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Monocular amblyopia and higher order aberrations

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Abstract

This study compared the corneal and total higher order aberrations between the fellow eyes in monocular amblyopia. Nineteen amblyopic subjects (8 refractive and 11 strabismic) (mean age 30 ± 11 years) were recruited. A range of biometric and optical measurements were collected from the amblyopic and non-amblyopic eye including; axial length, corneal topography and total higher order aberrations. For a sub-group of eleven non-presbyopic subjects (6 refractive and 5 strabismic amblyopes, mean age 29 ± 10 years) total higher order aberrations were also measured during accommodation (2.5 D stimuli). Amblyopic eyes were significantly shorter and more hyperopic compared to non-amblyopic eyes and the interocular difference in axial length correlated with both the magnitude of anisometropia and amblyopia (both $p < 0.01$). Significant differences in higher order aberrations were observed between fellow eyes, which varied with the type of amblyopia. Refractive amblyopes displayed higher levels of 4^{th} order corneal aberrations C(4,0)(spherical aberration), C(4,2)(secondary astigmatism) and C(4, -2)(secondary astigmatism along 45 degrees) in the amblyopic eye compared to the non-amblyopic eye. Strabismic amblyopes exhibited significantly higher levels of C(3,3)(trefoil) in the amblyopic eye for both corneal and total higher order aberrations. During accommodation, the amblyopic eye displayed a significantly greater lag of accommodation compared to the non-amblyopic eye, while the changes in higher order aberrations were similar in magnitude between fellow eyes. Asymmetric visual experience during development appears to be associated with asymmetries in higher order aberrations, in some cases proportional to the magnitude of anisometropia and dependent upon the amblyogenic factor.

Key words: higher order aberrations, amblyopia, strabismus

1. Introduction

Amblyopia is defined as a unilateral or bilateral decrease in visual acuity in the absence of ocular pathology. Disruption of the retinal image during early life due to uncorrected refractive error, form deprivation (e.g. cataract, ptosis), or binocular inhibition due to strabismus inhibits the normal development of the visual pathway. This results in a range of visual deficits in addition to reduced visual acuity in the amblyopic eye, including reduced accommodation (Ciuffreda et al., 1984; Ciuffreda & Rumpf, 1985; Hokoda & Ciuffreda, 1982; Hung et al., 1983; Ukai, Ishii & Ishikawa, 1986), contrast sensitivity (Abrahamsson & Sjostrand, 1988) and depth perception (McKee, Levi & Movshon, 2003). Hyperopic anisometropia is the most common cause of refractive amblyopia and an interocular difference of as little as one dioptre may result in amblyopia in the more hyperopic eye (Abrahamsson & Sjostrand, 1996). Amblyopia as a result of myopic anisometropia is less common, since the myopic eye may still receive clear vision at close working distances.

Higher order aberrations (HOA) could influence refractive development by degrading retinal image quality or by altering the image focal plane. Numerous studies have investigated the association between aberrations and the magnitude or type of refractive error with conflicting conclusions (Carkeet et al., 2002; Collins, Wildsoet & Atchison, 1995; He, Burns & Marcos, 2000; He et al., 2002; Kwan, Yip & Yap, 2009; Llorente et al., 2004). The changes in aberrations during (Cheng et al., 2004; Collins, Wildsoet & Atchison, 1995; Ghosh et al., 2011; He, Burns & Marcos, 2000) or following accommodation tasks (Buehren, Collins & Carney, 2005) or as a result of eyelid forces acting upon the cornea during downward gaze (Buehren, Collins & Carney, 2003; Collins et al., 2006) have also been investigated. However, few studies have examined the optics of amblyopic eyes, with an early study suggesting that vision loss in amblyopia is primarily neural and not influenced by HOA (Hess & Smith, 1977).

A recent case report (Prakash et al., 2007) proposed that interocular differences in HOA may explain the reduced visual acuity observed in cases of idiopathic amblyopia (reduced visual acuity in the absence of any identifiable cause or amblyogenic factor), a refractive entity termed 'aberropia' (Agarwal et al., 2009). Other studies examining HOA in amblyopes have typically shown similar levels of corneal (Plech et al., 2010) and total aberrations (Kirwan & O'Keefe, 2008) between fellow eyes which are in agreement with studies reporting a high degree of interocular symmetry in aberrations in non-amblyopic populations (Castejon-Mochon et al., 2002; Lombardo, Lombardo & Serrao, 2006; Porter et al., 2001; Vincent et al., 2011; Wang et al., 2003). However, of the previous amblyopia studies, only the most recent study (Prakash et al., 2011) corrected for enantiomorphism (midline symmetry) when comparing the HOA profile between fellow eyes. In addition, recent studies of aberrations in animals (Coletta, Marcos & Troilo, 2010) and children (Zhao et al., 2010) suggest that HOA such as trefoil and coma may be linked with form deprivation myopia and reduced visual acuity in amblyopia.

Although altered accommodative responses in amblyopic eyes have been well documented, the nature of aberrations in amblyopic subjects during accommodation has not been reported. Additionally, few studies have examined the biometrics of amblyopic eyes in detail. Previous studies have retrospectively examined the association between refractive error type and a range of different ocular conditions resulting in low vision, but did not have access to biometric data (Du et al., 2005; Nathan et al., 1985). Excluding studies of growth patterns following surgery for congenital cataract, only a small number of studies have examined axial length asymmetry in amblyopic eyes (Cass & Tromans, 2008; Lempert, 2008; Patel, Simon & Schultze, 2010; Weiss, 2003; Zaka-Ur-Rab, 2006).

In this study, we have examined corneal and total higher order aberrations in subjects with unequal visual acuity following asymmetric visual experience (monocular amblyopia) related to anisometropia or strabismus. We hypothesised that HOA may be different between the amblyopic and non-amblyopic eyes and may either contribute to or be altered during disrupted

emmetropisation. However, since this was a cross sectional study and not longitudinal, we cannot be certain if the differences between the eyes represent a possible cause or consequence of altered visual development. In the case of strabismic amblyopia it seems more likely that a difference in HOA between fellow eyes would be the result of altered visual development. Nonetheless, the differences between amblyopic and fellow non-amblyopic eyes may provide useful information regarding the development of asymmetric eye growth and the possible link between the optics of the eye and its growth.

2. Methods

2.1 Subjects and screening

Nineteen healthy subjects aged between 14 and 55 years (mean age 30 ± 11 years) with a history of asymmetric visual experience were included in this study. The subjects were primarily recruited from the staff and students of QUT (Queensland University of Technology, Brisbane, Australia). Eleven of the 19 subjects were female and the majority of subjects were Caucasian with 4 subjects of Asian descent. Eight subjects had refractive amblyopia (7 hyperopic anisometropes and 1 myopic anisometrope without strabismus) and 11 had strabismic amblyopia (strabismus with or without anisometropia including; 7 esotropes, 2 exotropes and 2 with vertical deviations). All subjects had unilateral amblyopia with an interocular difference in best-corrected visual acuity of 0.10 logMAR or greater.

Before testing, subjects underwent a screening examination to determine subjective refraction, binocular vision and ocular health status. All subjects exhibited central fixation in both eyes, which was assessed with visuoscopy monocularly, using the internal graticule target of a direct ophthalmoscope, and steady foveal fixation was observed in both the amblyopic and non-amblyopic eyes. No subject exhibited significant ocular or systemic disease. Fourteen subjects had a prior history of amblyopia therapy (penalisation or occlusion) for at least one month and six had a history of strabismus surgery. No subjects were rigid contact lens wearers. Six soft contact lens wearers

were included in the study but ceased lens wear for 36 hours prior to participation. Approval from the QUT Human Research Ethics Committee was obtained before commencement of the study and subjects gave written informed consent to participate. All subjects were treated in accordance with the tenets of the Declaration of Helsinki.

2.2 Data collection procedures

Biometric and optical measurements were collected from the amblyopic and non-amblyopic eye of each subject including; axial length, corneal topography and total higher order aberrations.

2.2.1 Axial length

Axial length (defined as the distance from the anterior corneal surface to the retinal pigment epithelium) was measured using the IOLMaster (Carl Zeiss Meditec, Inc., Jena; Germany). The IOLMaster is a non-contact instrument based on the principle of partial coherence laser interferometry and has been found to provide precise, repeatable measurements of axial length in children (Carkeet et al., 2004) and adults (Lam, Chan & Pang, 2001; Sheng, Bottjer & Bullimore, 2004). Five measures of axial length with a signal-to-noise ratio of greater than 2.0 were taken and averaged for each eye.

2.2.2 Corneal Topography

Corneal topography was measured using the E300 videokeratoscope (Medmont Pty. Ltd., Victoria, Australia) based on the Placido disc principle. Four measurements, captured according to the manufacturer's recommendations, were performed on each eye.

2.2.3 Total higher order aberrations

The total monochromatic aberrations of each eye were measured using a Complete Ophthalmic Analysis System (COAS) wavefront aberrometer (Wavefront Sciences, New Mexico, USA). The system was modified to allow fixation of an illuminated external target at 6 metres via a beam

splitter between the eye and the wavefront sensor. The subject's distance prescription was inserted into a lens holder outside of the path of the COAS beam (after taking into account the change in vertex distance) to allow a clear view of the fixation target. The eye not being measured was occluded. Subjects had natural pupil sizes without pharmacological dilation during COAS measurements. Room illumination was kept in the mesopic range to maximize the pupil size and to optimise the visibility of the externally illuminated distance target during measurements.

For subjects under forty years of age (n = 11, 6 refractive and 5 strabismic amblyopes), total higher order aberrations were also measured for each eye during accommodation (2.5 D stimuli). The near fixation target was the centre of a high-contrast Bailey-Lovie logMAR chart with diffuse background illumination. Care was taken to ensure the corrected accommodation stimuli was 2.5 D for each eye, taking into account spectacle lens effectivity as outlined in a previous study (Buehren & Collins, 2006). One hundred wavefront measurements (4 x 25 frames) were taken for each eye during distance and near fixation and later averaged.

2.3 Data Analysis

2.3.1 Corneal topography

Following data collection, corneal refractive power and height data were exported from the videokeratoscope. Topography maps that displayed poor focus or local irregularities such as tear film instability were excluded from analysis. Topography data were analysed using custom written software. Corneal height data were used to calculate the corneal wavefront error using a ray tracing procedure (Buehren, Collins & Carney, 2003). Zernike polynomials were fitted to the wavefront error (up to and including the eighth radial order) and expressed using the double index notation (Optical Society of America [OSA] convention) (Thibos et al., 2000). The image plane was at the circle of least confusion and the wavelength used was 555 nm. The corneal wavefront was centred on the line of sight by using the pupil offset value from the pupil detection function in the videokeratoscope as the reference axis for the wavefront. This procedure was conducted for 4

measurements per eye and the mean and standard deviations were calculated. Corneal diameters of 4 and 6 mm were chosen for analysis purposes to approximate mean pupil sizes in photopic and mesopic conditions respectively.

2.3.2 Total higher order aberrations

Wavefront data from the COAS was fitted with an 8th order Zernike expansion and exported for further analysis. Using customised software, the 100 wavefront measurements were rescaled to a set pupil diameter of 4 mm (Schwiegerling, 2002) and then the coefficients of the Zernike polynomials were averaged. Wavefront data were also converted to refractive power maps in order to calculate the best-fit spherocylinder during distance and near fixation. Pupil size scaling was only conducted to convert from a larger natural pupil size to a smaller pupil which has been shown to be associated with only very small errors that are not expected to be optically significant (Schwiegerling, 2002). The corneal and ocular wavefront analysis was conducted for right and left eye data, taking into account enantiomorphism. Corneal and ocular wavefront data for the left eye was flipped about the vertical axis to correct for enantiomorphism (i.e. the sign of the Zernike coefficients for all non-radially symmetric terms was reversed) (Smolek, Klyce & Sarver, 2002). Although corneal and ocular wavefronts were fit with 8^{th} order Zernike expansions, given that the predominant higher order aberrations are 3^{rd} and 4^{th} order terms (Porter et al., 2001; Wang et al., 2003) we limited our analysis up to and including the 4^{th} order. Analysis was carried out for the 3^{rd}, 4^{th} and higher order root mean square (RMS) values, as well as for the individual 3^{rd} and 4^{th} order Zernike terms.

2.3.3 Statistical analysis

Two tailed paired t-tests were used to assess the statistical significance of the mean interocular difference between the non-amblyopic and amblyopic eye of each subject. Pearson's correlation coefficient was used examine the association between the magnitude of anisometropia or amblyopia and the interocular difference in the variable of interest.

3. Results

3.1 Overview

An overview of the mean refraction, visual acuity and axial length of the strabismic and refractive amblyopes are presented in Table 1. In general, the amblyopic eyes were significantly shorter in axial length and more hyperopic in comparison to fellow eyes (all $p < 0.01$). There were statistically significant differences between the fellow eyes for both the spherical component and spherical equivalent refractive error (both $p < 0.01$). The magnitude of refractive astigmatism (cylinder) was slightly greater in the amblyopic eyes but this difference did not reach statistical significance ($p = 0.10$). The magnitude of anisometropia was highly correlated with the interocular difference in axial length between fellow eyes (for all amblyopes r = -0.96, p < 0.0001, axial anisometropia = -0.36 x SEq anisometropia -0.02) (Figure 1) and moderately correlated with the magnitude of amblyopia (i.e. the interocular difference in visual acuity) (for all amblyopes r = 0.62, p < 0.01, amblyopia = 0.10 x SEq anisometropia +0.21). The strabismic and refractive amblyopes showed similar trends to those of the total amblyope group.

3.2 Corneal aberrations

Corneal aberrations for the 6mm corneal diameter are presented in Table 2, however the results for the 4 mm analysis were similar. For the analysis of RMS values, when all subjects were included in the analysis, differences between eyes in terms of third, fourth and higher order RMS did not reach statistical significance. However, examination of the refractive amblyopes separately ($n = 8$) revealed significantly greater amounts of fourth and higher order RMS values in the amblyopic eyes, for the 6 mm analysis diameter. Strabismic amblyopes ($n = 11$) displayed a different pattern, with a trend for greater third, fourth and higher order RMS values in the non-amblyopic eye. However, these interocular RMS differences did not reach statistical significance for the strabismic amblyopes.

Examination of individual Zernike terms describing the corneal wavefront revealed several small but statistically significant differences between fellow eyes. Figure 2 displays the average corneal

wavefront error maps for the amblyopic and non-amblyopic eye in the refractive and strabismic cohorts. Strabismic subjects displayed an interocular difference in corneal aberrations with a significantly higher level of trefoil C(3,3) in the amblyopic eye. Refractive amblyopes did not exhibit the same interocular differences in third order terms, but rather they displayed significant interocular differences in fourth order terms C(4,2) secondary astigmatism, C(4,-2) secondary astigmatism along 45 degrees and C(4,0) spherical aberration. The amblyopic eyes of the refractive amblyopes had significantly more positive spherical aberration and significantly less (more negative values) of the secondary astigmatic terms.

3.3 Total higher order monochromatic aberrations

Valid data were obtained for all 19 subjects during distance fixation and for 11 younger subjects (5 strabismic and 6 refractive amblyopes) during near fixation. An overview of the mean refraction, visual acuity and axial length of the strabismic and refractive amblyopes used for the accommodation task are presented in Table 3. Zernike wavefront coefficients and RMS values for the amblyopic and non-amblyopic eyes during distance fixation are presented in Table 4 averaged over a 4 mm pupil diameter. Figure 2 also displays the average total wavefront error maps for the amblyopic and non-amblyopic eye in the refractive and strabismic cohorts. In a similar fashion to the corneal aberrations, the strabismic amblyopes displayed higher levels of trefoil C(3,3) which reached statistical significance (p = 0.05). However, refractive amblyopes did not exhibit significant interocular difference in any of the total ocular aberration terms.

During near fixation (2.5 D accommodative demand) spherical aberration C(4,0) changed significantly from distance fixation levels in both the amblyopic and fellow eyes of the subjects. Zernike wavefront coefficients, RMS values and the lag of accommodation for the amblyopic and non-amblyopic eyes during near fixation are presented in Table 5 averaged over a 4 mm pupil diameter. On average, spherical aberration shifted in the negative direction in both amblyopic (-0.013 ± 0.017 microns) and non-amblyopic eyes (-0.020 ± 0.024 microns). This magnitude of change

was not statistically different between fellow eyes. However, the interocular difference in the accommodative response (1.7 times greater in the non-amblyopic eye) was similar to the interocular difference in the change in spherical aberration (1.5 times greater in the non-amblyopic eye). The change in the spherical component of refraction (amblyopic -1.04 ± 1.11 D, non-amblyopic -1.76 ± 0.71 D) and best sphere M (amblyopic -1.02 ± 1.09 D, non-amblyopic -1.73 ± 0.70 D) was significantly different between the fellow eyes (both $p < 0.05$). Although both eyes displayed a lag of accommodation for the 2.5 D stimulus, the non-amblyopic eyes exhibited a significantly larger accommodative response. This trend was consistent between the refractive and strabismic amblyopes, with the amblyopic eye displaying a greater lag of accommodation in both sub-groups (refractive 0.71 D and strabismic 0.70 D lag). There was a moderate correlation between the interocular difference in accommodative response with the magnitude of spherical equivalent anisometropia which approached statistical significance ($r = -0.52$, $p = 0.10$). The between eye difference in accommodative response was significantly correlated with the magnitude of amblyopia ($r = -0.69$, $p = 0.02$).

3.4 Internal higher order aberrations

The internal higher order aberrations (centred on the line of sight) were also calculated over a 4 mm pupil diameter by subtracting the Zernike coefficients of the anterior corneal wavefront from the total ocular wavefront for each subject (Artal et al., 2001). The average internal HOA maps for the amblyopic and non-amblyopic eyes of the refractive and strabismic amblyopes are shown in Figure 2 and display a moderate degree of symmetry between the fellow eyes as reported in a non-amblyopic population (Wang et al., 2005). There were no significant interocular differences between the fellow eyes of the refractive or strabismic groups for individual Zernike coefficients up to the 4^{th} order, or higher order RMS values (all p values > 0.05).

3.5 Interocular difference in HOA and magnitude of anisometropia/amblyopia

We examined the association between the interocular difference in both corneal and total ocular HOA up to the 4th order with the magnitude of spherical equivalent anisometropia and amblyopia. For corneal HOA, weak correlations were observed for third order Zernike term C(3,1) horizontal coma with respect to the degree of anisometropia (r = -0.39, $p < 0.05$) and amblyopia (r = -0.41, $p < 0.05$) when including all amblyopic subjects (Figure 3). The negative slope of the regression line indicates that the less hyperopic (or more myopic) of the two eyes (irrespective of whether the eye was amblyopic) typically had a greater amount of horizontal corneal coma than the fellow eye. For total ocular HOA, the interocular difference in spherical aberration, 3rd, 4th and higher order RMS increased in direct proportion to the magnitude of anisometropia when examining all amblyopic subjects (p values ≤ 0.05). For the strabismic subjects, this trend was also observed for Zernike terms C(3,-1) and C(4,0).

A weak correlation was also observed between the interocular difference in total spherical aberration C(4,0) and the magnitude of amblyopia (all subjects, r = 0.43, p = 0.03) (Figure 4), although no significant differences were observed between the fellow eyes using the paired t-test analysis. In contrast to corneal coma, the positive slope of the regression equation indicates that the more hyperopic (or less myopic) of the two eyes had a greater magnitude of total spherical aberration.

4. Discussion

As expected, the magnitude of anisometropia was strongly correlated with the interocular difference in axial length in our cohort of amblyopic subjects. The amblyopic eye was typically shorter than the fellow non-amblyopic eye suggesting that the disruption of visual input resulted in axial growth retardation rather than excessive axial elongation. The amblyopic eye was the more myopic in only four subjects, three of whom were strabismic amblyopes.

Previous studies have reported a high degree of interocular symmetry of corneal aberrations in isometropic populations (Lombardo, Lombardo & Serrao, 2006; Wang & Koch, 2003) and also in non-amblyopic anisometropes (Vincent et al., 2011). We observed greater amounts of astigmatism in the amblyopic eye, as reported previously (Plech et al., 2010), however, we also found some significant interocular differences in corneal aberrations between the fellow eyes. Examination of the corneal wavefronts of the strabismic subjects revealed a significantly higher level of trefoil in the amblyopic eye compared to the fellow eye. Refractive amblyopes did not exhibit the same interocular differences in third order terms but displayed significant interocular differences in fourth order terms C(4,2) secondary astigmatism, C(4,-2) secondary astigmatism along 45 degrees and C(4,0) spherical aberration. These findings suggest that the interocular asymmetry in corneal aberrations of monocular amblyopes may differ depending on the cause of amblyopia that may be indicative of some form of feedback between the visual experience of the amblyopic eye and corneal optics.

Corneal aberrations were generally greater than total ocular aberrations in both the amblyopic and non-amblyopic eyes of our subjects (Tables 2 and 4). This is consistent with previous studies that have shown that the internal optics (primarily the crystalline lens) partially compensate for the aberrations of the cornea (Artal, Benito & Tabernero, 2006; Artal et al., 2001). While hyperopic eyes typically display greater levels of corneal and lenticular lateral coma due to greater horizontal pupil decentration, the magnitude of trefoil is similar (or slightly less) in hyperopes compared to myopes for corneal, lenticular and total ocular aberrations (Artal, Benito & Tabernero, 2006). In our cohort of subjects, the majority of whom were hyperopic anisometropes, we observed similar levels of mean corneal coma between the fellow eyes, however, in the strabismic cohort trefoil C (3,3) was significantly different between the fellow eyes, most notably for the cornea, but also for total ocular aberrations.

We undertook additional analyses to verify that the interocular differences observed in third order terms of the strabismic amblyopes were not due to differences in fixation during the measurement

of corneal topography. If strabismic subjects were fixating eccentrically during topography measurements, one might expect a larger amount of coma or trefoil due to the rotation of the eye (visual axis) relative to the videokeratoscope (measurement axis) for a cornea with a normal prolate elliptical shape. We compared the average horizontal pupil offsets from the Medmont E300 data (the horizontal distance between the pupil centre and the geometric centre of the cornea) between the amblyopic and non-amblyopic eyes after accounting for enantiomorphism. Horizontal pupil offsets were not significantly different between the fellow eyes for strabismic (interocular difference 0.08 ± 0.17 mm) or refractive amblyopes (interocular difference 0.11 ± 0.23 mm). This supports the assumption that fixation was controlled in the amblyopic eyes during the measurement procedures and confirms the central monocular fixation found with direct ophthalmoscopy in the subject screening process. In addition, no significant correlations were found between the horizontal pupil offset and the amount of primary horizontal coma or trefoil for the amblyopic and non-amblyopic eyes of both refractive and strabismic subjects. These findings suggest the interocular differences observed in the strabismic amblyopes were not an artefact of eccentric fixation in the amblyopic eye.

It has been reported previously that extraocular muscle tension may influence refractive astigmatism (Bagheri, Farahi & Guyton, 2003). To investigate the potential role of extraocular muscle tension producing changes in corneal topography and larger amounts of coma or trefoil in the amblyopic eye of the strabismic subjects, we examined the relationship between the magnitude of horizontal deviation strabismus (measured by prism cover test) and the amount of primary horizontal corneal coma or trefoil. The correlations were weak and not statistically significant (both $p > 0.05$). However, 6 of the 11 strabismic subjects had undergone strabismus surgery, so this will have influenced the magnitude of horizontal deviation and therefore the correlation between the factors. In addition, we observed no significant difference in the magnitude of third or fourth order aberrations in the amblyopic eyes of strabismic subjects who had undergone strabismus surgery and those who had not ($p > 0.05$, unpaired t-test). Therefore, since the interocular differences in corneal

aberrations we observed in the strabismic subjects do not appear to be related to eccentric fixation, extraocular muscle tension/surgery or horizontal pupil offset, they could potentially be related to altered corneal development during or following altered visual experience. A previous study of aberrations in children reported higher levels of total trefoil RMS in the amblyopic eye of both strabismic and refractive amblyopes; however the interocular difference did not reach statistical significance (Kirwan & O'Keefe, 2008). In our strabismic cohort, for both corneal and total aberrations, the mean Zernike coefficient C(3,3) (trefoil) was positive in the amblyopic eye and negative in the fellow eye, suggesting that the sign of the aberration may be a factor related to asymmetric ocular growth or amblyopia. Additional comparison of higher order aberrations in a non-amblyopic cohort of hyperopes and emmetropes may help to identify whether interocular asymmetries in aberrations such as trefoil arise due to altered visual experience or are an artefact of the ocular dimensions of the hyperopic eye (e.g. a larger horizontal pupil decentration).

Alterations in the magnitude of corneal astigmatism has been observed in young chicks following various manipulations of visual input (Kee & Deng, 2008) and it is conceivable that similar mechanisms could operate in humans. We examined the relationship between the interocular difference in corneal and total ocular aberrations for each Zernike coefficient up to the fourth order and the degree of spherical equivalent anisometropia and magnitude of amblyopia to test for any such association. Small but statistically significant correlations were observed between the interocular difference in corneal coma and the magnitude of both anisometropia and amblyopia. Several total ocular aberration terms (primary spherical aberration, 3rd order RMS, 4th order RMS and higher order RMS) also increased in proportion with increasing levels of anisometropia.

Smaller interocular differences in both corneal coma (Figure 3) and total spherical aberration (Figure 4) tended to correspond with a low degree of SEq anisometropia (approximately 0 to 1 D). The greater the magnitude of anisometropia, irrespective of the sign (i.e. whether the amblyopic eye was more myopic or more hyperopic compared to the fellow eye) the larger the interocular difference in

corneal coma and total spherical aberration. This suggests that the interocular differences observed for corneal coma and total spherical aberration may be related to eye size (refractive error) rather than the magnitude or type of amblyopia. Previous work has shown that hyperopic eyes display greater levels of corneal lateral coma due to greater horizontal pupil decentration compared to myopes and emmetropes (Artal, Benito & Tabernero, 2006).

A study of marmosets observed that form deprived eyes had significantly higher levels of trefoil C(3,-3) and 5^{th} and 7^{th} order RMS compared to their fellow control eyes (Coletta, Marcos & Troilo, 2010). In addition, the magnitude of anisometropia induced following form deprivation was significantly correlated with the interocular difference in RMS values for 5^{th} and 6^{th} order aberrations. While several chick studies using a monocular deprivation paradigm have demonstrated an increase in aberrations following monocular altered visual experience (Garcia de la Cera, Rodriguez & Marcos, 2006; Kisilak et al., 2006; Tian & Wildsoet, 2006) this recent marmoset model (Coletta, Marcos & Troilo, 2010) is the first to report an association between the magnitude of induced anisometropia and the interocular difference in HOA. We observed a similar trend in our experiment when including all amblyopic subjects for both corneal (horizontal coma) and total (primary spherical aberration, 3^{rd}, 4^{th} and higher order RMS) aberrations. Of interest is the association observed between the interocular differences in corneal primary horizontal coma and total spherical aberration and the interocular difference in visual acuity. As the magnitude of amblyopia increased, the amblyopic eye displayed greater levels of negative horizontal corneal coma and positive spherical aberration (Figures 3 and 4). The sign of the aberration, in addition to the magnitude, could potentially play a role in the development of asymmetric refractive errors or amblyopia with respect to directional eye growth cues. A large study of children, also found that comatic aberrations may be associated with amblyopia (Zhao et al., 2010). Given that studies with other animals have shown an increase in higher order aberrations following altered visual experience, it seems more likely that the variations we observed in the aberration profile associated with the type

and magnitude of amblyopia are also a result of abnormal eye growth rather than a cause of abnormal growth.

We also measured the total aberrations of the amblyopic and fellow eye during near fixation in a small sub-group of the amblyopes. Overall, the total HOA did not change significantly during accommodation, except for spherical aberration which underwent the anticipated negative shift. The change in higher order aberrations during accommodation, in particular spherical aberration, is related to the change in crystalline lens shape, dimensions and position (i.e. an increase in lens thickness and a steepening of the anterior and posterior lens surfaces) (Rosales et al., 2008). While we observed a significant interocular difference in the accommodative response, the change in spherical aberration during accommodation was not significantly different between the amblyopic (-0.013 µm) and non-amblyopic eyes (-0.020 µm). Given that we have controlled for pupil size during analysis procedures, this suggests there could potentially be an asymmetric change in the shape or dimensions of the crystalline lens between the two eyes during accommodation in our amblyopic subjects which results in a relatively similar change in higher order aberrations between the fellow eyes but an unequal accommodative response.

To our knowledge the changes in the ocular biometrics of amblyopic eyes during accommodation have not been previously examined. Cass and Tromans (2008) compared unaccommodated crystalline lens biometrics between the fellow eyes of amblyopic children using ultrasound during cycloplegia. Lens thickness was similar between amblyopic and non-amblyopic eyes, but made up a significantly larger proportion of the axial length in the amblyopic eye. Calculated lens power was also significantly higher in the amblyopic eye of both refractive (anisometropic) and strabismic (isometropic) amblyopes. The authors suggested that abnormal visual experience may influence the normal thinning of the lens during ocular development.

A significant asymmetry in the lag of accommodation for a 2.5 D stimulus was observed, with the amblyopic eye showing a reduced accommodative response (mean interocular difference 0.71 D).

This finding is within the relatively wide range of lags reported by previous studies (approximately 0.5 - 2 D interocular difference) that have employed a variety of methodologies to examine the accommodation response (Ciuffreda & Rumpf, 1985; Hokoda & Ciuffreda, 1982). Hokoda and Ciuffreda (1982) used dynamic retinoscopy to compare the accommodation between the fellow eyes in a small group of predominately strabismic amblyopes and observed a significant lag in the amblyopic eye (mean interocular difference 2.17 D) during binocular viewing. Under monocular viewing conditions, Ciuffreda and Rumpf (1985) observed accommodative lags of 1.62 D and 1.15 D for amblyopic and fellow non-amblyopic eyes respectively, similar to the values reported in our strabismic cohort. However, these values were for a 5 dioptre accommodation demand (spatial frequency 4 c.p.d.) compared to our 2.5 D stimuli. Both Ciuffreda et al (1984) and Ukai et al (1986) used an autorefractor to measure the monocular accommodation stimulus-response slope in amblyopic subjects. Accommodation was significantly reduced in amblyopic eyes, with the slope of the stimulus response curve approximately 1.27 times greater in the fellow non-amblyopic eye in both studies. Our results are consistent with the trends observed in these earlier studies; however the magnitude of the lag of accommodation is slightly higher in our amblyopic cohort. This may be due to differences in instrumentation, as we used an aberrometer to calculate the accommodative response, unlike previous studies.

Several studies have shown that higher order aberrations may influence the accommodative response. Inducing increased levels of positive spherical aberration and coma, either with contact lenses (Collins, Goode & Atchison, 1997; Lopez-Gil et al., 2007) or adaptive optics (Gambra et al., 2009; Gambra et al., 2010) broadens the depth of focus and typically results in a greater lag of accommodation. We observed increased levels of positive corneal trefoil and positive spherical aberration in the amblyopic eyes of the strabismic and refractive amblyopes respectively, which also had a significantly larger accommodative lag. Although the mean interocular difference in these Zernike terms for total ocular aberrations was not significantly different, there was a moderate correlation between the interocular difference in the accommodative response and the interocular

difference in the ocular spherical aberration which approached statistical significance ($r = 0.53$, $p = 0.09$). Gambra et al (2010) observed that a large increase in higher order aberrations (e.g. 1 µm of spherical aberration, coma or trefoil) is required to reduce the accommodative response in healthy non-amblyopic subjects. However, in amblyopic eyes, it may be possible that the presence of increased levels of aberrations, combined with other factors such as diminished neural sensitivity, may reduce the accommodative response.

While studies have suggested that a lag of accommodation may be associated with the development of myopia due to hyperopic retinal defocus (Gwiazda et al., 1995; Gwiazda et al., 1993), we observed a greater lag in the amblyopic eyes (mean lag 1.46 ± 1.11 D) compared to the fellow non-amblyopic eyes (mean lag 0.74 ± 0.71 D). In other words, during accommodation the amblyopic eye is typically exposed to a hyperopic stimulus (lag of accommodation) compared to the non-amblyopic eye, yet it typically shows diminished eye growth not excessive eye growth. This suggests that the impaired neural function (e.g. reduced high spatial frequency contrast sensitivity) of the amblyopic eye could interfere with ocular growth signals leading to a shorter (hyperopic) eye.

The reduced accommodative response in amblyopic eyes has been investigated in detail previously (Ciuffreda et al., 1984; Hokoda & Ciuffreda, 1982; Hung et al., 1983) and is thought to be a result of abnormal visual experience during the development of the visual pathway which affects the neural input associated with accommodation. Reduced sensitivity to a defocused retinal image (which typically contributes to the stimulus for accommodation) is also thought to result in reduced accommodative response. The asymmetry in the accommodative response between fellow eyes was moderately correlated with the magnitude of anisometropia and significantly associated with the magnitude of which has been reported previously (Ukai, Ishii & Ishikawa, 1986).

We observed small yet statistically significant interocular differences in corneal aberrations between the fellow eyes of our amblyopic cohort; however the total ocular aberrations were relatively symmetric. Consequently, the visual impact of this corneal interocular difference is probably small

in magnitude. While the total ocular aberrations were similar between the fellow eyes of our amblyopic subjects, we cannot rule out the possibility that there was a greater asymmetry in the corneal or total eye aberrations during the critical stages of eye growth which may have disrupted the development of normal binocular vision.

Brunnette et al (2003) observed that a second order polynomial (a 'V pattern' quadratic) best described the change in magnitude of higher order monochromatic aberrations with age. That is, the optical quality of the eye is reduced in children and in the elderly and peaks during early adulthood (age 21-40). The authors suggested that throughout ocular development during childhood, higher order aberrations also undergo a fine tuning in synchrony with the emmetropisation of lower order aberrations while lenticular changes contribute to the observed increase in HOA later in life. Future longitudinal studies examining the changes in aberrations over time in strabismic and anisometropic cohorts, particularly in early childhood, are required to better understand the natural time course of change in aberrations in these populations and will help to clarify the potential impact of higher order aberrations upon the development of amblyopia.

Since our study was also cross sectional in design it is difficult to comment on the causal nature of the relationship between higher order aberrations and amblyopia. In addition, our data was restricted to measurements taken along the visual axis. It is likely that peripheral vision also plays a role in the regulation of eye growth (Smith et al., 2005; Smith et al., 2007). Future studies examining the interocular symmetry of peripheral optics and biometrics may provide additional information regarding the development of asymmetric refractive errors. Longitudinal studies examining ocular and corneal aberrations during development should also provide further insights into whether alterations in higher order aberrations are a cause or consequence of altered visual experience.

5. Conclusion

In subjects with a history of asymmetric visual experience, the interocular difference in axial length is the primary cause of anisometropia and it also correlates with the magnitude of amblyopia. Overall,

corneal and total higher order aberrations were similar between fellow eyes, but significantly higher levels of trefoil and coma in the amblyopic eye suggest that non-rotationally symmetric aberrations may be caused by abnormal ocular development as reported in monocular deprivation paradigms in other animal species.

(Jimenez et al., 2008)

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Figure captions

Figure 1: Correlation between spherical equivalent anisometropia (D) and interocular difference in axial length (mm) for all amblyopic subjects (*n* = 19). Interocular differences calculated as the amblyopic eye minus the non-amblyopic eye.

Figure 2: Average corneal (top), internal (middle) and total (bottom) higher order wavefront aberration maps for the amblyopic and non-amblyopic eyes of strabismic and refractive amblyopes over a 4 mm pupil diameter, centred on the line of sight. Left eye aberration profiles have been rotated to account for enantiomorphism. Interocular difference calculated as the amblyopic eye minus the non-amblyopic eye. Note: The y-axis scale differs for corneal, internal and total wavefronts.

Figure 3: Correlation between the interocular difference in corneal horizontal coma C(3,1) (microns) and spherical equivalent anisometropia (D) (right) and magnitude of amblyopia (logMAR) (left). Interocular differences calculated as the amblyopic minus the non-amblyopic eye.

Figure 4: Correlation between the interocular difference in total spherical aberration C(4,0) (microns) and spherical equivalent anisometropia (D) (right) and magnitude of amblyopia (logMAR) (left). Interocular differences calculated as the amblyopic minus the non-amblyopic eye.

Table

	All amblyopes (*n* = 19)			Strabismic amblyopes (*n* = 11)			Refractive amblyopes (*n* = 8)		
	Amblyopic	**Non-amblyopic**	**Paired t-test *(p)***	**Amblyopic**	**Non-amblyopic**	**Paired t-test *(p)***	**Amblyopic**	**Non-amblyopic**	**Paired t-test *(p)***
Sphere (D)	1.73 ± 4.02	0.21 ± 3.18	< 0.01	1.98 ± 2.89	0.39 ± 1.93	0.06	1.50 ± 5.63	-0.06 ± 4.68	0.02
Cylinder (D)	-1.00 ± 0.98	-0.74 ± 0.60	0.10	-1.07 ± 1.04	-0.68 ± 0.59	0.15	-1.00 ± 0.97	-0.81 ± 0.69	0.20
SEq (D)	1.23 ± 4.20	-0.16 ± 3.31	< 0.01	1.44 ± 2.76	0.05 ± 1.96	0.08	1.00 ± 6.06	-0.47 ± 4.91	0.04
VA (logMAR)	0.36 ± 0.42	-0.14 ± 0.14	< 0.001	0.43 ± 0.50	-0.01 ± 0.03	0.01	0.28 ± 0.33	-0.01 ± 0.09	0.02
AxL (mm)	23.02 ± 1.64	23.54 ± 1.35	< 0.01	22.87 ± 1.09	23.40 ± 0.97	0.07	23.21 ± 2.36	23.74 ± 1.88	0.05

Table 1: Overview of the amblyopic and non-amblyopic eyes. Data presented as mean ± *SD.* SEq - spherical equivalent refractive error, VA - best corrected visual acuity, AxL - axial length.

	Strabismic amblyopes (*n* = 11)			Refractive amblyopes (*n* = 8)		
Zernike coefficient	**Amblyopic**	**Non-amblyopic**	**Paired t-test (*p*)**	**Amblyopic**	**Non-amblyopic**	**Paired t-test (*p*)**
(3,-3)	0.018 ± 0.096	0.065 ± 0.160	0.49	0.016 ± 0.144	0.058 ± 0.121	0.16
(3,-1)	-0.135 ± 0.201	-0.210 ± 0.254	0.38	-0.144 ± 0.085	-0.164 ± 0.098	0.67
(3,1)	-0.163 ± 0.158	-0.113 ± 0.144	0.26	-0.231 ± 0.139	-0.159 ± 0.136	0.21
(3,3)	**0.041 ± 0.139**	**-0.091 ± 0.232**	**0.009**	0.016 ± 0.102	-0.001 ± 0.056	0.37
(4,-4)	0.003 ± 0.004	0.007 ± 0.060	0.76	0.018 ± 0.048	0.003 ± 0.039	0.21
(4,-2)	-0.030 ± 0.042	-0.004 ± 0.023	0.11	**-0.033 ± 0.033**	**0.006 ± 0.027**	**0.001**
(4,0)	0.178 ± 0.083	0.202 ± 0.124	0.43	**0.169 ± 0.042**	**0.130 ± 0.045**	**0.0002**
(4,2)	0.008 ± 0.071	-0.023 ± 0.115	0.46	**-0.13 ± 0.055**	**0.049 ± 0.063**	**0.006**
(4,4)	-0.004 ± 0.066	-0.018 ± 0.114	0.66	0.013 ± 0.020	0.001 ± 0.026	0.29
3rd order RMS	0.381 ± 0.131	0.448 ± 0.175	0.46	0.353 ± 0.070	0.294 ± 0.123	0.12
4th Order RMS	0.249 ± 0.048	0.301 ± 0.111	0.26	**0.196 ± 0.032**	**0.166 ± 0.033**	**0.05**
Total HOA RMS	0.493 ± 0.134	0.573 ± 0.216	0.45	**0.417 ± 0.066**	**0.355 ± 0.110**	**0.04**

Table 2: Corneal higher order aberrations (Mean ± *SD* Zernike coefficients, microns) for the amblyopic and non-amblyopic eyes (6 mm corneal diameter analysis). Bold numbers indicate a significant difference between the fellow eyes ($p \leq 0.05$).

	All amblyopes (*n* = 11)			Strabismic amblyopes (*n* = 5)			Refractive amblyopes (*n* = 6)		
	Amblyopic	**Non-amblyopic**	**Paired t-test *(p)***	**Amblyopic**	**Non-amblyopic**	**Paired t-test *(p)***	**Amblyopic**	**Non-amblyopic**	**Paired t-test *(p)***
Sphere (D)	1.64 ± 2.62	0.02 ± 2.09	0.01	1.55 ± 3.08	0.55 ± 1.46	0.35	1.71 ± 2.47	-0.42 ± 1.05	0.01
Cylinder (D)	-0.68 ± 0.42	-0.59 ± 0.46	0.55	-0.70 ± 0.51	-0.45 ± 0.62	0.43	-0.67 ± 0.38	-0.71 ± 0.33	0.77
SEq (D)	1.30 ± 2.57	-0.27 ± 2.08	0.01	1.20 ± 2.89	0.33 ± 1.24	0.38	1.38 ± 2.56	-0.77 ± 1.19	0.01
VA (logMAR)	0.32 ± 0.28	-0.02 ± 0.06	< 0.01	0.41 ± 0.38	0.00 ± 0.01	0.08	0.24 ± 0.14	-0.04 ± 0.08	< 0.001
AxL (mm)	22.99 ± 1.19	23.61 ± 0.96	0.01	23.13 ± 1.51	23.47 ± 1.16	0.32	22.87 ± 0.97	23.74 ± 0.44	0.02

Table 3: Overview of the amblyopic and non-amblyopic eyes of participants in the accommodative task. Data presented as mean ± *SD*. SEq - spherical equivalent refractive error, VA - best corrected visual acuity, AxL - axial length.

	Strabismic amblyopes (*n* = 11)			Refractive amblyopes (*n* = 8)		
Zernike coefficient	**Amblyopic**	**Non-amblyopic**	**Paired t-test (*p*)**	**Amblyopic**	**Non-amblyopic**	**Paired t-test (*p*)**
(3,-3)	-0.011 ± 0.060	0.007 ± 0.059	0.30	0.009 ± 0.049	-0.002 ± 0.037	0.38
(3,-1)	-0.028 ± 0.056	-0.040 ± 0.047	0.48	-0.031 ± 0.040	-0.015 ± 0.063	0.46
(3,1)	0.006 ± 0.032	0.019 ± 0.061	0.55	-0.023 ± 0.047	-0.011 ± 0.052	0.18
(3,3)	**0.029 ± 0.043**	**-0.004 ± 0.072**	**0.05**	0.008 ± 0.030	0.010 ± 0.045	0.92
(4,-4)	-0.006 ± 0.021	0.004 ± 0.014	0.30	0.000 ± 0.017	-0.001 ± 0.014	0.80
(4,-2)	-0.003 ± 0.014	-0.001 ± 0.010	0.66	0.004 ± 0.021	-0.002 ± 0.015	0.53
(4,0)	0.030 ± 0.021	0.030 ± 0.022	0.94	0.033 ± 0.040	0.026 ± 0.031	0.27
(4,2)	-0.013 ± 0.027	-0.013 ± 0.016	0.95	0.005 ± 0.027	0.019 ± 0.009	0.25
(4,4)	0.017 ± 0.015	0.019 ± 0.010	0.70	0.011 ± 0.008	0.005 ± 0.014	0.30
3rd order RMS	0.048 ± 0.020	0.058 ± 0.022	0.25	0.042 ± 0.016	0.046 ± 0.016	0.67
4th Order RMS	0.024 ± 0.009	0.021 ± 0.008	0.27	0.026 ± 0.012	0.021 ± 0.008	0.09
Total HOA RMS	0.121 ± 0.035	0.140 ± 0.038	0.16	0.113 ± 0.038	0.116 ± 0.039	0.87

Table 4: Total monochromatic ocular aberrations (Mean ± *SD* Zernike coefficients, microns) for the amblyopic and non-amblyopic eyes (distance fixation) (4 mm pupil diameter). Bold numbers indicate a significant difference between the fellow eyes ($p \leq 0.05$).

	Strabismic amblyopes (*n* =5)			Refractive amblyopes (*n* = 6)		
Zernike coefficient	**Amblyopic**	**Non-amblyopic**	**Paired t-test (*p*)**	**Amblyopic**	**Non-amblyopic**	**Paired t-test (*p*)**
(3,-3)	0.000 ± 0.043	0.001 ± 0.061	0.95	0.026 ± 0.028	0.012 ± 0.032	0.51
(3,-1)	-0.062 ± 0.058	-0.056 ± 0.043	0.81	-0.046 ± 0.046	-0.022 ± 0.066	0.63
(3,1)	-0.003 ± 0.028	-0.009 ± 0.010	0.66	0.002 ± 0.031	-0.003 ± 0.045	0.80
(3,3)	0.034 ± 0.038	0.011 ± 0.067	0.19	-0.006 ± 0.015	0.001 ± 0.038	0.72
(4,-4)	0.002 ± 0.015	0.005 ±0.005	0.80	0.002 ± 0.007	0.008 ± 0.006	0.45
(4,-2)	-0.001 ± 0.011	0.003 ± 0.010	0.62	0.006 ± 0.016	-0.001 ± 0.014	0.17
(4,0)	0.017 ± 0.035*	0.023 ± 0.028*	0.65	-0.011 ± 0.030*	-0.023 ± 0.042*	0.33
(4,2)	-0.002 ± 0.011	-0.009 ± 0.016	0.33	0.002 ± 0.030	0.010 ± 0.008	0.66
(4,4)	0.019 ± 0.027	0.019 ± 0.017	1.00	0.004 ± 0.022	0.011 ± 0.019	0.62
3rd order RMS	0.092 ± 0.055	0.102 ± 0.037	0.49	0.066 ± 0.046	0.077 ± 0.043	0.80
4th Order RMS	0.050 ± 0.017	0.041 ± 0.023	0.30	0.045 ± 0.013	0.045 ± 0.028	0.95
Total HOA RMS	0.118 ± 0.051	0.123 ± 0.021	0.76	0.090 ± 0.040	0.107 ± 0.031	0.57
Lag	**1.66 ± 0.94**	**0.96 ± 0.99**	**< 0.05**	**1.32 ± 1.27**	**0.62 ± 0.36**	**< 0.05**

Table 5: Total monochromatic aberrations (Mean ± *SD* Zernike coefficients*,* microns) and lag of accommodation (Mean ± *SD,* D) for the amblyopic and non-amblyopic eyes (near fixation, 2.5 D accommodation demand) (4 mm pupil diameter). Significant differences between amblyopic and non-amblyopic eyes highlighted in bold, * denotes a significant change from distance fixation ($p \leq 0.05$).

Figure 1

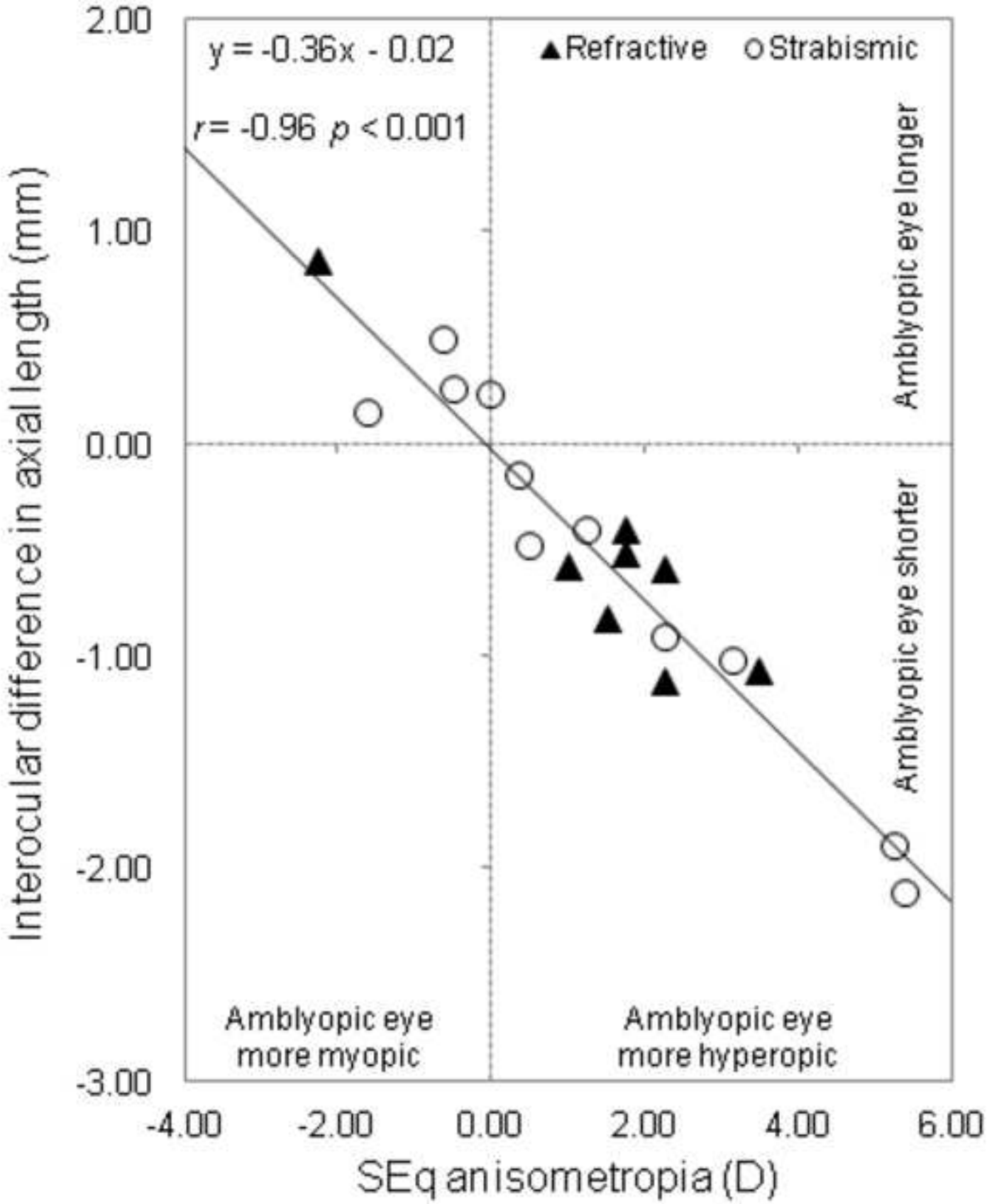


Figure 2

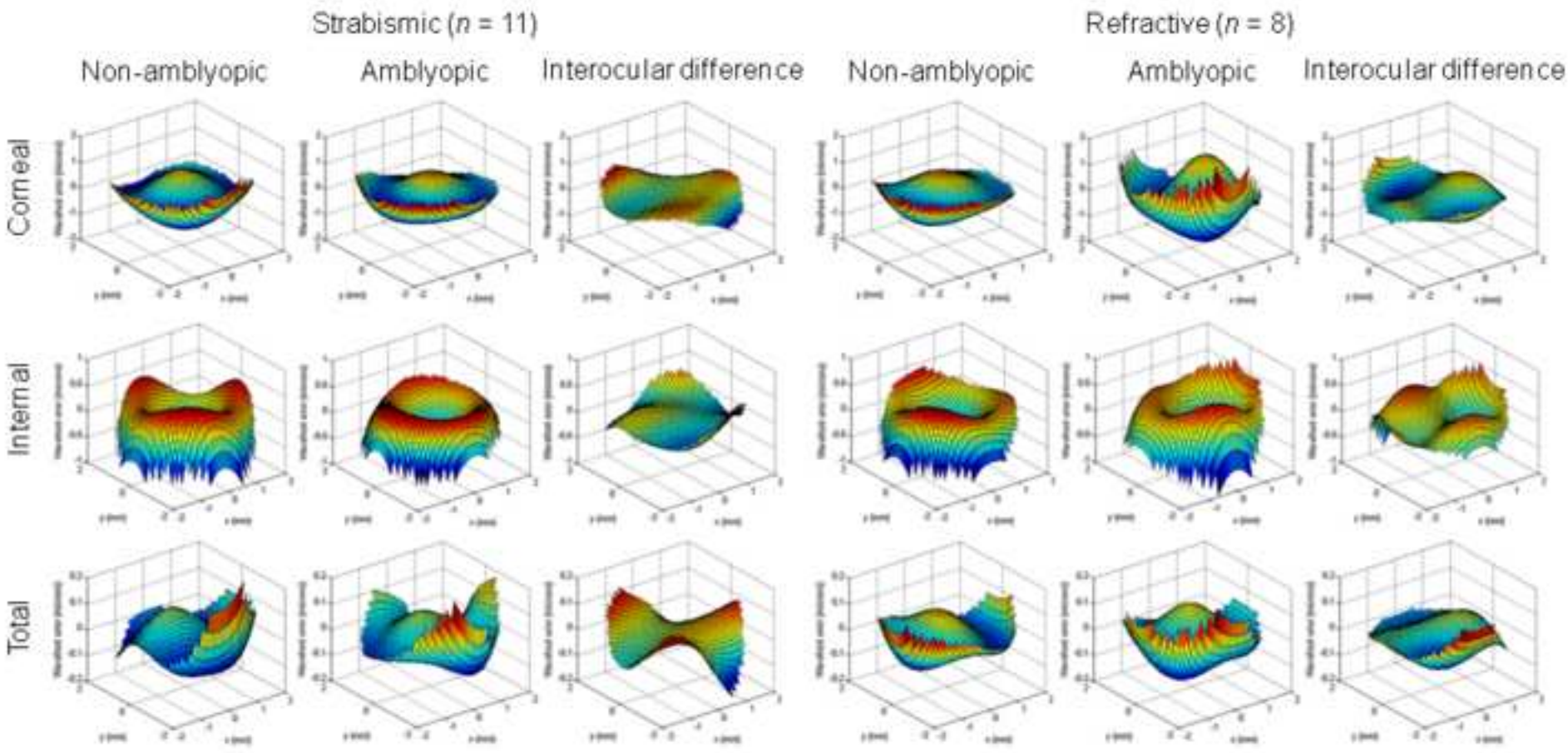


Figure 3A

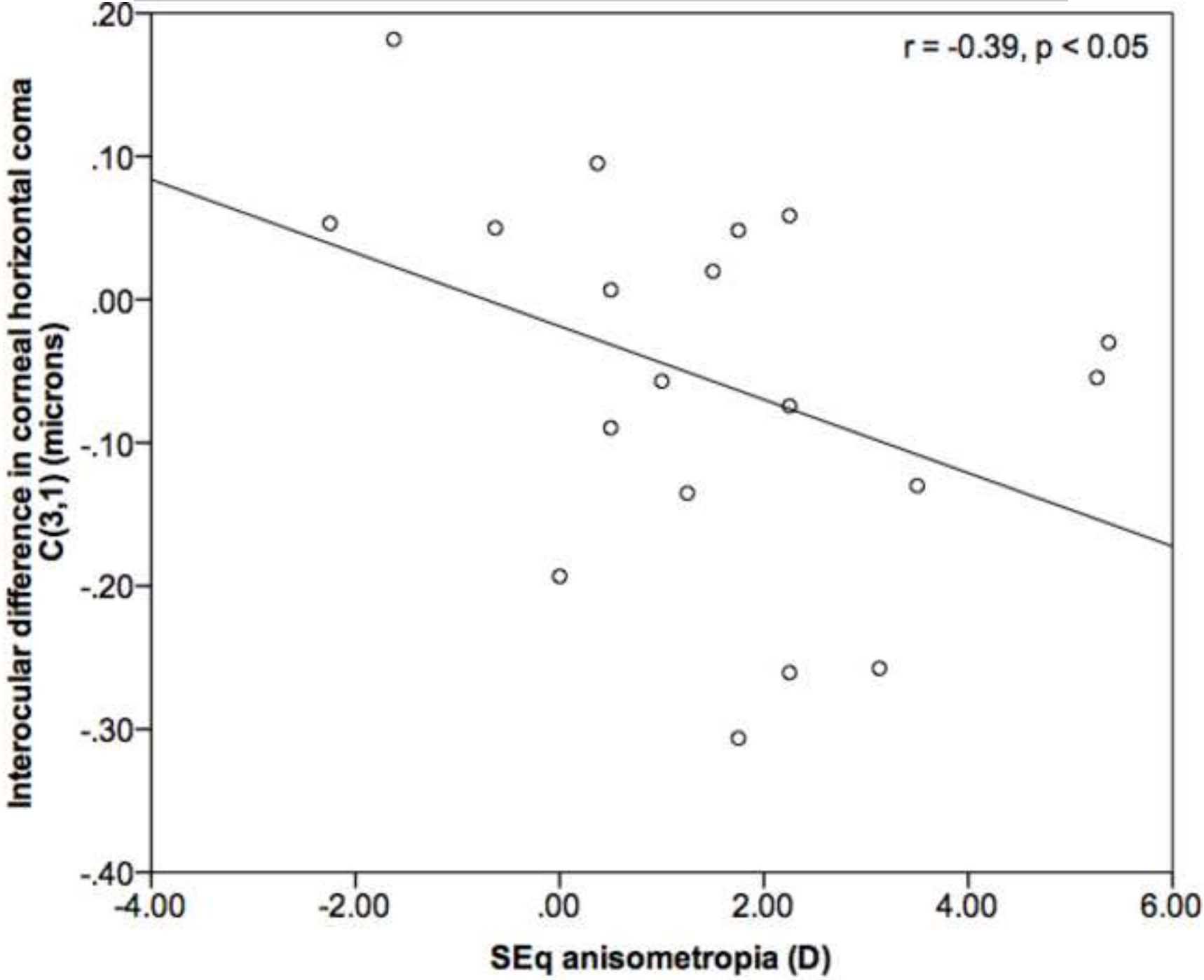


Figure 3B

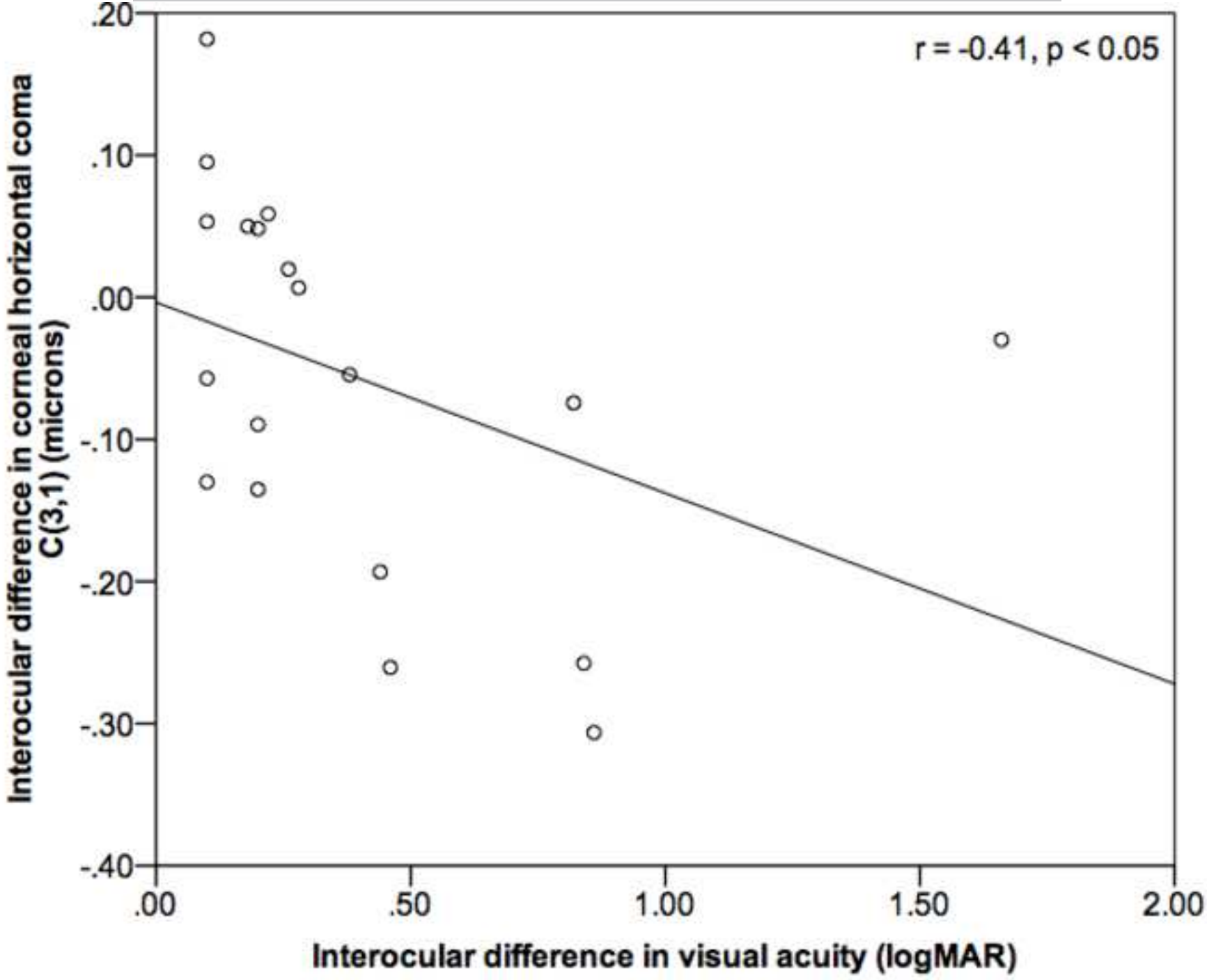


Figure 4A

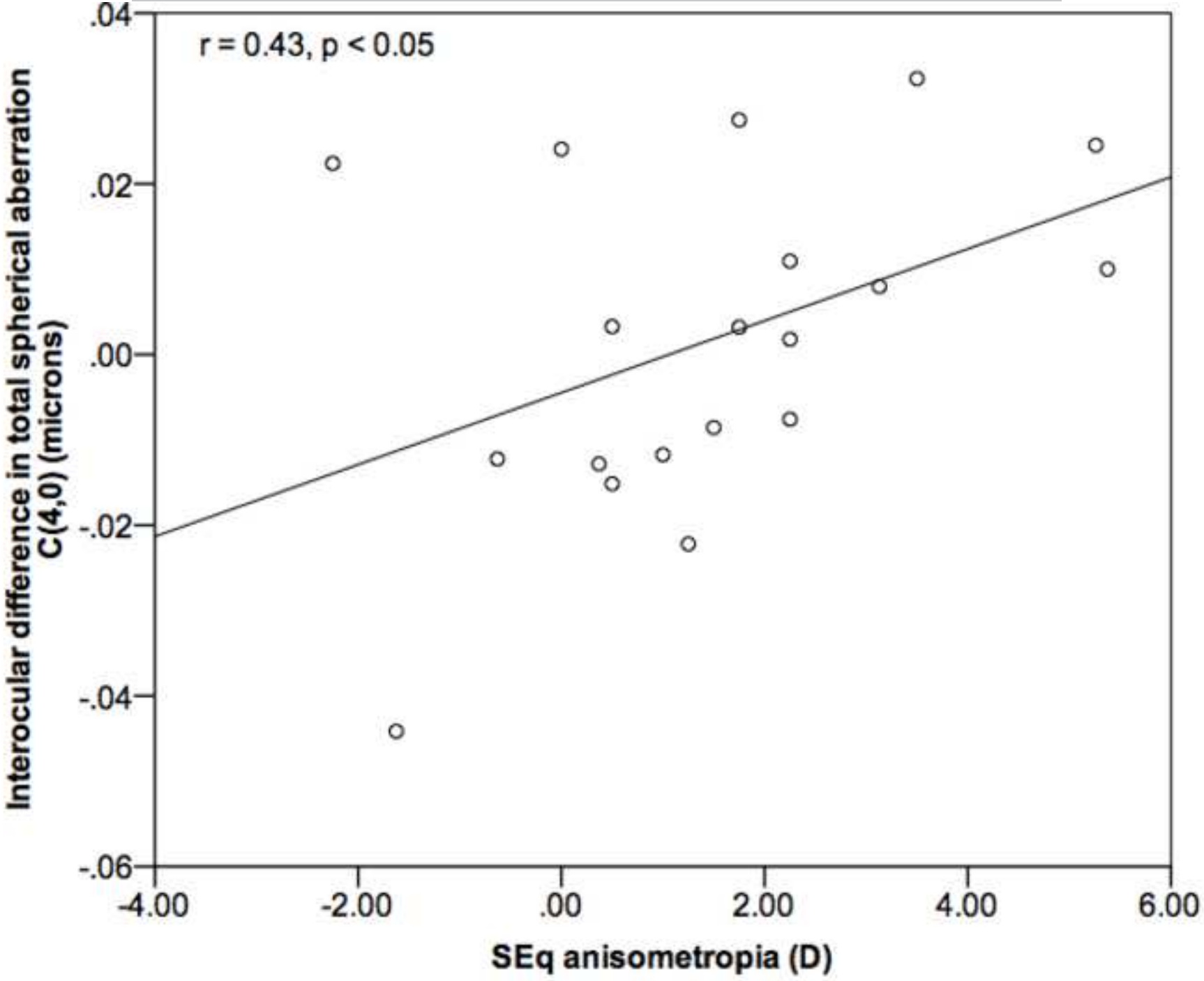
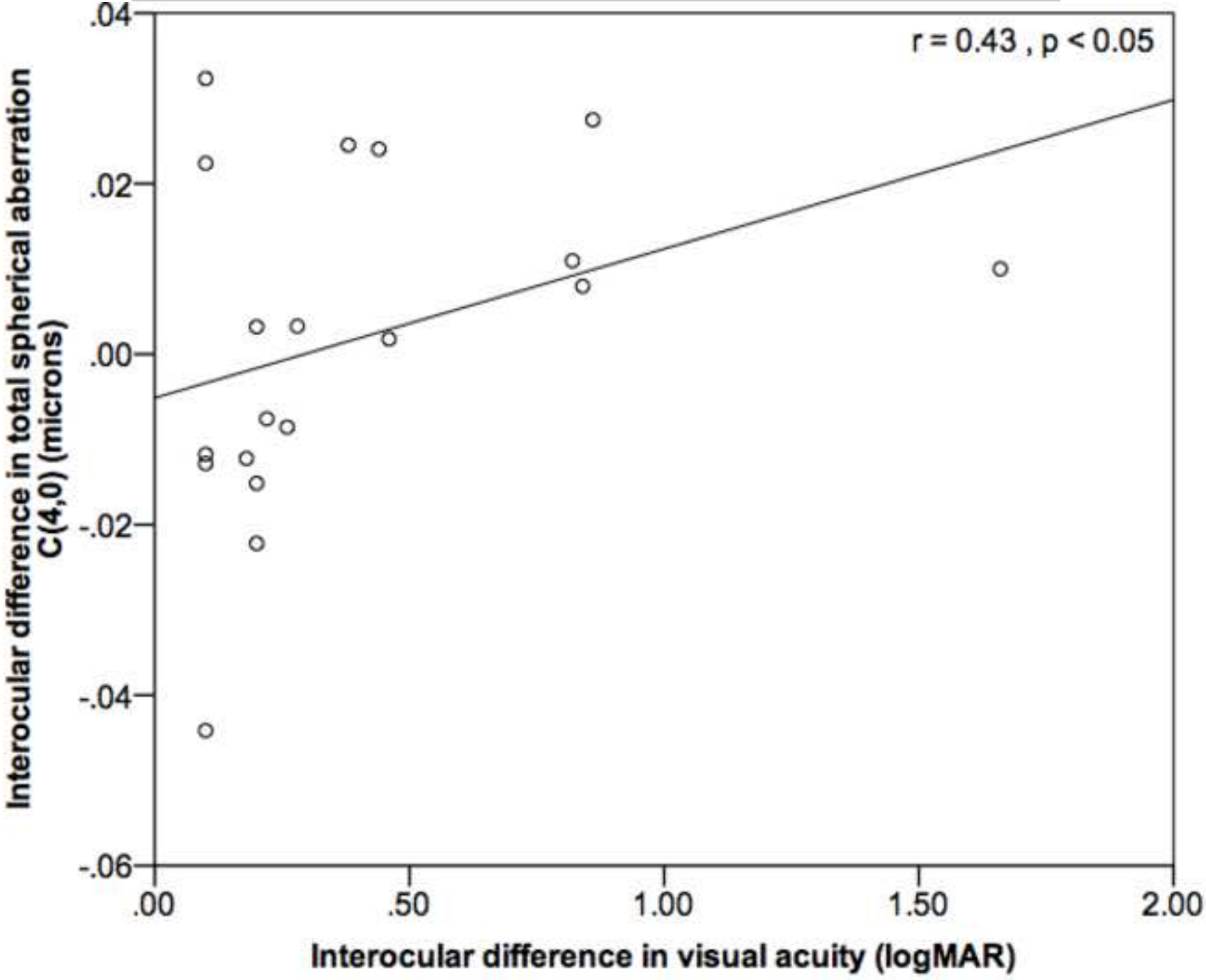


Figure 4B



Highlights

*Corneal and total HOA were compared between the fellow eyes of monocular amblyopes

*Interocular differences in HOA vary with the type and magnitude of amblyopia

*Interocular asymmetry in coma or trefoil may be caused by abnormal ocular development