# Higher-order aberrations in amblyopia: An analysis of pre- and post-wavefront-guided laser refractive correction

by

Anne T Salmon

BSc Physio-Pharm

BSc (hons) Optom

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Aston University

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# Preface

No part of this thesis, in any form, has been submitted for any degrees or other qualification at any university or college.

This thesis was a retrospective analysis of ophthalmic records pertaining to adult amblyopic and visually-normal patients who underwent wavefront-guided laser refractive correction at the London Vision Clinic, Harely Street, between May 2003 and September 2008. All pre- and post-operative measurements of visual acuity, contrast sensitivity and higher order aberrations were carried out by the team of practitioners at the London Vision Clinic prior to commencement of this study.

A. Salmon.

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## Thesis Summary

Thesis Title: Higher-order aberrations in amblyopia: An analysis of pre- and post-wavefront-guided laser refractive correction

Student Name: Anne T Salmon

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For more than a century it has been known that the eye is not a perfect optical system, but rather a system that suffers from aberrations beyond conventional prescriptive descriptions of defocus and astigmatism. Whereas traditional refraction attempts to describe the error of the eye with only two parameters, namely sphere and cylinder, measurements of wavefront aberrations depict the optical error with many more parameters. What remains questionable is the impact these additional parameters have on visual function.

Some authors have argued that higher-order aberrations have a considerable effect on visual function and in certain cases this effect is significant enough to induce amblyopia. This has been referred to as 'higher-order aberration-associated amblyopia'. In such cases, correction of higher-order aberrations would not restore visual function.

Others have reported that patients with binocular asymmetric aberrations display an associated unilateral decrease in visual acuity and, if the decline in acuity results from the aberrations alone, such subjects may have been erroneously diagnosed as amblyopes. In these cases, correction of higher-order aberrations *would* restore visual function. This refractive entity has been termed 'aberropia'.

In order to investigate these hypotheses, the distribution of higher-order aberrations in strabismic, anisometropic and idiopathic amblyopes, and in a group of visual normals, was analysed both before and after wavefront-guided laser refractive correction.

The results show: (i) there is no significant asymmetry in higher-order aberrations between amblyopic and fixing eyes prior to laser refractive treatment; (ii) the mean magnitude of higher-order aberrations is similar within the amblyopic and visually normal populations; (iii) a significant improvement in visual acuity can be realised for adult amblyopic patients utilising wavefront-guided laser refractive surgery and a modest increase in contrast sensitivity was observed for the amblyopic eye of anisometropes following treatment (iv) an overall trend towards increased higher-order aberrations following wavefront-guided laser refractive treatment was observed for both visually normal and amblyopic eyes. In conclusion, while the data do not provide any direct evidence for the concepts of either 'aberropia' or 'higher-order aberration-associated amblyopia', it is clear that gains in visual acuity and contrast sensitivity may be realised following laser refractive treatment of the amblyopic adult eye. Possible mechanisms by which these gains are realised are discussed.

Visual gain, anisometropic, strabismus, idiopathic amblyopia, laser eye surgery.

# Contents

# Chapter One

## 1.1 Introduction

The principal aim of this thesis was to analyse the distribution of higher-order aberrations in a population of amblyopes to determine whether such aberrations contribute to abnormal visual development. It has been proposed that binocular asymmetry in higher-order aberrations could lead to the development of amblyopia proper (i.e. neural dysfunction). If this was the case, correction of such higher-order aberrations would not lead to a restoration of visual acuity. Such cases have been termed 'higher-order aberration-associated amblyopia' (Prakash et al., 2007). Others have reported that patients with binocular asymmetric aberrations have been mistakenly labeled as amblyopes and that the unilateral decrease in visual acuity associated with an asymmetrical distribution of higher-order aberrations is purely refractive in origin. If this was the case, it has been suggested that the correction of such aberrations with wavefront-guided laser refraction surgery would restore visual acuity. These cases have appeared in non peer reviewed papers and have been termed 'aberropia' (Agarwal et al., 2002). To address these issues, the distribution of higher-order aberrations in strabismic, anisometropic and idiopathic amblyopes, and in a group of visual normals, was analysed both before and after wavefront-guided laser refractive correction.

This Introduction will begin with an overview of lower- and higher-order optical aberrations and the known effects of optical aberrations on visual function. This will be followed by discussions on strabismic and anisometropic amblyopia, higher-order

aberration-associated amblyopia and aberropia. An overview of laser refractive surgery will also be given, to include the effects of refractive surgery on higher-order aberrations and a discussion of the clinical protocol used on the cohort of subjects reported in this study.

### 1.1.1 Optical aberrations

The quality of a retinal image formed by the human optical system is limited by optical aberrations. If the eye were a perfect optical system, light from an object of regard would converge to a single point (see figure 1.1a). In the normal human eye, light rays passing through ocular media are distorted and deviate away from the principal course (see figure 1.1b). This departure of optical performance from the predictions of paraxial optics is termed optical aberration.

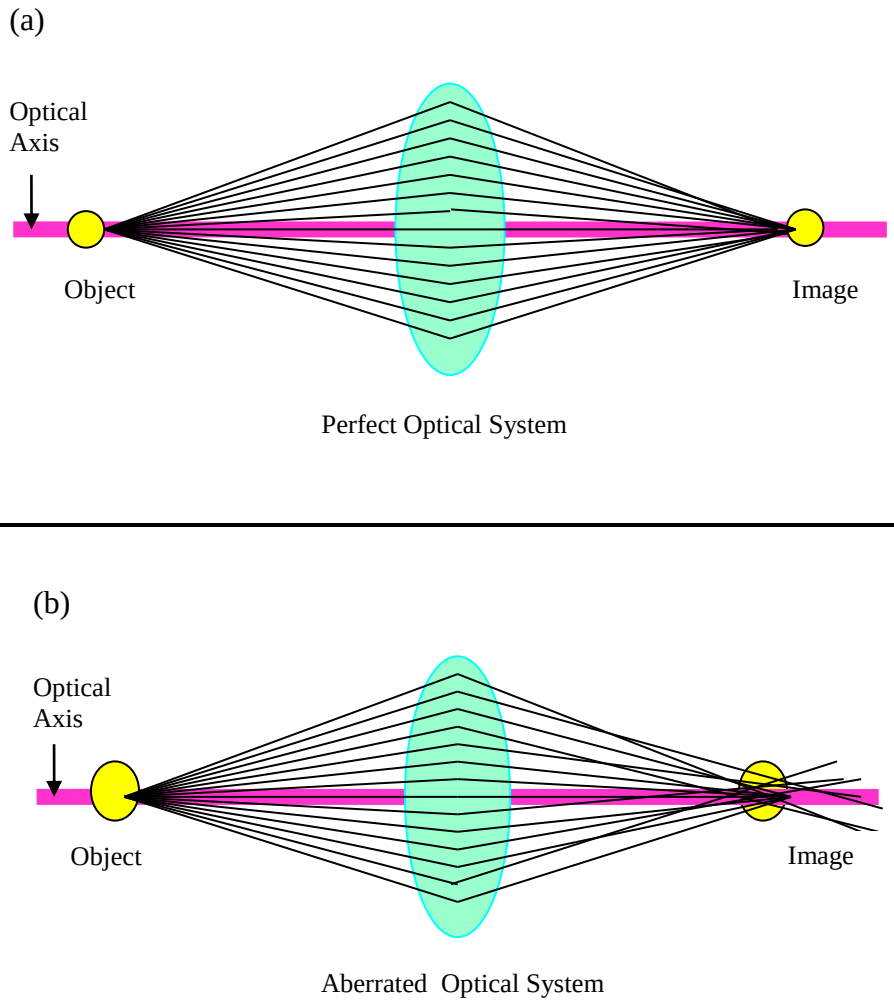



**Figure 1.1** (a) *The perfect optical system following assumptions of paraxial optics. (b) The aberrated human optical system.*

- **Lower-order aberrations**

Lower-order aberrations account for approximately 90% of the overall aberrations in the eye (Meister, 2010; Salmon et al., 2005). In the normal population, the dominant lower-order aberrations are the second-order sphero-cylindrical errors of myopia (positive defocus), hyperopia (negative defocus) and regular astigmatism. Note that first-order aberrations, such as tip and tilt, are reported to be visually insignificant (Meister, 2010; Liang et al., 1997; Williams et al., 2000). Lower- order aberrations are fully correctable with spectacle lenses, contact lenses or refractive surgery.

- **Higher-order aberrations**

The advent of adaptive optics, aberrometers and wavefront-guided refractive surgical techniques have unveiled a host of higher-order aberrations that describe more completely the aggregate effects of the ocular optical system on light passing through the eye. Such higher-order aberrations cannot be corrected with conventional spectacles, contact lenses or routine kerato-refractive surgical correction.

The impact of higher order aberrations on image quality may be described by image quality metrics such as point spread function (PSF), and modulation transfer function (MTF) and wave front error (WFE).

**Point spread function.** If the visual system had perfect optics the image of a spot or point of light on the retina would be identical to the original spot or point light source. Thus a plot of relative intensity of this point of light as a function of distance, on the retina, would result in a straight line, as illustrated in figure 1.2 by the dashed, vertical, green line. However, the eye's optics are not perfect, and thus the relative intensity of the point of light is distributed across the retina as shown by the red curve. This curve is called the "point spread function" (PSF). The degree of spread (blur) of the point object is a measure for the quality of an imaging system.


**Figure 1.2** *Illustrates point spread function. The dashed green line depicts the relative intensity of a point of light as a function of distance for a perfect optical system. The red curve depicts the spread of light intensity across the retina when the imperfections of the human visual system are considered (image taken from* http*://www.yorku.ca).*

The PSF describes the effects of diffraction and all optical aberrations. This may be depicted in two or three dimensional form, as illustrated in figure 1.3. The Strehl ratio may also be used to describe image quality using the PSF. The Strehl ratio is computed by taking the ratio of the height of the central core of the actual system PSF with respect to the central core of an aberration free PSF.

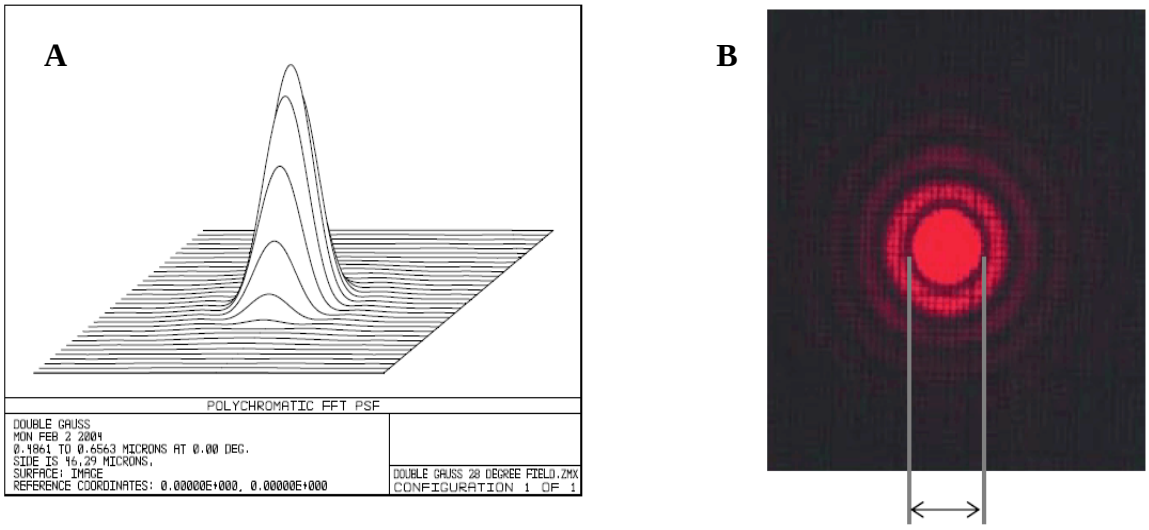



**Figure 1.3** *A) A three dimensional representation of point spread function. B) a two dimensional representation of point spread function. (adapted from Santamaría et al., 1987)*

**Modulation Transfer Function**. The limitation of point spread function as a descriptor of image quality is that it only describes the spread induced for point light source. Modulation transfer function describes the degradation of more complex square wave gratings (figure 1.4) as they pass through an optical system.

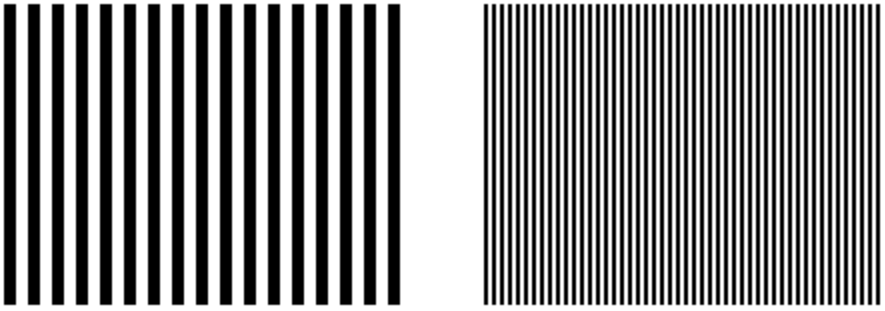


**Figure 1.4** *Square wave gratings. Grating on the left having a lower spatial frequency than grating on the left.*

Modulation may be defined according to the equation:

$$\text{Modulation} = (L_{max} - L_{min}) / (L_{max} + L_{min}).$$

Where: $L_{max}$ = the maximum luminance of the grating

$L_{min}$ = the minimum luminance of the grating.

When modulation is defined in terms of light it is frequently referred to as Michelson contrast, as the ratio of the illumination from the light and dark bars of the grating is essentially a measure of contrast. If a square wave grating stimulus of a specific

frequency (v) and modulation (contrast) is imaged through the optical system, the modulation of the image can now be measured.

The modulation transfer function (MTF) is defined as the modulation, Mi, of the image divided by the modulation of the object, Mo.

$$MTF(v) = Mi / M0$$

Thus MTF is the modulus of the Fourier transformation of the point spread function (PSF) as illustrated in figure 1.5.

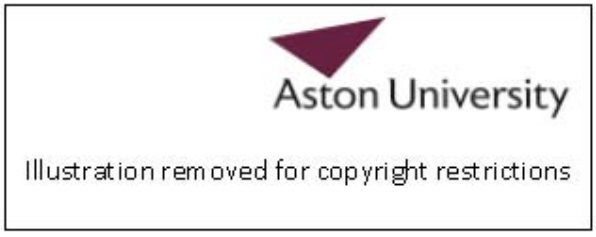



**Figure 1.5** *Modulation of an image as a function of spatial frequency. (Adapted from Santamaría et al., 1987)*

A MTF equal to one would be a perfect image of the grating, while an MTF of zero would be a uniform blur. The MTF is a very sensitive measure of aberration, a lens with only a quarter-wavelength spherical aberration would have its MTF reduced by approximately thirty percent.

**Wavefront error.** Higher-order aberrations may also be described in terms of 'wavefront errors'. This is perhaps one of the most widely used geometric methods for measuring image quality and the method used in the current study. The wavefront is a cross section of light rays traveling through the ocular media. In a perfect optical system, all rays are parallel and the wavefront cross-section is perfectly flat. Deviation from this flat reference plane is referred to as wavefront error, as depicted in figure 1.6 and 1.7.


**Figure 1.6 (a)** *Illustrates an ideal aberration free eye, where all rays of light entering the pupil converge onto the same retinal loci, forming a localised point spread function (psf) and flat, uniform wavefront mapped at the pupil plane. (b) Illustrates the normal aberrated eye, where rays of light entering the pupil strike the retina at different loci forming a point spread and a wavefront error mapped at the pupil plane.* (taken from Marcos, 2001).

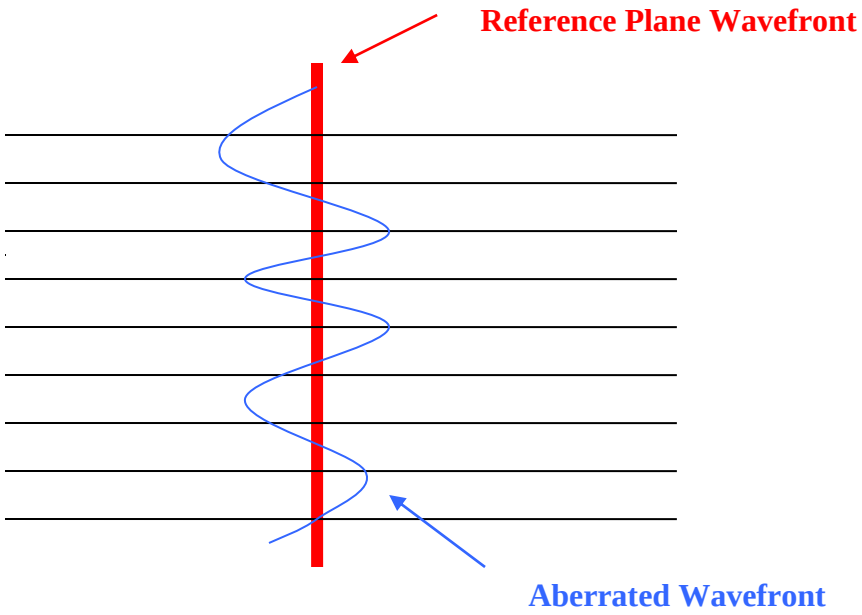
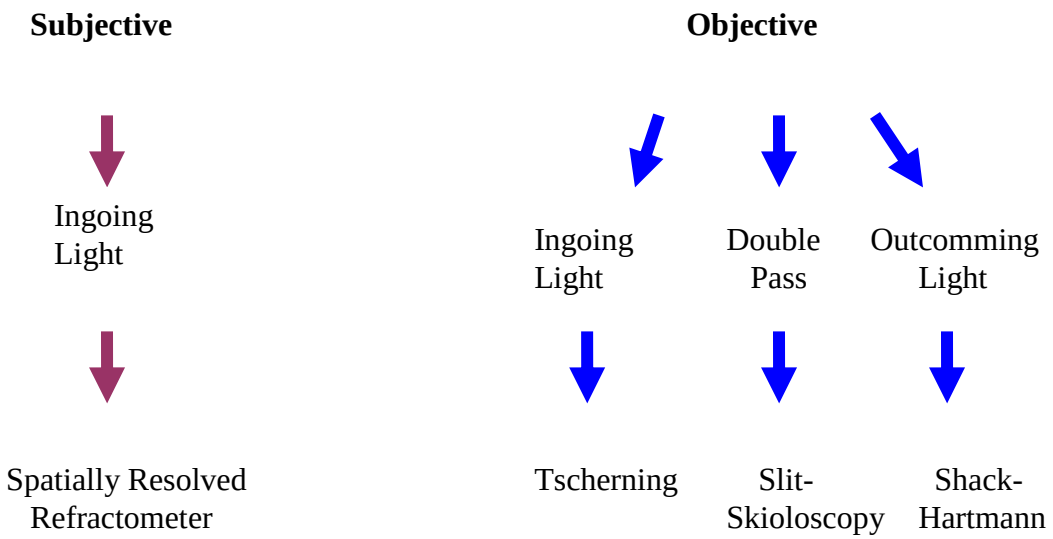



**Figure 1.7** *Illustrates the optical deviations of the wavefront from a flat reference plane.*

**Measuring the wavefront error.** The mechanisms for measuring higher order aberration wavefront errors may be broadly divided into 4 main categories.




1) **Spatial resolved refractometery** utilises an ingoing adjustable method of determining wavefront pattern. The ingoing light rays are manually adjusted by the patient until a central retinal focus is achieved. This patient adjustment allows for subjective determination of wavefront pattern.

2) **Tscherning** based devices utilise the retina to obtain the ocular wavefront pattern. A grid of laser energy is shone into the eye and projected onto the retina. The manor by which the grid deviates as it enters the eye and is imaged on the retina defines the wavefront pattern.

3) **Double pass** method uses both ingoing and outgoing light and analysis the wavefront pattern by slit skioscopy employing retinoscopic principles.

4) **Shack-Hartmann** principle. This method was utilised in the current study and involves measuring the displacement of outgoing light from a perfect lattice of lenslets. A small beam of light is projected along the ocular line of sight onto the retina. The retina reflects this light outwards through the lens and the cornea. Outgoing light is then directed through a set of lenslets. For the perfect unaberrated eye, the reflected plane of the wave of light will be focused into a perfect lattice of point images, each image falling on the optical axis of its corresponding lenslet. However for the aberrated eye a distorted wavefront will be reflected. The local slope of the wavefront will now be different for each lenslet. By measuring the displacement of each spot from its corresponding lenslet axis the slope of the aberrated wavefront can be deduced.

**Describing higher order aberrations.**

Once a wavefront error has been measured the data elicited is presented in its raw form termed centroids. Conversion of raw data to a usable description of the wavefront error involves the application of different mathematical techniques in order to describe the optical surface in three dimensions and to quantify these optical abnormalities or aberrations. The 3 primary mathematical integrations used are Siedel, Zernike, and Fourier algorithms.

**Siedel.** Seidel describes five monochromatic aberrations, which are, spherical aberration, coma, oblique astigmatism, curvature of field and distortion.


**Figure 1.8** *Illustrates the 5 Seidel aberrations (Spherical aberrations, Coma, Astigmatism, Curvature of Field and Distortion). (Image taken from http://www.quadibloc.com/science/opt0505.htm).*

**Spherical aberration.** Spherical aberration is the most common higher-order aberration encountered in the human visual system. It arises due to light rays reaching the retina from the curved periphery of the lens and cornea, producing a shorter or longer focal length than those entering from the central apical portions. The more spherical the peripheral curve is in relationship to the central or apical curve, the more spherical aberration is produced. Figure 1.15 illustrates the effect of spherical aberrations on point spread function (PSF) and retinal image quality.

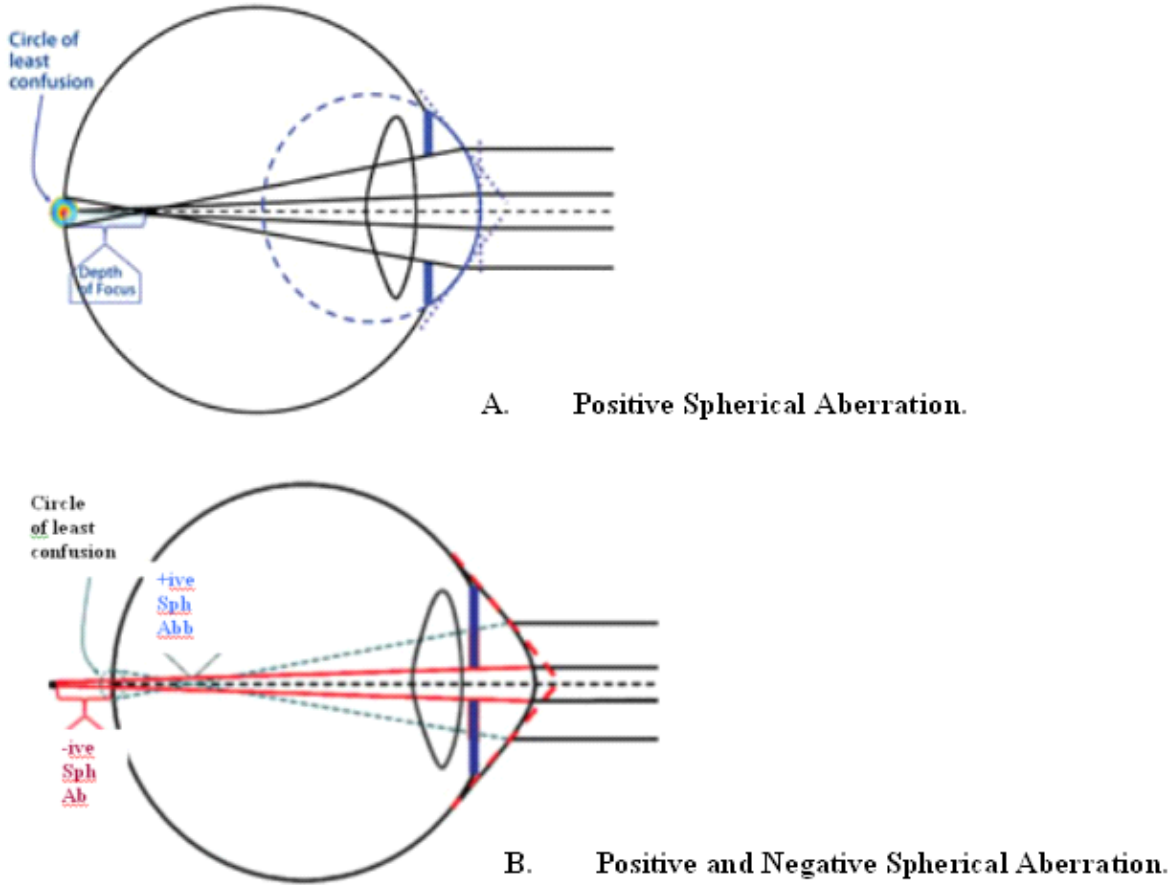



**Figure : 1.9** *Illustrates the formation of positive and negative spherical aberration.*

Spherical aberration may be described as positive or negative. With positive spherical aberration, the cornea / lens is more oblate in nature and thus peripheral light rays converge in front of the retina, inducing effects similar to that of myopia (see figure 1.9 A). With negative spherical aberrations the cornea / lens are more prolate shaped, inducing an insufficient convergence of peripheral rays. Hence, negative spherical aberrations will produce minimal reduction of distance vision but will not produce depth of focus for near (see figure 1.9 B).

**Coma**. The ability of the eye and visual system to replicate an identical image of an object of regard is termed the 'optical transfer function'. The optical transfer function is dependent upon the percent loss of contrast as a function of spatial frequency, termed the modulation transfer function, and on the phase of light transmission through the optical media, termed the phase transfer function. Axial coma arising from misalignment of the cornea and lens induce distortions which produce a wavefront that is comet shaped, as illustrated in figure 1.10.

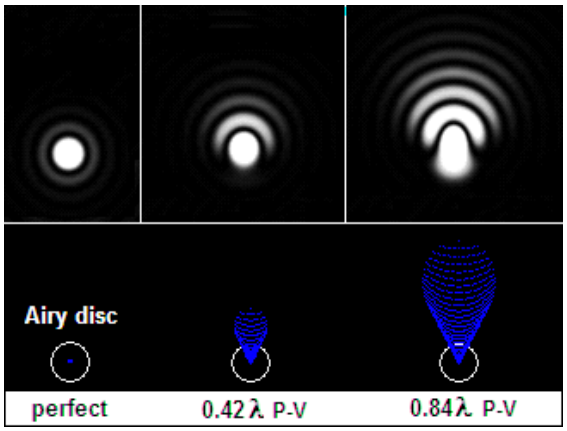



**Fig: 1.10**
*Coma aberration.*

*Right: Perfect image replication without the presence of coma.*

*As coma error increases, right to left best focus location shifts from the centre of the airy disc to form a coma shaped wavefront deformation*

**Oblique Astigmatism**. Arsis from the inability of the eyes optical system to form a point image of an oblique point object, due to the non-spherical radii of curvature of the eye's refracting surfaces. Instead of the rays reuniting in a single image point, they form two line foci at right angles to one another with a disk of least confusion in-between, where the refracted pencil has its least cross-sectional area, somewhere between the two foci. The plane containing the optical axis of the surface is referred to as the tangential plane and the plane at right angles to the tangential plane is referred to as the sagittal plane (see figure 1.11). Thus oblique astigmatism is an aberration of off-axis rays.


**1.11** *Top: Illustrates the tangential and sagittal error created by off axis oblique astigmatism. Below: the effects of oblique astigmatism on a point light source (Image taken from http://www.astrosurf.com).*

**Distortion.** Distortion represents the inability of an optical system to create a rectilinear image of the subject. Distortion occurs when light from points on the object are not focused in a linearly proportional distance from the optical axis, but instead brought together on the image plane at erroneous distance from the optical axis, resulting in parts of the image being more magnified than others. This aberration manifests with two main effects: barrel and pincushion, also referred to positive and negative distortion, as illustrated below in figure 1.12. The barrel shows a central image bigger than the edges, the magnification decreases with the off-axis object distance. The pincushion is the inverted phenomenon that is the edges of the field are bigger than the central area, the magnification increasing with the off-axis distance of the object. Distortion does not affect image quality but rather image lateral position and shape.

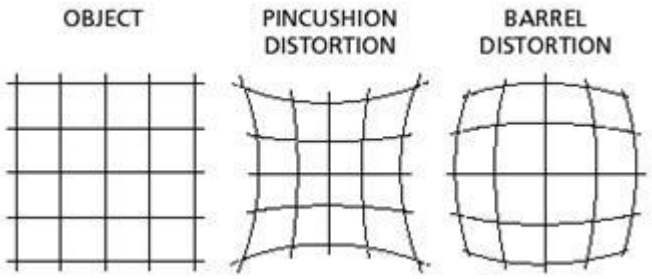



**Figure 1.12** *Depicts the affects of Siedel aberration; distortion.*

**Zernike.** Wavefront data produced by the eye is fitted to an allegoric circular polynomial first describe by Zernike in 1934. This expresses mathematically the three dimensional wavefront deviation from a unit circle of zero mean utilising circle polynomials. Deviations from zero mean are determined as a function of change in radial order height

(p) and angular frequency (θ). ρ is the normalised distance from the pupil centre. Normalising ρ means it has a maximum value of one at the edge of the pupil. Therefore, for a 6mm pupil, a point 3mm from the centre would have a ρ value of 0.5. θ is the angular subtense of the imaginary line joining the pupil centre and the point of interest to the horizontal. Thus aberration output data is dependent on pupil size. Therefore, all wavefront measures must be referenced to a pupil size.

$$W(\_,\theta) = \sum C^{m}_{n} Z^{m}_{n}(\_,\theta)$$

Wavefront Aberration — Zernike Co-efficient — Zernike Polynomial

Zernike co-efficients are determined using a least square fit to a grid of exact ray data, such that the individual aberrations within the polynomial are organised into a hierarchy of Zernike terms. This may be graphically represented as a pyramid resulting from Zenike term expansion as a function of radial order (n) and angular frequency (m). The terms are ordered and enumerated according to the specifically defined ordering number (j). The Zernike pyramid, as defined by American national standards institute (ANSI), is shown in figure 1.13 below. Zernike mode influence on visual function is reflective of their location in the aberration pyramid: terms located at the periphery of the aberration pyramid will have less impact on vision than modes located centrally. For example, spherical aberrations and coma exert a greater influence on visual performance than quadrafoil and pentafoil. The Zernike pyramid may also be presented pictorially using wavefront shape and a reference wavefront cross-section which is perfectly flat, known

for reference as piston. The measure of difference between the actual wavefront shape and the ideal flat-shaped piston represents the amount of aberration in the wavefront. Figure 1.14 illustrates various forms of higher-order aberrations.

The advantage of Zernike description is that at the lower end of aberration terms clinical familiar descriptions, such as defocus, astigmatism and spherical aberrations, are used. The total amount of optical aberrations may be reported as the root mean square (RMS) by combining Zernike coefficients. This allows for quick comparison of aberration profiles, gives an overall indication of the aberration level of the eye under consideration and is generally a relatively good indicator of the deviation of the wavefront form the ideal. This strategy works well for the more common lower-order shapes but is less accurate in eyes with highly aberrated wavefronts, as it only utilizes a subset of the acquired data points (typically the amount necessary to produce a 6th order image) and also does not apply any 'weighting' to the data, thus the affect of all aberrations (up to $6^{th}$ order) are treated as having the same impact on visual function. Thus different combinations of aberrations may have equal RMS across the pupil but have different effects on vision; hence, RMS error is a poor indicator of visual performance.

When fitting more complex patterns this mathematical model induces averaging and smoothing. Thus the data captured lose fidelity beyond nine orders of Zernike terms, and more noise than information is introduced into the solution beyond 10 orders. Also Zernike polynomials are also mathematically unable to describe a straight line. This

limitation has implications in terms of analyzing visual aberrations that result from striae and cap amputations that have a linear quality.


**Figure 1.13** *Zernike terms expansion pyramid. Aberrations are ordered as a function of radial order (n) and angular frequency (m). The 'j' number or Zernike mode determines placement within the pyramid. J = n(n=2) +m / 2; where n = radial order and m = angular frequency. (taken from telescope-optics http://www.telescope-optics.net).*


**Figure: 1.14** *Illustrates shapes of aberration profiles created when a wavefront of light passes through an eye. The piston describes the wavefront of a theoretical perfect aberration free eye (Image: Alcon Inc.www.alcon.com).*

**Fourier transformation analysis** uses a mathematic process of harmonic analysis that does not split the visual system into individual terms but rather creates a description of the whole wavefront. This involves the use of a series of chosen sine waves and thus overcomes the difficulty in reconstructing a complex or irregular patterns, as a series of sine waves can be taken and simply added together in order to describe any given shape. Similarly there is ease of breaking down a complex pattern into its component sine waves in a process termed Fourier analysis. Thus it has been suggested that Fourier synthesis is roughly equivalent to a 20th-order Zernike polynomial (Brint and Vukich, 2005). The disadvantage of Fourier description of wavefront error is that it presumes that the data from all lenslets are equally reliable and there is no way to weight data points or to evaluate and/or discard highly suspect points. In addition the Fourier model presumes a perfect and repeatable image but it is known that the effects of the tear film, accommodation, and fixation will to produce some variability.

The Optical Society of America, charged with the task of developing recommendations on definitions, conventions, and standards for the reporting of optical aberrations of human eyes has recommended adopting the use of Zernike Polynomial (Thibos et al., 2000), suggesting that this approach is best-suited for our current treatment technologies, providing the necessary accuracy without introducing artefacts or being overly sensitive to noise in the measurement and subsequent treatment. Thus Zernike RMS of aberration in addition to Siedel aberrations Coma and Spherical aberration were used in the current study in order to describe and compare the overall wavefront error of eyes under analysis.

Coma and Spherical aberration were chosen as it has been shown that with respect to their effect on visual performance, these are two most common and most troublesome forms of higher-order aberrations (Applegate et al., 2002).


**Figure 1.15** *Illustrates the differing effects of higher order aberrations coma and spherical aberration on point spread function and retinal image quality (taken from Karpecki, 2007)*

- **Distribution of higher-order aberrations within the normal population**

It has been shown that the normal human visual system is far from a perfect optical system (Castejon-Mochon et al., 2002), but rather suffers from optical aberrations inherent in its high plus design. However, there also exist several innate mechanisms to reduce the effects of these intrinsic aberrations on every day visual function.

Firstly the anatomy of the eye minimises the affect of spheriacl aberrations. The corneas prolate shape and the anterior corneal surface being flatter peripherally than centrally (aplanatic surface), results in less refractive power at the periphery therefore reducing refraction of peripheral light rays. The nucleus of the eyes crystalline lens has higher refractive index than the lens cortex, so that again central rays of light are refracted more than peripheral. The Iris acts as stop down aperture to reduce spherical aberration. Average pupil size is approximately 3-4mm in photopic illumination, at which the pupil edge coincides with the peak of spherical aberration. In scotopic conditions, where pupil size enlarges, rod activity predominates rendering the effects of spherical aberrations on visual function negligible. On accommodation pupil size is reduced and the central anterior lens surface bulges forward while the peripheral edges flatten, increasing the refractive power more centrally and reducing spherical aberration. In addition the Stiles Crawford effect, which describes the directional sensitivity of cones, capturing photons of light most effectively when incident directly along the cone axis and light striking cones at larger angles of incidence being less effective at stimulation, thus peripheral light rays that are refracted more due to spherical aberration will be less troublesome.

Secondly, it has been shown that within the visually normal population it has been shown that right and left eye higher-order aberrations display significant correlation, exhibiting mirror symmetry in type and magnitude (see figure 1.17) (Castejon-Mochon et al., 2002; Porter et al., 2001; Applegate, 2002; Thibos et al., 2002). On binocular viewing there is unification of these two mirror images into a single percept, which has been shown to reduce the adverse impact of monocular higher-order aberrations on visual performance (see figure 1.18). This enhancement is believed to be associated with neural summation at a cortical level, where there is convergence of monocular input (Prakash et al., 2007; Fam and Lim, 2004). Those higher order aberrations that have been shown to have the greatest effect on visual performance - spherical aberrations and coma - have also been shown to have higher percentages of binocular summation (Fam and Lim, 2004). Experimental models using adaptive optics systems illustrate that the reverse also holds true, in that by inducing higher-order aberrations that do not display mirror symmetry, binocular summation and visual performance are adversely affected, as exemplified in figure 1.18 (Fam and Lim, 2004).


**Figure: 1.16** *Illustrates mirroring symmetry between right and left higher order aberrations, utilizing three dimensional wavefront plots of surface aberrations of two observers (image taken from Ling and Williams 1997).*


**Figure 1.17** *Percentage binocular summations according to Zernike mode. Coma and Spherical like aberrations showing the greatest influence on binocular summation. Error bars represent one standard error (Image taken from Fam and Lim 2004).*


**Figure 1.18** *Aberration induced loss in monocular visual acuity (top) and binocular visual acuity (bottom). A greater loss in binocular visual acuity is observed on introduction of 2$^{nd}$, 3$^{rd}$, and 4$^{th}$ order aberrations. Measurements taken utilizing aberrated and unaberrated LogMar acuity charts. Error bars show one standard deviation (Image taken from Fam and Lim 2004).*

- **Distribution of higher-order aberrations within the amblyopic population**

Blake et al. (1973) stated that the cardinal feature of the binocular visual system is unification of the two separate monocular views into a cyclopean view that betrays little trace of its monocular origins. Within the amblyopic population the two monocular views presented to the visual system are so disparate, unification into a single precept cannot be achieved. The unveiling of the presence of higher order aberrations within the human visual system has led to the question of whether a disparate distribution of higher order aberrations contribute to the development of amblyopia (Agarwal et al., 2010 Prakash et al., 2011).

However, little is known about the pattern of higher-order aberrations within the amblyopic population. Moreover, the limited data which does exist displays little agreement. Kirwan and O Keefe (2008) found no statistically significant difference between the fellow and amblyopic eyes of either strabismic or anisometropic amblyopes. However, Yu et al. (2009) did report a statistically significantly difference between eyes of amblyopic subjects. Prakash et al. (2011), in a cross sectional observational trial, found no statistically significant difference in comparison of mean Zernike coefficients between normal and amblyopic eyes, although the interrelation between Zernike coefficients was significantly different between amblyopic and fellow eyes.

- **The effect of higher-order aberrations on visual function**

It has been demonstrated that higher order aberrations exert more effect on contrast sensitivity than visual acuity. Liang and colleagues (1994) were the first to illustrate that higher-order aberrations affected visual performance and could be corrected using adaptive optics systems. Utilising a deformable mirror, they demonstrated a six fold increase in contrast sensitivity when higher-order aberrations were corrected. Yoon and Williams (2002) repeated Liang's experiment using the same adaptive optics system, evaluating the effect of aberrations on letter acuity as well as contrast sensitivity. Their findings are depicted in figure 1.19 and 1.20 below. They reported a five-fold improvement in contrast sensitivity, but only a modest improvement in letter visual acuity. Likewise, Li et al (2009) found a mean improvement in visual acuity of only 1.9% after correction of spherical aberrations, while a 13.5% increase in contrast sensitivity was reported.


**Figure: 1.19** *Change in contrast sensitivity function following correcting of low order aberrations only (x symbols), chromatic aberrations (open triangles), monochromatic aberrations (open circles), all aberrations (solid circles) (Image taken from Yoon and Williams, 2002).*


**Figure: 1.20** *Effect of correcting higher order aberrations on Snellen visual acuity. Visual acuity measurements taken at retinal luminance level of 474Td, with a 6mm pupil size. The error bars represent one standard error of the mean (Image taken from Yoon and Williams, 2002).*

It has been proposed that the difference in measurable benefit gains between contrast sensitivity and visual acuity, following correction of higher order aberrations, are due to neural factors limiting acuity improvement even when enhancement in retinal image quality are realised. That is, foveal cone spacing will ultimately impose a limit of approximately 60 cycles per degree; nonetheless an increase in retinal image contrast at spatial frequencies below this sampling limit will still provide improved image quality (Williams et al., 2000). Conjecture on the matter by other authors suggests that it may be neural transfer function which is the limiting factor in achieving visual acuity

enhancement (Applegate et al., 2003). Another suggestion is that the Stiles–Crawford effect halts acuity gain that may be realised by correcting aberrations at the corneal plane (Gao et al., 2008). This phenomenon describes how cone photoreceptors have directional sensitivity and capture photons of light most effectively when the beam of light is incident directly along its axis. Light which strike cones at larger angles of incidence are less effective at stimulating cones. Thus the gain in correcting all aberrations across the corneal surface may be lost due to oblique angles of incidence of light, as shown in figure 1.21

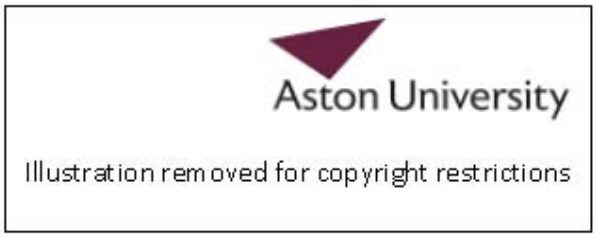



**Figure**:**1.21** *Gray scale plot (A) and surface plot (B) illustrating the Styles Crawford Effect. (Vision Science II - Monocular Sensory Aspects of Vision. http://www. learningace.com.)*

Perhaps the simplest explanation is that visual acuity per se is not a sufficiently sensitive measure to access improvements gained by correcting higher-order aberrations. This may be so because the contrast sensitivity function is too steep at the acuity limit, and thus

large changes in contrast sensitivity may have little effect on acuity, as illustrated in figure 1.22.


**Figure: 1.22** *Illustrates the relationship between contrast sensitivity and visual acuity. The lower part of the curve reflects traditional acuity letter charts. The slope of the curve is relatively steep, thus improving contrast from 25% to 100% results in little effect on the visual acuity measurement. To determine point 'b', a high contrast variable letter size chart is used (conventional acuity chart). To determine point 'c', a low contrast letter chart is required (Image taken from Precision-Vision, 2012).*

Thus in the current study, measures of both of visual acuity and contrast sensitivity pre- and post- wavefront-guided laser refractive correction were considered.

## 1.2 Amblyopia

Amblyopia is normally defined as a reduction in visual acuity in one or both eyes that cannot be corrected by refraction and is not associated with any ocular pathology or structural abnormality of the eye. Based on the evidence presented by various studies (Badell et al., 1981, Ciuffreda wt al., 1979, Kirschen et al., 1981, Stuart et al., 1962, Flom et al., 1963, Brock et al., 1952, Hess et al., 1977, Wood et al., 1975) the American Optometric Association (AOA, 2004) has suggested that this definition of amblyopia should be expanded to include deficits not only in visual acuity but also contrast sensitivity. Table 1.1 shows the syndrome of compromising deficits in amblyopia, as defined by the AOA. Table 1.2 outlines the characteristics of amblyopia as defined by the AOA.

| **Syndrome of Compromising Deficits in Amblyopia Defined by American Optometric Association** | |
|---|---|
| • Increased sensitivity to contour interaction effects. | • Abnormal spatial distortions and uncertainty. |
| • Unsteady and inaccurate monocular fixation. | • Poor eye tracking ability. |
| • Reduced contrast sensitivity. | • Inaccurate accommodative response. |

**Table 1.1** *Syndrome of Compromising Deficits in Amblyopia*

| **Characteristics of Amblyopia.**<br>**Defined by American Optometric Association** | |
|---|---|
| • Decreased best corrected visual acuity in the absence of any pathology. | • Increased sensitivity to contour interaction effects. |
| • First and last letter are most readily identified. | • Abnormal spatial distortions. |
| • Reduced contrast sensitivity. | • Reduced hyperacuity. |
| • Reduced vergence eye movements. | • Increased accommodative latency. |
| • Diminished papillary response amplitude. | • Acuity improves with isolated letters and is relatively reduced when presented with a row of letters: crowding phenomenon. |
| • Pursuit and saccade abnormalities:<br>○ Increased latency in saccadic eye movements.<br>○ Reduced gain in pursuit eye movements.<br>○ Asymmetric pursuit eye movements.<br>○ Abnormal saccadic substitution.<br>○ Asymmetric optokentic nystagmus. | |

**Table 1.2** *Characteristics of Amblyopia*

- **Pathophysiology of amblyopia**

Early work using animal models suggested the primary defect in amblyopia may exist at the level of the retina (Ikeda et al.,1974,1976; Crewther et al., 1982). However, later electrophysiological studies (Gottlob et al., 1987, Hess et al., 1985) demonstrated normal physiological function in the retina of amblyopic human eyes.

Similarly, the lateral geniculate nucleus (LGN) was put forth as a possible site of defect based on morphologic changes noted in animal amblyopic models (Von Noorden 1973,1975; Kupfer, 1965; Hickey et al., 1977; Guillery, 1972; Tremain et al.,1982). However, neurophysiological studies reported no evidence for LGN dysfunction in amblyopia (Levitt et al., 2001; Blakemore et al., 1986; Derrington et al., 1981; Sasaki et al., 1998). Functional magnetic resonance imaging (fMRI) allowed quantitative analysis of the function of the LGN in human amblyopes. Although functional deficiencies in LGN activity have been reported in amblyopes (Hess et al., 2009), the current consensus of opinion is that this reduction in LGN activity is reflective of a reduction in feedback from higher cortical areas (Levitt et al., 2001, Blakemore et al., 1986, Derrington et al., 1981, Sasaki et al., 1988).

Today, the visual cortex is considered to be the primary site of dysfunction in human amblyopia, as suggested by the pioneering work by Hubel and Wiesel (1962). Their work demonstrated that amblyopia is a developmental problem in the visual cortex rather than an intrinsic, organic neurological problem in the eye. They further established that age

was an important factor in the development of amblyopia, and put forth the concept of a 'critical period' during which connections in the cortex are particularly susceptible to change. They showed that sensory input from each eye competes for representation within the visual cortex, and that the eye which competes most successfully establishes ocular dominance (Hubel and Wiesel, 1970).

Modern day functional imaging studies provide support for the original work of Hubel and Wiesel (Anderson and Swettenham, 2006; Furmanski et al., 2004; Maertens et al., 2005; Neary et al., 2005; Barnes et al., 2000; Muckli et al., 2006; Li et al., 2007). Functional magnetic resonance imaging (fMRI), positron emission tomography (PET) and magnetoencephalography (MEG) have been the primary neuroimaging tools used to asses the site and nature of cortical deficits in amblyopia. A review of the literature indicates that the amblyopic visual cortex shows numerous areas of abnormal activity, including V1, V2, parieto-occipital and ventral temporal cortex (Roelfsema et al., 1994; Hess and Field, 1994; Levi and Klein, 1986; Levi et al., 1994). Based on a variety of experimental studies, the nature of this abnormal activity has been shown to include desynchronized cortical responses (Roelfsema et al., 1994), neural disarray (Hess and Field, 1994), neural under-sampling (Levi and Klein, 1986) and/or the loss of fine –scale spatial visual processing (Levi et al., 1994). It has been proposed that the type of amblyopia, amblyopic density, whether a refractive component exists and the age of treatment initiation will all serve to influence the site and nature of the cortical defect (Anderson and Swettenham, 2006).

- **Classification of amblyopia**

The classification of amblyopia is based on the clinical condition which gave rise to its development. These are briefly reviewed below.

***Form Deprivation Amblyopia.*** Form deprivation amblyopia occurs when a physical obstruction to vision occurs during the critical period of infant development (Ciuffreda and Levi, 1991). Causes include cataract, complete blepharoptosis, corneal opacity, hyphema, vitreous hemorrhage and over occlusion (Anderson et al., 1980; Harrad et al., 1988; Hardesty, 1959; von Noorden, 1981).

***Refractive Amblyopia.*** Anisometropia refers to unequal uncorrected refractive error in which the difference between the corresponding major meridian of the two eyes is at last 1D. The greater the degree of anisometropia the more severe the amblyopia (Jampolsky et al.,1955; Kivlin and Flynn, 1981; Tanlamai and Gross, 1979).

***Strabismic Amblyopia.*** Esotropia, exotropia, hypotropia, and hypertropia may all give rise to strabismic amblyopia. In order to avoid confusion or diplopia, the visual systems suppresses the image from the strabismic eye. This active inhibition disrupts binocular rivalry and in time results in reduced retinotopic mapping of the strabismic amblyopic eye at cortical level.

***Idiopathic Amblyopia.*** Idiopathic amblyopia refers to amblyopia which cannot be attributed to the presence of strabismus, uncorrected refractive error or form deprivation, thus termed a 'diagnosis of exclusion'. Such patients display reduced visual acuity with no sustained improvement utilising conventional refractive correction or occlusion. With the introduction of wavefront analysis technology, the possibility of asymmetrical higher-order aberration profiles acting as an amblyopiogenic factor in 'idiopathic amblyopia' has been suggested (Agarwal et al., 2002; Parakash et al., 2007). There are two distinct theories relating higher-order aberrations and idiopathic amblyopia, both of which are reviewed below.

- **Aberropia**

Agarwal (2002) proposed a new refractive entity termed Aberropia. Aberropia is defined as a refractive error that results in a decrease in visual acuity that can be attributed to higher order aberrations (Agarwal, 2002). Aberropia may be further classified as either congenital or acquired (see figure 1.23). Congenital aberropia describes a patient born with high amounts unilateral aberrations which, if large enough, may interfere with normal binocular interactions. Acquired aberropia describes a condition that is secondary to pathology such as keratoconus, lenticonus, subluxated lens, vitreous opacities, thickened posterior hyaloid, or fine epiretinal membrane that may arise secondary to corneal or lenticular surgery (Agarwal, 2003).


**Figure: 1.23** *Classification of Aberropia (Agarwal 2002)*

The suggestion of this novel clinical entity, aberropia, albeit in non-peered viewed papers, gave new impetuous to assessing and possibly correcting higher-order aberrations. As visual pathway development and cortical inhibition are not thought to be involved in the aetiology of aberropia, patients' age should not be a limiting factor for treatment. Thus, treatment of aberropia would not be confined to the critical period and manipulation of higher-order aberrations at the corneal plan would serve to improve visual acuity in the adult idiopathic amblyopic eye (Agarwal et al., 2010; Young, 2007).

- ***Higher-Order Aberration Associated Amblyopia***

Prakash and colleagues put forth a case hypothesizing 'higher-order aberration associated amblyopia'. Unlike Agarwal's 'aberropia', where vision was impaired by hitherto undetected higher-order aberrations, Prakash et al. suggested that between-eye differences in wavefront profiles results in the fellow eye gaining ocular dominance at a cortical level, and thus the fellow eye becoming truly amblyopic (Prakash et al., 2007; Argarwal et al., 2007) . They reported a case of asymmetrical higher-order aberrations in which the subject was diagnosed with 'idiopathic amblyopia'. In this case laser interferometry did not return a value of 6/6. It was therefore proposed that this finding would indicate that the amblyopia persists even after the obstacle to bifoveal fixation is no longer present and thus suggests a cortical origin of defect.

In a follow up cross sectional observational trial, Prakash et al. (2011) evaluated higher-order aberration profiles within a pediatric 'idiopathic' amblyopic population. It was found that interrelation between Zernike coefficients were significantly asymmetrical. Prakash and colleagues concluded that there would seem to be a strong possibility that a subset of 'idiopathic' amblyopia may be associated with loss of symmetry in wavefront patterns of the two eyes (Prakash et al. 2011). To illustrate this point, Prakash et al. (2011) asked the reader to consider a hypothetical situation where optometrists are only aware of spherical power (defous) and have no knowledge of astigmatism. In such a supposed scenario, patients with meridonal anisometropia would be labeled 'idopathic' amblyopes as there would be no known aetiology for their development of amblyopia –

this, he suggests, is akin to what has occurred with an amblyopic subgroup with asymmetrical higher-order aberration profiles.

In addition, Prakash et al proposed an emmetropization like tendency for higher order aberrations akin to the emmetropization pattern seen with lower-order spherocylindrical aberrations. Brunette et al. (2003) demonstrated a progressive decrease in higher order aberrations from childhood to adulthood and also suggest that the definition of emetropization be expanded to include reduction of higher order aberrations. Thus, Prakash et al put forward that this process of higher order aberration emetropization may be disrupted in subjects with higher order aberration associated amblyopia resulting in abnormal binocular interaction and amblyopia.

- **Amblyopia treatment**

The underlying principle in amblyopic treatment is restoration of visual acuity by promoting use of the amblyopic eye. This may be achieved by:

***Full refractive correction.*** Full refractive correction after cycloplegic refraction affords the best quality image to be formed on the retina. High degrees of anisometropia cause disparity in retinal image size between the two eyes (aneisokonia), and large amounts of aneisoknia may represent a barrier to fusion (Faber, 2002). In such cases contact lenses may be a useful alternative to spectacle treatment (Roberts and Adams, 2002). Refractive amblyopes often show significant improvement in visual acuity, contrast sensitivity and accommodative function following 4-6 weeks of full time continuous optical correction,

although it may take up to 24 weeks to see the full benefit of refractive correction (Mosley at al., 2002).

***Occlusion.*** The rationale behind occlusion therapy is that the occlusion of the fixing eye stimulates the amblyopic eye, enabling neural input to the visual cortex from the amblyopic eye and reducing cortical inhibition. A recent report by the Pediatric Eye Disease Investigator Group (PEDIG, 2003) suggested a prescribed patching regime of two hours for moderate amblyopia and six hours for severe amblyopia. Dose response evaluation indicated an 82% improvement in visual acuity achieved after 6 weeks of occlusion therapy, with further improvement gain up to 12 weeks (Stewart et al., 2004).

***Penalisation.*** Penalisation treatment involves 'hindering' the sound eye at near or distance or both in order to facilitate visual stimulation of the amblyopic eye. Penalisation may be achieved by the instillation of a cycloplegic drug into the sound eye, thus preventing accommodation and reducing depth of focus. In this way the amblyopic eye is used for near fixation. This method is generally employed in cases of moderate amblyopia or when the patient is uncooperative with conventional patching. Optical penalisation may be achieved by optimally correcting the amblyopic eye while placing a high powered over-correction before the fellow eye, thus reversing the visual relationship that existed previously between the two eyes. The PEDIG (2004) suggested that both penalisation and patch occlusion are effective treatments for moderate amblyopia.

***Perceptual Learning.*** Gibson (1963) defined perceptual learning as any relatively permanent and consistent change in the perception of a stimulus array following practice or experience with this array. Perceptual learning strategies for remediation of amblyopia involves intensive, active, supervised visual experience with feedback (Wong 2012).

The concept of utilising perceptual learning tasks for amblyopic therapy has gained some momentum over recent years. Employing such treatment strategies became attractive to practitioners for two reasons. First, conventional treatment of patching or penalisation does not promote binocular cooperation and many patients retain abnormal binocular vision despite improved acuity in the amblyopic eye. Conversely perceptual learning encourages binocular vision (O'Toole et al., 1992; Chen et al., 2008; Knox et al., 2012) Second, the effects of perceptual learning on visual performance extend beyond the critical period of visually development and thus can be effective in adult amblyopia (Huang et al., 2008; Zhou et al., 2006; Levi 2005; Polat et al., 2004; Li et a., 2004; Hussain et al., 2012). To date three small studies with control groups have investigated the effectiveness of perceptual learning as a therapeutic option (see Polat et al., 2004; Chen et al., 2008; and Liu et al., 2011). Although holding promise, randomised controlled clinical trials comparing conventional treatment with perceptual learning therapy are needed to address the true potential of this novel therapy.

***Laser Refractive Surgery.*** Traditional methods of correcting and rehabilitating anisometropic amblyopia through spectacle correction, occlusion and /or penalisation pose a challenge in a subset of amblyopic patients due to significant aniseikonia, compliance issues or both. Each diopter of spectacle refractive correction represents a

change in retinal image size of approximately 2%, thus inducing a degree of aniseikonia (Wilson et al., 2008). Anisometropia greater than 3.5D may represent a barrier to fusion and such patients are often left under corrected (Faber, 2002). Prismatic difference between the two spectacle lenses may also induce ansiotropia in different directions of gaze. These issues may be circumnavigated by correction with contact lenses at the corneal plane. However, difficult maintenance regimes, contact lens intolerance, lack of adaptation, frequent loss of contact lenses, cost, poor compliance and higher risk of microbial keratitis infection have been cited as restricting the role of contact lens correction, particularly amongst the pediatric amblyopic population. (Wilson et al., 2008; Autrata and Rehurek, 2004; Paysse et al., 2006).

Refractive correction at the corneal plane can also be achieved through laser refractive surgery. In recent years several studies have investigated laser refractive correction as a method of anisometropic correction for pediatric amblyopes where conventional therapies have failed. Table 1.3 summaries the findings of said studies.

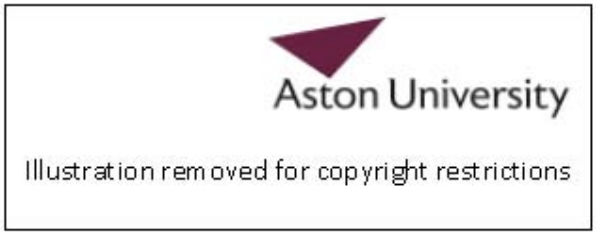



**Table 1.3.** *Summary of studies evaluating laser refractive treatment for anisometropic amblyopia. # pts = number of patients. SE = spherical equivalent. FU = follow up. Complic = complications. NR = not reported (taken from Paysse, 2007).*

Some authors have investigated whether an improvement in visual acuity, beyond that achieved with conventional treatment, may also be possible in adult amblyopes following laser refractive surgery. For example, Roszkowska (2006) reported a one / more line gain in 82.5% of anisometropic amblyopes included in their study and Barequet et al. (2004) reported a 3 line gain in a similar patient cohort. Sakatani et al. (2004) and Lanze et al. (2004) cited a statistically significant improvement in BSCVA in both adult anisometropic and strabismic amblyopes following laser refractive treatment. However Orucoglu et al. (2011) is the only study thus far in which a control group was employed. In this retrospective analysis, the fixing eye of the amblyopic subjects was used for control measures. Note, however this remains a controversial practice because it is unclear whether the fixing eye of amblyopes can be deemed 'normal' (see section 2.2).

The reasons why a superior gain in acuity is afforded following laser eye treatment of the adult amblyopic eye are not fully understood. A number of factors have been suggested, including a sustained refractive correction by surface laser ablation, a reduction in aneisokonia and a reduction in spectacle aberrations (Orucoglu –Orucov et al., 2011; Sakatani et al., 2004; Barequet et al., 2004; Lanza et al., 2005). It has also been postulated that a reduction in higher-order aberrations may be the reason behind this greater visual gain. The suggestion of the novel clinical entity 'aberropia' has resulted in a growing interest relating to assessment and correction of higher-order aberrations within the amblyopic population. Should Agarwals' theory of 'aberropia' hold true, manipulation of higher-order aberrations at the corneal plane may serve to restore aberration symmetry and thus improve visual acuity, increase contrast sensitivity and allow binocular summation to be established in the adult amblyopic eye.

## 1.3 History of laser refractive surgery

The first description of surgical manipulation of the cornea in order to allow correction of refractive error was from Sato (1933). Following observation of corneal flattening secondary to acute breaks which developed in Descement's membrane in keratoconic patients, Sato embarked on elimination of myopia and astigmatism by making several corneal incisions (Sato,1939). Fyodorov and Durneva (1972) refined Sato's techniques, and produced a formula for the number of radial corneal incisions that would provide a more predictable outcome for individual patients. Barraquer (1981) pronounced that "the correction of refractive defects should not depend on hopeful placement of incisions and cicatrical retraction of wound healing, but a process that permitted a predetermined result of the greatest possible accuracy on an organ in permanent regeneration". He named his new procedure keratomileusis, derived from the Greek words keratos (outer layer) and mileusis (carving).

Talamo (1997) and Seiler (1995) were the first to utilise the excimer laser to create keratotomy incisions. Initial results of laser keratotomy were poor, with Seiler reporting better results when excising over the whole corneal area. This technique was termed photorefractive keratotomy (PRK).

As the uptake of PRK increased, significant corneal haze, regression of refractive effect and poor predictability became apparent (Seiler, 1995). It was theorized that such complications could be attributed to surface ablation possibly severing of the corneal neural network and destruction of Bowman's layer. Buratto and Pallikaris (1989)

proposed the theoretical advantages of combing Barraquers intra stromal keratomileusis technique with Seilers PRK by creation of a hinged flap containing epithelium, Bowmanns layers and the anterior stroma and then applying excimer to produce 3-mm-diameter circular ablations on the central part of the exposed stromal bed. Once ablation was complete the flap was repositioned and held in place via the action of the endothelial pump. This new technique, coined Laser in Situ Keratimileusis (LASIK), avoided trauma to Bowmans layer (Pallikaris et al., 1990).

Retrospective evaluation of patient satisfaction and visual outcomes following LASIK procedures revealed that although the majority of patients were satisfied with the level of 'day-to day' uncorrected vision achieved, reports of post operative glare, haloes, star bursts and reduction in contrast sensitivity remained (Holladay at al., 1999). Clinically it was found that such patients suffered from a reduction in contrast sensitivity and increased glare recovery times (Ghaith, 1998). It was considered that the above signs may be attributed to the creation of higher-order aberrations during the ablation process (Marcos, 2001).

Traditional laser refractive treatment involves altering the curvature of only the central corneal area, flattening it for myopes and steepening it for hyperopes. Central ablation contours dramatically change corneal asphericity and thus change the aberration profile for the optical system of the eye. Such ablation induced increases in higher-order aberrations required consideration when planning treatment profiles. This led to

incorporation of aberrometer systems into laser platforms, and the introduction of wavefront-guided laser refractive treatment.

Wavefront-guided treatments involve the utilization of aberrometers to measure the aberrations of the entire optical system, thus affording refractive surgeons the opportunity to consider both lower-order aberrations (spherical and cylindrical refractive error) as well as higher-order aberrations when compiling their ablation profiles. Rather than creating a sharp central ablation zone with a circular laser beam, wavefront-guided surgery utilize a system of smaller beam scanning spot lasers to deliver the laser energy in a pre-determined customized pattern. The introduction of iris registration hardware into wavefront-guided programmers have helped improve the transfer of pre-operative aberrations profile data to in-situ surgical application (Chernyak, 2004). Such refinement has been achieved by not only reducing the incidence of misalignment of ablation profiles but also accounting for physiologically induced cyclorotation when the patient changes from a seated position for corneal mapping to a supine position for surgical correction (Chernyak, 2004).

Despite the popularity of wavefront-guided ‘customised laser treatment’, there has been no unanimous opinion about its definitive clinical benefit. A review of the literature indicates that, although utilisation of wavefront-guided systems has served to reduce the amount of laser refractive induced aberrations, there are still limits to the achievement of an aberration-free eye (Mrochen 2000).


**Table 1.4:** *Reported results of Snellen visual acuity, contrast sensitivity and higher-order aberration outcomes for comparative studies of wavefront-guided (W) versus conventional (C)LASIK procedures. (NR= not reported) (taken from Schallhorn et al., 2008).*

Table 1.4 shows the level of refractive accuracy, Snellen visual acuity, changes in contrast sensitivity function and changes in higher order aberrations for several comparative studies of wavefront-guided (W) versus conventional (C) LASIK procedures (Schallhorn et al., 2008). The results of these studies indicate that refractive accuracy and snellen visual acuity outcomes improve with the assistance of wavefront-

guided procedures. However, there is considerable variability in the reported effectiveness of wavefront-guided procedures in reducing post operative higher-order aberrations.

It has been suggested that such variability may be attributed to shifting of the pupillary centre with illumination and postural changes, thus resulting in misalignment of proposed ablation pattern and in-situ application (Tantayakom et al., 2008). Kugler and Wang (2010) proposed that wavefront data, which describes optical properties of the entire ocular pathway, should be combined and considered alongside topography data in order to ascertain the most appropriate ablation pattern. Park et al. (2012) recommended that discrepancies between the visual and pupillary axes, that is angle kappa should also be considered to avoid the creation of decentred profiles. The pupillary axis is a line perpendicular to the surface of the cornea, passing through the centre of the pupil. The visual axis connects the fovea with the fixation point and this line passes the nodal point of the eye, which is a purely theoretical concept and cannot be measured. Therefore, clinically, the angle kappa was redefined as the angular distance between the line of sight and the pupillary axis; this was previously described as angle lambda in historical references (Artal at al. 2006).

A positive angle kappa refers to a corneal light reflex which appears on the nasal side of the corneal centre. This arsis from a foveal position just temporal to the anatomical axis of the eye. Thus light shone onto the cornea will cause a reflex just nasal to the pupil

centre. A negative angle kappa arises from a foveal position just nasal to the anatomical axis of the eye and a corneal reflex temporal to the pupil centre (see figure 1.24).


**Figure 1.24** *Illustrates angle kappa, the angle between the optical and visual axis. (Image taken from Park et al. 2012).*

Consideration of angle kappa has been shown to be particularly important when treating eyes with larger hypermetropic prescriptions. Larger angle kappa and smaller optical zone in hypermetropic ablation compared to myopic ablation renders laser refractive treatment of hypermetropic prescriptions more sensitive to decentration (Moshirfar et al., 2013). In such cases wavefront calculations at the entrance pupil centre would not represent the patient's true vision as the patient is not looking through the centre of the pupil and thus wave-front guided treatment could result in a number of visual complaints including glare, distortion, reduced visual acuity and diplopia (Reinstein et al. 2013).

Variation in individual corneal thickness has also been cited as a source of variability. Corneal water content increases from anterior to posterior. Corneal areas with lower water content will ablate more for each laser pulse than areas of higher water content. In addition corneal thickness will vary at different meridians, generally being thinnest inferior or inferiotemporaly, hence ablation rate will be higher in these zones (Lipshitz 2002).

The data in the current study was extracted from patient records held at the London Vision Clinic. Prior to inclusion in the study, each chart was assessed to ensure that: (i) corneal topography data and aberrations data was considered in combination prior to laser refractive treatment plans, (ii) measurements of corneal thickness and corneal anatomy were incorporated into the final ablation plan, (iii) iris registration technology was employed throughout the procedure to ensure alignment of pre-operative and in-situ ablation pattern, (iv) consideration was given to angle kappa in order to ensure against off-axis ablation. All of the above pre-operative assessments form part of the normal pre-operative protocol employed at the London Vision Clinic. Patient records devoid of any of the above were not considered analysis.

## 1.4 Pre and post operative protocol conducted by the London Vision Clinic

This thesis involved retrospective analysis of clinical records pertaining to adult amblyopic and visually normal subjects who elected for wavefront-guided laser refractive treatment at the London Vision Clinic. The following section briefly outlines the pertinent pre-and post- operative protocols employed at said clinic.

**Vision:** Vision was assessed using the Vector Vision ESV-3000 ETDRS LogMar acuity chart (Vector Vision, Ohio, USA). The 'letter scoring technique' was used, where each letter identified correctly was awarded a score of 0.02 log units. Such a method was employed as LogMar letter acuity scoring has been shown to display high repeatability and reliability (Montés-Micó and Charman, 2001; Arditi and Cogenello, 1993; Raasch and Bullimore, 1998; Dong et al., 2004; Raasch and Flom, 1994; Bailey et al., 1991; Ferris et al., 1982). With the LogMar chart, there exists uniform between-letter and between-row spacing, with a logarithmic progression of letter size (see figure 1.26). LogMar acuity charts minimise the detrimental effects of visual crowding, which is known to influence the legibility of letters, particularly in the amblyopic population (Elliott and Firth, 2009; Levi and Stanley, 1985; Giaschi et al. 1993). Pre-operative best corrected visual acuity was assessed with prescriptions obtained by manifest refraction, cycloplegic refraction and WASCA (Zeiss, Oberkochen, Germany) refraction (see below) as well as pin hole acuity. That which afford best visual acuity was labeled as such. In 98.3% of cases, best corrected visual acuity obtained by manifest refraction matched that obtained with pin hole (figure 1.25). Visual acuity was reassessed at time points of one day, one week, one month, three months, six months and twelve months post-operatively.

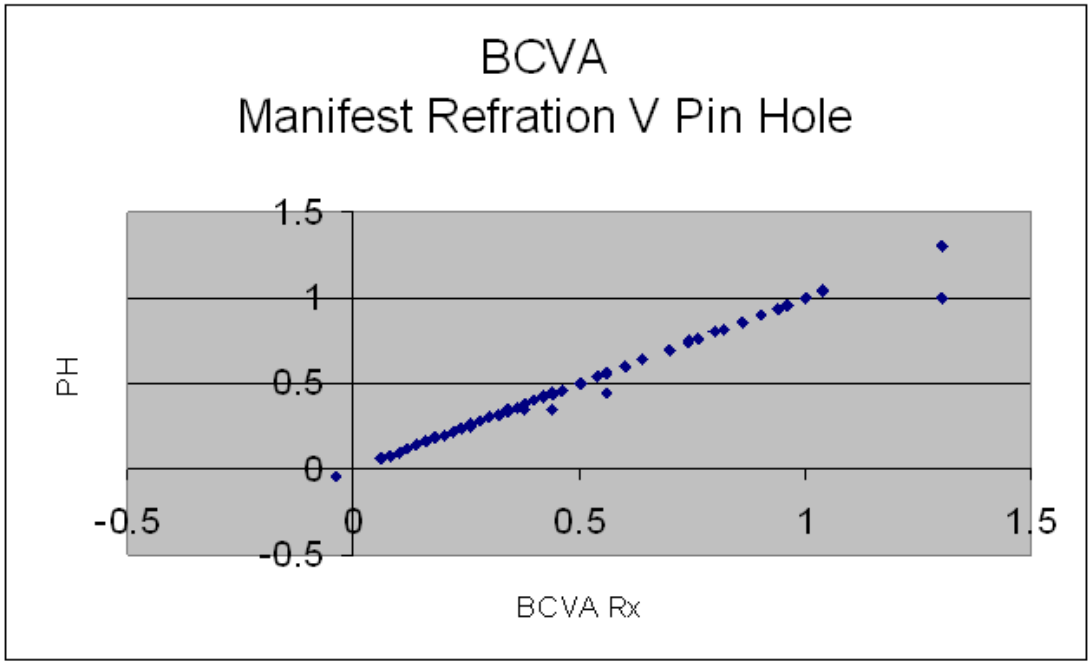



**Figure 1.25** *Illustrates that in 98.3% of cases, best corrected visual acuity obtained by manifest refraction matched that obtained with pin hole*


**Figure: 1.26 *:*** *ETDRS LogMar acuity chart. Each row has 5 letters. Rows are separated by 0.1 log units. Letters are spaced on a log scale with logarithmic progression of letter size.*

**Refraction.** All patients underwent a full subjective binocular refraction, objective cycloplegic refraction and a WASCA refraction (with and without cycloplegia) by qualified optometrists. Refraction was carried at one week prior to surgery and the day of surgery. Refraction was reassessed at one week, one month, three months, six months and twelve months post-operatively.

**WASCA: Aberrometry:** Abberometry was carried out using Carl Zeiss wavefront aberration supported corneal ablation system (WASCA). WASCA allows a measure of this wavefront function based on the Shack-Hartmann principle (see Thibos, 2000). Colour maps display total and higher-order aberrations, numerical lists show root mean square of the sum of all Zernike values, an example of which is shown in figure 1.27. All data was taken from pupils of 7mm diameter or above.

**WASCA: Refraction:** The WASCA apparatus allows measurement of large aberrations including spherical refractive between -15D and +7D, and astigmatic errors up to 6DC (Salmon et al., 2003). It has been shown that WASCA-determined refractive error is reliable, repeatable and displays a high level of accuracy with reported mean errors of +/- 0.1DS, +/- 0.1 DC and +/-2 degrees on cyl axis (Cheng et al., 2004; Reinstein et al. 2004) WASCA repeatability has been shown to improve with cycloplegia (Salmon et al., 2003). Thus, in the current study data from both cycloplegic and non cycloplegic WASCA was analysed for each subject recruited.


**Figure: 1.27** *Abberometry output from Carl Zeiss wavefront aberration supported corneal ablation system (WASCA). Displaying: WASCA determined refractive error, Zernike coefficients, colour maps reflecting the root mean square of total and higher-order aberrations, simulated aberrated letter E.*

**Contrast Sensitivity**. Contrast sensitivity functions were established utilising the CSV-1000 contrast sensitivity chart (Vector Vision, Ohio, USA), covering the range 3-18 cpd. The last correct response for each spatial frequency was taken as the contrast threshold and plotted using the LogMar to CSV score conversion chart provided on the CSV-1000 graph, an example of which is shown in figure 1.29. The y axis shows the CSV contrast score and the x axis the spatial frequency of the target. Contrast sensitivity was evaluated pre-operatively and at time points of three months, six months and twelve months post-operatively.

**Contrast Sensitivity Values for the CSV-1000E:**

| | S | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|---|
| Row (CPD) | | | | | | | | | |
| A (3.0) | 5 | 10 | 15 | 22 | 31 | 43 | 61 | 85 | 120 |
| B (6.0) | 8 | 16 | 24 | 36 | 50 | 70 | 99 | 138 | 193 |
| C (12.0) | 4 | 8 | 12 | 18 | 25 | 35 | 50 | 70 | 99 |
| D (18.0) | 1.5 | 3 | 4.5 | 7 | 9.5 | 13 | 18 | 25 | 36 |

**Contrast Sensitivity Values for the CSV-1000E in Log Units:**

| | S | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|---|
| Row (CPD) | | | | | | | | | |
| A (3.0) | .70 | 1 | 1.17 | 1.34 | 1.49 | 1.63 | 1.78 | 1.93 | 2.08 |
| B (6.0) | .91 | 1.21 | 1.38 | 1.55 | 1.70 | 1.84 | 1.99 | 2.14 | 2.29 |
| C (12.0) | .61 | .91 | 1.08 | 1.25 | 1.40 | 1.54 | 1.69 | 1.84 | 1.99 |
| D (18.0) | .17 | .47 | .64 | .81 | .96 | 1.10 | 1.25 | 1.4 | 1.55 |

**Figure: 1.28** *The above tables show contrast sensitivity scores for CSV-100 for both linear and log values.*


**Figure**: **1.29** *CSV-1000 contrast sensitivity plot. The contrast sensitivity curve is derived by determining the highest contrast sensitivity level a patient can detect for each spatial frequency and marking this on CSV-1000 score chart from 1-8. The curve is plotted by connecting each score marked. The x axis shows the spatial frequency of the target and y axis shows the level of contrast in log units. Conversion to LogMar contrast sensitivity is provided (taken from Jirásková, et al.,* 2012).

**Corneal Topography:** Corneal topography data obtained from Pentacam (Oculus, Wetzlar, Germany). The Pentacm instruments utilising rotating Scheimpflug imaging technology to provide measurements of the anterior and posterior corneal curvature, pachymetry, corneal topography, astigmatism and Scheimpflug photography of the lens. The system is comprised of two cameras, one stationary to detect pupil size, orientation and to control for fixation, the second, rotating to capture images of the anterior segment. This rotational element allows a three dimensional image of the anterior corneal surface to be rendered and also allows the centre of the corneal to be precisely located. A total of 138,000 true elevation points are extracted for both anterior and posterior corneal surfaces, from limbus to limbus, including central cornea (Jain, R. 2013).

Corneal topography obtained from Pentacam was considered alongside aberrations data in compiling aberration profiles. (see figure 1.30).


**Figure 1.30** *Screen shot of Pentacam corneal topagraphy output. Upper right Sagittal map, lower right corneal thickness mapping. Left; Anterior and posterior corneal surface elevation maps. also available; tangential-radial maps, refractive maps and net power calculation of corneal refractive power (Image taken from Ambrosio et al., 2006)*

**Corneal thickness:** Measurements of corneal thickness and corneal anatomy obtained from Artemis (UltraLink L.L.C., Arizona, USA) very high frequency digital ultrasound were incorporated into the final ablation plan (see figure 1.31).


**Figure 1.31** *Screen shot of Artemis control panel. Upper right panel displays ultrasound echo data. Lower right panel demonstrates that this patient's angle kappa results in a geometrical tilt of the anterior segment relative to the visual axis (green line). (Probust 2004)*

**Laser refractive treatment:** Laser refractive treatment was delivered via Carl Zeiss MEL-80 excimer laser platform (Zeiss, Oberkochen, Germany). The Carl Zeiss group claims this system "allows for the finest corrections of higher-order aberrations" via provision of a fully programmable customised treatment options, integrating refraction results, corneal topography and wavefront analysis. Eight hundred spot resolution and Gaussian beam delivery facilitates large overlap of laser spot zones yielding smooth ablation profiles. Aberration smart ablation (ASA) generates aspherical profiles to allow optimal mesocopic vision and tissue saving algorithm (TSA) conserves the stromal bed. Active eye tracking allows a laser pulse to be delivered within 2-6 milliseconds of detection of eye position and eye registration software permits compensation for torsion in order to prevent decentration of ablation profiles. In addition, closed loop monitoring controls for fluctuations in laser beam energy delivered to the cornea during treatment.

## 1.5 Thesis Aims

The goal of this thesis was to analyse the distribution of higher-order aberrations in a population of amblyopes in order to determine whether such aberrations contribute to abnormal visual development. Specifically, evidence was sought for the proposed entities of 'aberropia' and 'higher-order aberration-associated amblyopia'. These issues were addressed in four experimental chapters:

- In chapter three the aim was to determine whether the pre-operative profile of higher-order aberrations between the fixing and amblyopic eyes of strabismic, anisometropic, and idiopathic amblyopes are symmetrical or asymmetrical. In addition, the distribution of aberrations in prescription-matched eyes of normally-sighted individuals was assessed and compared with that in the cohort of amblyopes.

- In chapter four the change in post-operative visual acuity (at 1 day, 1 week, 1 month, 3 months, 6 months and 12 months) within the amblyopic and visually-normal populations was assessed.

- Chapter five details the change in post-operative contrast sensitivity (at 3 months, 6 months and 12 months) within the amblyopic and visually-normal populations.

- Chapter six details the change in post-operative higher-order aberration profiles (at 3 months, 6 months and 12 months) within the amblyopic and visually-normal populations.

# Chapter Two

## Methods

### 2.1 General methods

This was retrospective study that involved analysis of records pertaining to adult amblyopic and visually-normal patients, male and female, who underwent wavefront-guided laser refractive correction at the London Vision Clinic, Harely Street, between May 2003 and September 2008.

Patients suitable for inclusion in this study were identified by searching the patient database held at the London Vision Clinic.

Prior to treatment at the London Vision Clinic, all patients were approached for their consent to allow data pertaining to their treatment to be used for research purposes. It was made clear to all participants that:

- They were not under any obligation to take part in any study.
- There would be no consequence whatsoever to their continued care at the London Vision Clinic should they decide to consent or not.
- Research involves data pertaining to pre- and post-operative measurements only.
- Involvement would not warrant any additional visits to the London Vision Clinic beyond their scheduled after care appointments.

- Patient privacy and confidentially would be protected at all times during research analysis.
- Risk of breach of confidentiality would be minimized by coding data and no patient names would be used in any study.
- The rights, safety and wellbeing of patients would be safeguarded at all times.
- Volunteers would receive no direct benefit from participating in research studies.
- Patients would be made aware of any publications made following completion of research.
- Any further information could be sought by contacting the London Vision Clinic directly.

## 2.2 Patient details

**Amblyopic subjects.**

A cohort of four hundred and sixty eight patients (936 eyes) were identified as adult amblyopes prior to laser refractive treatment. Amblyopic subjects were identified as those who were found to have an intraocular difference in visual acuity of two lines or more, that could not be corrected by refraction and did not have any associated ocular pathology or structural abnormality of the eye. Note that, based on this classification, two subjects were deemed amblyopic because their 'poor 'eye had a visual acuity of - 0.01 Log Mar while their fellow fixing eye had a visual acuity of -0.3 Log Mar (i.e. two lines difference).

Patients within this cohort were excluded from the study if: the presenting amblyopia was found to be secondary to trauma or ocular pathology; the patient was under 18 years of age at time of treatment; the pre-operative record was deemed incomplete for research purposes; the patient was deemed to have learning difficulties; the patient suffered any cognitive disorder; the patient suffered from dementia or mental illness; or the patient suffered from dyslexia (see table 2.1 and 2.2).

| **London Vision Clinic.**<br><br>**Criteria for Consideration Prior to Laser Refractive Surgery.** | | |
|---|---|---|
| **Exclusion** | **Caution** | **Inclusion** |
| • Active ocular pathology.<br>• Keratoconus or forme fruste keratoconus.<br>• Dry eye, active meibomian gland dysfunction or blepharitis.<br>• Sjorgens Disease.<br>• Pregnant or best feeding.<br>• Residual stromal thickness of less than 250μm.<br>• Under 18 yaers of age.<br>• Cognitive disorder, dementia or un controlled mental illness. | • Previous ocular surgery.<br>• Well managed dry eye, meibomian gland dysfunction or blepharitis.<br>• Autoimmune diseases (eg. lupus, rheumatoid arthritis),.<br>• Immunodeficiency states (eg. HIV)<br>• Diabetes.<br>• Collagen or vascular disorders.<br>• Systemic medications likely to affect wound healing such as retinoic acid and steroids.<br>• Pupilslarger than 8.5mm in mesocopic conditions. | • Sufficient pachymetry for treatment i.e. residual stromal thickness ≥250μm.<br>• Age 18 years or over.<br>• Stable Rx for one year.<br>• Healthy Retina<br>• IOP within normal range.<br>• No corneal pathology.<br>• No recent history of an ocular (eye) herpes, eye infection or inflamation, excessive corneal disease/scarring or severely dry eyes. |

**Table 2.1** *Criteria for selection of candidates suitable for laser refractive treatment at the London Vision Clinic.*

| Criteria For Amblyopic Patient Selection. | |
|---|---|
| **Inclusion** | **Exclusion** |
| • Intraocular acuity difference of two lines or more.<br>• No gain in VA with accurate refraction or pin hole.<br>• No ocular pathology.<br>• No structural abnormality of the eye.<br>• Adult patient ( over 18 years).<br>• Availability of prescription matched control subject.<br>• Complete patient record to include; history of amblyopic treatment; pin hole acuity; pre and post operative measurements of VA, contrast sensitivity and higher order aberrations. | • Amblyopia secondary to pathology or trauma.<br>• Pre-operative record deemed incomplete for research purposes.<br>• Blended vision surgery for treatment of presbyopia.<br>• Any further surgical treatment for pathology / strabismus following laser refractive treatment.<br>• Pathology identified following laser refractive treatment.<br>• Patient under the age of 18 years at time of surgery.<br>• Patient was deemed to have learning difficulties; suffered any cognitive disorder; dementia; mental illness; or dyslexia. |

**Table 2.2** *Criteria for selection of amblyopic eyes included in this study.*

Of the 468 records identified as having pre-operative amblyopia, 182 patients were removed from the study as their surgery involved blended vision treatment for presbyopic correction, 33 were removed due to identification of ocular pathology (details in table 2.3), 5 records were deemed incomplete for research purposes (details in table 2.4), 12 patients could not be matched with control data (details table 2.5) and 1 had strabismic surgery following laser refractive treatment. Thus 235 (468 eyes) complete records of adult amblyopic patients who underwent laser refractive correction were subject to statistical analysis in order to evaluate pre–operative changes in higher-order aberrations, best corrected visual acuity and contrast sensitivity.

The pre-operative ocular status of the remaining 235 subjects is reported in Table 2.6.

| ***Reason for removal due to ocular pathology.*** | |
|---|---|
| Planned 2 stage LASIK surgery, Rx -8.00. At 8 mths post op horse shoe tear noted, referred and prophylactic laser treatment applied before second stage of LASIK surgery. | Rx -8.00. Suffered retinal detachment secondary to PVD at 8mths post op, also developed cataract, referred for cataract extracted and IOL inserted. Posterior capsule opacification ensued. |
| Hypertopia secondary to paralysis of 7$^{th}$ nerve following spinal cord injury. | Patient professional boxer. Traumatic cataract and RPE clumping noted. |
| Congenital cataract. | Blue dot cataract |
| Epiretinal membrane formation | Glaucoma suspect, referred. |
| Area of chorioretinal atrophy at macula. | Two corneal ulcers pre-operatively. Small stromal scar noted at pre-op assessment. |
| Patient reports 1/12 premature, poor vision since birth. Pre-op assessment revealed nystagmus, alternating SOT, depigmented macula, peripheral retinal sound. | Patient reports advised "congenitally poor vision". RPE thinning and mottled, very attenuated retinal vasculature at periphery, waxy disc, bone spincules. Likely RP. |
| Patient reports traumatic ocular injury in 2001, "bleed at back of LE". Fundus exam normal, corneal clear, small scar noted lower left lid. | Planned 2 stage, Rx +8.75. Lagopathalmos treated between first and second stage of LASIK treatment. |
| Trachoma as a child. | Retinal detachment at age 15, now 45. Patient reports delay in repair. |
| 7 cases of nystagmus noted in pre-op assessment. | Patient reports stone hit RE at 10 year, reduced vision since. |
| Patient developed cataract 9 mths post op. | Diabetic retinopathy. |
| Old corneal scar due to metal foreign body. | Previous uveitis, visible ABMD and posterior orbital pseudotumour. |
| Early cataract noted at pre op. | Punctate inner choriodopathy. |
| Two cases of drusen at macula. | Peripheral retinal detachment noted at pre op dilated fundus examination. |
| | |

**Table 2.3** *List of specific ocular pathologies that resulted in subjects being excluded from this study.*

| ***Reason for deeming charts incomplete for research purposes.*** | |
|---|---|
| Patient examined elsewhere for 3 mths post op. No data on contrast sensitivity, aberrations provided. | Planned 2 stage. Patient returned to Pakistan following first stage. Had not returned for second stage at time of study. |
| Patient relocated to Sydney after 6 mths post op, aftercare carried out elsewhere with no facility for contrast sensitivity / aberrometery. | Planned 2 stage. Patient happy with visual outcome after stage 1, decided not to follow up on second stage. |
| Patient relocated to Australia, 5 mth post op data received from optometrist in Australia, no data since this time point. | |

**Table 2.4** *Outlines the reasons subjects were removed from the study when the patient's record was deemed incomplete for research purposes.*

| ***Reasons for unmatched data.*** | |
|---|---|
| 11 cases where fellow, non amblyopic eye was 0.00 LogMar or better prior to surgery, therefore no surgery undertaken on fellow eye. | 1 case of -17.00 where match could not be made with normal control data. |

**Table 2.5** *Outlines reasons subjects were removed from the study when there was an inability to acquire a prescription-matched control subject.*

| ***Ocular Status of Cohort.*** | |
|---|---|
| 151 subjects presented with hypermetropic Rx. | 84 subjects presented with myopic Rx. |
| 131 subjects presented with anisometropic amblyopia. | 104 subjects presented with strabismic amblyopia. |
| 101 subjects had previous occlusion therapy for amblyopia. | 31 subjects had previous surgical treatment for amblyopia |
| 159 subjects were prescribed refractive treatment during critical period. | |
| 162 subjects presented in full refractive correction for amblyopic eye. | 72 presented with balance correction for amblyopic eye. |

**Table 2.6** *Describes the ocular characteristics of the amblyopic cohort included in this study.*

**Idiopathic amblyopic subjects**

Following pre-operative examination, if the cause of presenting asymmetrical best corrected visual acuity could not be ascribed to anisometropia, strabismus or pathology, patients were considered to be amblyopic without identity, often times referred to in the literature as 'idiopathic amblyopes' (Von Noorden, 1985).

**Control subjects**

When establishing a control group for this study, the question of whether the non amblyopic eye of the amblyopic patients could be considered as 'normal', and therefore act as control, was addressed.

The non amblyopic eye is by convention referred to as the 'sound' or 'normal' eye based on the fact that it has a normal level of visual acuity. However, high contrast letter visual acuity is but one of the parameters used to describe visual function. There exists some evidence to suggest that other visual function parameters depart from 'normal' in the non-amblyopic eye of amblyopic patients (Giaschi et al., 1992).

It has been reported that the non amblyopic eye of both anisometropic and strabismic amblyopes demonstrate reduced contrast sensitivity at high spatial frequencies when compared to age matched normals with binocular fixation (Leguire et al., 1990). In addition it has been reported that the non amblyopic eye of amblyopic patients displayed departure from the norm in the later stages of dark adaptation, horizontal eccentricity of fixation and ability to recognize motion-defined letters (Giaschi et al., 1992). Others have

reported no significant difference in contrast sensitivity function between non amblyopic eyes of amblyopes and normal binocular controls (Katz et al., 1984; Sjostrad, J. 1981).

In view of the above conflicting reports, the current study employed two controls for the amblyopic eye under investigation; 1) the fellow fixing eye of the 235 amblyopic patients identified for inclusion in the study, and 2) 235 prescription-matched control eyes from normally sighted observer with binocular fixation.

## 2.3 Data analysis

Sample size power calculation was carried out utilising: http://www.psycho.uni-duesseldorf.de/abteilungen/aap/gpower3/. Calculations were based on an alpha level of 0.05, a beta level of 0.2 and a small effect size of 0.25. A small effect size was chosen as it is currently unknown what level of higher order aberration asymmetry may induce higher order aberration associated amblyopia or 'aberropia'.

Once suitable patients were identified, data pertaining to pre and post operative higher-order aberrations, best corrected visual acuity and contrast sensitivity was extracted from patient records. Data was entered into SPSS 15.0 for statistical analysis.

In order to eliminate:

- Confounding factors, that is a situation in which the effect of laser refractive surgery could be distorted by the presence of another variable such as previous treatment undertaken.
- Effect modifier variables that may differentially modify either positively or negatively the observed effect of laser refractive, for example current refractive correction; full Rx or balance Rx.
- Temporal relationships, the relationship between the cause of amblyopia and the effect of laser refractive surgery.

Date was stratified according to:

- Type of refractive error: myopic and hypermetropic.
- Type of amblyopia: strabismic, anisometropic, idiopathic.
- Previous treatment undertaken: spectacle treatment, occlusion therapy, surgical treatment.
- Current refractive correction: full refection, balance prescription only.

Statistical analysis was preformed on stratified data using paired t-tests at a 95% confidence interval to compare pre-operative and post-operative measurements of higher-order aberrations, best corrected visual acuity and contrast sensitivity. A one way analysis of the variance (ANOVA) and Tukey's Honesty Significance Difference (HSD) test post-hoc analyses were utilised to assess the effect of eye condition (amblyopic, fixing and control) on magnitude of pre-operative higher order aberrations.

## 2.4 Ethics and Data Protection

The design protocol of this study adhered to the Deceleration of Helsinki and the Data Protection Act, and received ethical approval from the Auidology / Optometry Research Ethics Committee (AOREC) at Aston University on the 13th January 2010 (see appendix).

The main ethical issues raised by the scientific design of this protocol was the electronic recording of data pertaining to patients visual function. Although this aspect of the study meant that the protocol had some ethical issues, the scientific information to be gained was important as it will allow optometrists / ophthalmologists to provide a more informed view point to adult amblyopic patients considering laser refractive correction. The risks to research participants were that confidential data relating to their visual function could be revealed to parties other than those directly involved in this study. It would have been impossible however to analyse data without the use of an electronic database. Therefore to mange appropriately the ethical issues inherent in this study, it was necessary to put the following additional protections of the study population in place:

- Informed consent was obtained prior to any analysis of patient data.
  (see appendix London Vision Clinic, patient consent forms section 17 & 18).
- Only those involved directly in the study had access to the patient database.
- Patient record number rather than patient names were used in analysis undertaken.
- Data pertaining to this study was held off line, in password protected electronic files on encrypted laptops and PC's.

# Chapter Three

**Pre-operative profile of higher-order aberrations.**

## 3.1 Introduction

In this chapter, the pre-operative profile of higher-order aberrations between the fixing and amblyopic eyes of strabismic, anisometropic, and idiopathic amblyopes was examined to determine whether they are symmetrical or asymmetrical. The profile of aberrations within prescription-matched eyes of normally-sighted individuals was also assessed.

In order to investigate the plausibility of both higher-order aberration associated amblyopia (Prakash et al., 2001; Prakash et al., 2007) and aberropia (Agarwal et al., 2002; Agarwal et al., 2003; Agarwal et al.,2007, Agarwal et al., 2010), it must first be established whether the profile of higher order aberrations between amblyopic and non-amblyopic eyes differ. In addition it must be ascertained whether the composition of higher-order aberrations within the amblyopic population differs significantly from that within the normal binocular population. The experiments described in this chapter address these issues.

The higher order aberrations under consideration were coma, spherical aberration and root mean square of aberration up to the fourth order. The rational in choosing these particular higher-order aberrations for evaluation was threefold. First, such aberrations have been shown to be the most common aberrations present in the human visual system

(Castejon – Mochon et al., 2002; Applegate et al., 2002, Applegate et al., 2003). Second, their location in the Zernike pyramid indicates that these aberrations cause greater loss in acuity due to their wavefront error being concentrated near the center of the pupil (Applegate et al., 2002; Thibos et al., 2002; Fan and Lim 2004). Finally, these Zernike modes have been shown to display the highest amount of binocular summation (Fam and Lim, 2004).

## 3.2 Methods

In this chapter, a retrospective analysis of pre-operative higher-order aberrations pertaining to 131 anisometropic, 104 strabismic adult amblyopic eyes, 17 idiopathic amblyopic eyes, 252 fellow fixing eyes and 252 prescription matched controls were evaluated.

Abberometry had been performed utilising the Carl Zeiss wavefront aberration supported corneal ablation system (WASCA) (see section 1.4).

Hypermetropic data was segregated from myopic data prior to analysis of aberration data, which avoided the nulling effect that is necessarily incurred when adding oppositely-signed spherical aberrations.

Data was further segregated into those who presented for treatment with anisometropic amblyopia (n=131), those who presented with manifest strabismic amblyopia (n=104) and those for whom the cause of amblyopia could not be identified (i.e. idiopathic amblyopes, n=17).

## 3.3 Results

Figure 3.1 shows the pre-operative magnitude of (a) coma, (b) spherical aberrations and (c) root mean square (RMS) of total aberrations (up to $4^{th}$ order) in the amblyopic and fixing eyes of hypermetropic anisometropes (n = 73), and in prescription-matched control eyes of normally-sighted individuals (n = 73).

The group-mean magnitude of coma was 1.77 µm (+/- 0.08) for amblyopic eyes, 1.69 µm (+/- 0.07) for fixing eyes and 2.08 µm (+/- 0.08) for prescription-matched control eyes (Figure 3.1a). A one-way analysis of variance showed no main effect of eye condition (amblyopic, fixing or control eye) on the pre-operative magnitude of coma (F = 1.508, p = 0.224).

The magnitude of spherical aberration was -3.26 µm (+/- 0.12) for amblyopic eyes, -2.78 µm (+/- 0.12) for fixing eyes and -2.37 µm (+/- 0.14) for control eyes (figure. 3.1b). Note that there was a main effect of eye condition on the level of spherical aberrations (ANOVA: F = 3.1, p = 0.047). Post-hoc analyses using Tukey's Honesty Significance Difference (HSD) test indicated a significant difference in spherical aberrations between amblyopic and prescription-matched control eyes of 0.9 µm (p = 0.036).

The magnitude of RMS was 0.41 µm (+/- 0.01) for amblyopic eyes, 0.39 µm (+/- 0.01) for fixing eyes and 0.42 µm ( +/- 0.01) for control eyes (Fig. 3.1c). There was no main effect of eye condition on pre-operative magnitude of RMS (ANOVA: F = 0.604, p = 0.547).

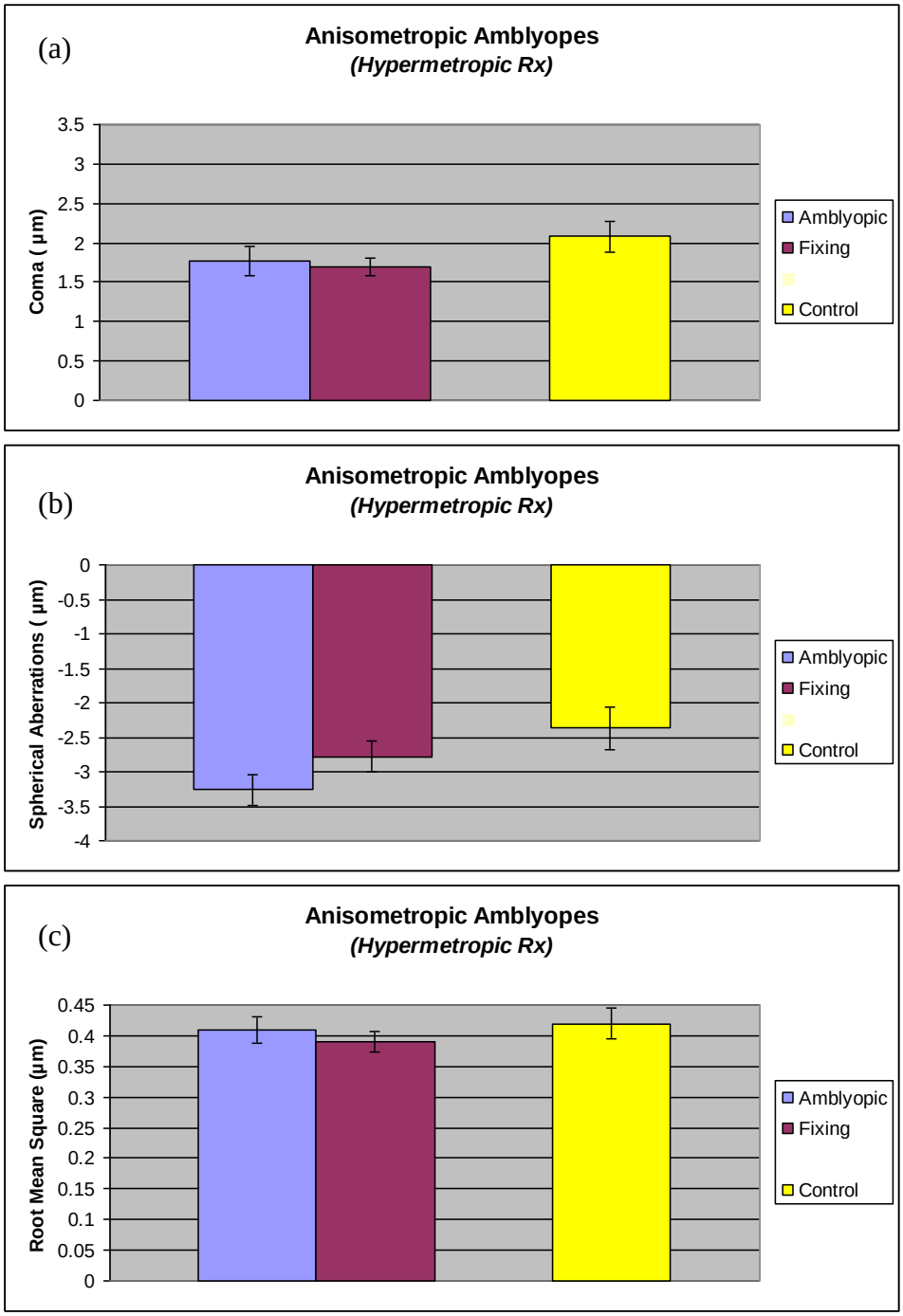



**Figure 3.1** *Pre-operative assessment of the group-mean higher-order aberrations in the amblyopic (blue) and fixing (purple) eyes of hypermetropic anisometropes (n = 73), and in prescription-matched control eyes (yellow) of normally-sighted individuals (n =73). Results are shown for (a) coma, (b) spherical aberrations and (c) RMS of total aberrations (up to 4$^{th}$ order). The vertical error bars show +/- one standard error of the mean. Results of statistical analyses are reported in the text.*

Using the same graphical format, Figure 3.2 depicts the results for myopic anisometropes (n = 58) and prescription-matched controls (n = 58). The group-mean magnitude of coma was 1.69 µm (+/- 0.09) for amblyopic eyes, 1.45 µm (+/- 0.1) for fixing eyes and 1.73µm (+/- 0.09) for prescription-matched control eyes (figure 3.2 a). The magnitude of spherical aberration was -1.72 µm (+/- 0.15) for amblyopic eyes, -1.65 µm (+/- 0.2) for fixing eyes and -1.84 µm (+/- 0.14) for control eyes (figure 3.2 b). And the magnitude of RMS was 0.35 µm (+/- 0.01) for amblyopic eyes, 0.33 µm for fixing eyes (+/- 0.013) and 0.35 µm (+/- 0.01) for control eyes (figure. 3.2 c). As found with hypermetropes, no main effect of eye condition on the pre-operative magnitude of coma ($F = 0.785$, $p = 0.458$), spherical aberrations ($F= 0.135$, $p = 0.874$) or RMS ($F = 0.297$, $p = 0.743$) was detected.

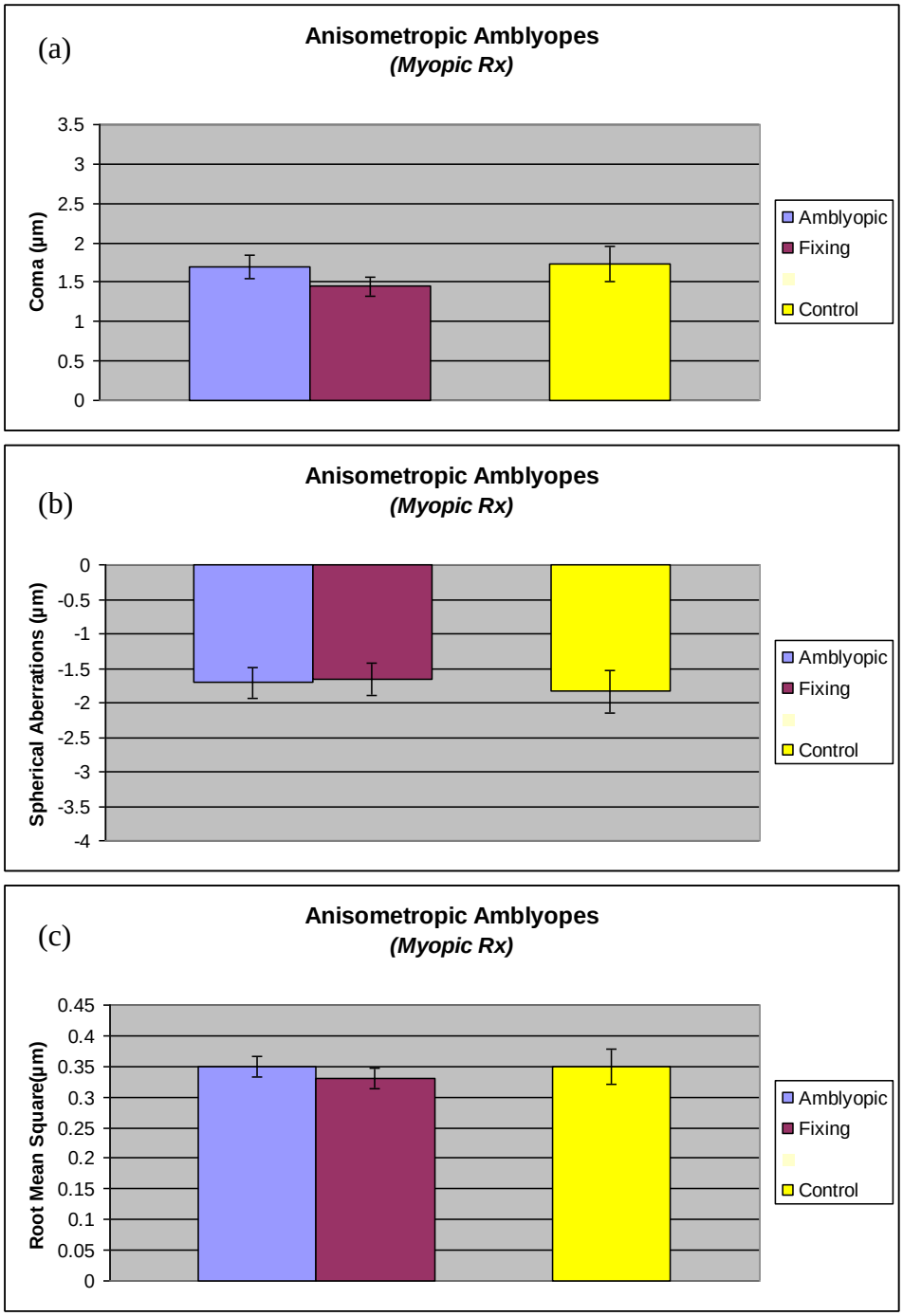



**Figure 3.2** *Pre-operative assessment of the group-mean higher-order aberrations in the amblyopic (blue) and fixing (purple) eyes of myopic anisometropes (n = 58), and in prescription-matched control eyes (yellow) of normally-sighted individuals (n =58). Results are shown for (a) coma, (b) spherical aberrations and (c) RMS of total aberrations (up to 4$^{th}$ order). The vertical error bars show +/- one standard error of the mean. Results of statistical analyses are reported in the text.*

Figure 3.3 shows the results for hypermetropic strabismic amblyopes (n = 79) and prescription-matched controls (n = 79). The group's mean magnitudes pertaining to pre-operative coma, spherical aberrations and root mean square of total aberrations are depicted. Note that a one-way analysis of variance showed no main effect of eye condition (amblyopic, fixing or control eye) on the pre-operative magnitude of coma ($F = 0.685$, $p = 0.505$), spherical aberrations ($F = 0.828$, $p = 0.438$), or RMS ($F = 1.338$, $p = 0.264$).

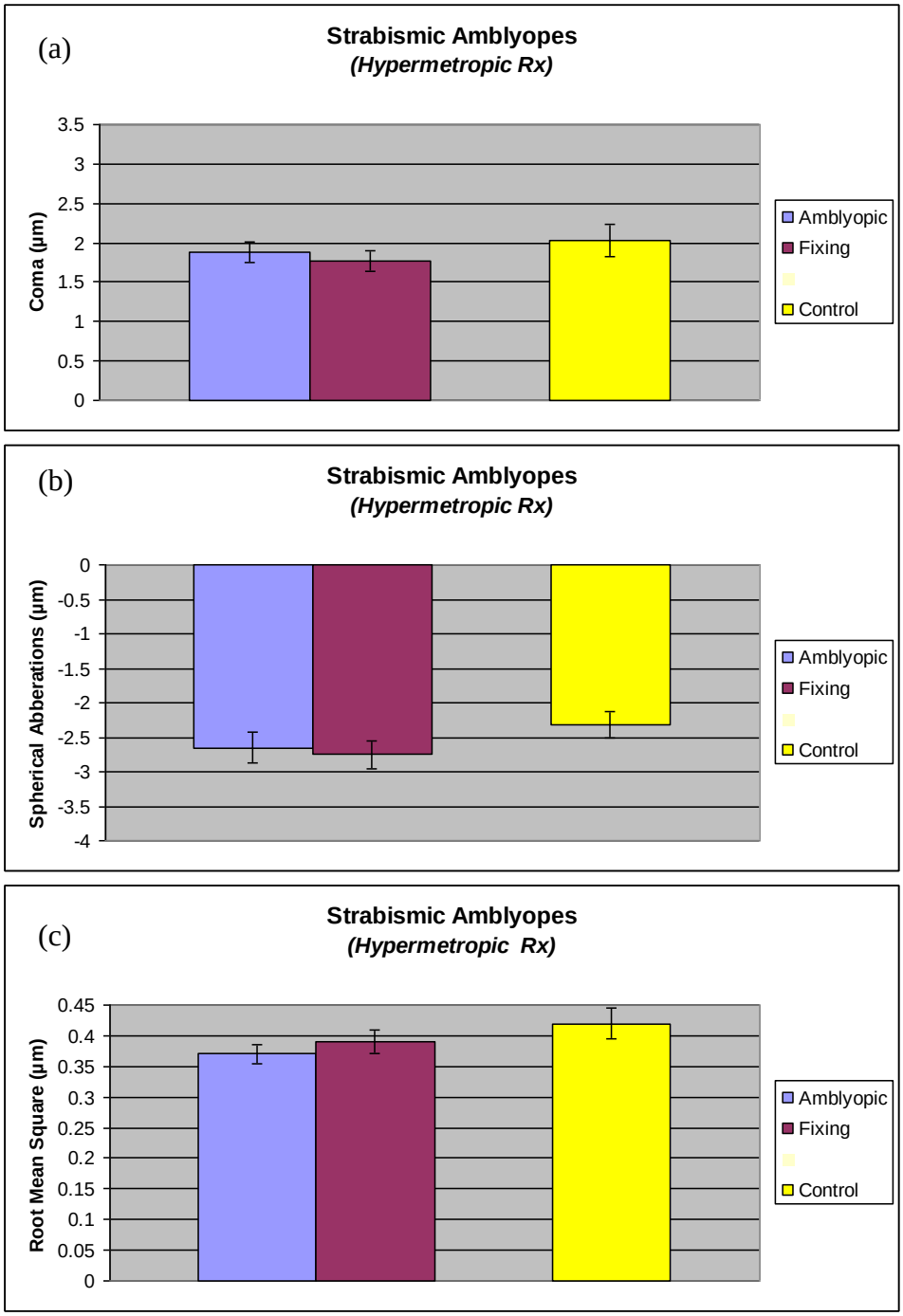



**Figure 3.3** *Pre-operative assessment of the group-mean higher-order aberrations in the amblyopic (blue) and fixing (purple) eyes of hypermetropic strabismic amblyopes (n = 79), and in prescription-matched control eyes (yellow) of normally-sighted individuals (n = 79). Results are shown for (a) coma, (b) spherical aberrations and (c) RMS of total aberrations (up to 4$^{th}$ order). The vertical error bars show +/- one standard error of the mean. Results of statistical analyses are reported in the text.*

Figure 3.4 shows the results for myopic strabismic amblyopes (n = 25) and prescription-matched controls (n = 25). The group-mean data analysis revealed a coma magnitude of 1.45 µm (+/- 0.1) for amblyopic eyes, 1.49 µm (+/- 0.1) for fixing eyes and 1.67 µm (+/- 0.15) for control eyes (figure 3.4 a); spherical aberration was -2.12 µm (+/- 0.17) for amblyopic eyes, -1.80 µm (+/- 0.17) for fixing eyes and -1.65 µm (+/- 0.24) for control eyes (figure 3.4 b); RMS was 0.32 µm (+/- 0.01) for amblyopic eyes, 0.32 µm (+/- 0.01) for fixing eyes and 0.33 µm (+/- 0.02) for control eyes (figure 3.4 c). Again, a one-way analysis of variance showed no main effect of eye condition (amblyopic, fixing or control eye) on the pre-operative magnitude of coma ($F = 0.222$, $p = 0.802$), spherical aberrations ($F= 0.366$, $p = 0.695$) or RMS ($F = 0.052$, $p = 0.949$) for the myopic strabismic cohort.

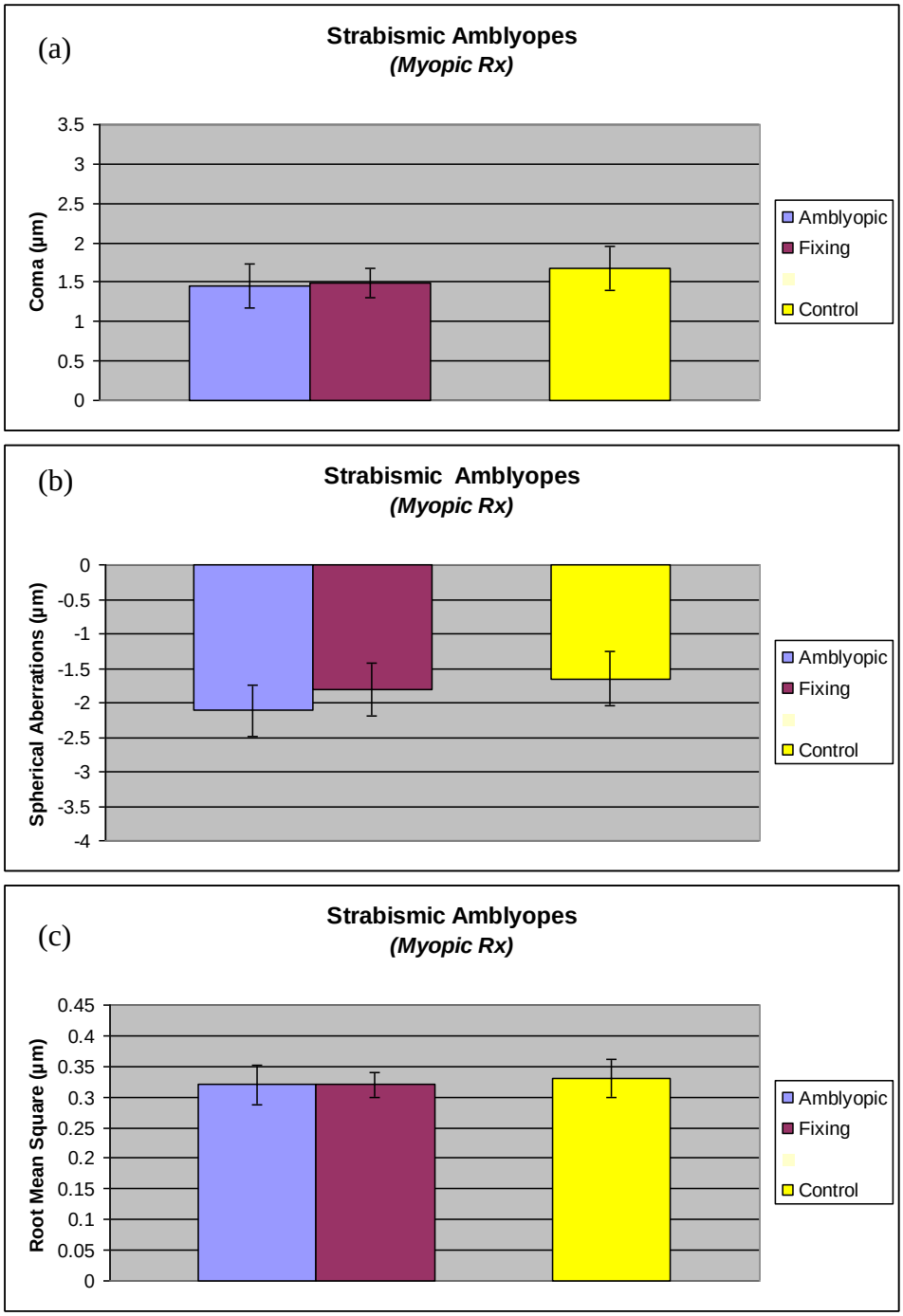



**Figure 3.4** *Pre-operative assessment of the group-mean higher-order aberrations in the amblyopic (blue) and fixing (purple) eyes of myopic strabismic amblyopes (n = 25), and in prescription-matched control eyes (yellow) of normally-sighted individuals (n = 25). Results are shown for (a) coma, (b) spherical aberrations and (c) RMS of total aberrations (up to 4$^{th}$ order). The vertical error bars show +/- one standard error of the mean. Results of statistical analyses are reported in the text.*

Figure 3.5 outlines the group-mean pre-operative magnitude of higher-order aberrations in the amblyopic and fixing eyes of hypermetropic idiopathic amblyopes (n = 7), and in prescription-matched control eyes of normally-sighted controls (n = 7). The magnitude of coma was 2.87 µm (+/- 0.3) for amblyopic eyes, 2.14 µm (+/- 0.17) for fixing eyes and 1.99 µm (+/- 0.3) for prescription-matched control eyes (figure 3.5 a). The magnitude of spherical aberration was -2.84 µm (+/- 0.1) for amblyopic eyes, -2.21 µm (+/- 0.5) for fixing eyes and -2.15 µm (+/- 0.6) for control eyes (figure 3.5b). RMS was 0.49 µm (+/- 0.45) for amblyopic eyes, 0.42 µm (+/- 0.3) for fixing eyes and 0.3 µm (+/- 0.04) for control eyes (figure 3.5c). A one-way analysis of variance showed no main effect of eye condition on the pre-operative magnitude of coma ($F = 2.323$, $p = 0.127$), spherical aberrations ($F= 0.154$, $p = 0.858$) or RMS ($F = 3.168$, $p = 0.066$) within the idiopathic cohort.

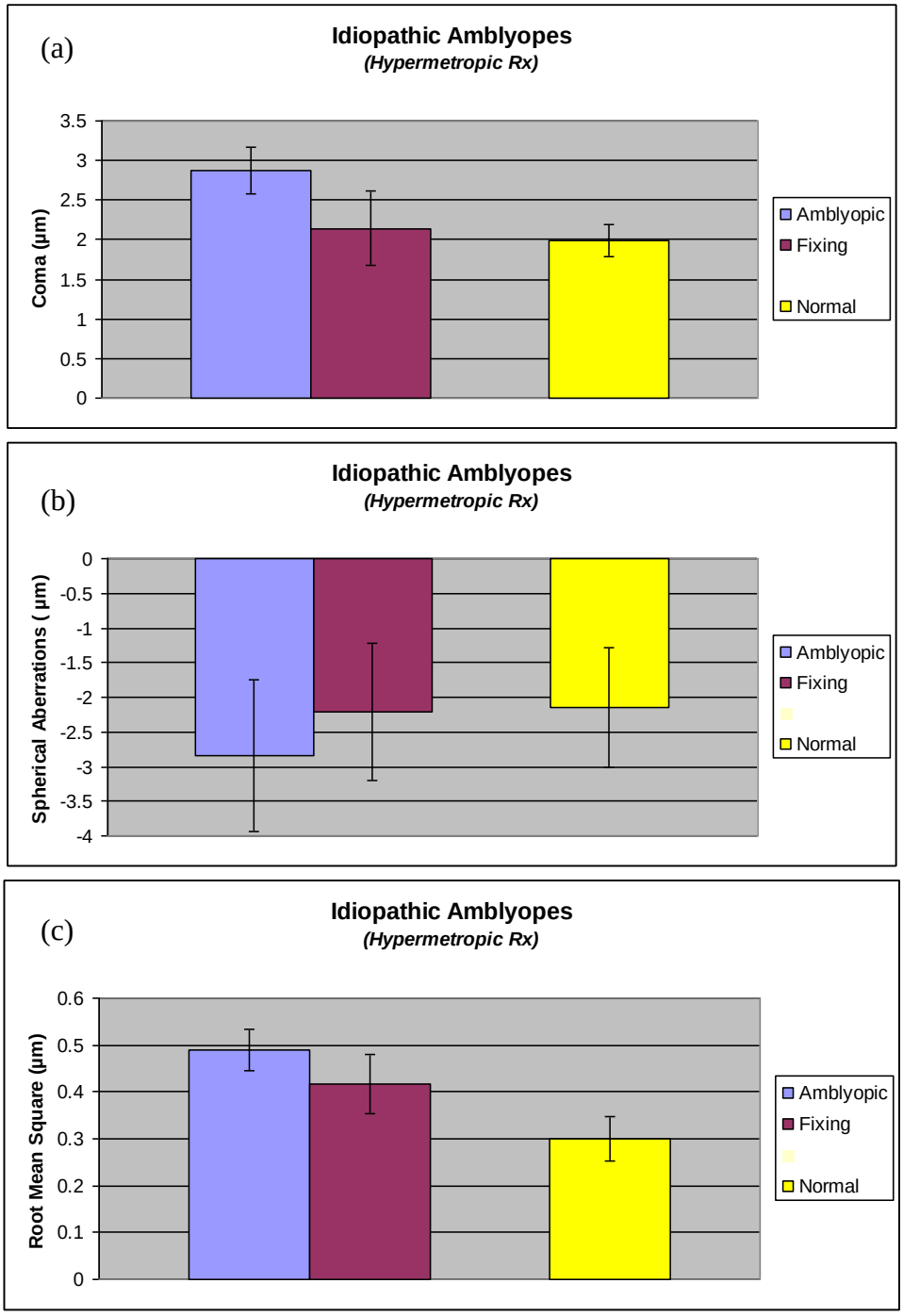



**Figure 3.5** *Pre-operative assessment of the group-mean higher-order aberrations in the amblyopic (blue) and fixing (purple) eyes of hypermetropic idiopathic amblyopes (n = 7), and in prescription-matched control eyes (yellow) of normally-sighted individuals (n = 7). Results are shown for (a) coma, (b) spherical aberrations and (c) RMS of total aberrations (up to 4$^{th}$ order). The vertical error bars show +/- one standard error of the mean. Results of statistical analyses are reported in the text.*

Figure 3.6 shows the group-mean data for myopic idiopathic amblyopes (n = 10) and prescription-matched controls (n = 10). As with the hypermetropic idiopathic amblyopes, a one-way analysis of variance showed no main effect of eye condition (amblyopic, fixing or control eye) on the pre-operative magnitude of coma ($F = 0.074$, $p = 0.929$), spherical aberrations ( $F= 1.495$, $p = 0.242$) or RMS ( $F = 0.111$, $p = 0.896$) for the myopic idiopathic cohort.

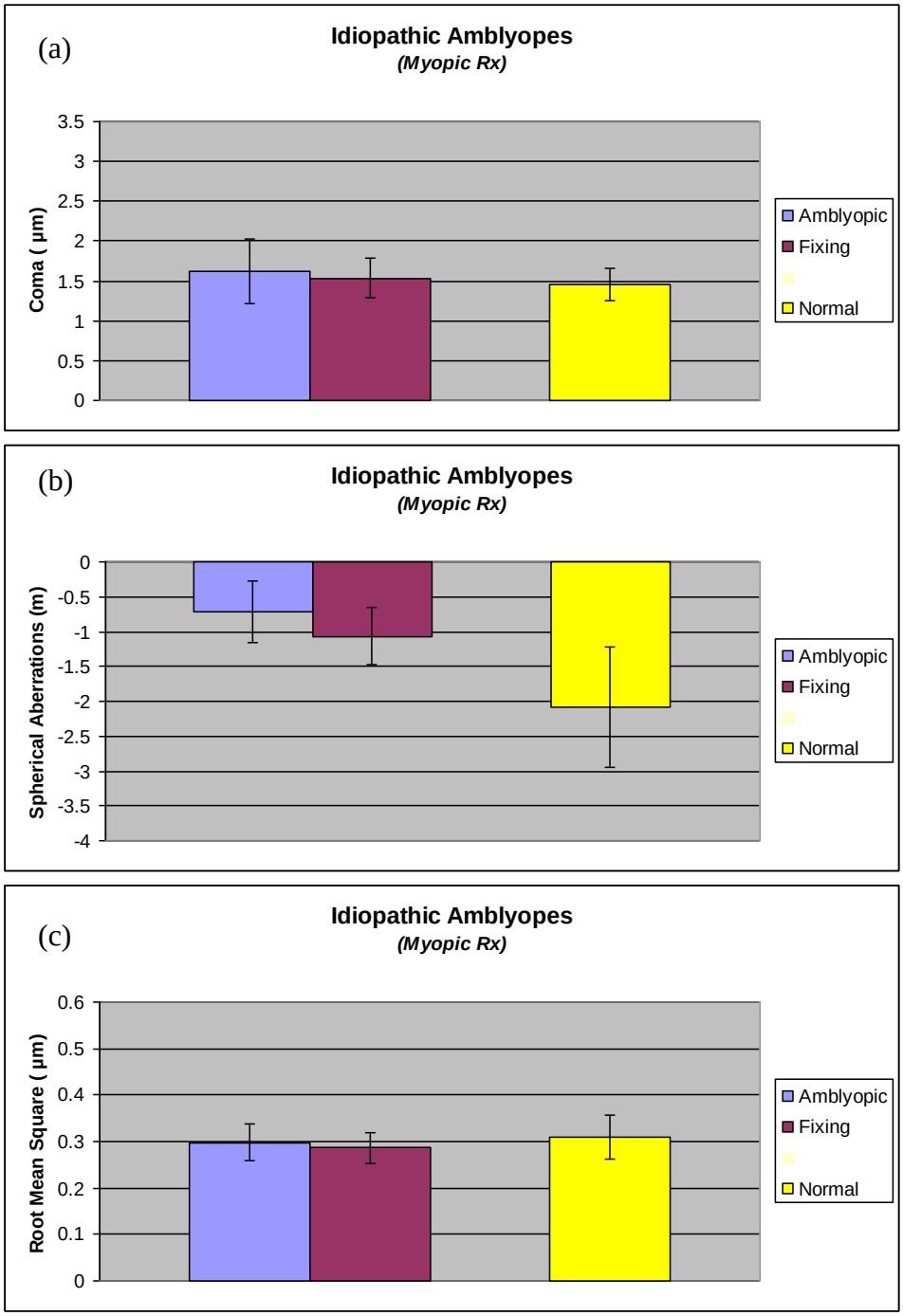



**Figure 3.6** *Pre-operative assessment of the group-mean higher-order aberrations in the amblyopic (blue) and fixing (purple) eyes of myopic idiopathic amblyopes (n =10), and in prescription-matched control eyes (yellow) of normally-sighted individuals (n =10). Results are shown for (a) coma, (b) spherical aberrations and (c) RMS of total aberrations (up to 4$^{th}$ order). The vertical error bars show +/- one standard error of the mean. Results of statistical analyses are reported in the text.*

The following tables (3.1 and 3.2) provide a summary of the above findings.

| **Difference in Pre-Operative Magnitude of HAO between Amblyopic, Fixing and Control Eyes.**<br><br>**Hypermetropic Cohort.** | | | |
|---|---|---|---|
| **Eye** | **Coma** | **Spherical Aberration** | **RMS of Aberrations** |
| **Anisometropic:**<br>Amblyopic<br>Control<br>Fixing | No statistical significant difference. | Difference of 0.9 µm between amblyopic and control eyes .<br><br>No difference | No statistical significant difference. |
| **Strabismic:**<br>Amblyopic<br>Control<br>Fixing | No statistical significant difference. | No statistical significant difference. | No statistical significant difference. |
| **Idiopathic:**<br>Amblyopic<br>Control<br>Fixing | No statistical significant difference. | No statistical significant difference. | No statistical significant difference. |

**Table 3.1** *Summaries the difference in pre-operative magnitude of higher order aberrations between amblyopic, fixing and control eyes for the hypermetropic cohort under investigation.*

| **Difference in Pre-Operative Magnitude of HAO between Amblyopic, Fixing and Control Eyes**<br><br>**Myopic Cohort** | | | |
|---|---|---|---|
| **Eye** | **Coma** | **Spherical Aberration** | **RMS of Aberrations.** |
| **Anisometropic:**<br>Amblyopic<br>Control<br>Fixing | No statistical significant difference. | No statistical significant difference. | No statistical significant difference. |
| **Strabismic:**<br>Amblyopic<br>Control<br>Fixing | No statistical significant difference. | No statistical significant difference. | No statistical significant difference. |
| **Idiopathic:**<br>Amblyopic<br>Control<br>Fixing | No statistical significant difference. | No statistical significant difference. | No statistical significant difference. |

**Table 3.2** *Summaries the difference in pre-operative magnitude of higher order aberrations between amblyopic, fixing and control eyes for the myopic cohort under investigation.*

## 3.4 Discussion

The results of this chapter provide evidence that there is no significant asymmetry in the magnitude of coma, spherical aberrations or RMS between the fixing and amblyopic eyes of either strabismic or anisometropic amblyopes. In addition, the mean magnitude of aberrations in both groups was similar to prescription-matched controls. These findings are in general agreement with previous studies by Kirwan and O' Keefe (2008) and Gray et al. (2004), who reported no significant asymmetry in wavefront profiles for strabismic or anisometropic amblyopes.

Prakash et al. (2007) suggested that an asymmetry in higher-order aberrations would not be expected in cases where the primary reason for amblyopia was anisometropia or strabismus (see section 1.2). They claimed that 'higher-order aberration associated amblyopia' only applies to idiopathic amblyopes, where no amblyogenic factor can be identified and no gain in BCVA can be elicited with conventional amblyopic treatment. In the current study, seventeen patients met Prakash et als criteria for classifying amblyopes as idiopathic. The group-mean magnitudes of higher-order aberrations for these subjects are shown in Figures 3.5 and 3.6. Note that, similar to all the other groups of amblyopes examined, no significant asymmetry in higher-order aberrations (in terms of coma, spherical aberrations or RMS) was observed. Therefore, an asymmetry of higher-order aberrations cannot be the cause of the amblyopia exhibited in this cohort.

Agarwal et al (2002) suggested a new clinical entity, termed aberropia, to describe a refractive condition in which abnormally large amounts of uncompensated higher-order aberrations degrade the retinal image quality to such an extent that they gives rise to pseudo-amblyopia. However, the lack of asymmetry in higher-order aberrations between the fixing and amblyopic eyes of the idiopathic cohort, and the lack of any significant difference in the mean magnitude of aberrations between the idiopathic amblyopes and prescription-matched controls, would suggest that idopathic amblyopes do not exhibit larger amounts of higher order aberrations than normally sighted eyes. This argues against Agarwal's hypothesis Agarwal et al (2002). This issue will be addressed further in chapter six.

In conclusion, the results of this first study suggest that asymmetry in higher-order aberrations is unlikely to play a role in the development of strabismic, anisometropic or idiopathic amblyopia. Furthermore, it does not seem likely that abnormally large amounts of higher-order aberrations have a role in compromising visual performance of idiopathic amblyopic eyes.

# Chapter Four

**Visual acuity outcomes following wavefront-guided laser refractive surgery on adult amblyopic eyes**

## 4.1 Introduction:

In this chapter, pre-operative best corrected visual acuity (BCVA) was compared with post-operative BCVA within the amblyopic and visually-normal populations.

To date, only a limited number of studies have investigated the use of laser refractive surgery in adult amblyopia ( Sakatani et al., 2004; Lanza et al., 2004; Orucoglu et al., 2011; Roszkowska et al., 2006; Barequet et al., 2004; Argarwal et al., 2007; Prakash et al., 2007). All have reported a gain in BCVA following laser refractive treatment of the adult amblyopic eye. The mechanism by which this gain in visual acuity was realized remains unclear. It has been postulated that permanent correction of spherocyclinrical errors, reduction of anisokonia and reduced spectacle aberrations, may play a role in improving acuity (Orucoglu-Oruvoc et al., 2001). Some authors have postulated that such acuity gains may also be attributed to the correction of higher-order aberrations.

The past decade has seen an increased understanding of the nature and composition of ocular higher-order aberrations. What remains an open question is the effect correction of these higher order aberrations have on conventional measures of visual function.

In this chapter, the change in measurements of logMar visual acuity following wavefront-guided laser refractive correction within a population of strabismic, anisometropic and idiopathic amblyopes and within a population of visually normal binocular subjects is evaluated.

## 4.2 Methods

This was a retrospective analysis of pre- and post -operative BCVA pertaining to 131 anisometropic, 104 strabismic adult amblyopic eyes, 17 idiopathic amblyopic eyes, 252 fellow fixing eyes and 252 prescription matched controls who elected for wavefront-guided laser refractive surgery at the London Vision Clinic. Visual acuity had been recorded utilising the Vector Vision ESV-300 ETDRS LogMar acuity chart.

Data relating to pre-operative visual acuity achieved with manifest, cycloplegic and WASCA refection, as well as visual acuity recorded with pin hole, was extracted from each patient record. That which afforded best corrected visual acuity (BCVA) was labeled as 'pre-operative BCVA'. Visual acuity data at time points of 1 day, 1 week, 1 month, 3 months, 6 months and 12 months post-surgery was analysed using SPSS 15.0 .

As in the previous chapter, data was stratified to reflect those whose amblyopia was of strabismic origin, anisometropic origin and those for which the origin of amblyopia could not be determined (i.e. idiopathic amblyopes). Data was further stratified according to presenting refractive correction and previous amblyopic treatment.

## 4.3 Results

Figure 4.1 shows the pre-operative versus post-operative measurements of BCVA for all amblyopic eyes included in this study (n=234) at time points from one day to one year (subplots a-f). The broken diagonal red line in each plot shows the 'line of no effect' (i.e. the same BCVA pre- and post-operatively).

Figure 4.1a shows that, on the first day after treatment, there was a significant reduction in mean BCVA of 0.029 LogMar ($t = -3.62$, $p < 0.01$). This is reflected in the general shift of the data above the line of no effect. At one week ($t = 3.417$, $p < 0.01$) and one month ($t = 5.86$, $p < 0.01$) post-surgery, a significant mean increase in BCVA of 0.045 LogMar was observed. Note, however, that only 51 subjects returned for review at 1 week. A sustained increase of 0.56 LogMar was observed at three months ($t = 7.89$, $p < 0.01$), six months ($t = 7.09$, $p < 0.01$) and 12 months ($t = 6.54$, $p < 0.001$) post-surgery.

The remaining figures in this chapter were constructed using the same graphical format as that shown in Figure 4.1.

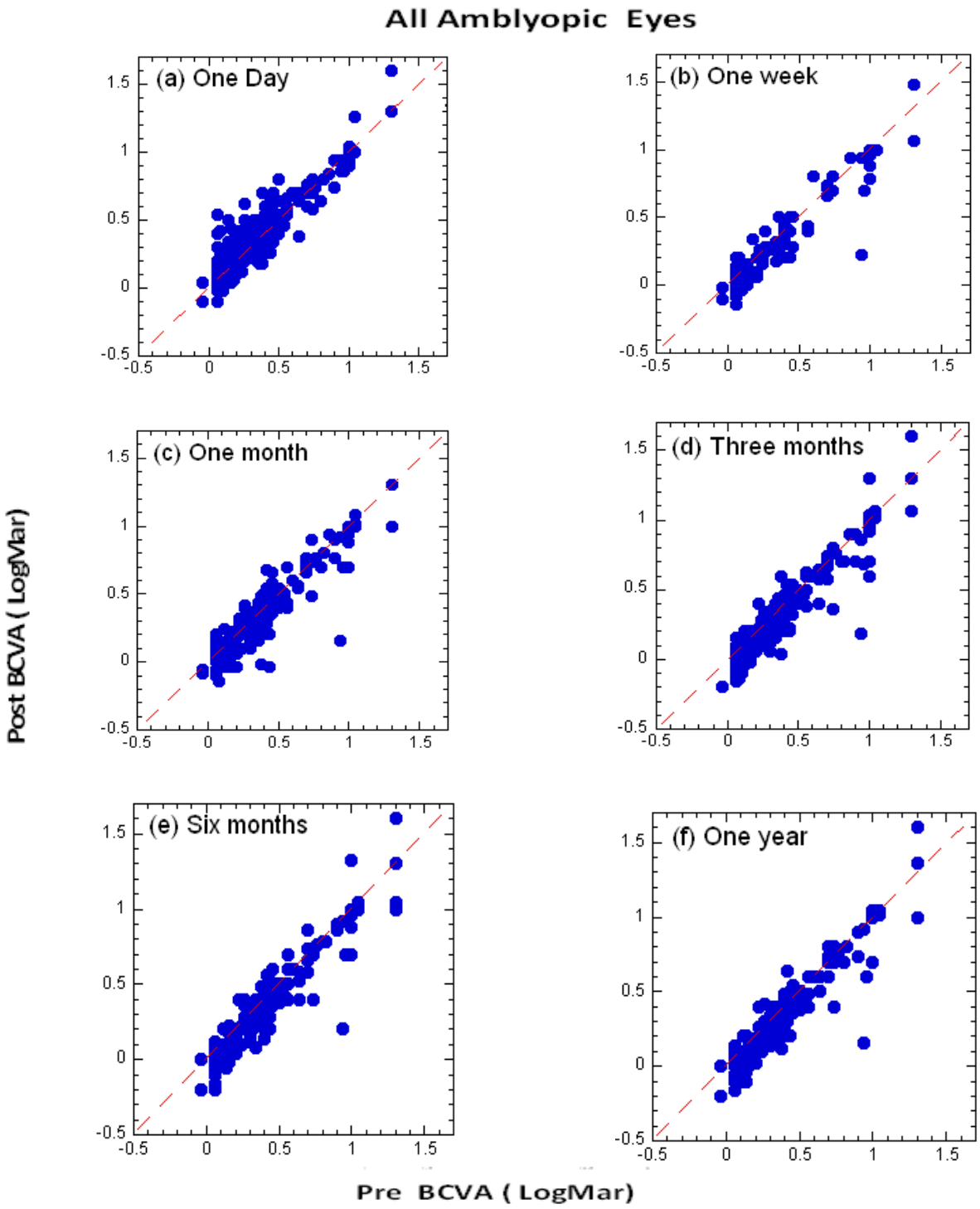



**Figure 4.1** *Pre-operative versus post-operative assessment of best corrected visual acuity (LogMar units) for all amblyopic eyes. (n=234). The straight line through each data set shows the line of no effect. A statistically significant reduction in best corrected visual acuity was observed at one day post treatment (p <0.01). No significant change was detected at one week post-operatively. All other time points show a statistically significant increase in best corrected visual acuity (p < 0.01).*

Figure 4.2 illustrates the pre-operative versus post-operative measurements of BCVA for the fellow fixing eye of amblyopic subjects (n=234). At one day post-treatment, there was a significant reduction in mean BCVA of 0.072LogMar ($t = -6.56$, $p < 0.001$). At both one week and one month post-treatment, no significant change in BCVA was observed, although again it should be noted that only 51 subjects returned for assessment at one week. At all other post-operative reviews, the entire patient cohort was evaluated. At post-operative time points of 3 mths, 6 mths and 12mths, a significant mean gain in BCVA of 0.016 ($t = 3.26$), 0.024 ($t = 4.19$) and 0.021 LogMar ($t = 3.68$), respectively, was observed for the fellow fixing eye of this cohort ($p = <0.01$).

## Fixing Eyes

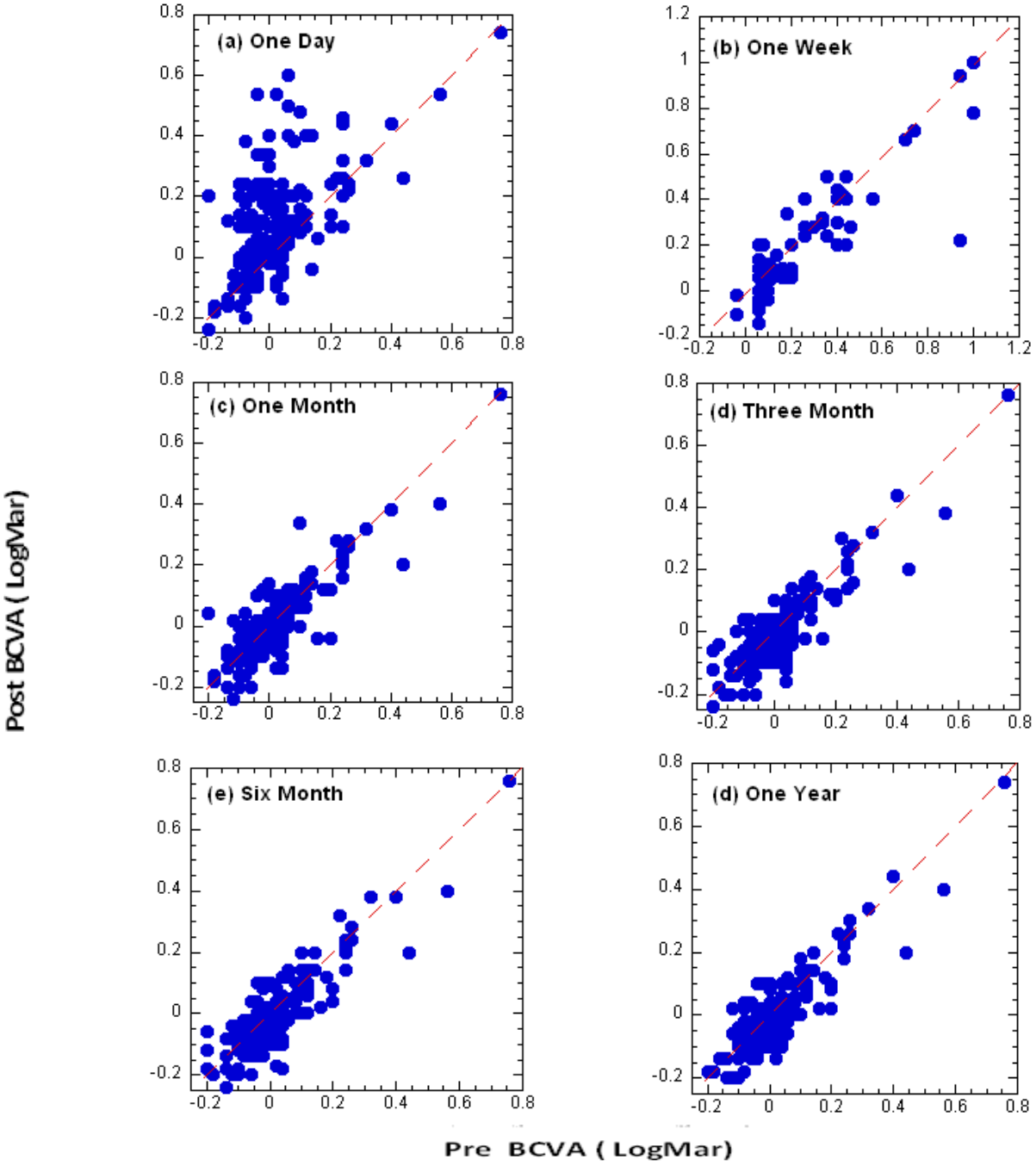



**Figure 4.2** *Pre-operative versus post-operative assessment of best corrected visual acuity (LogMar units) for fellow fixing eyes of all amblyopic subjects (n=234). ). The straight line through each data set shows the line of no effect. A statistically significant reduction in best corrected visual acuity was observed at one day, one week and one week post-operatively (p <0.01). No significant change was detected at one month or three months post-treatment. A significant increase in BCVA was observed at six and 12 months (p < 0.05).*

Figure 4.3 shows the pre-operative versus post-operative measurements of BCVA for the prescription matched control eyes (n=234). Again the broken red line in each plot is the 'line of no effect'. Data above the line indicates a reduction in acuity post-operatively, while data below the line indicates an improvement in BCVA post-operatively. There was a significant mean reduction in BCVA of 0.12 LogMar ($t = -10.16$, $p < 0.01$) and 0.04 LogMar ($t = -2.83$, $p < 0.01$) at 1 day and 1 week post-treatment, respectively. No significant change in BCVA was observed at 1 month or 3 months. At the 6 month follow up, a significant increase in mean BCVA of 0.01 LogMar was noted ($t = 2.06$, $p = 0.041$). Finally, at 12 months post-surgery a significant increase of 0.019 LogMar was observed ($t = 2.13$, $p = 0.035$).

**Control Eyes**

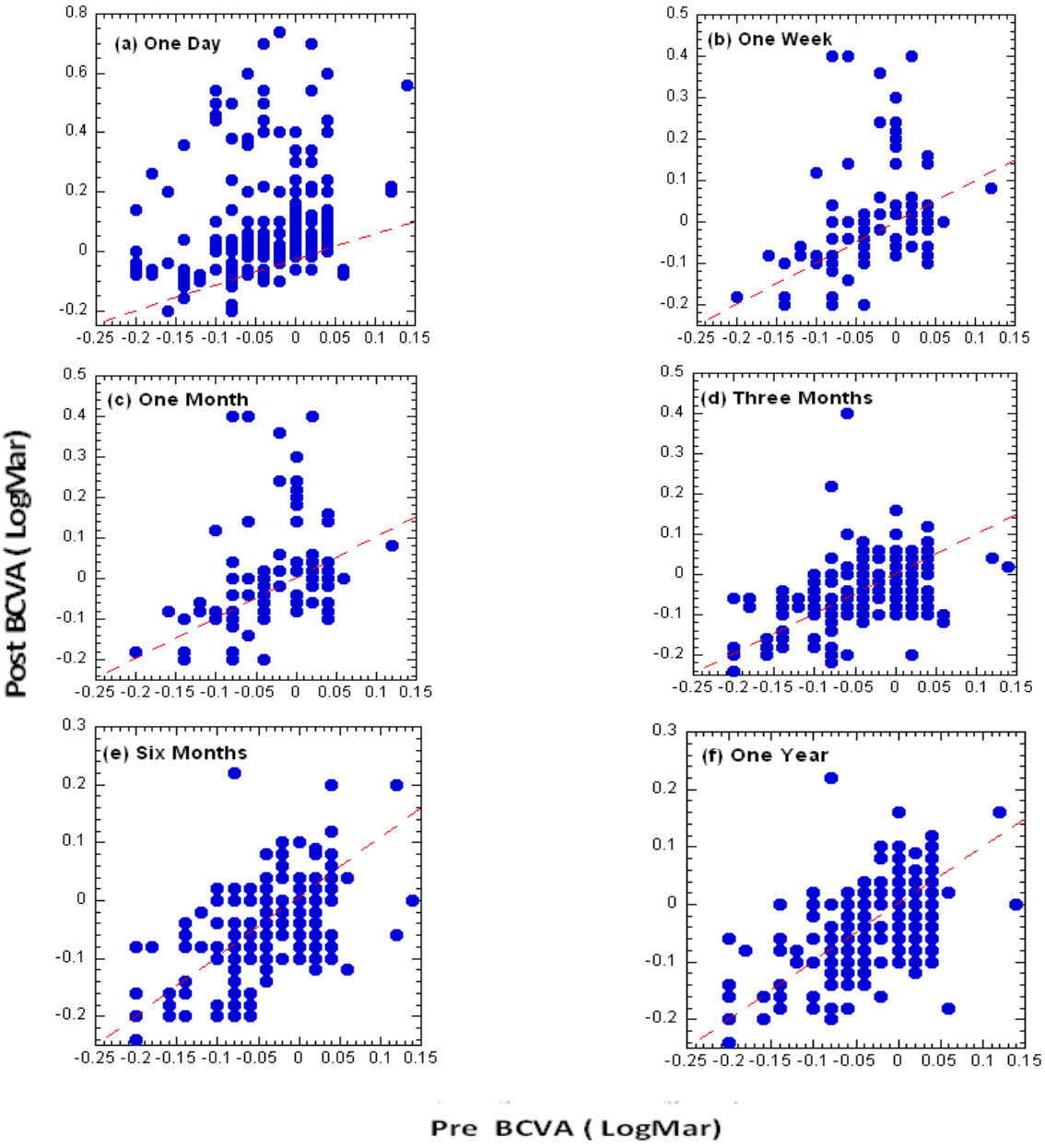



**Figure 4.3** *Pre-operative versus post-operative assessment of best corrected visual acuity (Log Mar units) prescription matched control eyes of normal binocular observers (n=234). ). The straight line through each data set shows the line of no effect. A significant reduction in best corrected visual acuity was observed at one day and at one week (p < 0.01)) post-operatively. No statistically significant change in visual acuity occurred at one month or three month post operative. An improvement in BCVA was observed at six months and one year post operative (p < 0.05).*

Figure 4.4 shows the pre-operative versus post-operative measurements of BCVA for the anisometropic amblyopic eyes evaluated in this study. There was an initial reduction in BCVA of 0.03 LogMar at one day post-treatment ($t = -2.989$, $p = 0.03$), followed by a sustained improvement in BCVA at 1 week (0.05 LogMar, $t= 3.71$, $p < 0.01$), 1 month (0.06 LogMar, $t= 5.48$, $p < 0.01$), and a mean increase of 0.08 LogMar BCVA at all other time points post-operatively ($p < 0.01$).

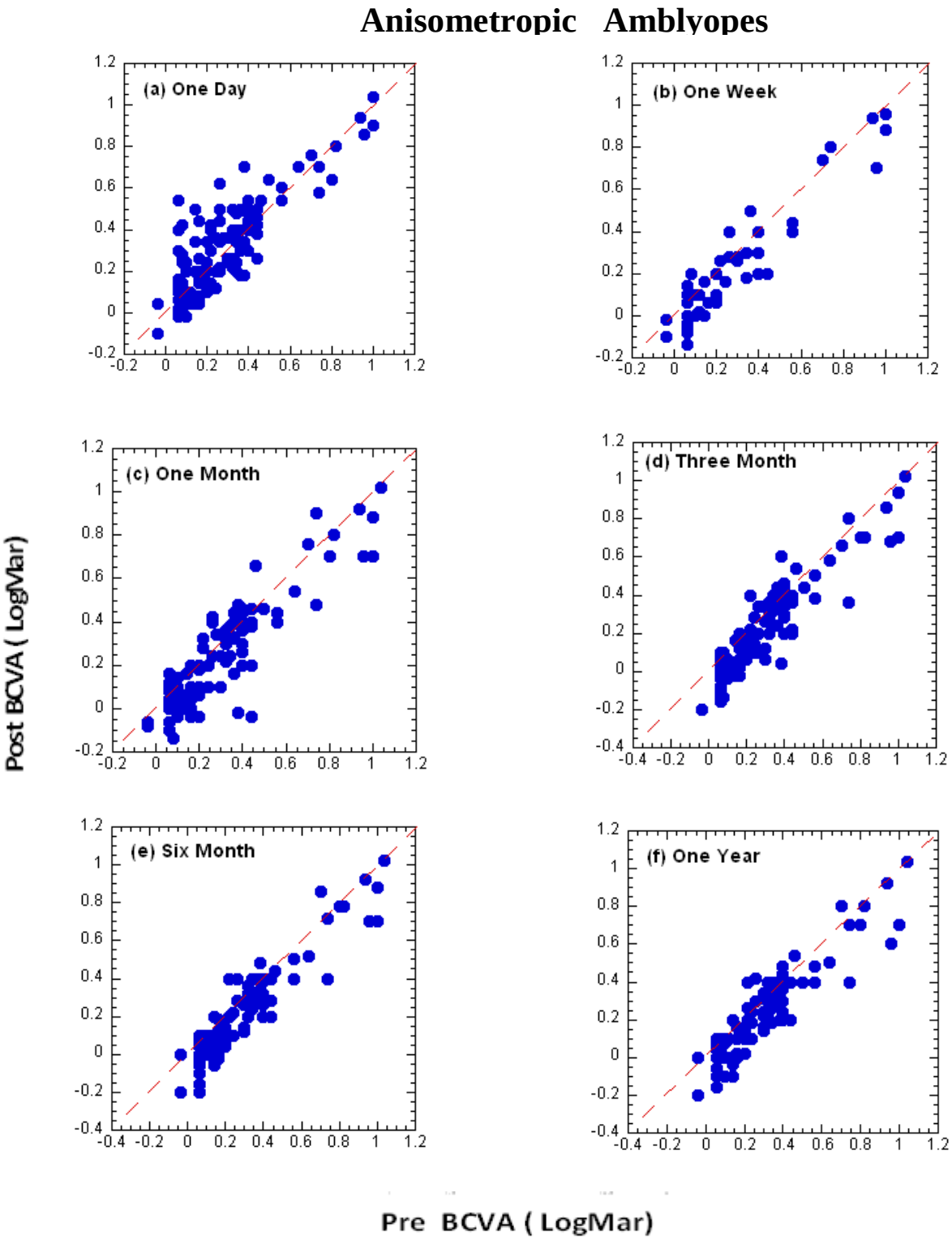



**Figure 4.4 Pre**-*operative versus post-operative assessment of best corrected visual acuity (Log Mar units) anisometropic amblyopic eyes (n=131).The straight line through each data set shows the line of no effect. A statistically significant (p < 0.05) reduction in one day post-operative best corrected visual acuity was observed. A statistically significant improvement in BCVA was observed at other time points (p < 0.05).*

Figure 4.5 shows the pre-operative versus post-operative measurements of BCVA for strabismic amblyopic eyes (n=104). Up to one week post-operatively, there was no significant difference in mean BCVA. At 1 month following treatment, a significant increase of 0.03 LogMar was observed ($t = 2.86$, $p = 0.05$), and this level of improvement was maintained at both three months ($t = 3.44$, $p < 0.01$) and six months ($t = 3.24$, $p < 0.01$) post-operatively. However, by 12 months there was no significant change in BCVA ($t = 2.71$, $p = 0.08$).

Note that the outliner towards the bottom right-hand corner of plots b-f pertains to data from a 15 prism diopter esotropic amblyope with a pre-operative refraction of -5.50 / -1.00 X 35. This subject presented with a balanced prescription and had a pre-operative BCVA of 0.95 LogMar. At 12 months post-operatively, this subject's visual acuity improved dramatically to 0.15 LogMar.

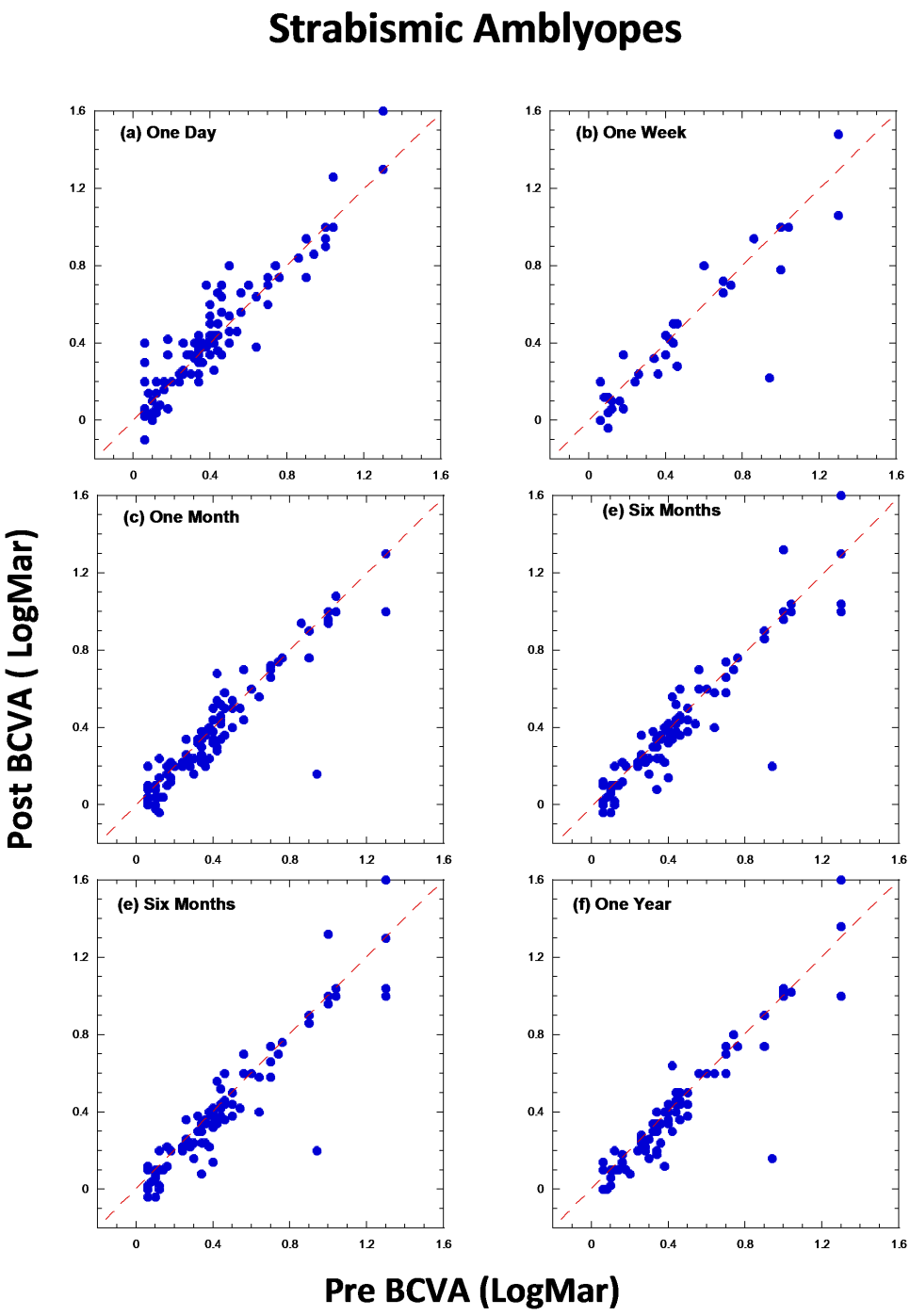



**Figure 4.5** *Pre-operative versus post-operative assessment of best corrected visual acuity (LogMar units) strabismic amblyopic eyes (n=104). The straight line through each data set shows the line of no effect. No statistically significant change in visual acuity occurred at one day or one week post-operatively. A significant improvement in BCVA was observed at 3, 6 and twelve months post-treatment ($p < 0.05$). No improvement was detected at 12 months ($p = 0.08$)*

Figure 4.6 depicts the pre-operative versus post-operative measurements of BCVA for those subjects classified as idiopathic amblyopes (n=17). No significant change in BCVA was observed the day after surgery. However, a significant increase in BCVA of 0.084 LogMar was evident at one month post-surgery ($t = 2.49$, $p = 0.025$), and this level of improvement was maintained at three months ($t = 3.76$, $p = 0.002$), six months ($t = 4.65$, $p = < 0.01$) and 12 months ($t = 3.49$, $p = 0.003$) post-surgery. Note that too few subjects returned for analysis at one week post-surgery.

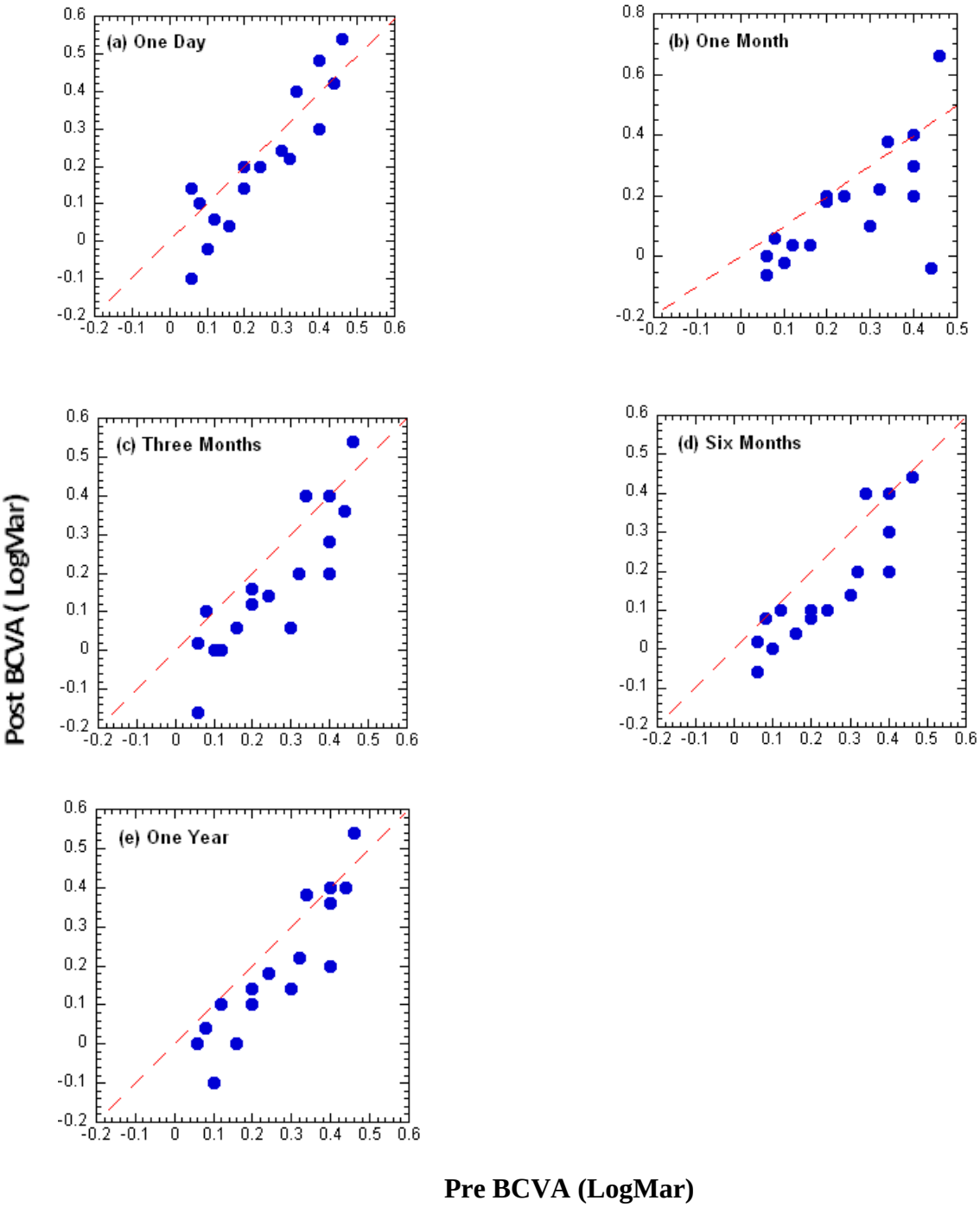



**Figure 4.6** *Pre-operative versus post-operative assessment of best corrected visual acuity (Log Mar units) 'idiopathic' amblyopic eyes (n=17). The straight line through each data set shows the line of no effect. No significant change in visual acuity occurred at one day post treatment. A significant improvement in BCVA was observed at all other time points ($p < 0.05$).*

Tables 4.1- 4.4 provide a summary of the main findings reported in this chapter.

| Amblyopic Eyes: Mean Post- Operative Change in Visual Acuity | | | | |
|---|---|---|---|---|
| **Time Point** | **Mean Reduction in VA** | **Mean Increase in VA** | **t** | **p** |
| One Day | 0.029LogMar | | -3.62 | <0.01 s |
| One Week | | 0.045 LogMar | 3.42 | <0.01 s |
| One Month | | 0.045 LogMar | 5.86 | <0.01 s |
| Three Months | | 0.056 Log Mar | 7.89 | <0.01 s |
| Six Months | | 0.056 LogMar | 7.09 | <0.01 s |
| One Year | | 0.056 LogMar | 6.54 | <0.01 s |

**Table 4.1** *Mean change in best corrected visual acuity (Log Mar units) following laser refractive treatment of amblyopic eyes (n=234). s = statistically significant at p <0.01.*

| Fixing Eyes: Mean Post- Operative Change in Visual Acuity | | | | |
|---|---|---|---|---|
| **Time Point** | **Mean Reduction in VA** | **Mean Increase in VA** | **t** | **p** |
| One Day | 0.072 LogMar | | -6.56 | <0.01 s |
| One Week | 0.009 LogMar | | -1.16 | 0.555 |
| One Month | | 0.063 LogMar | 1.13 | 0.260 |
| Three Months | | 0.016 LogMar | 3.26 | <0.01 s |
| Six Months | | 0.024 LogMar | 4.19 | <0.01 s |
| One Year | | 0.021 LogMar | 3.68 | <0.01 s |

**Table 4.2** *Mean change in best corrected visual acuity (Log Mar units) following laser refractive treatment fixing eye (n=234). s = statistically significant.*

| Control Eyes: Mean Post- Operative Change in Visual Acuity | | | | |
|---|---|---|---|---|
| **Time Point** | **Mean Reduction in VA** | **Mean Increase in VA** | **t** | **p** |
| One Day | 0.12 LogMar | | -10.16 | <0.01 s |
| One Week | 0.04 LogMar | | -2.83 | 0.006 s |
| One Month | | 0.0003LogMar | 0.06 | 0.950 |
| Three Months | | 0.007 Log Mar | 1.52 | 0.130 |
| Six Months | | 0.011 LogMar | 2.06 | 0.041 s |
| One Year | | 0.019 LogMar | 2.13 | 0.035 s |

**Table 4.3** *Mean change in best corrected visual acuity (Log Mar units) following laser refractive treatment of the prescription matched control eyes of normally sighted subjects (n=234). s = statistically significant.*

| Idiopathic Amblyopic Eyes : Mean Post- Operative Change in Visual Acuity | | | | |
|---|---|---|---|---|
| **Time Point** | **Mean Reduction in VA** | **Mean Increase in VA** | **t** | **P** |
| One Day | | 0.033 LogMar | 1.65 | 0.120 |
| One Month | | 0.084 LogMar | 2.48 | 0.025 s |
| Three Months | | 0.084 Log Mar | 3.76 | 0.002 s |
| Six Months | | 0.084 LogMar | 4.65 | < 0.01 s |
| One Year | | 0.070 LogMar | 3.49 | 0.003 s |

**Table 4.4** *Mean change in best corrected visual acuity (Log Mar units) following laser refractive treatment of 'idiopathic' amblyopic eyes (n= 17). s = statistically significant.*

Table 4.5 outlines the mean change in BCVA one year post wavefront-guided laser refractive correction. Data pertaining to anisometropic, strabismic and 'idiopathic' amblyopes have been discussed above. In addition, Table 4.5 outlines the mean change in BCVA observed for those subjects who presented for treatment with hypermetropic and myopic refractive error. Hypermetropic amblyopes showed a significant mean gain in BCVA of 0.019 Log Mar ($t = 2.39$, $p = 0\ .018$). No significant change in mean BCVA was observed for the fellow fixing eye of this cohort. Myopic subjects showed a significant mean gain in BCVA of 0.11 Log Mar ($t = 7.47$, $p < 0.01$) and 0.04 Log Mar ($t = 4.84$, $p = <0.01$) for the amblyopic eye and fixing eye, respectively

| Eye | BCVA Gain At 1 Yr | Significance. | |
|---|---|---|---|
| **Anisometropic:** | | | |
| **Amblyopic Eye** | **0.079 LogMar** | **p= <0.01** | **s** |
| **Fixing Eye** | **0.036 LogMar** | **p= <0.01** | **s** |
| **Control Eye** | **0.018 LogMar** | **p = 0.035** | **s** |
| **Strabismic:** | | | |
| **Amblyopic Eye** | **0.035 LogMar** | **p = 0.08** | **s** |
| **Fixing Eye** | **0.006 LogMar** | **p = 0.248** | |
| **Control Eye** | **0.011 LogMar** | **p = 0.041** | **s** |
| **Idiopathic:** | | | |
| **Amblyopic Eye** | **0.07 LogMar** | **p = 0.003** | **s** |
| **Fixing Eye** | **0.065 LogMar** | **p = 0.172** | |
| **Control Eye** | **0.007 LogMar** | **p = 0.130** | **ns** |
| **Hypermetropic:** | | | |
| **Amblyopic Eye** | **0.019 LogMar** | **p = 0.018** | **s** |
| **Fixing Eye** | **0.00017 LogMar** | **p = 0.972** | |
| **Myopic:** | | | |
| **Amblyopic Eye** | **0.11 LogMar** | **p= <0.01** | **s** |
| **Fixing Eye** | **0.04 LogMar** | **p= <0.01** | **s** |

**Table 4.5** *Mean gain in best corrected visual acuity at a time point of one year following laser refractive treatment. s = statistically significant.*

Table 4.6 outlines the mean change in BCVA for data grouped according to any previous amblyopic treatment undertaken. A significant increase in BCVA of 0.036 Log Mar was observed for those subjects who had undergone previous occlusion therapy ($p < 0.01$), while an increase of 0.043 Log Mar was observed for those who had refractive correction during childhood ($p < 0.01$). No acuity gain was observed for those subjects who had surgical treatment or no treatment during childhood.

| **Previous Treatment** | **BCVA Gain At 1 Yr** | Significance. |
|---|---|---|
| **Occlusion** | 0.036 LogMar | p = 0.004 s |
| **Surgical** | 0.043 LogMar | p = 0.240 |
| **Spectacle** | 0.043 LogMar | p < 0.01 s |
| **No Treatment** | 0.00042 LogMar | p = 0.39 |

**Table 4.6** *Mean gain in best corrected visual acuity at a time point of one year following laser refractive treatment. s = statistically significant.*

The mean gain in BCVA for data grouped according to the amount of refractive error corrected prior to laser refractive treatment is shown in table 4.7. A significant increase of 0.051 Log Mar was observed for those subjects who presented for treatment in full refractive correction ($p < 0.01$). A similar level of BCVA gain, 0.056 Log Mar, was observed in those who presented with a balance prescription only ($p = 0.01$).

| **Rx** | **BCVA Gain At 1 Yr** | Significance. |
|---|---|---|
| **Full Rx** | 0.051 LogMar | P < 0.01 s |
| **Balance Rx** | 0.056 .LogMar | P = 0.01 s |

**Table 4.7** *Mean gain in best corrected visual acuity at time point of one year following laser refractive treatment. s = statistically significant.*

Table 4.8 shows the pre- and post-operative BCVA for 16 subjects where the gain in visual acuity following treatment was such that the subjects would no longer be deemed to have amblyopia, as defined by the American Optometric Association (see section 1.2).

| Pre – Op BCVA Amblyopic Eye | Post-OP BCVA Amblyopic Eye | Pre – Op BCVA Fixing Eye | Post – Op BCVA Fixing Eye |
|---|---|---|---|
| 0.8 LogMar | 0.00 LogMar | 0.02 LogMar | 0.02 LogMar |
| 0.1 LogMar | 0.00 LogMar | -0.06 LogMar | -0.06 LogMar |
| 0.06 LogMar | 0.00 LogMar | -0.2 LogMar | -0.1 LogMar |
| 0.06 LogMar | 0.00 LogMar | -0.3 LogMar | -0.08 LogMar |
| 0.1 LogMar | 0.00 LogMar | -0.3 LogMar | -0.2 LogMar |
| 0.08 LogMar | 0.04 LogMar | -0.2 LogMar | -0.02 LogMar |
| 0.86 LogMar | 0.00 LogMar | -0.2 LogMar | -0.12 LogMar |
| 0.08 LogMar | 0.00 LogMar | -0.2 LogMar | -0.14 LogMar |
| 0.08 LogMar | 0.00 LogMar | -0.2 LogMar | 0.00 LogMar |
| 0.16 LogMar | 0.00 LogMar | -0.1 LogMar | 0.00 LogMar |
| 0.06 LogMar | 0.00 LogMar | -0.3 LogMar | -0.12 LogMar |
| 0.14 LogMar | -0.04 LogMar | -0.18 LogMar | -0.02 LogMar |
| 0.08 LogMar | 0.00 LogMar | -0.34 LogMar | -0.14 LogMar |
| 0.06 LogMar | 0.00 LogMar | -0.32 LogMar | -0.12 LogMar |
| 0.04 LogMar | 0.00 LogMar | -0.34 LogMar | -0.12 LogMar |
| 0.16 LogMar | 0.00 LogMar | -0.2 LogMar | -0.02 LogMar |

**Table: 4.8** *Pre- and post-operative BCVA of subjects no longer be deemed to have amblyopia following laser refractive treatment.*

## 4.5 Discussion

The results show an initial decrease in visual acuity following laser refractive treatment for both amblyopic and control eyes. This may be attributed to surgically-induced corneal epithelial injury which sets in motion a cascade of wound healing events in the stroma and epithelium (see Wilson et al. 2001). Following surgical recovery, the data show that a significant improvement in visual acuity can be realised for adult amblyopic patients treated with wavefront-guided laser refractive surgery. These findings are in agreement with the limited number of previous studies investigating the use of laser refractive correction in adult amblyopia (Orucoglu et al., 2011: Lanza et al., 2005; Barequet et al., 2004; Roszkowska et al., 2006; Sakatani et al., 2004).

Although the majority of the cohort would still be deemed amblyopic following treatment, 15 subjects would no longer be classified amblyopic. The pre- and post-operative BCVA of said subjects are shown in Table 4.8. Note that, with exception of one patient (Pre BCVA 0.8 LogMar), subjects within this group were only mildly amblyopic, with a pre-operative BCVA ranging from 0.16 to 0.06 LogMar. The results indicate that the eradication of 'amblyopia' in this particular subset of patients arises because of an improvement in acuity in the amblyopic eye combined with a reduction in acuity in the fellow fixing eye. Wali et al. (1991) described this effect as the "pull – push phenomenon" where, in order to balance inputs from the two eyes, the treated amblyopic eye may first cause a decrement in visual function of the dominant eye. This theory is underpinned by the assumption that amblyopia is a binocular abnormality, and that the amblyopic eye influences the fellow eye through binocular intraocular interactions.

The proposed theory of minification bias (Orucoglu et al., 2011) is supported by the data in this study, in that those subjects with pre-operative myopia demonstrated a larger gain in post-operative visual acuity than those with pre-operative hypermetropia (see table 4.5).

It has been argued that post-operative gain in BCVA following laser refractive treatment of the amblyopic eyes represents a return to a level of acuity previously achieved with treatment during the critical period (Kirwan and O' Keefe 2008). To asses this, in this study data was grouped to reflect those subjects who underwent conventional amblyopic treatment versus those who did not undertake any treatment during childhood (see table 4.6). A significant improvement in BCVA was observed for patients who had previous treatment with occlusion therapy and/or spectacles in childhood. However, no significant improvement was observed for those who had undergone previous strabismus surgery or for those subjects who had no treatment in childhood. Thus, the data supports the hypothesis that previous amblyopic treatment positively influences the visual outcome of amblyopic eyes following laser refractive treatment.

In addition, data was grouped to reflect those subjects who presented for laser refractive treatment with either a full refractive correction or a balanced prescription. Here, a significant improvement in post-operative visual acuity was realised for both subject groups (Table 4.7).

It has been suggested that a 0.14 Log unit improvement of visual acuity is clinically significant (Dong et al., 2004). Assessment of the data currently under consideration reveals that 43 of the 234 (18%) amblyopic eyes investigated improved beyond 0.14 log units. Of these 43 patients, 22 presented for laser refractive correction with anisometropic amblyopia and 21 with strabismic amblyopia. Twenty nine subjects had previous occlusion treatment for amblyopia, whereas only 5 of this group had previous surgical treatment. Thirty six subjects had spectacle correction during the critical period and thirty subjects presented for pre–operative assessment in their full refractive correction.

Therefore, the results show that for the cohort of amblyopic patients under investigation, occlusion therapy during the critical period combined with optimal refractive correction is advantageous in gaining a clinically significant improvement in acuity with laser refractive treatment.

The final hypothesis to consider is that visual acuity gain in the amblyopic eye arises secondary to relief from higher-order aberrations following wavefront-guided refractive correction at the corneal plane. This is explored in Chapter Six.

# Chapter Five

**Contrast Sensitivity outcomes following laser refractive surgery on adult amblyopic eyes**

## 5.1 Introduction

In this chapter, the change in post-operative contrast sensitivity (at 3 months, 6 months and 12 months) within the amblyopic and visually-normal populations following wavefront-guided laser refractive surgery was evaluated.

By convention, amblyopia is defined and detected clinically by a decrease in visual acuity. However, visual acuity only measures one aspect of visual function. Several studies have demonstrated that amblyopic patients not only have reduced visual acuity but also display other functional abnormalities, including reduced contrast sensitivity (Bradley et al., 1981).


**Figure: 5.1** *Illustrates the effect of increasing amounts of spherical aberration and coma aberrations on contrast sensitivity. The image of the test chart was viewed through a ascending levels of induced spherical aberrations and coma, SC0 to SC4 (image taken from Perez et al., 2009).*

It has been shown that higher-order aberrations exert a greater influence on measures of contrast sensitivity than on measures of visual acuity (Liang et al., 1994; Yoon et al., 2002; Li et al., 2009). Figure 5.1 illustrates the effect of higher-order aberration terms coma and spherical aberrations, on contrast sensitivity (see section 1.1.1).

In this chapter the effect of wavefront-guided laser refractive treatment on contrast sensitivity in the amblyopic eye was evaluated. For comparison, measures were also completed on both fellow fixing eyes and prescription-matched control eyes.

## 5.2 Methods

A retrospective analysis of pre- and post-operative measurements of contrast sensitivity pertaining to 96 anisometropic, 79 strabismic adult amblyopic eyes, 17 idiopathic amblyopic eyes, 188 fellow fixing eyes and 188 prescription-matched controls was conducted.

Contrast sensitivity had been measured utilising the vector vision CSV-1000 contrast sensitivity chart. Contrast sensitivity was plotted on a scale from 1-8 at spatial frequencies of 3, 6, 9, 12 and 18 cycles per degree. An example of conversion from this 1-8 scale to both linear and log units is shown below.

Example conversion: At 3 cycles per degree, the patient scores 8. Conversion tables show this to be a contrast sensitivity value of 120. Therefore, contrast = 1/120 = 0.0083. And the $\text{Log}_{10}(0.0083) = 2.08$.

**Contrast Sensitivity Values for the CSV-1000E:**

| | S | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|---|
| Row (CPD) | | | | | | | | | |
| A (3.0) | 5 | 10 | 15 | 22 | 31 | 43 | 61 | 85 | 120 |
| B (6.0) | 8 | 16 | 24 | 36 | 50 | 70 | 99 | 138 | 193 |
| C (12.0) | 4 | 8 | 12 | 18 | 25 | 35 | 50 | 70 | 99 |
| D (18.0) | 1.5 | 3 | 4.5 | 7 | 9.5 | 13 | 18 | 25 | 36 |

**Contrast Sensitivity Values for the CSV-1000E in Log Units:**

| | S | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|---|
| Row (CPD) | | | | | | | | | |
| A (3.0) | .70 | 1 | 1.17 | 1.34 | 1.49 | 1.63 | 1.78 | 1.93 | 2.08 |
| B (6.0) | .91 | 1.21 | 1.38 | 1.55 | 1.70 | 1.84 | 1.99 | 2.14 | 2.29 |
| C (12.0) | .61 | .91 | 1.08 | 1.25 | 1.40 | 1.54 | 1.69 | 1.84 | 1.99 |
| D (18.0) | .17 | .47 | .64 | .81 | .96 | 1.10 | 1.25 | 1.4 | 1.55 |

Data was grouped in accordance with amblyopic pathophysiology (strabismic, anisometropic and ‘idopathic’), previous amblyopic treatment (refractive, surgical, occlusion, no treatment) and the level of pre-operative refractive correction (i.e balanced or full prescription).

Pre-operative contrast sensitivity data, as well as data obtained at three, six and twelve months post-treatment, was analysed using SPSS 15.0.

## 5.3 Results

Figure 5.2 shows the change in mean contrast sensitivity following wavefront-guided laser refractive treatment of all amblyopic eyes included in this study (n = 188). There was no significant change in contrast sensitivity at 3 months or 6 months post-operatively when compared with pre-operative measurements ($p > 0.05$). However, at one year post-operatively, there was a significant improvement in contrast sensitivity at periodicities of 3 cycles per degree ($t = -2.54$, $p = 0.013$), 6 cycles per degree ($t = -2.63$, $p = 0.011$), 12 cycles per degree ($t = -2.30$, $p = 0.024$) and 18 cycles per degree ($t = -2.70$, $p = 0.009$).

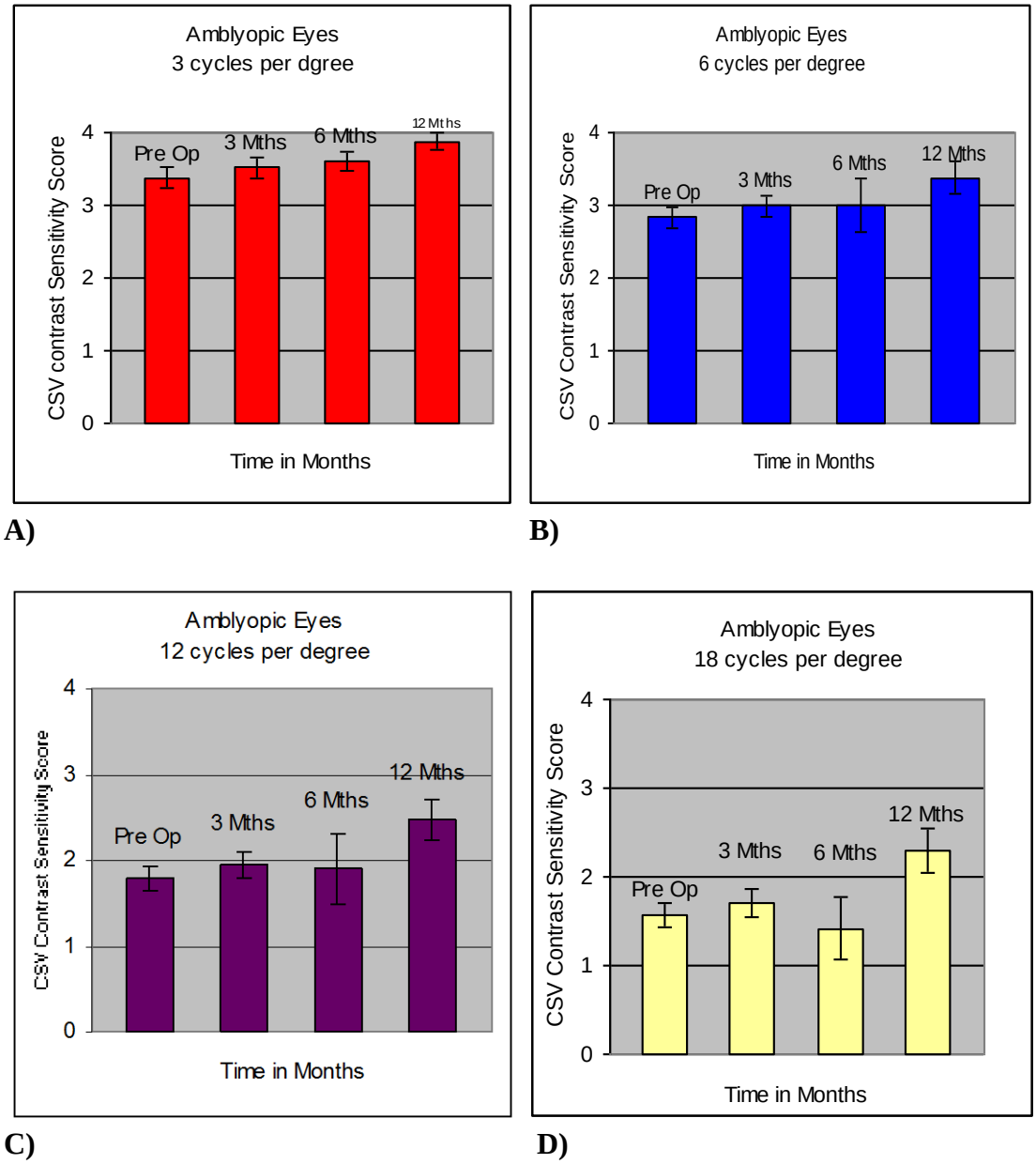



**Figure 5.2** *Mean contrast sensitivity for the amblyopic eye (n = 188), for test periodicities (a) 3, (b) 6, (c) 12 and (d) 18 cycles per degree. For each test spatial frequency, group mean contrast sensitivity is shown pre-operatively and three months, six months, twelve months post-operatively. The vertical error bars show +/- one standard error of the mean. Results of statistical analyses are reported in the text.*

Using the same graphical format, figure 5.3 illustrates the change in mean contrast sensitivity of the fellow fixing eyes of amblyopic subjects (n = 188). Note that there was no significant difference between pre- and post-operative sensitivity measures at any time point from 3 to 12 months post-surgery ($p > 0.05$).

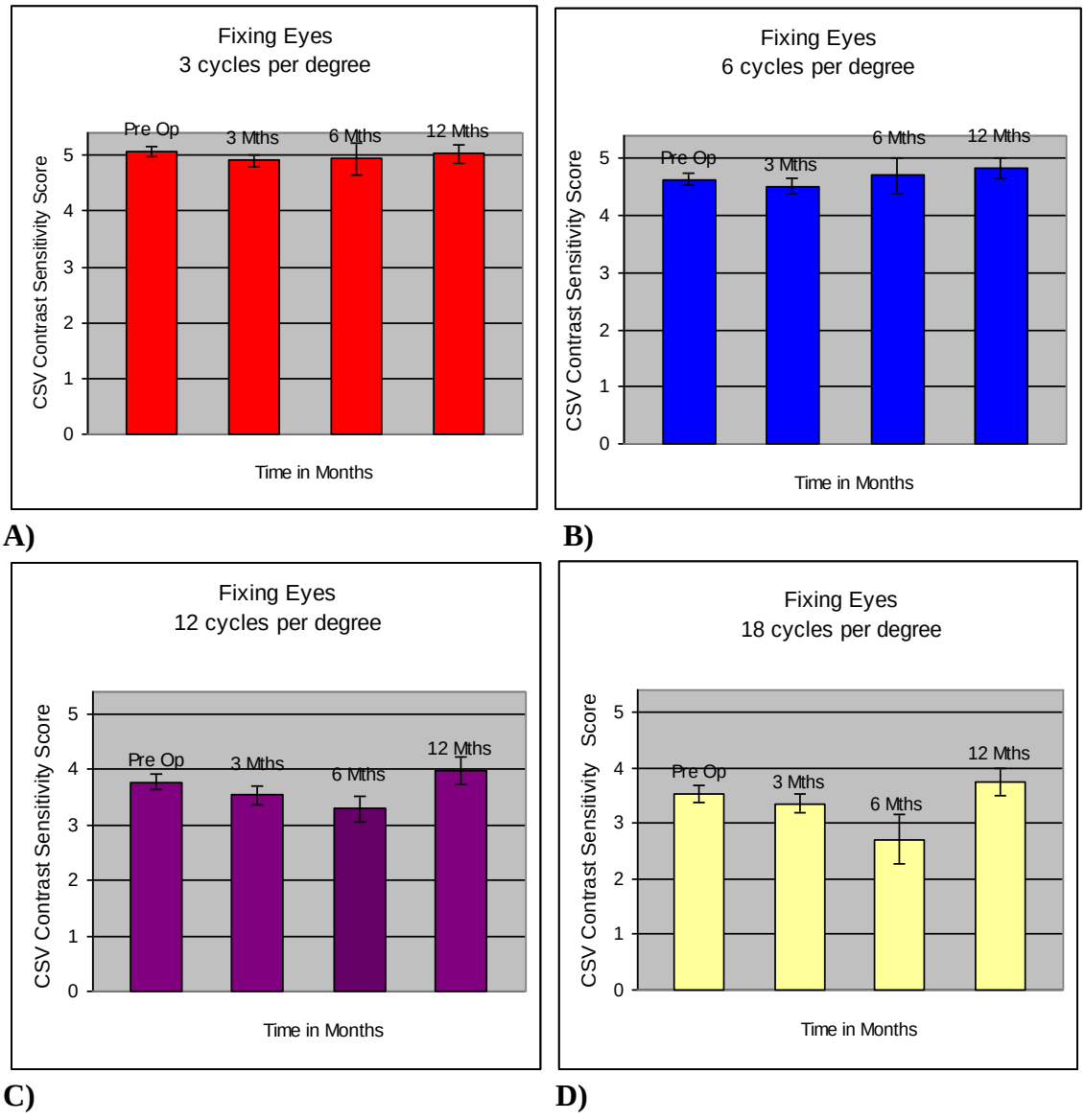



**Figure 5.3** *Mean contrast sensitivity for the fellow fixing eyes of amblyopic subjects (n = 188), for test periodicities (a) 3, (b) 6, (c) 12 and (d) 18 cycles per degree. For each test spatial frequency, group mean contrast sensitivity is shown pre-operatively and three months, six months, twelve months post-operatively. The vertical error bars show +/- one standard error of the mean. Results of statistical analyses are reported in the text.*

Figure 5.4 shows the change in mean contrast sensitivity for all prescription-matched control eyes (n = 188). A significant reduction in sensitivity was observed at 3 months post-operatively for 6 cycles per degree (t = 5.0, < 0.01), 12 cycles per degree (t = 4.69, p = <0.01) and 18 cycles per degree (t = 3.44, p = 0.01). No significant change in contrast sensitivity was observed at 6 months across any spatial frequency. A significant reduction in contrast sensitivity was observed at 12 months for 6 cycles per degree (t = 2.38, p = 0.02), 12 cycles per degree (t = 2.24, p = 0.028) and for 18 cycles per degree (t = 2.12, p = 0.037).

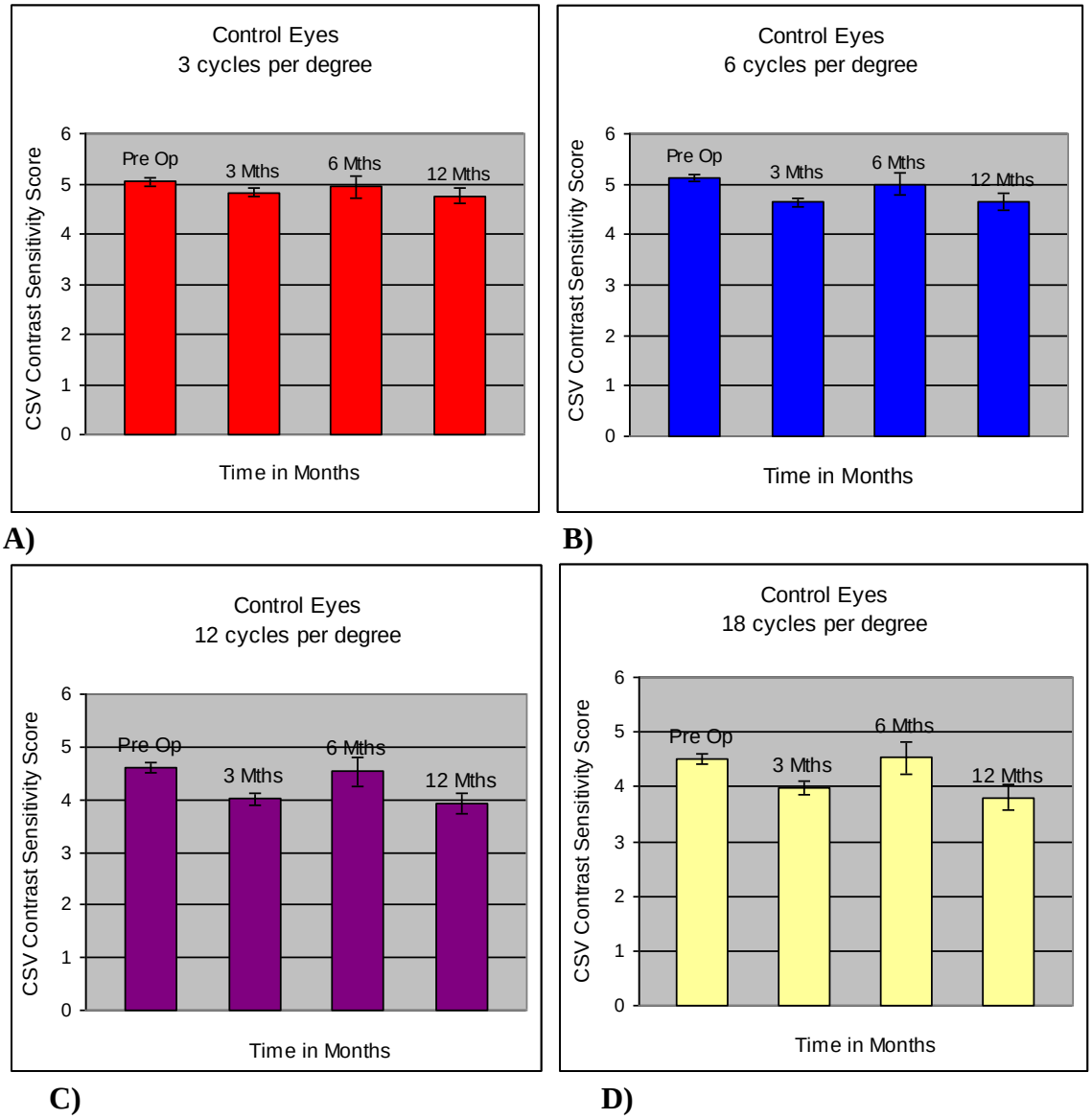



**Figure 5.4** *Mean contrast sensitivity for independent prescription matched control eyes (n = 188), for test periodicities (a) 3, (b) 6, (c) 12 and (d) 18 cycles per degree. For each test spatial frequency, group mean contrast sensitivity is shown pre-operatively and three months, six months, twelve months post-operatively. The vertical error bars show +/- one standard error of the mean. Results of statistical analyses are reported in the text.*

Figure 5.5 shows contrast sensitivity recorded pre- and post-operatively for anisometropic amblyopic eyes (n = 96). There was no significant change in contrast sensitivity at any time point from 3 to 12 months for test periodicities 3, 6 or 12 cycles per degree. However, at 12 months follow up, a significant improvement in sensitivity was noted at 18 cycles per degree ($t = -2.18$, $p = 0.036$).

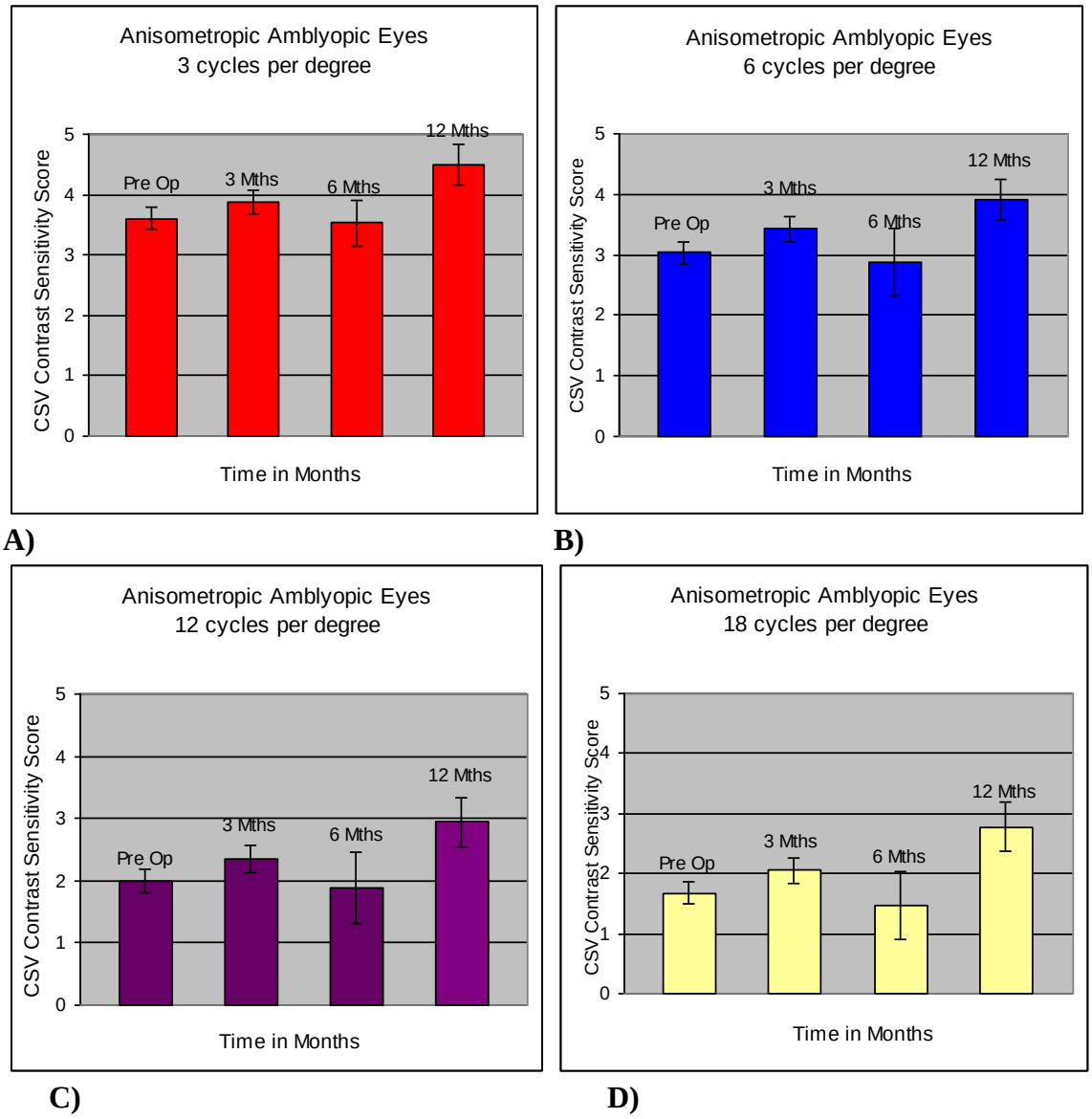



**Figure 5.5** *Mean contrast sensitivity for the anisometropic amblyopic eyes (n = 96), for test periodicities (a) 3, (b) 6, (c) 12 and (d) 18 cycles per degree. For each test spatial frequency, group mean contrast sensitivity is shown pre-operatively and three months, six months, twelve months post-operatively. The vertical error bars show +/- one standard error of the mean. Results of statistical analyses are reported in the text.*

Figure 5.6 shows the results for strabismic amblyopes (n = 79). Wavefront-guided correction of refractive error had no effect on contrast sensitivity for this patient cohort at any time point post-surgery. This was true for all spatial frequencies assessed (3 – 18 cycles per degree).

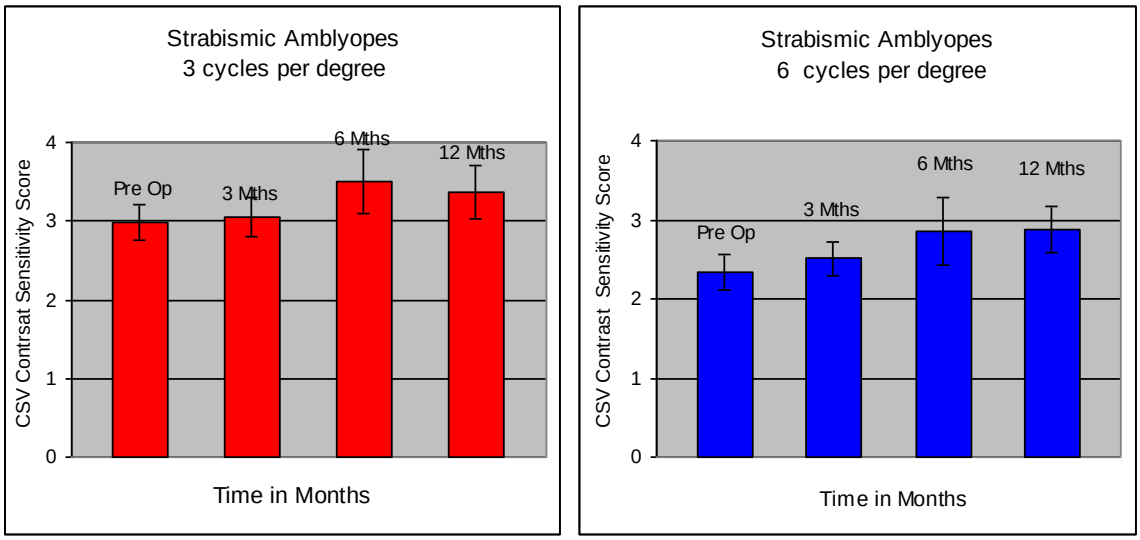



**Figure: 5.6** *Mean contrast sensitivity for the anisometropic amblyopic eyes (n = 79), for test periodicities (a) 3, (b) 6, (c) 12 and (d) 18 cycles per degree. For each test spatial frequency, group mean contrast sensitivity is shown pre-operatively and three months, six months, twelve months post-operatively. The vertical error bars show +/- one standard error of the mean. Results of statistical analyses are reported in the text.*

Figure 5.7 shows the results for the 'idiopathic' amblyopic cohort (n = 17). Again, no significant difference in pre- and post-operative contrast sensitivity measures was detected at any spatial frequency evaluated. Note, however, that insufficient data was available for analysis at 6 months post-treatment.

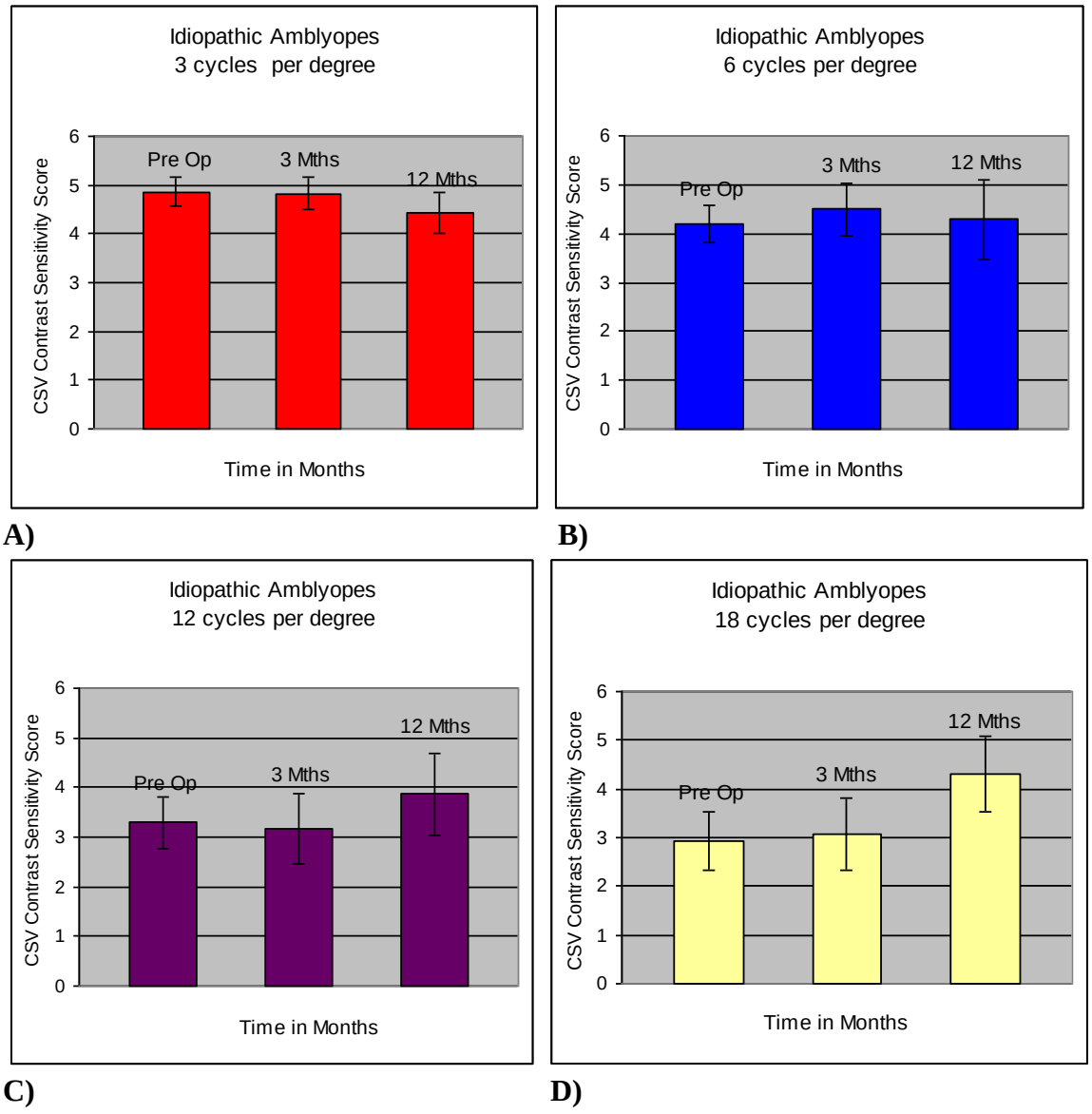



**Figure 5.7** *Mean contrast sensitivity for the idiopathic amblyopic eyes (n = 17), for test periodicities (a) 3, (b) 6, (c) 12 and (d) 18 cycles per degree. For each test spatial frequency, group mean contrast sensitivity is shown pre-operatively and three months, six months, twelve months post-operatively. The vertical error bars show +/- one standard error of the mean. Results of statistical analyses are reported in the text.*

Table 5.1 shows a summary of the mean change in contrast sensitivity, one year after wavefront-guided laser refractive correction, for data grouped according to the previous amblyopic treatment undertaken. A significant gain in contrast sensitivity at 3 cycles per degree was observed for amblyopic eyes that had previous surgical treatment ($t = -2.4$, $p = 0.033$). Subjects that had reported refractive treatment during childhood demonstrated a significant gain in sensitivity at 18 cycles per degree ($t = -2.1$, $p = 0.04$). No significant gain in contrast sensitivity was observed for those subjects that had not undergone any treatment for amblyopia in childhood.

| **Previous Treatment** | **Contrast Sensitivity Gain At 1 Yr** | Significance. |
|---|---|---|
| Occlusion | • 0.36 at 3 cpd<br>• 0.42 at 6cpd<br>• 0.49 at 12 cpd<br>• 0.31 at 18 cpd | • P = 0.156<br>• P = 0.148<br>• P = 0.140<br>• P = 0.223 |
| Surgical | • 1.15 at 3 cpd<br>• 0.70 at 6cpd<br>• 0.77 at 12 cpd<br>• 0.38 at 18 cpd | • P = 0.033 s<br>• P = 0.281<br>• P = 0.281<br>• P = 0.406 |
| Spectacle | • 0.40 at 3 cpd<br>• 0.48 at 6 cpd<br>• 0.57 at 12 cpd<br>• 0.49 at 18 cpd | • P = 0.057<br>• P = 0.060<br>• P = 0.066<br>• P = 0.040 s |
| No Treatment | • 0.26 at 3 cpd<br>• 0.32 at 6cpd<br>• 0.31 at 12 cpd<br>• 0.18 at 18 cpd | • P = 0.412<br>• P = 0.209<br>• P = 0.179<br>• P = 0.280 |

**Table 5.1** *Mean gain in CSV contrast sensitivity measures at one year following laser refractive treatment. s = statistical significance achieved.*

Table 5.2 shows the change in sensitivity one year post-surgery for subjects who presented with either full or balanced prescriptions prior to laser refractive treatment. Those that had a full refractive correction demonstrated a significant increased contrast sensitivity at 18 cycles per degree ($t = -2.07$, $p = 0.044$), where as those that had a balanced lens demonstrated a significance increase in contrast sensitivity at spatial frequencies of 3 ($t = -2.67$ , $p = 0.010$) and 6 cycles per degree ($t = -2.69$, $p = 0.010$).

| **RX** | **Contrast Sensitivity Gain At 1 Yr** | **Significance** |
|---|---|---|
| Full Rx | • 0.35 at 3 cpd | • P = 0.159 |
| | • 0.31 at 6cpd | • P = 0.200 |
| | • 0.48 at 12 cpd | • P = 0.109 |
| | • 0.47 at 18 cpd | • P = 0.044 s |
| Balance Rx | • 0.43 at 3 cpd | • P = 0.010 s |
| | • 0.55 at 6cpd | • P = 0.010 s |
| | • 0.31 at 12 cpd | • P = 0.176 |
| | • 0.22 at 18 cpd | • P = 0.225 |

**Table 5.2** *Mean gain in CSV measures of contrast sensitivity at one year following laser refractive treatment. s = statistical significance achieved.*

## 5.4 Discussion

In a closed loop laboratory setting, a five- to six-fold increase in contrast sensitivity may be realised following correction of higher-order aberrations utilising adaptive optics systems (Liang et al., 1997). However, this has not been realised *in situ*. Rather, previous studies on visual normals have reported a reduction in sensitivity following laser correction (Cardona Ausina et al., 2000). The current study is in agreement with these reports: at twelve months post-surgery, a modest reduction in sensitivity was evident in visual normals at all spatial frequencies examined (see figure 5.4).

It has been argued that the reduction in sensitivity in visual normals may be attributed to the biomechanics of corneal wound healing following surgery. Altered morphology of corneal keratocytes (Pedersen et al., 2000), loss in corneal cell transparency (Ambrosio et al., 2001), stromal microfolds and striae (Pisella et al., 2001) and cellular debris (Vesaluoma et al., 2000) have all been suggested as reasons for the post-operative decline in contrast sensitivity.

In summary, it appears that the gain in contrast sensitivity observed utilizing adaptive optic correction is not realised *in-situ* because the beneficial effects of aberration reduction is negated by the physiological response of the cornea to surgical trauma.

The contrast sensitivity results on amblyopes were qualitatively different to that on visual normals. Sensitivity measures on the fellow fixing eyes of either strabismic or

anisometropic amblyopes were unchanged at 12 months post-surgery (Figure 5.3). Similarly, sensitivity measures on the amblyopic eye of strabismus patients were unchanged at 12 months (Figure 5.6). However, a modest increase in contrast sensitivity was observed for the amblyopic eye of anisometropes at 12 months post-surgery (Figure 5.5). The latter is in agreement with Roszkowska et al. (2006). The reasons for the improvement in sensitivity in anisometropes remain an open question. One possibility is that the gain in sensitivity follows from a reduction in higher-order aberrations in the amblyopic eye following laser surgery (Agarwal et al., 2010; Prakash et al., 2007). This is explored in the following chapter.

# Chapter Six

**Higher Order Aberration Profiles following wavefront-guided laser refractive surgery**

## 6.1 Introduction

The primary aim of laser refractive surgery is to correct lower-order aberrations of focus and astigmatism. However, the correction of lower-order aberrations by conventional corneal ablation techniques, PRK and LASIK, may lead to an increase in higher-order aberrations (Oshika et al., 2002; Pallikaris et al., 2002).

The application of adaptive optics principles into laser treatment platforms has afforded surgeons the ability to provide a wavefront-guided ablation pattern that considers correction of both higher- and lower-order aberrations. However, there has been no agreement on the effectiveness of these procedures in reducing post-operative higher-order aberrations within visual normals (see Table 1.4 and 1.5).

Some studies have reported that the beneficial effect of wavefront-guided laser refractive is more evident within the amblyopic population (Agarwal et al., 2010).

Here, pre- and post-operative higher-order aberration profiles within a cohort of visual normals and within a population of amblyopic subjects were assessed.

## 6.2 Methods

A retrospective analysis of pre- and post-operative higher-order aberrations in 235 amblyopic eyes (anisometropic and strabismic), 17 idiopathic amblyopic eyes, 252 fellow fixing eyes and 252 prescription matched controls was made.

Note that hypermetropic data was segregated from myopic data prior to analysis of aberration data, which avoided the nulling effect that is necessarily incurred when adding oppositely-signed spherical aberrations.

## 6.3 Results

Figure 6.1 shows the pre- and post-operative magnitude of (a) coma, (b) spherical aberrations and (c) RMS in the amblyopic and fixing eyes of hypermetropic subjects (n = 151).

In amblyopic eyes, the group's mean magnitude of coma was 1.86 µm pre-operatively, rising to approximately 5 µm at three months following laser treatment and staying at that level until at least 12 months post-surgery. The results for the fixing eye were both qualitatively and quantitatively similar (figure 6.1a). The increase in post-operative coma was significant at three months ($t = -13.06$, $p < 0.01$), six months ($t = -4.55$, $p < 0.01$) and 12 months ($t = -9.46$, $p < 0.01$) for the amblyopic eyes. Similarly, the increase in coma was significant at three months ($t = -12.99$, $p < 0.01$), six months ($t = -3.93$, $p < 0.01$) and at 12 months ($t = -10.51$, $p < 0.01$) for the fixing eyes.

Figure 6.1b shows the mean change in spherical aberrations for the amblyopic and fellow fixing eyes of hypermetropes. Pre-operatively, the group-mean magnitude of spherical aberrations was approximately -3 µm in both the amblyopic and fixing eyes. Post-operatively, spherical aberrations in the amblyopic eyes were of similar magnitude but of opposite sign; the same overall trend was true for the fixing eyes (see 6.1b for details). The change in post-operative spherical aberrations was significant for each eye and for each time period assessed [three months ($t = -19.32$, $p < 0.01$), six months ($t = -7.76$, $p < 0.01$), 12 months ($t = -4.28$, $p < 0.01$) for amblyopic eyes; three months ($t = -4.11$, $p < 0.01$), six months ($t = -3.32$, $p < 0.01$), 12 months ($t = -3.50$, $p < 0.01$) for fixing eyes].

The change in root mean square (RMS) of total aberrations is shown in figure 1.6c. Again, pre-operative measures of RMS were similar for both amblyopic and fixing eyes, at a level of approximately 0.4μm. Following treatment, both eyes a showed a similar increase in RMS. This increase was shown to be significant at 3 months ($t = -15.838$, $p = 0.00$), 6 months ($t = -4.28$, $p < 0.01$) and at 12 months ($t = -11.05$, $p < 0.01$) for amblyopic eyes. Likewise, this increase was significant at 3 months ($t = -13.85$, $p = 0.01$), 6 months (paired t-test: $t = -3.76$, $p = 0.01$) and at 12 months ($t = -11.03$, $p < 0.01$) for the fixing eyes.

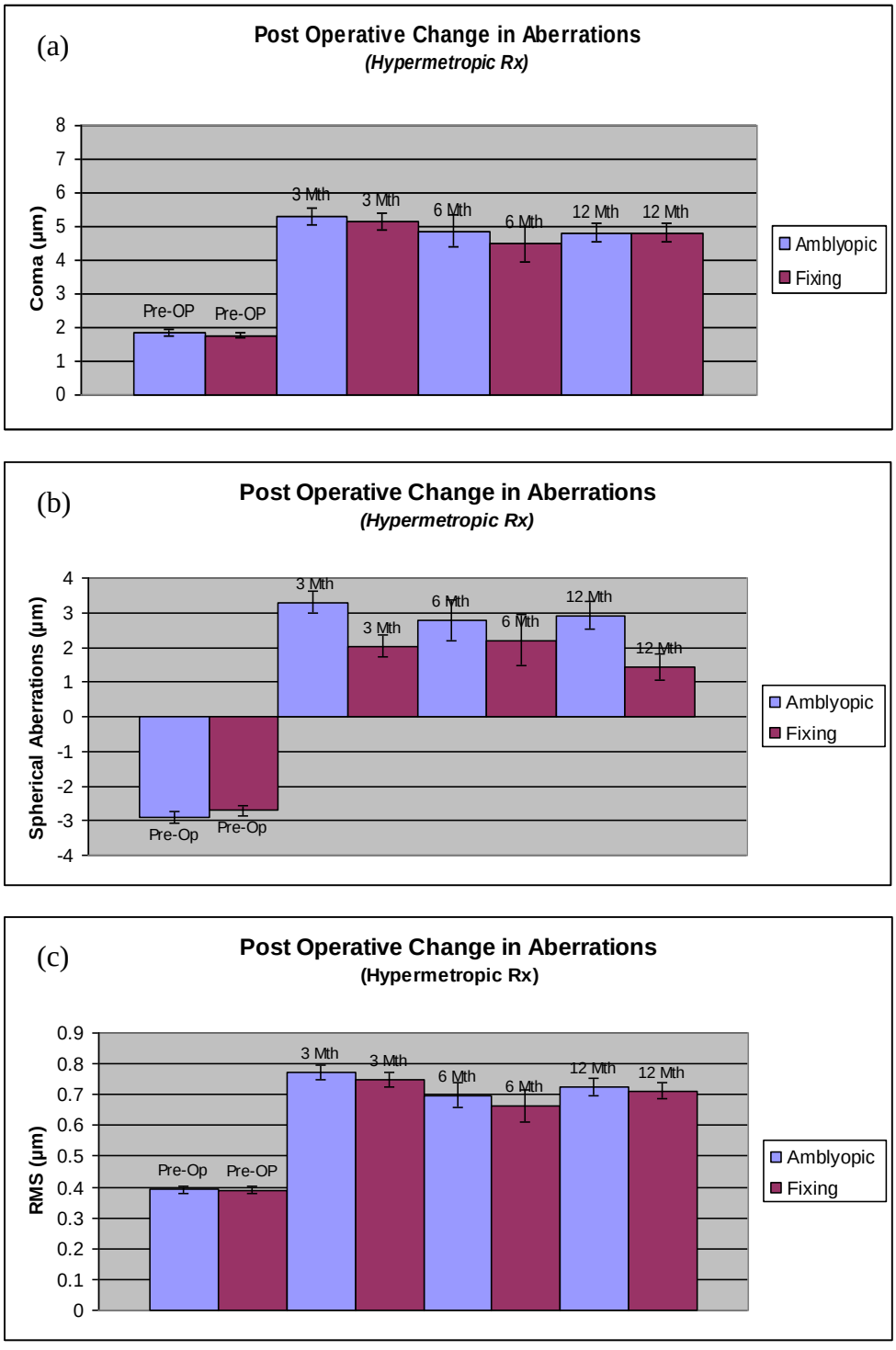



**Figure 6.1 Pre**-*operative and post-operative assessment of the group-mean higher-order aberrations in the amblyopic (blue) and fixing (purple) eyes of hypermetropic subjects (n = 151). Results are shown for (a) coma, (b) spherical aberrations and (c) RMS of total aberrations (up to 4th order). The vertical error bars show +/- one standard error of the mean. Results of statistical analyses are reported in the text.*

Figure 6.2 outlines the mean pre- and post-operative magnitude of (a) coma, (b) spherical aberrations and (c) RMS in the amblyopic and fixing eyes of myopic subjects (n = 84).

Figure 6.2a shows the group-mean data for coma aberrations for the amblyopic eye and fixing eye. The increase in coma observed in both eyes post-operatively was found to be significant at all time points evaluated [three months ($t = -3.10$, $p = 0.03$), six months ($t = -1.98$, $p = 0.04$), 12 months ($t = -1.22$, $p<0.01$) for amblyopic eyes; three months ($t = -4.16$, $p<0.01$), six months ($t= -2.15$, $p = 0.048$), 12 months ($t = -3.68$, $p = 0.01$) for fixing eyes ].

In figure 6.2b the pre-operative spherical aberrations is shown to be -1.70 µm for the myopic amblyopic eye and -1.65 µm for the fellow fixing eye. A significant increase in post-operative spherical aberrations was observed at 3 months ($t = 9.06$, $p < 0.01$), 6 months ($t = 3.86$, $p = 0.002$) and at 12 months ($t = 6.66$, $p = < 0.01$) for the amblyopic eyes. Likewise, a significant increase in post-operative spherical aberrations was observed at 3 months ($t = 8.05$, $p < 0.01$), 6 months ($t = 3.40$, $p = 0.004$) and at 12 months ($t = 6.10$, $p < 0.01$) for the fixing eyes.

Figure 6.3c shows the mean change in RMS. Both amblyopic and fellow fixing eyes had a similar level of total aberrations prior to surgery. Post treatment, an overall increase in RMS was observed. This reached significance at all time points for the amblyopic eye ($p < 0.00$). The fellow fixing eye showed a significant increase at both 6 months ($t = -6.29$, $p < 0.01$) and at 12 months ($t = -10.58$, $p< 0.00$) post-operatively.

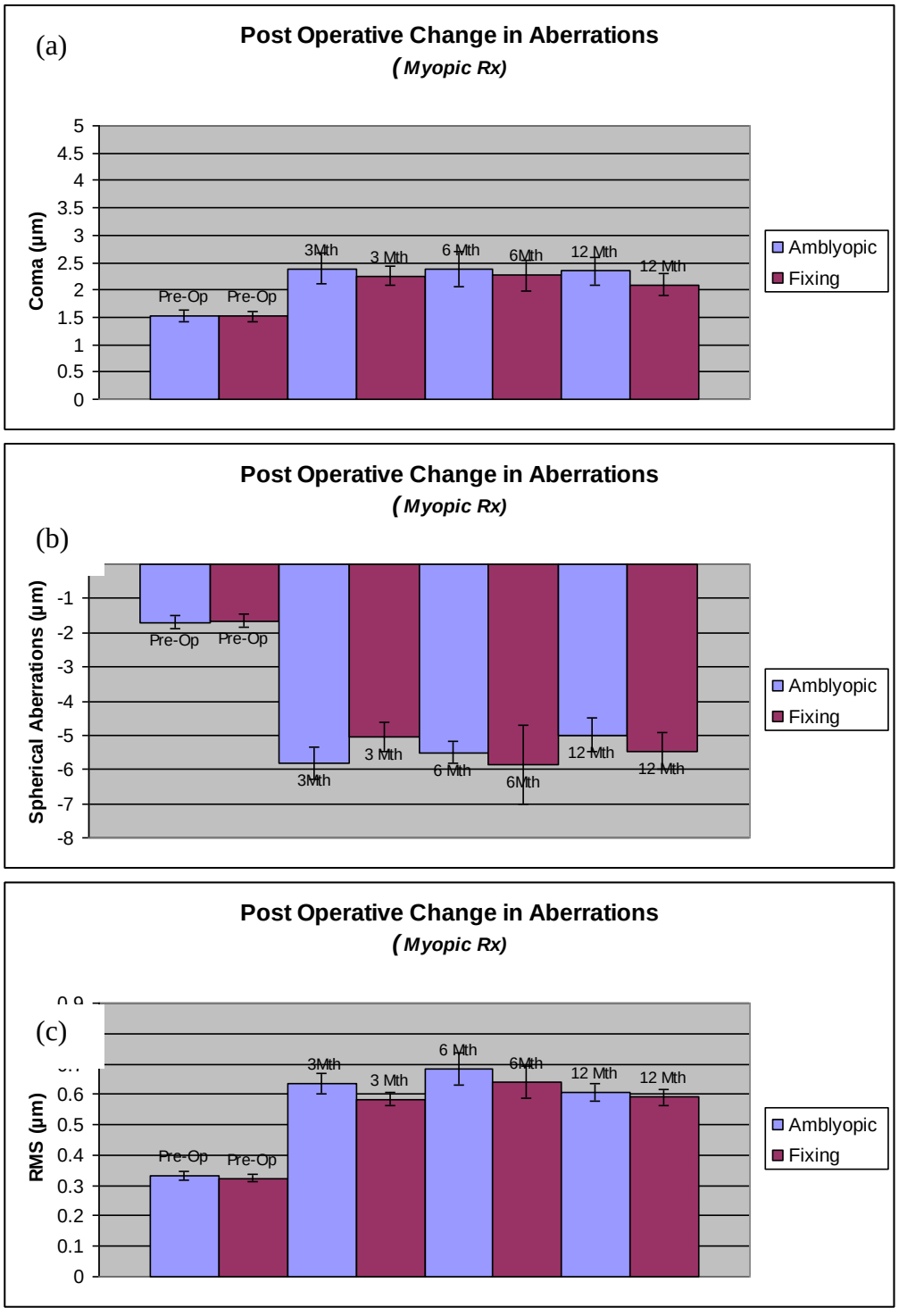



**Figure 6.2** *Pre-operative and post-operative assessment of the group-mean higher-order aberrations in the amblyopic (blue) and fixing (purple) eyes of myopic subjects (n =84). Results are shown for (a) coma, (b) spherical aberrations and (c) RMS of total aberrations (up to 4$^{th}$ order). The vertical error bars show +/- one standard error of the mean. Results of statistical analyses are reported in the text.*

Figure 6.3 illustrates the mean pre- and post-operative magnitude of (a) coma, (b) spherical aberrations and (c) RMS for the prescription-matched hypermetropic control eyes (n = 151).

Figure 6.3a shows a pre-operative magnitude of 1.97 µm for coma aberrations. A significant increase in post-operative coma to 5.52 µm was observed at 3 months ($t = -11.88$, $p < 0.01$), 4.39 µm at 6 months ($t = -5.04$, $p < 0.01$) and 5.44 µm at 12 months ($t = -9.15$, $p < 0.01$) for hypermetropic prescription-matched controls.

Figure 6.3b shows the group-mean data for spherical aberrations pre- and post-operatively. Note that there was a significant change in post-operative spherical aberrations at 3 months ($t = -11.15$, $p < 0.01$), 6 months ($t = -3.71$, $p = 0.01$) and 12 months ($t = -12.46$, $p < 0.01$).

Pre-operatively, RMS was reported as 0.41 µm. A significant post-treatment increase in RMS was shown to occur at three months ($t = -13.58$, $p < 0.01$), six months ($t = -5.77$, $p = 0.04$), and 12 months ($t = -10.87$, $p<0.01$)].

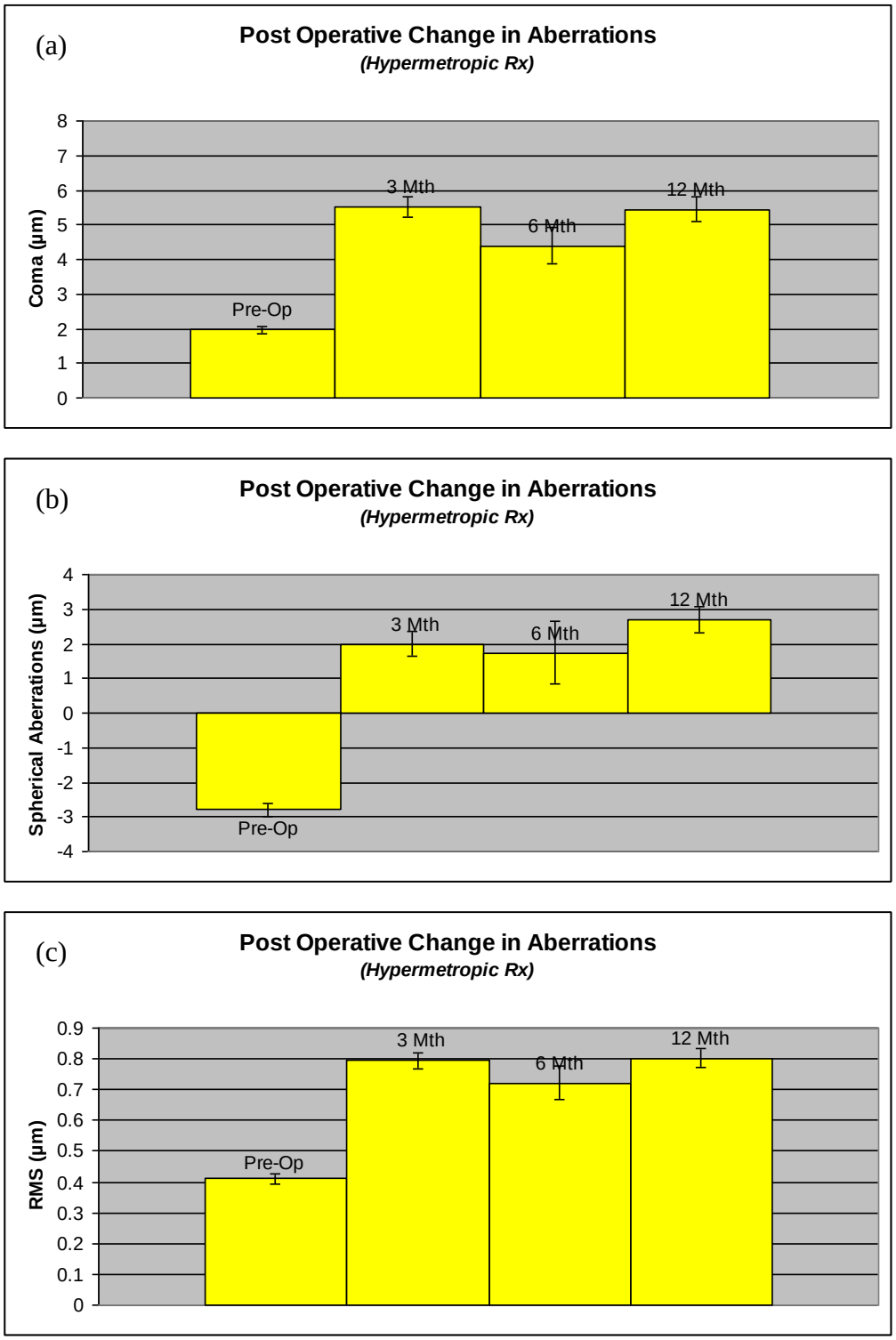



**Figure 6.3** *Pre-operative and post-operative assessment of the group-mean magnitude of higher-order aberrations in hypermetropic prescription matched control eyes. (n = 151). Results are shown for (a) coma, (b) spherical aberrations and (c) RMS of total aberrations (up to 4$^{th}$ order). The vertical error bars show +/- one standard error of the mean. Results of statistical analyses are reported in the text.*

Figure 6.4 illustrates the mean pre- and post-operative magnitude of (a) coma, (b) spherical aberrations and (c) RMS for the prescription-matched myopic control eyes. (n = 84).

The trend of the data indicates an approximate doubling in coma aberrations at 3 months ($t = -6.46$, $P < 0.01$), 6 months ($t=2.42$, $p = 0.026$) and 12 months ($t = -4.8$, $p < 0.01$) post-operatively (figure 6.4 a). Similarly, an approximate doubling in RMS was observed at all post-operative time points assessed [three months ($t = -10.65$, $p < 0.01$), six months ($t = -5.599$ $p < 0.01$), 12 months ( $t = -8.23$, $p < 0.01$) ] (figure 6.4 b).

Pre-operative spherical aberrations were measured at -1.81µm. The data shows a gradual decline in group-mean spherical aberrations over time. However, this decline did not achieve significance ($p > 0.05$).

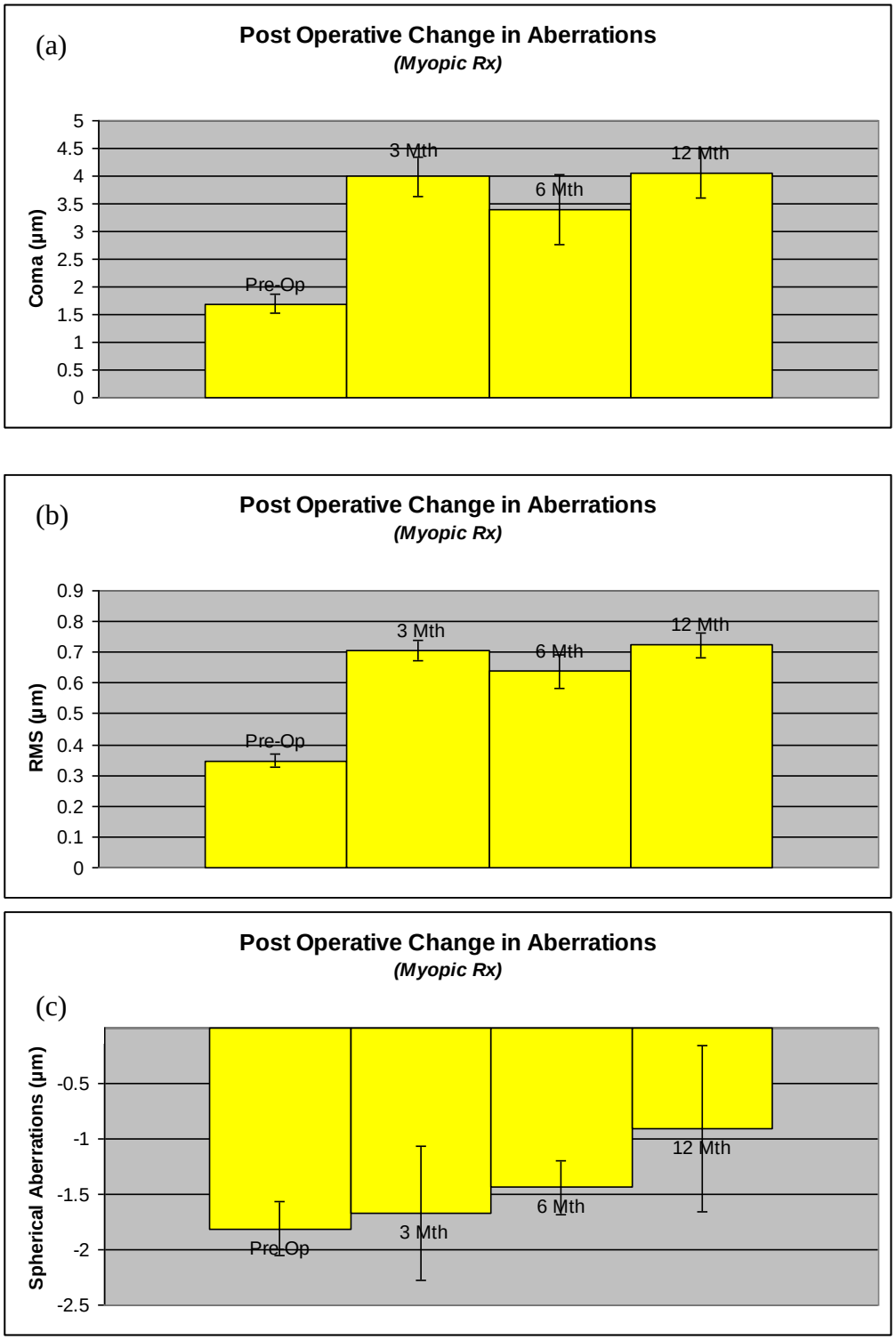



**Figure 6.4** *Pre-operative and post-operative assessment of the group-mean magnitude of higher-order aberrations in myopic prescription matched control eyes. (n = 84). Results are shown for (a) coma, (b) spherical aberrations and (c) RMS of total aberrations (up to 4$^{th}$ order). The vertical error bars show +/- one standard error of the mean. Results of statistical analyses are reported in the text.*

Figure 6.5 shows the mean pre- and post-operative magnitude of (a) coma, (b) spherical aberrations and (c) RMS for the hypermetropic idiopathic eyes and fellow fixing eyes (n = 7). Note that insufficient data was available at 6 months post-treatment for this patient cohort.

A significant increase in post-operative coma aberrations was observed at 3 months (t =-3.23, p = 0.022). However, at 12 months no significant change in coma was observed for the amblyopic eyes. Also, no significant change in post-operative coma was observed for the fellow fixing eyes (figure 6.5 a).

A significant increase in RMS was observed at 3 months for the idiopathic amblyopic eye only (t = -4.27, p = 0.008). At a time point of 12 months, however, no significant change was detected for either eye (figure 6.5c)

A significant reduction in spherical aberrations was observed at both 3 months ( t =-3.9, p = 0.011) and 12 months (t =-3.9, p = 0.011) for the amblyopic eye, whereas no significant change in spherical aberrations was observed for fellow fixing eye ( figure 6.5b).

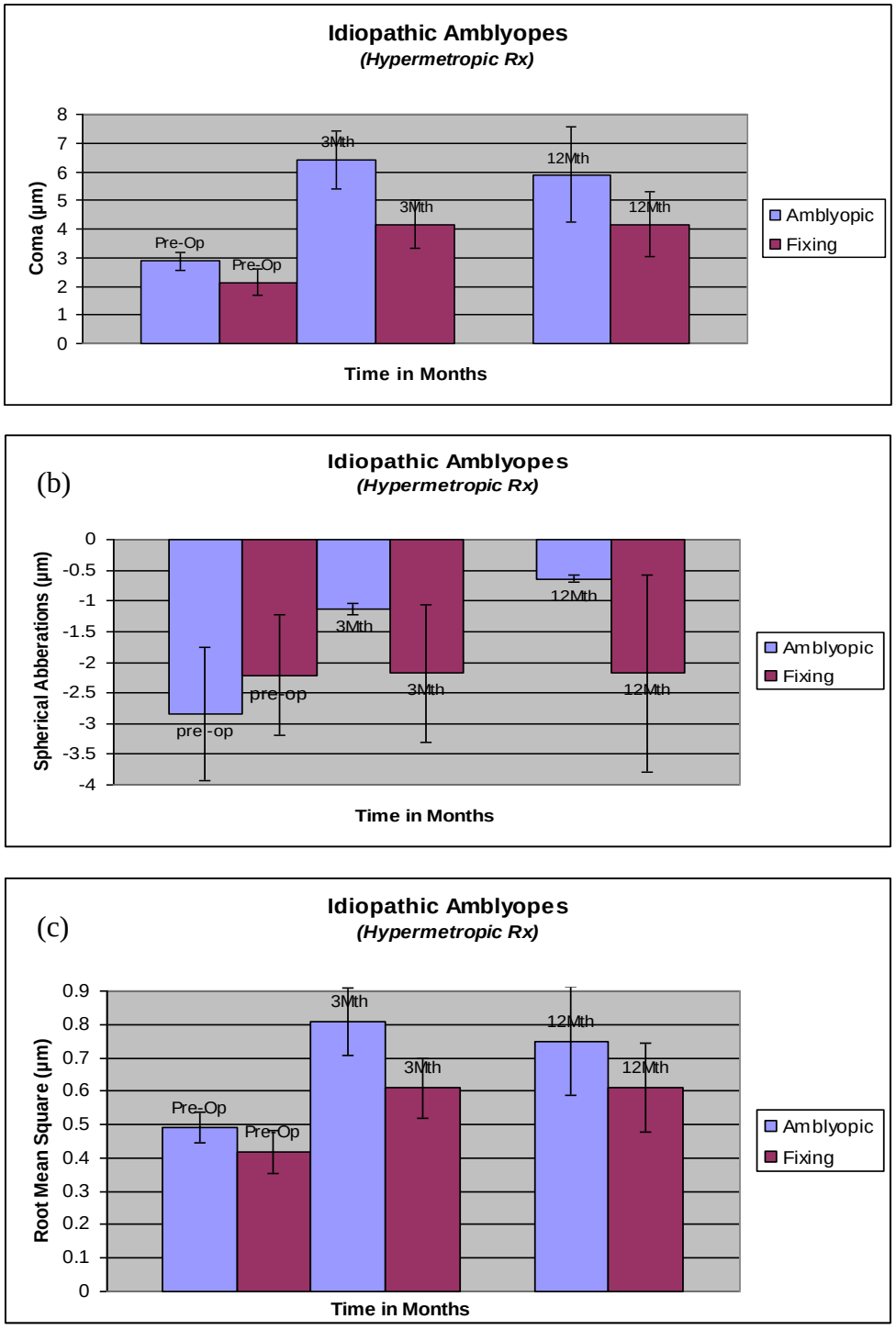



**Figure 6.5** *Pre-operative and post-operative assessment of the group-mean higher-order aberrations in the amblyopic (blue) and fixing (purple) eyes of hypermetropic idiopoathic subjects (n =7). Results are shown for (a) coma, (b) spherical aberrations and (c) RMS of total aberrations (up to 4$^{th}$ order). The vertical error bars show +/- one standard error of the mean. Results of statistical analyses are reported in the text.*

Figure 6.6 illustrates the mean pre- and post-operative magnitude of (a) coma, (b) spherical aberrations and (c) RMS in the myopic idiopathic eyes and fellow fixing eyes (n = 10). No significant change in post-operative coma aberrations was observed for either the amblyopic or fixing eye of this patient group ($p > 0.05$) (figure 6.6 a).

However, a significant increase in post-operative spherical aberrations was observed for fixing and idiopathic myopic eyes. Statistical analysis shows: (i) a 10-fold increase at 3 months ($t = 8.61$, $p = 0.001$), 11-fold increase at 6 months ( $t = 22.83$, $p = 0.011$) and a 9-fold increase at 12 months ($t = 5.45$, $p = 0.002$) for the amblyopic eyes, and (ii) a 6.5-fold increase at 3 months ($t = 28.97$, $p = 0.00$), a 9-fold increase at 6 months ($t = 2.45$, $p = 0.013$), and a 6.5-fold increase at 12 months ($t = 5.21$, $p = 0.002$) for the fixing eyes (figure 6.6 b).

Figure 6.6 c shows group-mean data for RMS of total aberrations. An approximate doubling in total aberrations was observed for both amblyopic and fellow fixing eyes. [three months ($t = -4.23$, $p = 0.013$), six months ($t = -2.92$, $p = 0.012$) and 12 months ($t = -5.07$, $p = 0.002$) for amblyopic eyes; and three months ($t = -13.03$, $p < 0.01$), six months ($t = -2.92$, $p = 0.012$), and 12 months ($t = -5.07$, $p = 0.002$) for fixing eyes].

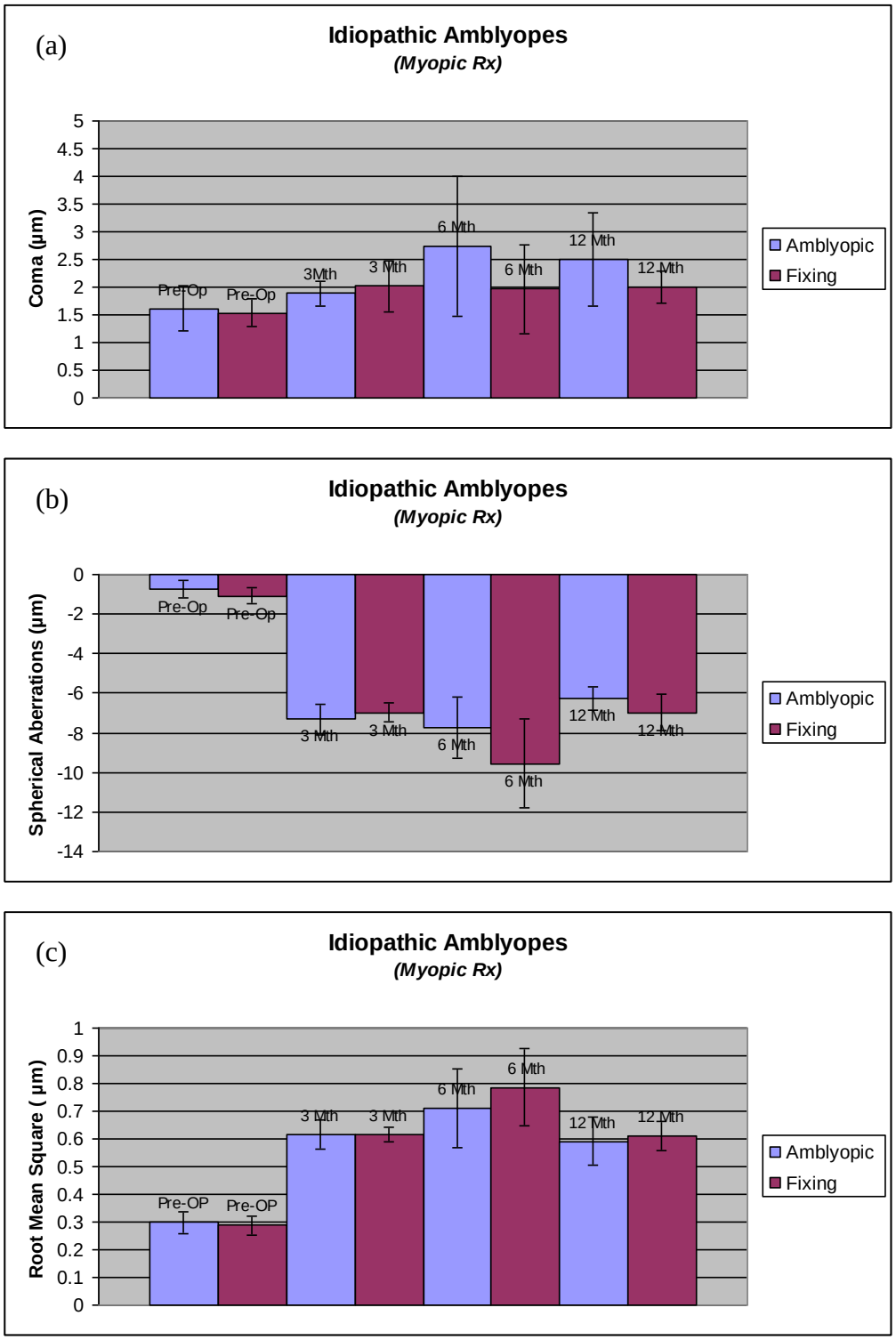



**Figure 6.6** *Pre-operative and post-operative assessment of the group-mean higher-order aberrations in the amblyopic (blue) and fixing (purple) eyes of myopic idiopoathic subjects (n =10). Results are shown for (a) coma, (b) spherical aberrations and (c) RMS of total aberrations (up to 4$^{th}$ order). The vertical error bars show +/- one standard error of the mean. Results of statistical analyses are reported in the text.*

Thus, the general trend of the data indicates that higher-order aberrations increase following laser refractive surgery for amblyopic eyes (anisometropic and strabismic), fellow fixing eyes and prescription-matched controls. Within the idiopathic amblyopic cohort, coma was unchanged while spherical aberrations increased significantly following wavefront-guided treatment. These findings are summarized in tables 6.1 and 6.2.

| Post Operative Change in Higher Order Aberrations. *Hypermetropic Cohort.* | | | |
|---|---|---|---|
| Eye | Coma | Spherical Aberrations | RMS |
| Amblyopic | ≈ x 3 fold increase at 3, 6 + 12 mths post-op | Mean change From negative to positive. | ≈ x 2 fold increase at 3, 6 + 12 mths post-op |
| Fixing | ≈ x 3 fold increase at 3, 6 + 12 mths post-op | Mean change From negative to positive. | ≈ x 2 fold increase at 3, 6 + 12 mths post- op |
| Rx Matched Control | ≈ x 3 fold increase at 3, 6 + 12 mths post-op | Mean change From negative to positive. | ≈ x 2 fold increase at 3, 6 + 12 mths post-op |
| Idiopthic Amblyopic | ≈ x 2 fold increase at 3 mths. No significant change at 12 mths. | ≈ x 2 fold reduction at 3 and 12 mths post – op | ≈ 1.5 fold increase at 3 mths. No significant change at 12 mths. |
| Fixing Eye of Idopathic | No significant change | No significant change | No significant change |

**Table 6.1** *Summary of the mean change in higher order aberrations following wavefront guided laser refractive treatment of hypermetropic eyes.*

| Post Operative Change in Higher Order Aberrations. *Myopic Cohort* | | | |
|---|---|---|---|
| Eye | Coma | Spherical Aberrations | RMS |
| Amblyopic | ≈ x1.5 fold increase at 3, 6 + 12 mths post-op | ≈ x 3 fold increase at 3, 6 + 12 mths post-op | ≈ x2 fold increase at 3, 6 + 12 mths post-op |
| Fixing | ≈ x1.5 fold increase at 3, 6 + 12 mths post-op | ≈ x 3 fold increase at 3, 6 + 12 mths post-op | ≈ x2 fold increase at 6 + 12 mths post-op |
| Rx Matched Control | ≈ x2.5 fold increase at 3, 6 + 12 mths post-op | No significant change | ≈ x2 fold increase at 3, 6 + 12 mths post- op |
| Idiopthic Amblyopic | No significant change. | ≈ x 10 fold increase at 3, 6 + 12 mths post-op | . ≈ x2 fold increase at 3, 6 + 12 mths post-op |
| Fixing Eye of Idopathic | No significant change. | ≈ x 7 fold increase at 3, 6 + 12 mths post-op | ≈ x2 fold increase at 3, 6 + 12 mths post-op |

**Table 6.2** *Summary of the mean change in higher order aberrations following wavefront guided laser refractive treatment of myopic eyes.*

## 6.4 Discussion

The results suggest an overall trend towards increased higher-order aberrations following wavefront-guided laser refractive treatment on the visually normal eye. This is in agreement with previous findings of Alio et al. (2006) and Schallhorn et al. (2008) who report that, although the amount of increase in higher-order aberrations with wavefront-guided surgery was less than that with conventional surgery, the achievement of a post-operative aberration-free eye remains elusive. Lipshitz (2002) suggested that misalignment due to cyclo rotation / changes in illumination during ablation may account for the increase in post-operative aberrations. However, the results of this study do not support this suggestion as iris tracking was used throughout the surgical procedure. Variation in ablation rate as a function of corneal thickness, as postulated by Manns et al. (2002) and Yoon et al. (2005), can also be discounted as corneal pachymetry was considered when establishing ablation profiles.

Previous studies evaluating visual outcome for strabismic and anisometropic amblyopic subjects following laser refractive treatment have postulated whether visual acuity and contrast sensitivity gain realised post treatment may be attributed to a reduction in higher-order aberrations (Sakatani et al. 2004). However, the data do not support this conclusion as higher-order aberrations were in general greater following wavefront-guided laser refractive treatment.

The suggestion that a specific subgroup of 'idiopathic' amblyopes may be afforded a visual gain following wavefront-guided laser refractive correction of higher-order aberrations was also considered. Data pertaining to this specific subgroup showed that higher-order aberration coma remained unchanged following treatment (figure 6.5a, 6.6a). Spherical aberrations reduced for hypermetropic subjects (figure 6.5 b) but increased for myopic subjects (fig 6.6 b). Root mean square of total aberrations was unchanged for hypermetropes (fig 6.5c) but increased for myopes (fig 6.6c).

Prakash et al. (2007) suggestion of 'higher-order aberration associated amblyopia' is not supported by the data in this study. Prakash described a circumstance where asymmetry in higher-order aberration profiles resulted in cortical changes inducing amblyopia. This hypothesis is not supported by the findings of this study because pre-operative assessment of higher-order aberration profiles pertaining to idiopathic amblyopes did not show asymmetry in wavefront profiles (see figures 3.5 and 3.6). Nonetheless, following wavefront-guided laser refractive treatment, visual acuity improved within the idiopathic amblyopic patient group (see figure 4.6).

Agarwal (2002) proposed a new refractive entity termed aberropia, which is described as a condition where there exists a large amount of unilateral higher-order aberrations or where a set of aberrations interact destructively to reduce visual acuity. Upon reduction or manipulation of such higher-order aberrations, visual function can be improved. While the data does not support the notion of extensive unilateral aberrations within idiopathic amblyopic subjects (see figures 3.5 and 3.6), it is possible that the overall combination of

higher-order aberrations present pre-operatively interacted in a more destructive manner that the set of higher-order aberrations created post-operatively.

# Chapter Seven

## 7.1 Principal Findings and Conclusions

The main aims of this thesis were: (i) to test the hypothesis that higher-order aberration profiles differ within normal and amblyopic populations; (ii) to establish whether or not the profile of higher-order aberrations differ within amblyopic subgroups (i.e. strabismic, anisometropic and idiopathic); (iii) to assess the merits or otherwise of the proposed clinical conditions of 'higher-order aberration-associated amblyopia' and 'aberropia'; and (iv) to determine whether wavefont-guided laser refractive surgery can correct higher-order aberrations and improve visual performance in amblyopes.

The results reported in this thesis provide evidence to suggest:

- The extent of higher-order aberrations does not differ within the normal and amblyopic populations (figure 3.1-3.6).

- The profile of higher-order aberrations between the amblyopic and fixing eyes of strabismic, anisometropic and idiopathic amblyopes is generally symmetrical (figures 3.1-3.6).

- It is unlikely that higher-order aberrations play a role in the development of amblyopia.

- Wavefront-guided laser refractive surgery does not correct/eliminate correct higher-order aberrations (figure 6.1 – 6.6), but may afford a more synergist combination of higher-order aberrations.

- A clinically significant gain in post-operative visual acuity (> = 0.14 Log units) may be realised in a small proportion of amblyopes (<20%) following laser refractive treatment of the amblyopic adult eye. This modest improvement should not be cited as a reason for surgery (figure 4.1).

- Amblyopes with a pre-operative myopic refraction realise a significantly greater gain in visual acuity post-operatively when compared to their hypermetropic counterparts.

- Gains in post-operative contrast sensitivity may be realised following laser refractive treatment of the amblyopic adult eye, and patients seeking treatment may be informed that post-operative gain in visual quality is a possible expectation (figure 5.2).

## 7.2 Higher-order aberration-associated amblyopia

Prakash et al (2007) proposed a novel amblyogenic factor termed 'higher-order aberration-associated amblyopia', where the presence of asymmetrical wavefront patterns during development leads to a cortical amblyopic deficit. It was suggested that this may explain the presence of some idiopathic amblyopes. In such cases, correction of higher-order aberrations in adult amblyopic eyes would *not* result in visual acuity.

The findings of this study indicate that the magnitude of higher-order aberrations between the amblyopic and fixing eyes of idiopathic amblyopes is *not* asymmetrical (figure 3.5, 3.6). The results further show that wavefront-guided laser refractive surgery serves to increase higher-order aberrations in idiopathic amblyopes (figures 6.5, 6.6). However despite this increase, a post-operative gain in visual acuity was realised within this patient cohort (figure 4.6). Possible reasons for this gain are given below.

## 7.3 Aberropia

Agarwal (2002) defined a new refractive entity termed 'aberropia'. This described a condition where there exist excessive unilateral higher-order aberrations, or where a set of aberrations interact destructively to reduce visual acuity. Again, it was suggested that aberropia may form the basis of some idiopathic amblyopes. However, unlike Prakash's suggestion of 'higher-order aberration associated amblyopia', Agarwal argued that the loss of vision in 'aberropia' was purely refractive in origin and that visual acuity could be restored following manipulation of the wavefront profiles. This could be achieved, it was claimed, by either eliminating higher-order aberrations or by creating a pattern of higher-

order aberrations that interacted in a self-cancelling manner (i.e. in a manner that served to improve visual function).

However, the existence of excessive unilateral higher-order aberrations within the idiopathic amblyopic cohort was *not* observed (figures 3.5, 3.6). Nonetheless, manipulation of higher-order aberrations following wavefront-guided laser refractive surgery did result in gains in visual acuity within this patient cohort.

## 7.4 Minification Bias

The proposed theory of minification bias (Orucoglu et al., 2011) is supported by the data in this study. That is, pre-operatively the high dioptre negative spectacle lenses of the myopic patient results in an apparent object size which is significantly reduced. Following laser refractive correction at the corneal plane a larger retinal image size is achieved, thus improving visual resolution. Conversely high powered plus lenses worn by hypermetropic subjects induce magnification of retinal image size. Following laser refractive correction at the corneal plane this induced magnification is lost.

In the current study, those subjects presenting with pre-operative myopia demonstrated a larger gain in post operative visual acuity than those with pre-operative hypermetropia (table 4.5). A five fold greater increase in best corrected visual acuity was shown for the myopic amblyopic cohort when compared to their hypermetropic counterparts. Likewise analysis of the data pertaining to the fellow fixing eye reveals a statistically significant

gain in post operative visual acuity for myopic subjects where as no statistically significant difference was identified for hypermetropic fixing eyes.

## 7.6 Conclusions

The findings of this study do not support the hypothesis that amblyopic eyes demonstrate larger magnitudes of higher-order aberrations than the fellow fixing eyes or prescription-matched control eyes. Thus, asymmetry in higher-order aberration profiles is unlikely to play a role in the development of amblyopia.

However, Argawal's hypothesis that wavefront-guided laser refractive treatment may be used to replace an interaction of aberrations that is destructive (resulting in acuity loss) with one that is constructive (resulting in acuity gain) cannot be out ruled (Argarwal et al., 2007). Based on the results reported here, it is the case that adult amblyopic patients who undertake wavefront-guided laser refractive treatment can expect post-operative changes in aberration profiles that yield gains in both visual acuity and contrast sensitivity.

There is a growing understanding that higher-order aberrations do not act in isolation but rather act synergistically to impact on visual function ( Applegate et al., 2003; Applegate et al., 2002; Yan Li et al., 2008; McLellan et al., 2006; Fam et al., 2004). A few recent studies have shown that the detrimental effect of some higher-order aberrations can be eliminated by the positive effect of others and that this interaction occurs independently of an overall increase or decrease in total higher-order aberrations (Applegate et al., 2002; Applegate et al., 2003; Mclellan et al., 2006; Li et al., 2008). In addition, it has

been shown that the modulation transfer function (MTF) is influenced by total interaction across the entire ensemble of aberrations rather than relations between specific pairs (McLellan et al. 2006). In a follow up to their initial case report, Prakash et al (2011) described that although comparison of Zernike coefficient means between normal and idiopathic amblyopic eyes showed no significant difference, the interrelation between coefficients was different. This discrepancy was proposed to influence both PSF and MTF and represent an amblyogenic factor.

To date, however, most higher -order aberration studies have concentrated their efforts on ways of measuring and reducing higher-order aberrations. This was due to the initial assumption that higher-order aberrations impacted on visual performance in a manner similar to lower-order aberrations – namely, that visual performance reduces as the net value of higher-order aberrations increases. Hence, little attention has been given to the interdependence of higher-order aberrations and the effect this has on visual performance. As such the mechanism(s) by which higher-order aberrations combine (either positively or negatively) is not yet fully understood.

In summary, wavefront-guided laser refractive treatment offers ophthalmic surgeons the ability to manipulate but not eliminate higher-order aberrations at the corneal plane. Future studies should be directed towards minimizing the creation combinations of aberrations that adversely affect visual performance in favor of those combinations that enhance visual performance.

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# Appendices

# COPY OF CONSENT FORM FOR PATIENTS

# ELECTING FOR LASER REFRACTIVE

# SURGERY AT THE LONDON VISION CLINIC

## London Vision Clinic

**138 Harley Street**
**London W1G 7LA**

## PATIENT CONSENT FORM (S)

**FOR**

## LASIK

**(LASER IN SITU KERATOMILEUSIS)**

and

## PRK

**(PHOTOREFRACTIVE KERATECTOMY)**

**last edited 1 June 2011**

1. I understand that I am a candidate for **LASIK (LASER IN SITU KERATOMILEUSIS) SURGERY**, a form of laser surgery where a surgeon will anaesthetise my eye with a topical anaesthetic, create a flap from my cornea using a specialised instrument, and use an excimer laser to reshape the cornea.
Patient Initial for **LASIK:** _____

***OR***

2. I understand that I am a candidate for **LASEK/PRK (LASER EPITHELIAL KERATOMILEUSIS/PHOTOREFRACTIVE KERATECTOMY) SURGERY**, a form of outpatient surgery in which a surgeon uses a device called an excimer laser to reshape the cornea.

Patient Initial for **LASEK/PRK**: _____

**LASIK** or **LASEK/PRK**, the identified surgery, is referred to as the "Procedure" in the following.

3. I understand Dan Z Reinstein MD MA(Cantab) FRCSC FRCOphth, at London Vision Clinic, will perform the Procedure on this _____day of _____ 2011

(i) both eyes [INITIAL] _____; **or**

(ii) on _____(DATE) my right eye

[INITIAL] _____; and on
_____ [DATE] on my left eye
[INITIAL] _____

4. I have reviewed the Surgical Information Package for **LASIK** surgery and for **LASEK/PRK** and I have discussed the Procedure that I am to receive with a nurse/counsellor, with an optometrist, and with my surgeon.

5. The nature of the Procedure, the possible complications and risks, as well as the possible benefits of the Procedure, the alternatives to the Procedure and the risks and benefits of those alternatives have been explained to me in language and using terminology that I understand. My surgeon has answered all of my outstanding questions about the Procedure.

6. I understand that this Procedure is an elective surgical procedure, and that there is no emergency or medical condition that requires that I have the Procedure.

7. Neither my surgeon, nor my optometrist, nor the Centre staff has made any promises or warranties or guarantees as to the success or effectiveness of the Procedure. I have been advised that after the Procedure, my vision may not be as clear and sharp as it was with glasses or contact lenses before the Procedure.

8. I understand that the Procedure may not eliminate the need for corrective lenses for all activities and that after the Procedure, I may need glasses or contact lenses for reading, driving or certain other activities, even if I did not wear them before. I also understand that the Procedure can unmask the need for reading glasses, and that I may have to use them after the Procedure, even if I did not wear them before.

9. I understand that after the Procedure I may experience side effects such as pain, discomfort and scratchiness, halos, blurry vision or fluctuations in vision, which may be temporary or could be permanent. I have been advised that I may find some of these side effects difficult to tolerate.

10. I understand that there are numerous risks and complications, both known and unknown connected with the Procedure, including but not limited to infection, hemorrhage, delayed healing, under or over correction, and other risks and complications that could affect my vision and my general health on a temporary or permanent basis, and could require additional surgery, including, but not limited to, retreatment or a cornea transplant. Those risks also include, but are not limited to, partial or total blindness, loss of a cornea, retinal damage or loss of an eye.

11. I understand that the Procedure is a relatively new procedure, and that little is known about its long-term safety and effectiveness.

12. I understand that the Procedure does not correct certain vision problems, including but not limited to amblyopia, strabismus, presbyopia, and cataracts.

13. I understand that the field of refractive surgery is continuing to evolve and that if I were to postpone my surgery there is the possibility that the LASIK and/or LASEK/PRK procedure might be improved or some other procedure might become available.

14. I understand that my surgeon is a medical doctor and a board certified ophthalmologist and ophthalmic surgeon who is experienced with LASIK and/or LASEK/PRK and has been credentialed to meet the standards required for certification by London Vision Clinic.

15. I understand that I will need certain post-operative care. The day after my surgery I will return to the Centre for a post-operative visit, which will include an examination by an eye care professional. An optometrist or other eye care professional at the Centre may provide additional post-operative care, with referral back to my surgeon if indicated. Post-operative care (24 hour, one week, one month, three month, six month and one year) at the Centre is included in my fee. I understand that if I so desire, I may make other arrangements for post-operative care at my own expense.

If this is my choice, I confirm that I have made arrangements to have my post-operative care provided by _____, who is an optometrist/ophthalmologist (delete as appropriate).

16. I have had the opportunity to ask questions about the Procedure and all of my questions have been answered satisfactorily.

17. I give my surgeon, my optometrist and London Vision Clinic permission to use data about my treatment for research purposes. I understand that my name and personal identifying information will remain confidential, unless I give written permission for the disclosure of such information.

18. I give my surgeon and London Vision Clinic permission to videotape or photograph the Procedure. I understand that my name and personal identifying information will remain confidential, unless I give written permission for the disclosure of such information.

19. If my surgeon, **Dan Reinstein,** MD MA(Cantab) FRCSC FRCOphth has advised me that I have a higher possibility of complications or risks arising from the procedure because I have certain medical conditions or risk factors, I understand that I am required to complete separate consent forms, which address my condition and/or risk factors.

20. I am not under the influence of any sedative. I am of clear mind and understand the nature of the Procedure and the possible risks related to the Procedure.

**I understand that by signing below, I am indicating that I have read and understood the information in this Patient Consent Form, that I have been verbally advised about the Procedure, that I have had an opportunity to ask questions, that I have received all of the information I desire concerning the Procedure, and that I authorise and consent to the performance of the Procedure and any different or further procedures which in the opinion of my surgeon are necessary due to an emergency.**

Patient's Name (please print): _____

Patient's Signature: _____

Surgeon's (Witness) Name (print): **Dan Z Reinstein MD MA FRCSC FRCOphth**

Surgeon's (Witness) Signature: _____

Date: _____ Time: _____

Patient Address: _____

_____

Patient Telephone Number (Day): _____

Patient Telephone Number (Evening): _____

Date of Birth: _____

## *CERTIFICATION OF SURGEON*

I, **Dan Z Reinstein MD MA(Cantab) FRCSC FRCOphth**, hereby certify that:

1. I have discussed and explained **LASIK (Laser in Situ Keratomileusis), *or* LASEK/PRK (Photorefractive Keratectomy) (please circle one),** referred to as the "Procedure", the risks and benefits of the Procedure, the alternatives to the Procedure and the risks and benefits of those alternatives with _____
(the "Patient").

2. The Patient is a suitable candidate for **LASIK or LASEK/PRK (please circle one)** given the ophthalmic findings and the Patient's physical, social, emotional and/or occupational needs.

3. I have discussed any special circumstances with the Patient and the additional potential risks posed by those special circumstances, including the following:
(TO BE COMPLETED BY SURGEON)

_____

_____

4. I have discussed the arrangements for post-operative care with the Patient, who has agreed to the plan for post-operative care.

5. I have answered all of the Patient's questions about the Procedure.

6. I have ascertained that the Patient fully understands the answers to questions that he/she posed to me.

7. I have ascertained that the Patient fully understands the risks, benefits and possible alternatives to the Procedure.

Name of Surgeon: **Dan Z Reinstein MD MA(Cantab) FRCSC FRCOphth**

Signature: _____

Date: _____

Aston University
Life & Health Sciences

**Response from AOREC**

13th January 2010

**Project title:** ***Adult Amblyopia: Are we seeing better now?***

**Reference Number:** Salmon OD
**Researchers:** Annie Salmon, Prof S.J. Anderson and Prof. D Reinstein

I am pleased to inform you that the Audiology / Optometry Research Ethics Committee has approved the above named project.

The details of the investigation will be placed on file. You should notify The Committee of any difficulties experienced by the volunteer subjects, and any significant changes which may be planned for this project in the future.

Yours sincerely

AOREC