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Hyperacuity deficits in anisometropic and strabismic amblyopes with known ages of onset

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Abstract

In order to evaluate the influence of etiology of amblyopia and of age at onset of amblyopia on the resulting constellation of spatial vision deficits, resolution/vernier and recognition/resolution acuity ratios were measured in groups of children with either strabismic amblyopia or anisometropic amblyopia with known ages of onset. Strabismic amblyopia with infantile onset (<9 months) and strabismic amblyopia with late onset (18–30 months) were both associated with abnormally low resolution/vernier and abnormally high recognition/resolution acuity ratios. Among amblyopes with infantile onset (<9 months), moderate amblyopia was associated with different resolution/vernier and recognition/resolution acuity ratios in anisometropic and strabismic groups. Infantile amblyopes with poor acuity outcomes included children who *initially* presented with anisometropia but later developed strabismus and children who *initially* presented with esotropia but later developed anisometropia; both subgroups with mixed amblyopia had poor resolution/vernier acuity ratios. Data from moderate amblyopes support the hypothesis that anisometropia and strabismus disrupt visual maturation in fundamentally different ways rather than simply at different stages in visual development.

Keywords: Hyperacuity; Amblyopia; Anisometropia; Esotropia

1. Introduction

There are converging lines of evidence that anisometropic and strabismic amblyopia are characterized by distinct constellations of deficits in spatial vision. Hyperacuity deficits of anisometropic amblyopes are comparable to their resolution deficits but strabismic amblyopes show hyperacuity deficits greater than can be predicted by resolution deficits (Levi & Klein, 1982, 1985). The difference in degree of hyperacuity deficit between anisometropic and strabismic amblyopes is not a result of differences between the groups in depth of amblyopia; differences persist even when patients are matched on the basis of resolution acuity, at least within the mild to moderate resolution range (Levi & Klein, 1985). Recognition acuity is also more severely compromised in strabismic than in anisometropic amblyopia when patients are matched on the basis of resolution acuity (Levi & Carkeet, 1993).

There are at least two hypotheses regarding the source of differences in visual performance between anisometropic and strabismic amblyopes. It may be that these differences in visual function reflect fundamentally different pathophysiological processes (etiology hypothesis; Levi, 1990); for example, anisometropic amblyopia may result from form deprivation due to defocus while strabismic amblyopia may result from interocular competition and suppression. A second hypothesis is that the different constellations of spatial deficits in anisometropic and strabismic amblyopia reflect the degree of visual maturation present at the onset of amblyopia (effective age hypothesis; Levi & Carkeet, 1993); that is, anisometropic amblyopia may arise at an age where visual maturation is more com-

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plete. This hypothesis predicts that visual functions which mature earliest will be less susceptible to disruption by abnormal visual experience. Much of the data from adult amblyopes is consistent with both of these ideas. A direct test of these alternative hypotheses has not been possible in studies of adults with amblyopia since complete clinical histories are rarely available to precisely document etiology and the time course over which amblyopia developed. The present study overcomes this limitation by evaluating vernier, resolution, and recognition acuities of amblyopic children who participated in prospective studies of visual acuity development throughout infancy and early childhood, i.e. amblyopes with known age of onset and etiology. If infantile strabismic amblyopia and infantile anisometropic amblyopia show similar patterns of spatial vision deficits while late onset strabismic amblyopia shows a different pattern of deficits, this finding would support the effective age hypothesis. If strabismic amblyopia shows the same pattern of spatial vision deficits regardless of whether onset occurred during infancy or not while anisometropic amblyopia shows a different pattern of deficits, this finding would support the etiology hypothesis. The latter alternative was supported in the present study.

2. Methods

2.1. Participants

Seventy-five children aged 6–9 years participated in the study (53 amblyopic children and 22 controls). The participants who met all inclusion and exclusion criteria for the present study were a small subgroup of a larger ongoing longitudinal study of over 1500 children with congenital or infantile visual disorders who were enrolled at time of their initial diagnosis by a collaborating pediatric ophthalmologist.

Fifteen children had a history of infantile anisometropia of >1.5 D (range 1.5–5.5 D spherical equivalent) and amblyopia with infantile onset (<9 months of age). While it is difficult to pinpoint the onset of anisometropic amblyopia, the age at diagnosis does set an upper limit; the mean age at time of diagnosis was 3.9 months (SD = 2.2 months). None of these children had astigmatism >1.25 D. Ten children in this group maintained orthoposition of the eyes throughout follow-up and had acuity of 20/40 to 20/80 in the amblyopic eye at age 6–9 years. The other five anisometropic children had poor acuity outcomes (20/100 to 20/400) and developed strabismus during follow-up (at 13–34 months).

Twenty-three children had a history of constant esotropia and amblyopia with infantile onset (<9 months). The mean age at time of diagnosis was 3.8 months (SD = 1.2 months). Fourteen children in this group maintained approximately equal refractive errors in the two eyes (within 1 D) and had acuity of 20/40 to 20/80 in the amblyopic eye at age 6–9 years. Nine esotropic children with infantile onset had poor acuity outcomes (20/100 to 20/400) and developed anisometropia of >1.5 D during follow-up (at 15–46 months).

Fifteen children had a history of constant esotropia and amblyopia with late onset (18–36 months). The mean age at time of diagnosis was 21.9 months (SD = 5.7 months). All children in this group maintained approximately equal refractive errors in the two eyes (within 1 D) and had acuity of 20/40 to 20/80 in the amblyopic eye at age 6–9 years.

Twenty-two children age 6–9 years were healthy volunteers with normal eye findings. Data from the right eyes were used to provide normative ranges. None of the patients or volunteer children had congenital malformations or infections, other ocular abnormalities, or neurological dysfunction.

All patients were prescribed treatment according to the American Academy of Ophthalmology standard of care, including surgery for strabismus, optical correction of refractive error with spectacles and/or contact lenses, and occlusion therapy. However, based on their referring ophthalmologists' assessments of fixation preference (failure to maintain fixation with one eye when the other eye is uncovered) and/or acuity, each of the children who participated in this study had a history of amblyopia since the initial office visit and remained amblyopic throughout the longitudinal study.

Informed consent was obtained from one or both parents prior to the child's participation. This research protocol observed the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center.

2.2. Recognition acuity

Snellen acuity at 10 ft. viewing distance was measured with an approximate logMAR-based video acuity display (Mentor BVAT II-BVS) using presentation of a single lines of letters and 0.1 log unit progression: 20/125 (0.8 logMAR), 20/100 (0.7 logMAR), 20/80(0.6 logMAR), 20/60(0.5 logMAR), 20/50(0.4 logMAR), 20/40(0.3 logMAR), 20/30(0.2 logMAR), 20/25(0.1 logMAR), 20/20(0.0 logMAR), 20/15(-0.1 logMAR). This video system allows for randomization of letters presented over multiple trials so that the child cannot memorize the order of letters.

Testing began with the amblyopic eye and the 20/125 size optotype. Each time the child was correct in identifying three letters on a given line, the next smallest line was presented. When the child made three errors on a

line, the next trial presented optotypes 0.1 log unit larger to confirm that the child was able to complete this line and a second trial at the missed line to confirm that the child failed this line by making three or more errors. If confirmation was not obtained, testing continued until these criteria were met. If the child was unable to pass the 20/125 line, the child was moved in to 5 ft. (half the viewing distance) and tested. Recognition acuity was defined by the smallest optotype for which the child could correctly identify three letters on two trials. Snellen acuity in 20 ft. notation was converted to logMAR by the formula:

$$\text{logMAR recognition acuity} = \log_{10}(\text{Snellen denominator}/20)$$

2.3. Resolution acuity

Resolution acuity was determined by extrapolation of the contrast sensitivity function, fit by a two-parameter negative exponential model, $s = c\mathrm{e}^{-av}$, where s is sensitivity, c is a vertical scaling parameter (asymptotic sensitivity parameter), a is a roll-off parameter and v is spatial frequency. This model is based on the finding that log sensitivity at high spatial frequencies declines linearly with linear spatial frequency (Campbell & Green, 1965), to 0.0 log sensitivity and the minimal roll-off of the contrast sensitivity function at low spatial frequencies observed under our test conditions. Contrast sensitivity at 0.38, 1.5 and 6 c/deg was measured using D6 grating patches presented on a Macintosh high resolution color display ($14.6° \times 11°$ at the 1 m viewing distance). Background luminance matched the mean luminance of the grating patches (1.56 log cd/m^2). D6 (6th derivative of a Gaussian) patterns are spatially localized, are in negative cosine phase, have a spatial integral of zero, and have a spatial frequency bandwidth of 1.0 octave (Swanson, Wilson & Giese, 1984). In order to keep the stimulus length equal to a constant number of cycles, D6 patterns were multiplied by vertical Gaussians with space constants 0.8 times the peak frequencies of the D6s, yielding approximately circular stimuli. We chose to use these spatially localized patterns because it maximized the likelihood that the macula mediated measured thresholds, it minimized the confounding effects of probability summation, and it allowed us to measure resolution and vernier acuity with comparable stimuli. Data were gathered using a spatial two-alternative forced-choice staircase protocol with interleaved staircases (Birch, Swanson, Stager, Woody & Everett, 1993; Birch & Stager, 1996). On each trial, the child moved a joystick to indicate whether the grating patch appeared to the left or to the right of the center of the display. Task comprehension was verified by a series of practice trials prior to the test. A fourth data point for each contrast sensitivity function was obtained by setting contrast to 0.50 and varying spatial frequency. All thresholds were determined by performing maximum likelihood estimation on the staircase data sets using a three-parameter model of the psychometric function (Swanson & Birch, 1992). Resolution acuity in D6 peak frequency c/deg was converted to logMAR by the formula:

$$\text{logMAR resolution acuity} = \log_{10}(30/\text{cycles per deg})$$

2.4. Vernier acuity

Vernier acuity was measured at high contrast ($>$ 0.98) using 1.5 c/deg D6 grating patches in which a central 0.4° strip of the patch was offset. Vernier stimuli were presented on the same display system used for resolution acuity. A spatial two-alternative forced-choice interleaved staircase protocol was used (Birch & Stager, 1996). Briefly, the child moved a joystick to indicate whether the offset in the D6 grating patch was to the left or to the right. Task comprehension and visibility of the grating patch was verified by a series of practice trials prior to the test. All thresholds were determined by performing maximum likelihood estimation on the staircase data sets using a three-parameter model of the psychometric function (Birch & Swanson, 1992). Some children were unable to respond consistently even to the largest offset; in these cases they were assigned a vernier threshold one octave larger than the the largest offset available. Vernier acuity (s) was converted to logMAR by the formula:

$$\text{logMAR vernier acuity} = \log_{10}(\text{s}/60)$$

3. Results

3.1. Vernier acuity

The mean ($\pm$ SD) vernier acuity of the age-matched normal sample was -0.22 ± 0.45 logMAR (36.2 s) and of the nonamblyopic eyes of the patient group as a whole was -0.074 ± 0.36 logMAR (50.6 s). The vernier acuity of non-amblyopic eyes was not significantly different from normal ($t = 1.46$, $P > 0.14$). The mean vernier acuity of the amblyopic eyes of the patient group as a whole was 0.41 ± 0.70 logMAR (154.2 s), significantly poorer than that of the normative cohort ($t_{73} = 3.85$, $P < 0.001$) and of the nonamblyopic eyes ($t_{52} = 4.50$, $P < 0.001$).

3.2. Resolution/vernier acuity ratio

The mean resolution/vernier acuity ratio for the age-matched normal sample was 8.0($\pm$ 1.2):1. Resolution and vernier acuities for the individual patients are shown in Fig. 1. Children with anisometropic ambly-

opia are shown in panel A. Those with moderate acuity outcomes in the amblyopic eye (20/40 to 20/80) show similar deficits in both resolution acuity and vernier acuity so that the normal resolution/vernier acuity ratio of 8:1 is approximately maintained. Children with strabismic amblyopia are shown in panel B. Both infantile onset and late onset strabismic amblyopes tended to show greater deficits in vernier acuity than in resolution acuity regardless of acuity outcome; most strabismic children had resolution/vernier acuity ratios that were much lower than normal. Children with poor acuity outcomes in the amblyopic eye ($<20/100$) had both anisometropia and strabismus and showed substantially larger deficits in vernier acuity than in resolution acuity.

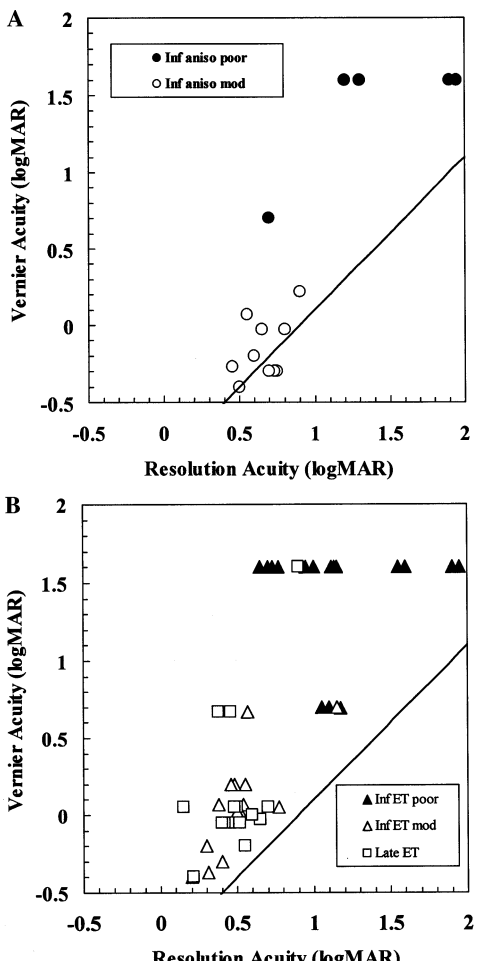

Fig. 1. Resolution and vernier acuities for children with anisometropic amblyopia (panel A) and moderate acuity outcomes (20/40 to 20/80; ○) and poor acuity outcomes (20/100 to 20/400; ●) or strabismic amblyopia (panel B) and moderate acuity outcomes (20/40 to 20/80; with infantile onset – △, with late onset – □) and poor acuity outcomes (20/100 to 20/400; ▲). The solid line shows the predicted relationship if comparable deficits are present for both vernier and resolution acuity so that the normal resolution/vernier acuity ratio of 8:1 is maintained. Note that vernier acuities plotted at 1.58 logMAR are default values assigned when the child was unable to discriminate even the largest vernier offset available (1.28 logMAR; 1150 s).

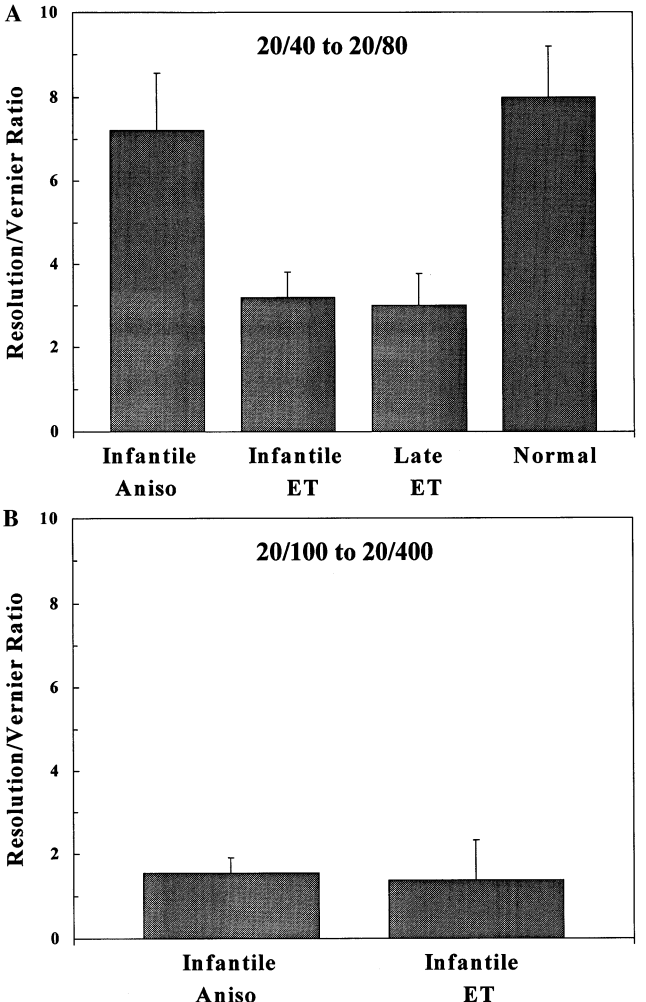

Fig. 2. Resolution/vernier acuity threshold ratios of anisometropic and strabismic amblyopes with infantile (<9 months) or late (18–30 months) age of onset and moderate acuity outcomes (20/40 to 20/80; panel A) or poor acuity outcomes (20/100 to 20/400; panel B). The normal range is shown as a shaded area. Vertical lines indicate 1 SEM.

As a result, their resolution/vernier acuity ratios were much lower than normal.

Mean resolution/vernier acuity ratios for each patient group are summarized in Fig. 2. Children with moderate acuity outcomes in the amblyopic eye (20/40 to 20/80) are shown in panel A. Regardless of age of onset, children with strabismic amblyopia had resolution/vernier acuity ratios which were significantly below normal (mean $\pm$ SD $= 3.1 \pm 1.3$ infantile esotropia; 3.0 ± 1.7 late onset esotropia; 8.0 ± 1.2 normal; infantile esotropia versus normal: $t_{34} = 1.94$, $P < 0.03$; late onset esotropia versus normal: $t_{35} = 2.05$, $P < 0.02$). Anisometropic amblyopes with moderate acuity outcomes had normal recognition/vernier acuity ratios (mean $= 7.2 \pm 3.0$; $t_{30} = 0.26$, $P > 0.35$). Children with poor acuity outcomes (20/100 to 20/400) had both strabismus and anisometropia. Mean resolution/vernier acuity ratios for each patient group are shown in panel

B of Fig. 2. In conjunction with poor acuity outcomes, both the children who *initially* presented with anisometropic amblyopia and the children who *initially* presented with strabismic amblyopia had resolution/vernier acuity ratios which were significantly below normal (mean $\pm$ SD = 1.5 ± 1.0; $t_{34} = 2.62$, $P < 0.007$).

3.3. Recognition/resolution acuity ratio

The mean recognition/resolution acuity ratio (MAR ratio) for each patient group and for normals is shown in Fig. 3. Children with moderate acuity outcomes in the amblyopic eye (20/40 to 20/80) are shown in panel A. Regardless of age of onset, strabismic amblyopes had recognition/resolution acuity ratios which were significantly above normal (mean $\pm$ SD = 1.4 ± 0.4 infantile esotropia; 1.4 ± 0.6 late onset esotropia; 1.1 ± 0.2 normal; infantile esotropia versus normal: $t_{34} = 2.57$, $P < 0.007$; late onset esotropia versus normal: $t_{35} = 2.25$, $P < 0.02$). Anisometropic amblyopes with moderate acuity outcomes in the amblyopic eye had normal recognition/resolution acuity ratios (mean = 1.1 ± 0.4; $t_{30} = 0.62$, $P > 0.25$).

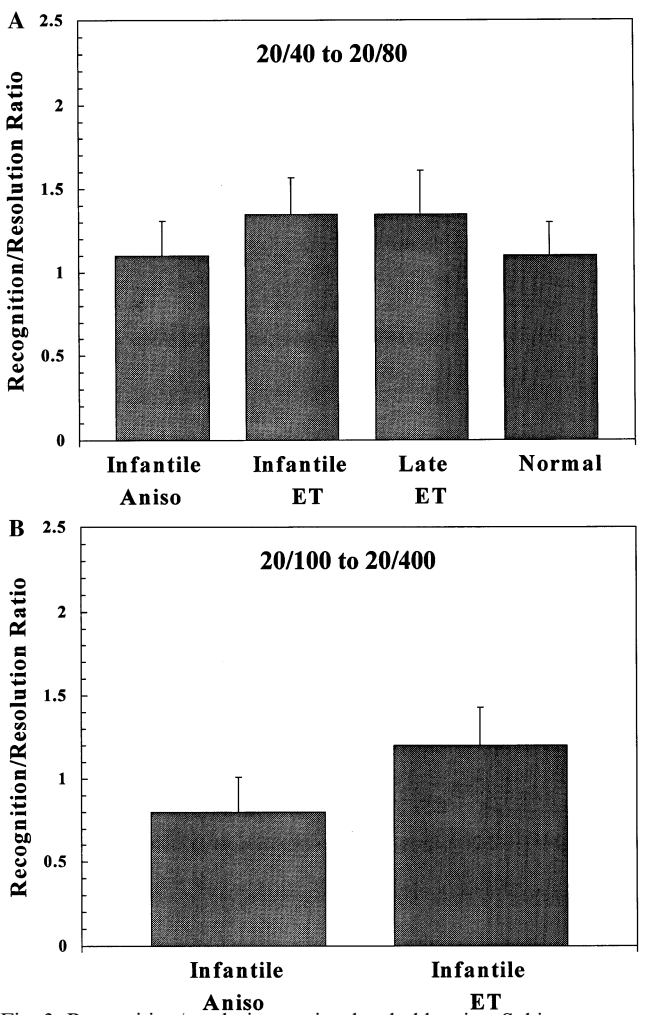

Fig. 3. Recognition/resolution acuity threshold ratios. Subject groups and graphing conventions are as per Fig. 1.

Mean recognition/resolution acuity ratios for children with poor acuity outcomes in the amblyopic eye (20/100 to 20/400) and for normals are shown in panel B of Fig. 3. In conjunction with poor acuity outcomes, the children who *initially* presented with anisometropic amblyopia and the children who *initially* presented with strabismic amblyopia had recognition/resolution acuity ratios which were not significantly different from normal (mean $\pm$ SD = 1.0 ± 1.0; $t_{34} = 0.01$, $P > 0.45$).

4. Conclusions

Strabismic amblyopia with infantile onset (< 9 months) and strabismic amblyopia with late onset (18–30 months) were both associated with abnormally low resolution/vernier and abnormally high recognition/resolution acuity ratios, i.e. age at onset of amblyopia alone does not determine the severity of hyperacuity and recognition acuity deficits. Among amblyopes with infantile onset (< 9 months), moderate amblyopia was associated with different resolution/vernier and recognition/resolution acuity ratios in anisometropic and strabismic groups, i.e. etiology of amblyopia played a major role in determining the severity of hyperacuity and recognition acuity deficits.

According to the effective age hypothesis proposed by Levi and Carkeet (1993), the resolution/vernier ratio of 2.5:1 observed in infantile strabismic amblyopia in the present study represents an effective age of about 0.5–1 year. This is consistent with the clinical findings of strong fixation preferences in these children during the first year of life, continued fixation preference during years 2–5, and amblyopia documented by recognition acuity tests beginning at 3 years of age. On the other hand, approximately the same resolution/vernier ratio was observed in late onset strabismic amblyopia; clearly, onset of amblyopia at 1.5–3.0 years is inconsistent with an effective age of 0.5–1 year. Finally, the ratio of 7:1 observed in infantile anisometropic amblyopia in the present study represents an effective age of about 5–7 years. This is inconsistent with the clinical findings of strong fixation preferences in these children during the first year of life, continued fixation preference during years 2–5, and amblyopia documented by recognition acuity tests beginning at 3 years of age. Taken together, these data suggest that the etiology of amblyopia is a more significant factor in determining the pattern of spatial vision deficits than the age at onset of amblyopia.

Two possible alternative interpretations of the data need to be considered. First, treatment was attempted for all of these amblyopic children, although it was judged unsuccessful since amblyopia persisted through-

out longitudinal follow-up. Nonetheless, it is possible that the attempted course of treatment did have some effect on visual development and that the effectiveness of treatment was, for whatever reason, different for anisometropic versus esotropic children. The difference was not apparent in recognition acuities, which were not significantly different for the two groups (mean $\pm$ SD logMAR $= 0.38 \pm 0.15$ for infantile anisometropic amblyopia and 0.32 ± 0.13 for infantile esotropic amblyopia). Even so, it is possible that the attempted course of treatment led to better vernier acuities in children with anisometropic amblyopia without affecting recognition acuity. Second, it is possible that, although both cases of esotropia and anisometropia with infantile onset were examined, anisometropia does not exert its amblyogenic effect until later in life when the optical and neural transfer functions are more mature. Note that this represents a hybrid etiology-effective age hypothesis. This hypothesis that anisometropic has no amblyogenic effects during infancy cannot be correct because all of the anisometropic infants enrolled in this study had clear clinical findings of amblyopia present during infancy. However, it is possible that, while fixation preference and acuity are affected by anisometropia during infancy, vernier acuity is not susceptible to the effects of anisometropia until the visual system is more mature.

Within the subgroups of infantile amblyopes with poor acuity outcomes, both resolution and recognition acuities were depressed by approximately 1.0 log unit relative to mean normal; vernier acuity showed even greater loss, averaging 1.6 log unit deficit relative to mean normal. Both children who *initially* presented with anisometropia and those who *initially* presented with esotropia had poor resolution/vernier acuity ratios. However, by an average age of 22 months, all of the children in these subgroups had both strabismus and anisometropia. Thus, the abnormal acuity ratios may have resulted from either or both of the amblyogenic factors.

Overall, the acuity ratios in the present study are similar to those in the literature; both the approximate 7:1 resolution/vernier acuity ratio in normals and anisometropic amblyopes and the 2.5:1 resolution/vernier acuity ratio in strabismic amblyopes are common findings (Levi & Klein, 1982, 1985; Levi & Carkeet, 1993). Abnormal recognition/resolution acuity ratios and 'crowding effects' have also been reported in association with strabismic amblyopia in adults (Levi & Klein, 1985; Levi, 1990; Levi & Carkeet, 1993). However, the resolution/vernier acuity ratio outcomes from children with infantile anisometropic amblyopia do differ from the ratios observed in a primate models of amblyopia (Kiorpes, Kiper & Movshon, 1993). Monkeys reared with experimental strabismus or monocular -10 D extended-wear soft contact lenses to simulate infantile anisometropia developed amblyopia and had abnormal resolution/vernier ratios regardless of etiology. However, two of the seven strabismic monkeys developed anisometropia and one of the five anisometropic monkeys developed a large angle strabismus. Whether other anisometropic monkeys developed microstrabismus was not determined. Therefore, the resolution/vernier acuity ratios in at least some of these amblyopic monkeys may be more comparable to those of our poor acuity outcome groups in which children developed secondary anisometropia or strabismus. In addition, it is possible that amblyopia associated with large degrees of anisometropia (10 D) may be different from amblyopia associated with the smaller degrees of anisometropia seen in the participants of this study (1.5–5.5 D).

Overall, the data from moderate amblyopes, which are uncomplicated by the development of secondary anisometropia or strabismus, are not consistent with the effective age hypothesis. It is more likely that anisometropia and strabismus disrupt visual maturation in fundamentally different ways rather than simply at different stages in visual development.

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