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Visual deficits in anisometropia

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ABSTRACT

Amblyopia is usually associated with the presence of anisometropia, strabismus or both early in life. We set out to explore quantitative relationships between the degree of anisometropia and the loss of visual function, and to examine how the presence of strabismus affects visual function in observers with anisometropia. We measured optotype acuity, Pelli-Robson contrast sensitivity and stereoacuity in 84 persons with anisometropia and compared their results with those of 27 persons with high bilateral refractive error (isoametropia) and 101 persons with both strabismus and anisometropia. All subjects participated in a large-scale study of amblyopia (McKee et al., 2003). We found no consistent visual abnormalities in the strong eye, and therefore report only on vision in the weaker, defined as the eye with lower acuity. LogMAR acuity falls off markedly with increasing anisometropia in non-strabismic anisometropes, while contrast sensitivity is much less affected. Acuity degrades rapidly with increases in *both* hyperopic and myopic anisometropia, but the risk of amblyopia is about twice as great in hyperopic than myopic anisometropes of comparable refractive imbalance. For a given degree of refractive imbalance, strabismic anisometropes perform considerably worse than anisometropes without strabismus – visual acuity for strabismics was on average 2.5 times worse than for non-strabismics with similar anisometropia. For observers with equal refractive error in the two eyes there is very little change in acuity or sensitivity with increasing (bilateral) refractive error except for one extreme individual (bilaterally refractive error of –15 D). Most pure anisometropes with interocular differences less than 4 D retain some stereopsis, and the degree is correlated with the acuity of the weak eye. We conclude that even modest interocular differences in refractive error can influence visual function.

1. Introduction

Amblyopia, a developmental disorder that degrades spatial vision and stereopsis, is usually associated with strabismus, anisometropia or their combination early in life (Ciuffreda, Levi, & Selenow, 1991). Although it is customary to classify amblyopes by the clinical conditions that are evident at the time that they are examined, the association may not always be causal. Both strabismus and anisometropia can *cause* amblyopia, and either can also be a *consequence* of amblyopia (Birch & Swanson, 2000; Kiorpes & Wallman, 1995; Lepard, 1975). In a previous paper (McKee, Levi, & Movshon, 2003), we detailed the visual functions of a large sample of individuals with amblyopia or risk factors for amblyopia, categorized according to their clinical attributes and history. Our results showed that there were important differences in the pattern of visual loss among the clinically defined categories.

Analyzing the patterns of visual loss in this large population revealed that anisometropes and those suffering from deprivation (defined by a history of blur or occlusion, e.g., infantile cataract or ptosis) display similar functional losses, suggesting that blurred vision in early life may provoke a particular pattern of functional loss. Both the prevalence and severity of amblyopia are related to the degree of anisometropia (e.g. Copps, 1944; Jampolsky, Flom, Weymouth, & Moses, 1955; Tanalami & Goss, 1979; Weakley, 2001), and stereoacuity may also be disrupted by anisometropia (Dobson, Miller, Clifford-Donaldson, & Harvey, 2008). However, the quantitative relationships between the degree of anisometropia and functional vision loss, more broadly defined, have not been fully explored. One purpose of the present paper is to examine the quantitative relationship between the degree of anisometropia, and the losses in three types of visual function: resolution (optotype acuity), contrast sensitivity and stereoacuity. This is of special importance because of the high prevalence of anisometropia in the population (≈12% in adults in Segovia, Spain (Antón, Andrada, Mayo, Portela, & Merayo, 2009); 10% in Singapore (Saw et al., 2008), and more than 4% in Hispanic and African American Children in the United States (MEPEDS Group, 2010)).

Optotype acuity worsens as the amount of anisometropia increases (Jampolsky et al., 1955; Kivlin & Flynn, 1981; Weakley, 2001), but it is not yet clear what causes this deficit, or how

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anisometropia *per se* influences other visual functions. Anisometropia can have several effects: it can result in one eye's retinal image being defocused some or all of the time, with an accompanying reduction in image clarity and image contrast and/or differences in retinal image size (aniseikonia). The most important consequence of amblyopia is that the signals that the two eyes send to the brain about a single object will be different. It has often been suggested that defocus *per se* can *cause* amblyopia. Thus, high uncorrected refractive errors (equal in the two eyes) can in extreme cases lead to isoametropic amblyopia (Ciuffreda et al., 1991; von Noorden, 1977). However, the amblyopia associated with bilateral defocus is milder than that occurring in anisometropia (Copps, 1944), suggesting it is the dissimilarity of the information in the two eyes, rather than defocus alone, that causes the loss of visual function that defines anisometropic amblyopia.

To illuminate these questions using a large and well characterized population, here we compare the visual functions of pure anisometropes, anisometropes with strabismus and observers with high, but equal refractive errors in the two eyes. We previously found that binocularity was a critical factor in determining the pattern of visual loss (McKee et al., 2003). Adults lacking central binocular function were significantly different from adults with residual binocular function. *Anisometropic* observers who lacked binocular function resembled *strabismic* observers in their patterns of functional visual loss (McKee, 1998). This leads to the suggestion that the loss of binocular function during early development modulates the pattern of visual loss. Thus a second purpose of this paper was to examine how the presence or absence of strabismus interacts with anisometropia to modulate visual function.

2. Methods

Our methods and procedures were detailed in our previous report (McKee et al., 2003).

2.1. Observers

The observers studied here represent three subgroups of the four hundred and ninety-five observers who participated in the large-scale study reported in McKee et al., 2003. Here we report on visual functions in 212 individuals, including:

84 pure anisometropes, defined as having:

- Unequal refractive error (with a difference in refractive error between the eyes of 1 D or more at the most anisometropic meridian
- No ocular deviation
- No non-centric fixation
- No deprivation
- No surgical history

The anisometropes were evenly divided between male and female (42 each). Approximately 69% were Caucasian; 6% African American; 17% Hispanic and 11% Asian. Note that this sums to slightly over 100% because two of the subjects fell into more than one category.

27 refractives, individuals with isoametropia defined as having:

- High refractive error (>3.00 D of mean vector blur) in both eyes
- No unequal refractive error
- No deprivation
- No non-centric fixation
- No surgical history

101 strabismic anisometropes, defined as having:

- Constant ocular deviation at near and far test distances
- No history of deprivation
- Unequal refractive error

Most observers were recruited by newspaper advertisements aimed at people between the ages of 8 and 40 with amblyopia or "lazy eye". Those included in the present study were drawn from a pool of 548 people who underwent clinical examination. 43 were excluded because of ocular pathology, bilaterally reduced vision, or poor responsiveness; 10 withdrew before completing the psychophysical testing. Each observer was given a complete battery of clinical tests performed by one of six study clinicians (3 ophthalmologists and 3 optometrists, who all underwent training in the standardized clinical protocol).

2.2. Visual function

We report here on the following measures of visual function:

1. Optotype (Snellen) acuity. We measured optotype acuity with a modified Bailey-Lovie (LogMAR) chart, as used in the early treatment diabetic retinopathy study (ETDRS Report, 1985).
2. Pelli-Robson contrast sensitivity. We measured contrast sensitivity with a Pelli-Robson contrast sensitivity chart (Pelli, Robson, & Wilkins, 1988).
3. Stereo-optical circles test. We measured stereopsis using the Randot "Circles" test (Stereo Optical Co, Chicago, IL).

All testing details are given in McKee et al. (2003). Subjects were fully corrected during the testing.

2.3. Specifying anisometropia

Our primary interest is in how visual function varies with the degree of anisometropia. There are several ways to specify the degree of anisometropia. In the figures and analyses that follow we specify the refractive error in terms of the maximally signed vector blur (Thibos, Wheeler & Horner, 1997; Harris, 1990; Raasch, 1995). This method of specifying sphero-cylindrical refractive error as a single value, was shown by Raasch to predict visual acuity quite accurately. The Vector Blur model combines spherical and cylindrical refractive errors into a single value using a dioptric vector addition model, computing vector blur as:

$$\frac{\sqrt{s^2 + sc + c^2}}{2}$$

where s is the spherical refractive error and c is the cylindrical refractive error. Traditionally, anisometropia was specified on the basis of the most anisometropic meridian (MAM, e.g. Jampolsky et al., 1955). Indeed, in our first publication on amblyopia (McKee et al., 2003), we classified participants as anisometropic if they had 1 D difference between the eyes at the most anisometropic meridian. The sample analyzed in this paper is the same group of anisometropes described in the first paper, but here the analysis is based on vector blur, rather than MAM. In Supplementary Figure S1, we show that, as expected, these two measures are very similar, but that vector blur anisometropia is, on average, about 0.5 D less than MAM. In many of the figures that follow, a few anisometropes (as classified by MAM) have less than 1 D of vector blur anisometropia. This is because MAM specifies the maximum anisometropia while vector blur and spherical equivalent assume that the anisometrope will chose to focus midway between the

two meridia. Using these two different methods of specifying anisometropia yield essentially the same results and conclusions.

3. Results

3.1. The distribution of refractive errors in anisometropia

Fig. 1 shows the distribution of refractive errors in each eye of the anisometropes (red), strabismic anisometropes (blue) and refractives (gray). We use this color code throughout. Symbol size coarsely codes visual acuity (Fig. 1A) and stereoacuity (Fig. 1B, discussed below). The coordinate system plots vector blur refractive error of the strong eye (abscissa) against the vector blur refractive error of the weak eye (ordinate). Note that we use "strong" and "weak" (defined on the basis of acuity) rather than "preferred" and "non-preferred" to avoid ambiguities related to preference or eye dominance. The solid gray lines mark zero refractive error for each eye. The green diagonal band marks equal refractive error in the two eyes (±1 D).

There is no generally accepted classification for the different optical forms of anisometropia, so we made one up and labeled the six regions of interest in the space. Our overall division of anisometropes into two groups is defined by the horizontal zero. All observers above this line are hyperopic in their weaker eye and are generically *anisohyperopes*. All below the line are myopic in their weak eye, and are generically *anisomyopes*. A slight majority of pure anisometropes is anisomyopic (46/84, 55%), but a majority of strabismic anisometropes is anisohyperopic (58/101, 57%). The upper right quadrant below the green diagonal represents "anomalous" anisohyperopes – individuals who have a smaller hyperopia in the weak eye then in the strong eye (6 of 185 subjects with anisometropia, 3%). This is "anomalous" because the eye with the smaller refractive error is usually the strong eye, and is seldom if ever accompanied by amblyopia. We have no explanation for this uncommon situation. Much more common, and more commonly amblyopic, are anisohyperopes whose strong eye has a smaller refractive error (48/185, 26%); these are in the top right quadrant above the green diagonal. The upper left and lower right quadrants represents hyperopic and myopic antimetropes, respectively. They are antimetropes because the two eyes have opposite-signed refractive errors, hyperopic in one eye, and myopic in the other. Myopic antimetropes are very rare (6/185, 3%), but hyperopic antimetropes are more common (41/185, 22%), and like other anisohyperopes are often amblyopic. In other words, among antimetropes, the hyperopic eye is much more likely to be the weak eye, perhaps reflecting a failure of emmetropization. Finally, the lower left quadrant contains anisomyopes. Anisomyopes below the diagonal have smaller refractive errors in the strong eye (54/185, 29%); anomalous anisomyopes above the diagonal have smaller refractive errors in the weak eye (30/185, 16%); these are relatively common compared to anomalous anisohyperopes.

3.2. Variation in the visual acuity (LogMAR) with anisometropia

To provide a graphical overview of the relationship between acuity and refractive error, acuity in the weak eye is coarsely coded by symbol size in Fig. 1A. The smallest symbols represent LogMAR < 0.3 in the weak eye (i.e., acuity of better than 20/40). The two larger symbol sizes represent LogMAR 0.3–0.6 and LogMAR > 0.6 respectively. By the usual definitions, the two larger symbol sizes represent individuals with amblyopia. Inspection of Fig. 1A reveals several points:

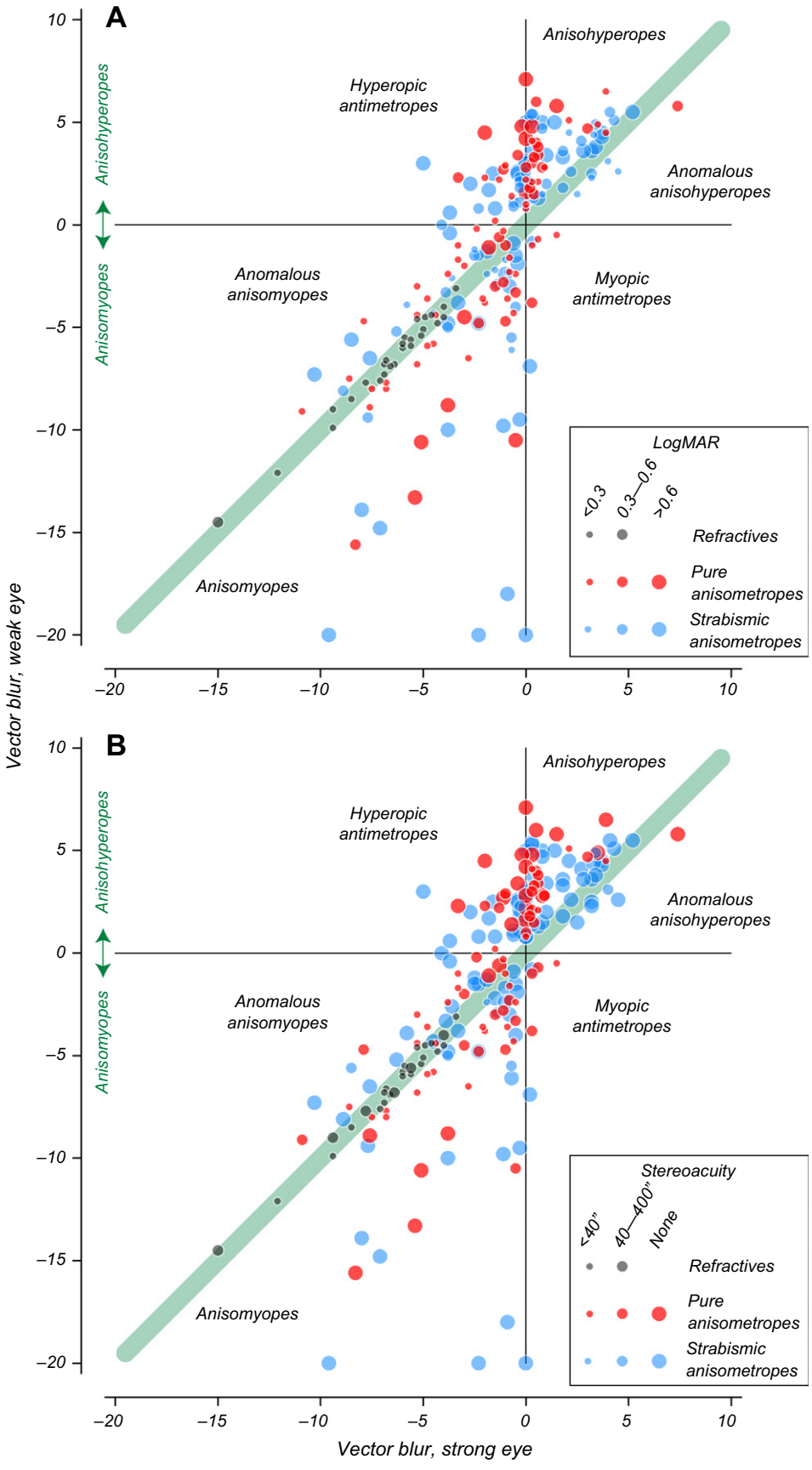
(1) Equal refractive error, as high as 12 D does not result in amblyopia. Only one refractive (−15 D) is amblyopic (LogMAR 0.3–0.6).
(2) As expected based on previous reports, amongst the pure anisometropes (red symbols) there is a substantial number of amblyopic anisohyperopes (including one anomalous anisohyperope).
(3) Perhaps more surprising is the substantial number of amblyopic anisomyopes, even with fairly small degrees of myopia in the weak eye. We will return to this point later. None of the pure anisometropes in the anomalous anisomyopia segment have amblyopia.
(4) Strabismic anisometropes (blue symbols) are overwhelmingly amblyopic except for the underpopulated regions labeled anomalous anisohyperopia and myopic antimetropia.

In a more quantitative assessment, Fig. 2A shows how optotype acuity in the weak eye varies with the degree of anisometropia (left panel) and with absolute mean refractive error (right panel). In this, and subsequent figures, we use negative values for anisometropia to indicate anisomyopes (see Fig 1), and positive values to indicate anisohyperopes. The meandering lines show the running mean acuity for each of the three groups (computed over seven adjacent data values).

Several points are obvious from inspection of Fig. 2A. Consider the left panel. Firstly, for the pure anisometropes, acuity falls off markedly with increasing anisometropia. The V-shape of the data show that visual acuity degrades rapidly with increases in *both* hyperopic and myopic anisometropia. Linear regression suggests that the fall-off of acuity with anisometropia is somewhat shallower in myopic than in hyperopic anisometropia. The slopes of the best fitting lines (calculated from the VA at zero anisometropia) are −0.55 ± 0.06 and 0.74 ± 0.1 for myopic and hyperopic anisometropia respectively. Secondly, at low values of anisometropia, the strabismic anisometropes have a wide range of performance, with many performing considerably worse than anisometropes with the same degree of refractive imbalance. For these observers, one could reasonably conclude that the presence of strabismus has a multiplicative effect on acuity. From the running means, it is clear that acuity is, on average, about 2.5 times worse in the strabismic anisometropes than in the pure anisometropes over the entire range of overlapping anisometropias. Thirdly, for the refractives (gray) there is very little change in any of the acuity measures, with increasing (bilateral) refractive error except for the one extreme individual (−15 D).

Inspection of the right panel of Fig. 2A reveals that, on average, even in anisometropes with substantial myopia, acuity is very much better than in strabismic anisometropes with similar degrees of myopia. The difference between anisometropes with and without strabismus diminishes with increasing hyperopia. We interpret this to mean that increasing blur in the image damages acuity as much as the presence of strabismus. Finally, the running means

Fig. 1. Distribution of refractive errors in each eye of anisometropes (red), strabismic anisometropes (blue) and refractives (gray). We use this color code in all subsequent figures. The vector blur refractive error of the strong eye (abscissa) is plotted against the vector blur refractive error of the weak eye (ordinate). The solid black lines denote zero refractive error (horizontal – weak eye; vertical – strong eye). The green diagonal band represents equal refractive error in the two eyes, ±1 D. The upper right quadrant above the red lines represents anisohyperopes – emmetropic or hyperopic in the strong eye, and more hyperopic in the weak eye. The upper right quadrant below the red line represents "anomalous" anisohyperopes – emmetropic or hyperopic in the strong eye, and less hyperopic in the weak eye. The lower right quadrant represents myopic antimetropes. The upper left quadrant represents hyperopic antimetropes – emmetropic or hyperopic in the weak eye, and myopic in the strong eye. The lower left quadrant contains anisomyopes. Anisomyopes below the red line – emmetropic or myopic in the strong eye, and more myopic in the weak; "Anomalous" anisomyopes above the red line – emmetropic or myopic in the strong eye, and less myopic in the weak eye. Symbol size is used to coarsely code visual acuity (A) and stereoacuity (B).



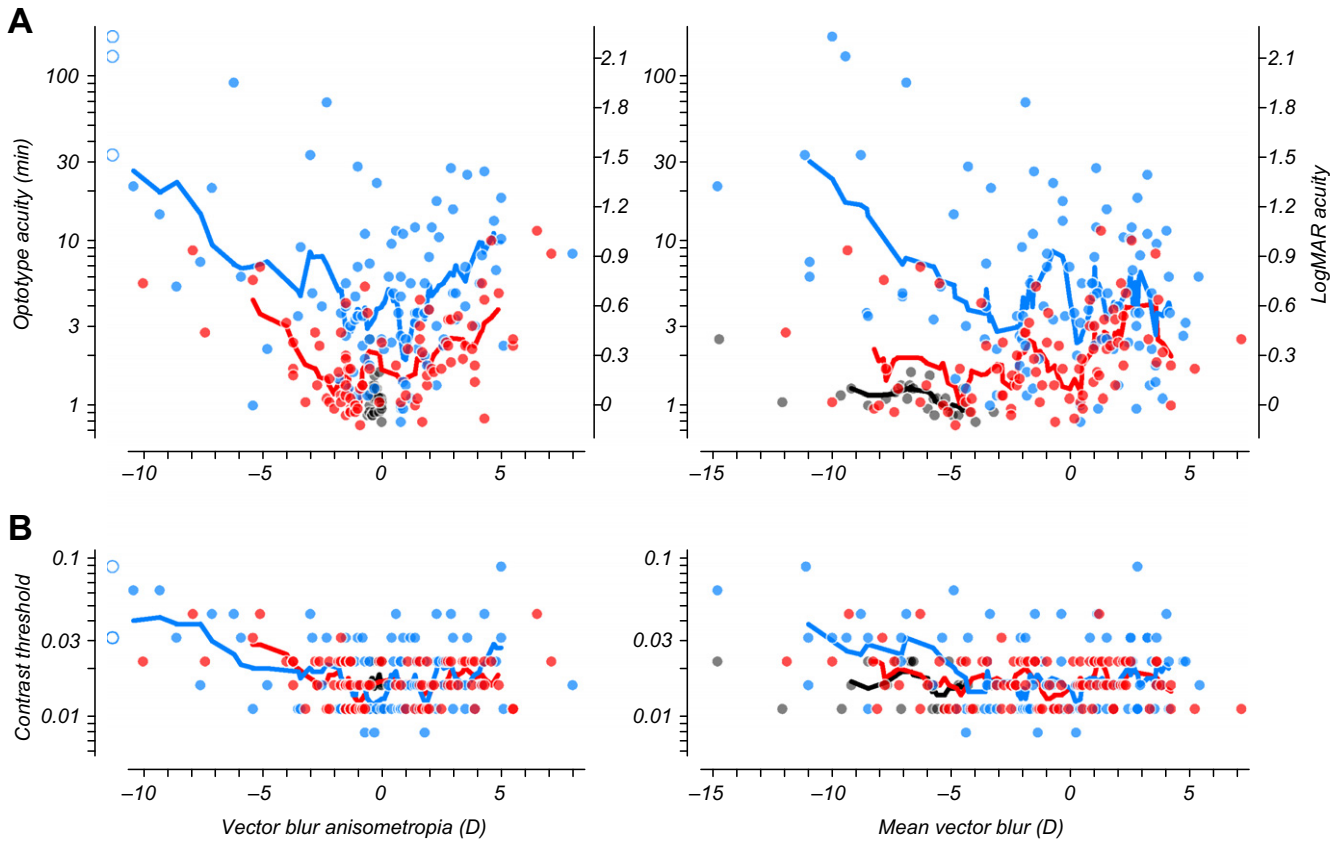


Fig. 2. Optotype acuity (A) and contrast threshold (B) vs. degree of anisometropia (left panel) and absolute refractive error (right panel). The meandering lines show the running mean acuity for each of the three groups. Vector blur anisometropia is defined as the absolute value of the difference in vector blur between the two eyes, given the sign of the refractive error of the weak eye.

of the pure anisometropes rise with increasing hyperopia, but remain flat with increasing myopia, reflecting the fact that many fewer myopes become amblyopic than hyperopes (see Fig. 4A).

3.3. Variation in contrast thresholds with anisometropia

While acuity falls off sharply with the degree of anisometropia, contrast sensitivity, as measured using the Pelli-Robson test (Fig. 2B) is much more tolerant of refractive imbalance in both pure and in strabismic anisometropes. Increasing bilateral refractive error (isoametropia) has almost no effect on contrast sensitivity.

3.4. Variation in stereoacuity with anisometropia

To assess stereopsis we measured stereoacuity (Circles test). Over 70% of our anisometropic subjects have measureable stereopsis: 56 of 84 (67%) have stereoacuity of 140 arc sec or better on the circles test – considered to be based on genuine stereopsis (Fawcett & Birch, 2003). Thirty-five of 84 (42%) showed stereoacuity of 50 arc sec or better. In contrast, only 6 of 101 strabismic anisometropes (6%) had stereoacuity of 140 arc sec or better, and just 1 of 101 (1%) 50 arc sec or better. Interestingly, the one strabismic anisometrope with 20 arc sec stereoacuity had early surgery (less than 6 months), and no patching.

Fig. 1B provides a graphical overview of the relationship between stereoacuity and refractive error, with stereoacuity coarsely coded by symbol size (the smallest symbols represent stereoacuity <40 arc sec, and the two larger symbol sizes represent stereoacuity of 40–400 arc sec and stereoacuity >400 arc sec (the upper limit of the test) respectively. The two larger symbols therefore represent individuals who have impaired and no stereopsis respectively. Inspection of Fig. 1B reveals several points:

(1) All observers with equal refractive error retain stereopsis – most achieving 40 arc sec or better.
(2) Amongst the pure anisometropes (red symbols) substantially fewer anisohyperopes retain stereoacuity of 40 arc sec or better than do anisomyopes. However, some anisomyopes, even with fairly small degrees of myopia in the weak eye show no measurable stereopsis.
(3) Strabismic anisometropes (blue symbols) are overwhelmingly stereoblind.
(4) While the two panels of Fig. 1 seem to mirror each other, a close comparison reveals that while there are 18 anisohyperopes with good acuity in the weak eye (LogMAR < 0.3, smallest red symbols in Fig. 1), there are only 3 with stereoacuity better than 40 arc sec (smallest red symbols in Fig. 1B). Thus, monocular blur appears to impair the development of good stereoacuity more than the development of good visual acuity.

Fig. 3 provides a quantitative assessment, showing how stereoacuity varies with the degree of anisometropia (left panel) and with absolute refractive error (right panel). The most striking difference between the anisometropes and the strabismic anisometropes is in their stereoacuity. As is evident in Fig. 3, most anisometropes between ±4 D have stereopsis, while most strabismic anisometropes do not (failure to demonstrate stereoacuity is plotted at the top of the graph – compare blue vs red symbols). For those anisometropes demonstrating measurable stereopsis, there is a broad scat-

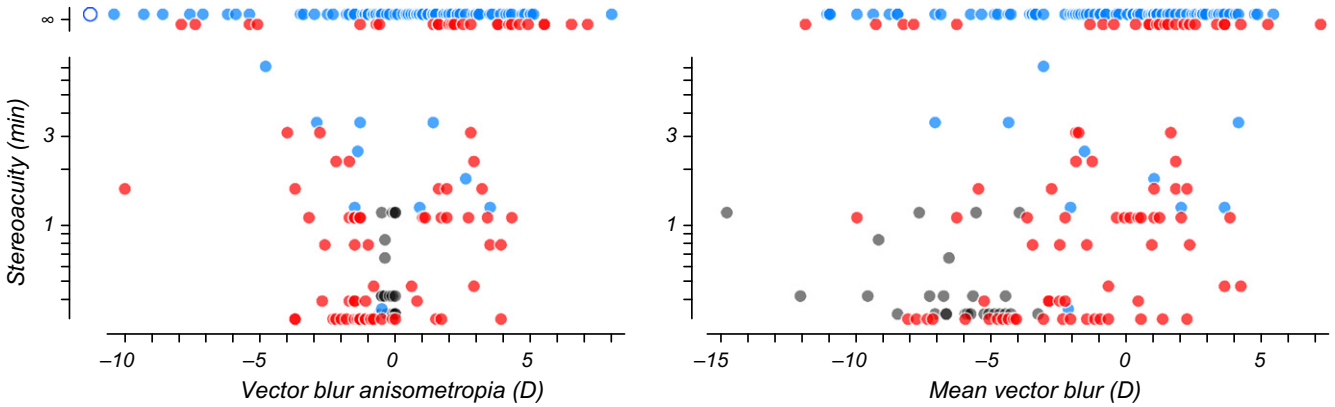


Fig. 3. Stereoacuity vs. degree of anisometropia (left panel) and absolute refractive error (right panel).

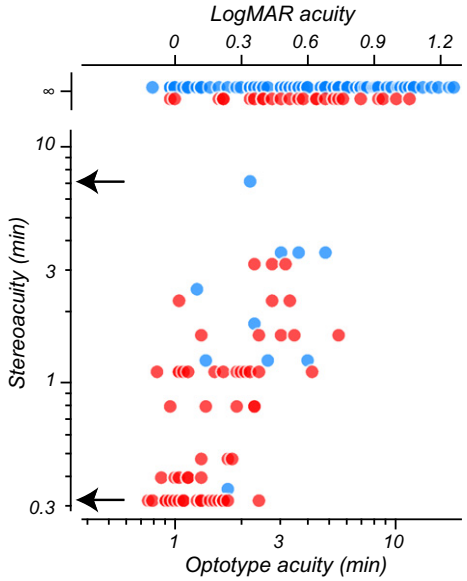


Fig. 4. The relationship between stereoacuity and MAR. The arrows show the upper and lower limits of the test. The data for strabmismic anisometropes (in blue) have been displaced for clarity.

ter (from 0.33 to 3.33 arc min [20–200 arc sec) in their stereoacuity. There is also a notable asymmetry between hyperopic and myopic anisometropia: only six out of 39 *hyperopic* anisometropes (≈15%) demonstrate stereoacuity of 30 arc sec or less, while 24 of 45 *myopic* anisometropes (≈53%, plus one strabismic myopic anisometrope) show stereoacuity in this range. Only one (out of 101) strabismic anisometrope demonstrated stereopsis of 0.5 arc min better. In contrast, all 27 isoametropes have measurable stereopsis, and more than half display stereothresholds of 20 arc sec, the limit of the test.

3.5. Does stereoacuity depend on optotype acuity (MAR)?

Fig. 4 shows that the relationship between stereoacuity and visual acuity is not straight-forward. Over the entire range of optotype acuities, there are some anisometropes who are essentially stereoblind (data plotted along the top of the graph). However, if we exclude those stereoblind anisometropes, there is a clear linear relationship between stereoacuity and LogMAR ($r = 0.54$). It is also interesting to note that there are anisometropes with excellent stereopsis (20 arc sec), with reduced optotype acuity in the weak eye (up to 2.5 arc min), and many with stereopsis better than 140 arc sec who have substantially reduced acuity (MAR up to 6 arc min or 20/120). As noted in our previous study, any stereopsis is better than none, and the total absence is correlated with extra visual losses in LogMAR and Vernier acuity that are not explained by their grating acuity deficit (McKee et al., 2003).

It is also worth noting that while most strabismic anisometropes (blue circles) were stereoblind, six showed stereoacuity of 2.33 arc min (140 arc sec) or better (including one observer with 0.33 arc min [20 arc sec] stereoacuity). Surprisingly, the few strabismic anisometropes who have measurable stereopsis show the same relationship with acuity as do the pure anisometropes.

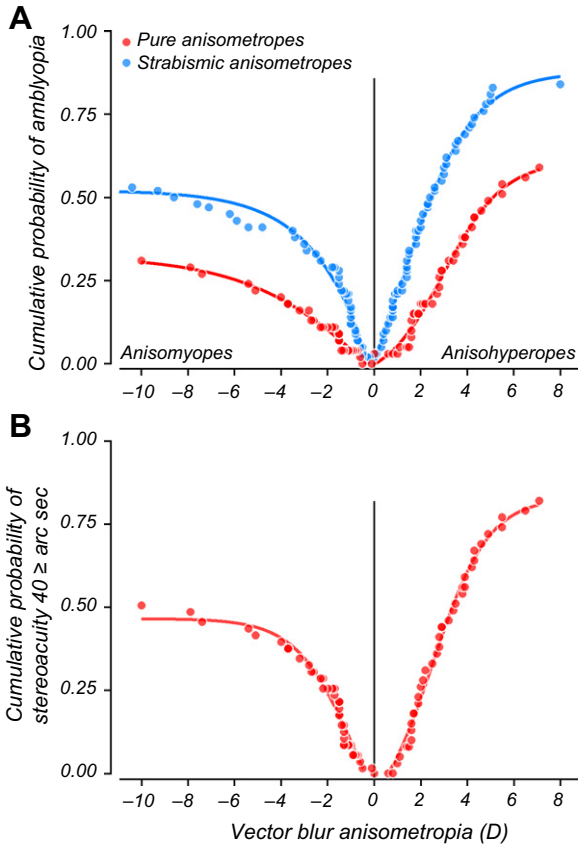


Fig. 5. (A) The cumulative probability of being amblyopic (defined as having acuity of 20/40 or worse in the weak eye) as a function of the absolute value of the amount of anisometropia. (B) The cumulative probability of stereo-acuity being 40 arc sec or worse. Cumulative probabilities for positive and negative values of vector blur anisometropia were computed separately, beginning at 0.

As noted above, ≈70% of the anisometropes retain stereopsis. Interestingly, about 20% of anisometropes with straight eyes fail the stereo test and also show no binocular function on a test of rudimentary binocular fusion, based on a coarse binocular integration test. These anisometropes have no binocularity, and that is supported by the fact that this rare group looks more strabismic-like on our other measures (see McKee et al., 2003).

4. Discussion

Our goal was to explore quantitative relationships between the degree of anisometropia and losses in visual acuity, contrast sensitivity, and stereopsis. Our results show that anisometropia is much more detrimental to acuity than it is to contrast sensitivity. We found that visual acuity falls off somewhat faster in hyperopic than in myopic anisometropia. Previous studies and clinical experience suggest that the prevalence of amblyopia (as defined by a visual acuity criterion) is lower with low degrees of myopic as compared with hyperopic anisometropia. To compare our results with previous studies, we've plotted the cumulative probability of being amblyopic (defined as visual acuity of 20/40 or worse in the weak eye) as a function of the absolute value of the amount of anisometropia (Fig. 5A).

For the pure anisometropes, myopia and hyperopia show rather different slopes (the lines are sigmoids fit to the data), so that by around 3 D of anisometropia, roughly 40% of hyperopic anisometropes are amblyopic (according to either criterion), whereas only about 15% of myopic anisometropes are amblyopic. Even with 10 D of myopic anisometropia, only ≈30% will become amblyopic. Strabismic anisometropes of both signs show a steeper increase in the probability of amblyopia than do pure anisometropes; however, even with very high myopic anisometropia, only ≈50% of strabismic anisometropes have amblyopia, whereas virtually all strabismic anisometropes are amblyopic with 8 D of hyperopic anisometropia.

There is also an asymmetry evident in the stereopsis data. Fig. 5B shows the cumulative probability of stereo-acuity being 40 arc sec or worse. With 3 D of anisometropia, 40% of both hyperopic and myopic anisometropes have reduced stereopsis (40 arc sec or worse). For hyperopic anisometropes, increasing anisometropia results in an increasing proportion of the population with reduced stereopsis. In contrast, the data for the myopic anisometropes saturate, so that even with substantial anisometropia (≈10 D), more than 50% of the myopic anisometropes retain stereoacuity of better than 40 arc sec. Only one of the 101 strabismic anisometropes has stereopsis of 40 arc sec or better, so 99% fail the criterion at all levels of anisometropia. We conclude that the loss of stereoacuity is a general feature accompanying strabismus, and occurs in anisometropia only when there is substantial unilateral defocus.

Our analysis of the prevalence of amblyopia and stereo-anomalies is consistent with previous studies in showing that amblyopia is associated with a large myopic defocus and a small hyperopic defocus. Taken together, our prevalence results are largely in agreement with previous studies (Copps, 1944; Jampolsky et al., 1955; Tanalami & Goss, 1979; and Weakley, 2001). In the most extensive study to date, Weakley reviewed the records of 361 patients with anisometropia, and 50 nonanisometropic controls. His patients were much younger (age ranged from ≈3 to 14.5 years) than ours (age range from 8 to 40 years). Because of emmetropization, we might expect our older population to be more myopic than Weakley's, and perhaps more myopic than they were when amblyopia developed. We suspect that our population also differs in ethnicity from the populations of previous studies. A large proportion of our anisometropes were Asian; Asians are also known to have a high prevalence of myopia (Saw et al., 2008). Despite these differences, Weakley concluded that spherical myopic anisometropia of greater than 2 D and spherical hyperopic anisometropia of more than 1 D resulted in a significant increase in amblyopia and a decrease in binocular function, in general agreement with our findings. Interestingly, both hyperopic and myopic cylindrical anisometropia of greater than 1.5 diopters resulted in an increased incidence of amblyopia and a decrease in binocular function. Most of the low myopic anisometropes with reduced acuity have astigmatism (Figure S1). This group of astigmatic myopes contributes to the high prevalence of reduced acuities and low tolerance for defocus seen in the group of amblyopes with low myopic spherical equivalent refractive errors. This is why MAM identifies a few amblyopes missed by the vector blur definition.

Importantly, our results, in agreement with Copps (1944), show that anisometropic amblyopia is not simply a consequence of passive form deprivation through defocus. Large bilateral refractive errors have only a small effect on visual performance. This is quite surprising because high myopia can result in significant structural changes (axial length; retinal stretching, etc.). We will return to the question of how monocular defocus degrades performance later in the Discussion.

A second goal of our study was to examine how the presence or absence of strabismus modulates visual function in persons with anisometropia. We found that strabismus can exacerbate the pattern of functional loss of acuity and contrast sensitivity, and typically devastates stereoacuity. As noted in the introduction, both strabismus and anisometropia can *cause* amblyopia, and either can also be a *consequence* of amblyopia (Lepard, 1975; Kiorpes & Wallman, 1995; Birch & Swanson, 2000). Our clinical "history" might have been helpful, but there are many reasons why estimates of onset age based on clinical history cannot be taken seriously; in particular, the age of onset is based on remembrance of times past, and is deeply and inextricably entangled with the age at which the child first saw an eye care professional. Nevertheless, it is interesting that of the 6 strabismic anisometropes who had any measurable stereopsis (200 arc sec or less), *all* had onset ages of 5 years or older. This is consistent with experiments in deprived monkeys that showed that binocularity is only retained when the onset of deprivation is late (Harwerth, Smith, Duncan, Crawford, & von Noorden, 1987).

4.1. How does monocular (but not binocular) defocus influence visual function?

In terms of its influence on visual development, monocular blur is much less well tolerated than binocular blur. Why does 4 D of defocus in one eye (whether myopic or hyperopic) result in substantial amblyopia, when the same degree of defocus in both eyes (isoametropia) has no effect on visual function? One might argue that isoametropes retain visual function because, by viewing at very close distances (e.g. for a 7 D myope, reading at a distance of 14 cm) they would have periods of clear vision. Note that our isoametropes are all myopic; nonetheless, it clear from Figs. 1 and 2 that myopic anisometropia also has a much greater effect on visual acuity than myopic isoametropia. In contrast to myopic anisometropia, a *hyperopic* anisometrope will generally accommodate to obtain a clear retinal image in the less hyperopic eye, and the fellow eye will *always* be out of focus, with an attendant degradation of high spatial frequencies in the retinal image. Indeed, the prevailing clinical wisdom suggests that for low to moderate amounts of *myopic* anisometropia, patients may use the more myopic eye for near viewing and the less myopic eye at distance, and therefore avoid amblyopia. This is the standard explanation for the lower prevalence of amblyopia in low degrees of myopic compared with hyperopic anisometropia. In this view, the amount of time that the retinal image is defocused as well as the magnitude

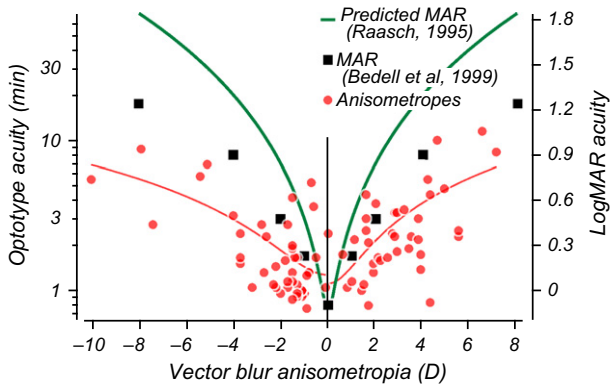


Fig. 6. The thick green lines shows the optotype acuity predicted from refractive blur by a dioptric vector addition model (Raasch, 1995 – see text). The squares show the effect of lens induced blur on optotype acuity (from Bedell et al., 1999). The circles replot the optotype acuity of our anisometopes (from Fig. 2). The red lines fit to the data are the defocus tolerance fits described earlier (see text).

of defocus, is important. To look more closely at the question of whether it is the defocus *per se*, below we ask whether the degree of visual loss in hyperopic anisometropia can be predicted simply on the basis of their current defocus. Note that we do not know how much defocus was present in early development, and resulted in the amblyopia; rather, what we are asking here is whether the defocus at the time of this study can predict the visual acuity measured in the study.

The thick green lines in Fig. 6 shows the optotype acuity predicted from refractive blur by a dioptric vector addition model (Raasch, 1995), and the squares show a similar, but somewhat smaller effect of induced blur on optotype acuity (data from Bedell, Patel, & Chung, 1999). The circles replot the optotype acuity of our anisometropes (from Fig. 2A). Interestingly, the preponderance of the anisometropes' data fall below both the acuity predicted from refractive error, and that based on induced blur. The red lines fit to the data are the defocus tolerance fits of the form:

$$A = A_0\sqrt{1 + (a/D_T)^2}$$

where A_0 represents the acuity when the anisometropia is equal to 0 diopters; a is the degree of anisometropia, and D_T is the defocus tolerance, i.e., for anisometropes, it is the observer's tolerance to unequal refractive error. This function is actually a form of the more familiar function that has been frequently used to quantify equivalent intrinsic noise (Barlow, 1962; Pelli, 1990), i.e., the amount of noise that must be added to a stimulus to elevate thresholds by $\sqrt{2}$. Levi and Klein (1990) used this parameterization, to quantify the amount of intrinsic blur in amblyopia, i.e., the amount of blur that had to be added to the stimulus to elevate thresholds by $\sqrt{2}$. This is effectively a measure of the amount of blur (or noise) one can tolerate before performance is degraded. Indeed, Chung and Levi (1997) used it to quantify amblyopes' tolerance to image motion. Here, we use it to quantify how much anisometropia is required to degrade performance by $\sqrt{2}$. The astute reader will note that the lines do not "look" like the conventional intrinsic noise function; however, that's because our data are plotted on semilogarithmic (rather than the usual double logarithmic) co-ordinates. Both the predicted acuity and acuity with induced blur show very little tolerance to defocus ($D_T \approx 0.3$–0.4 D). In contrast, vector blur tolerance in anisometropia is approximately 1.9 D for anisomyopia and 1.2 D for anisohyperopia, remarkably similar to the values suggested by Weakley (2001).

The main point of this analysis is to show that the visual performance of anisometropes for acuity is generally better than would be predicted strictly on the basis of retinal blur. This is somewhat surprising, because the monocular acuity of an eye that is optically blurred is worse when the (unblurred) fellow eye is open than when it is occluded, suggesting that the blurred eye is suppressed when both are open (Simpson, 1992). Moreover, anisometropic amblyopia (as indexed by a loss in contrast sensitivity) is uniform across the binocular visual field, but is absent in the monocular temporal field (Hess & Pointer, 1985), suggesting that binocular suppression is involved in anisometropic amblyopia. Perhaps performance in anisometropes is "spared" to some degree either because the anisometropia was less when it mattered in development than at the time of our measurements, or by periods of clear vision (e.g. using the more myopic eye for close viewing), by previous treatment, or by a period of development with no consequential monocular blur (as discussed below).

Stereopsis is also more degraded by monocular blur (or monocular contrast reduction) than by both eyes being blurred (Legge & Gu, 1989; Westheimer & McKee, 1980), so it is noteworthy that many anisometropes retain stereopsis. Holopigian, Blake and Greenwald (1986) found that anisometropic amblyopes have stereopsis at low, but not high spatial frequencies, meaning that their stereoacuity is not as good as normal but is nevertheless functional. Thus, the relationship between stereoacuity and MAR may be "explained" simply by assuming that binocularity is spared at those spatial frequencies that can be seen by both eyes (and where the two eyes have reasonably similar contrast sensitivity). For these anisometropes, stereoacuity would covary in direct proportion with MAR, as the data in Fig. 4 shows. The stereoacuity of anisometropic amblyopes may be as good as the resolution of their weaker eye permits, and this is given credence by the relationship between stereoacuity and MAR of the weak eye (Fig. 4). It also receives support from the finding that improvement in acuity in anisometropic amblyopes following perceptual learning (Levi & Li, 2009) or videogame play (Li, Ngo, Nguyen, & Levi, in press) results in improved stereoacuity.

4.2. What are the neural consequences of monocular blur?

In monkeys, obscured vision during early development leads to a loss of neurons driven by the deprived eye (Hubel, Wiesel & LeVay, 1977), and in humans, unilateral cataracts result in severe amblyopia if not treated in the first six weeks of life (Birch & Stager, 1996). Experimentally induced blur during development leads to a selective loss of neurons tuned to high spatial frequencies (Kiorpes, Carlson, Alfi, & Boothe, 1989; Movshon et al., 1987). Both manipulations lead to losses in behavioral contrast sensitivity (Harwerth et al., 1987; Kiorpes, Boothe et al., 1987; Kiorpes, Carlson et al., 1989). Interestingly, alternating monocular defocus early in life can lead to a specific loss of stereopsis at high spatial frequencies in the absence of monocular changes in contrast sensitivity (Wensveen, Harwerth, & Smith, 2003) with a commensurate loss of sensitivity of V1 neurons to interocular phase disparity at high spatial frequencies (Zhang et al., 2003). If we assume that the visual condition of adults reflects developmental history, our *anisometropes* are likely to have had abnormal experience that resulted in the attenuation of high spatial frequency information in one eye, and therefore a specific deprivation of binocular neurons tuned to high spatial frequencies.

Anisometropes and deprivationals have similar patterns of visual loss (McKee et al., 2003). The average contrast sensitivity and acuity of individuals in these categories was subnormal, presumably because the vision in their non-preferred eyes was compromised during development; however, as noted above, performance is compromised less than predicted directly on the basis of the refractive error (measured at the time of our psychophysical measurements). Without knowing the precise relation-

ship between interocular difference in signal strength and spatial frequency and the monocular deprivation effect, it is not possible to make more quantitative predictions.

4.3. The "natural history" of anisometropic amblyopia development

Several lines of evidence suggest that the period of susceptibility to amblyopia does not begin at birth, and this has raised interesting debates regarding when treatment should begin. For example, in monocularly deprived kittens, Hubel and Wiesel (1970) reported that the period of susceptibility in kittens began abruptly at about 4 weeks of age. In humans, neither congenital cataract, nor congenital esotropia produce a loss of acuity prior to 2 months of age (Taylor, Vaegan, Morris, Rogers, & Warland 1979; Maurer, Lewis, & Tytla, 1983; Mohindra, Jacobson, Thomas, & Held, 1979). It appears that the onset of amblyopia may not begin before the normal development of binocular interaction in striate cortex (Held, 1984). This notion receives further support from the finding that a prior period of prism rearing which severely disrupts binocular neurons, "protects" monkeys from the harmful effects of monocular lid suture (Smith et al., 1992). Moreover, there is frequently a period of uninterrupted continued parallel acuity development in the two eyes, following the onset of experimental strabismus. This can also be seen in the development of resolution in monkeys with experimental strabismus. (Kiorpes et al., 1989), providing some support for the notion that the development of amblyopia involves binocular competition and suppression (von Noorden, 1977).

While the signals from the two eyes are decorrelated in strabismic amblyopia they are positively correlated in anisometropia; however, if the image of one eye is blurred, and thus of lower contrast, its signal will be somewhat weaker. Thus, cortical neurons driven through the defocussed eye would be expected to have lower sensitivity, particularly for high spatial frequencies, since these are affected most by blur (Eggers & Blakemore, 1978; Levi & Klein, 1985; Movshon et al., 1987; Kiorpes, Kiper, O'Keefe, Cavanaugh, & Movshon, 1998; Wilson, 1991). Consider, for example, an anisometrope, whose one eye has a high hyperopic refractive error. The retinal image will be blurred, thus reducing high spatial frequencies in the retinal image. However, since high spatial frequency sensitivity is not present until fairly late in development (e.g. Norcia, Tyler, & Hamer, 1990), this blur will not influence neural processing, until it exceeds the "neural" blurring of the image by the developing visual nervous system. It is only at this stage of development that monocular defocus is likely to result in a binocular neural imbalance. As noted above, refractive blur actually predicts more loss than is manifest by our anisometropes, and we speculate that the neural blur early in development and a late onset of persistent anisometropia (see below) may contribute to sparing visual function in anisometropia.

Meridional amblyopia (associated with high degrees of astigmatism early in life), also does not develop in the first year of life, and perhaps not until age three (Mohindra et al., 1979; Teller, Allen, Regal, & Mayer, 1978). There is presently very little known about the development of anisometropia, and the literature is quite conflicting as to its prevalence (Almeder, Peck, & Howland, 1990; Flom & Bedell, 1985; Howland & Sayles, 1985; Laird, 1990). However, several points are now becoming clear. First, refractive error, and the emmetropization process do not seem to be so tightly linked in the two eyes early in life as previously thought (Abrahamsson, Fabian, Andersson, & Sjostrand, 1990). Consequently, anisometropia present at an early age may not persist (Abrahamsson et al., 1990; Almeder et al., 1990). Secondly, there appears to be a subgroup of young children, whose anisometropia does persist (Abrahamsson et al., 1990), and perhaps it is these children, exposed to continuous unilateral blur, who develop amblyopia. Abrahamsson et al. (1990) found that 14 of 33 patients with anisometropia at age one year, remained anisometropic at age four years, and 25% of these patients developed amblyopia. Those patients whose anisometropia did not persist showed no increased risk of amblyopia. This suggests that the development of anisometropic amblyopia may require a prolonged period of continuous unilateral blur. Our analysis suggests that periods of clear vision may help "protect" anisometropes from the full effect of defocus. It seems important for future studies to try to understand the role of the emmetropization process in anisometropia, and vice versa, since retinal image blur is a critical factor in determining the accuracy of the emmetopization process. Another avenue for future studies is to compare the optical properties of anisometropes and isoametropes in light of a recent case study suggesting that higher order aberrations may be an "amblyogenic" factor in some aniometropic patients (Prakash, Choudhary, Sharma, & Titiyal, 2007).

As shown in the present paper, there are a significant proportion of amblyopes, perhaps as many as 1/3 (Flom & Neumaier, 1966) who present with anisometropia and no strabismus. The vast majority of these maintain some degree of binocularity. These anisometropic amblyopes demonstrate different psychophysical losses than strabismic amblyopes (McKee et al., 2003) and anisometropes lacking in binocularity, and may show different prognosis with treatment (Kivlin & Flynn, 1981). Treating the binocular anisometropes early via optical correction may actually prevent the development of amblyopia. Importantly, perceptual learning and videogame play can also lead to improvements in acuity and stereopsis in adults with longstanding anisometropic amblyopia (Li, Provost, & Levi, 2007; Li et al., in press).

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.visres.2010.09.029.

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