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Visual Functions and Interocular Interactions in Anisometropic Children with and without Amblyopia

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Purpose. In uncorrected anisometropia, protracted dichoptic stimulation may result in interocular inhibition, which may be a contributing factor in amblyopia development. This study investigates the relationship between interocular interactions and anisometropic amblyopia.

Methods. Three visual functions (low-contrast acuity, contrast sensitivity, and alignment sensitivity) were measured in the nondominant eye of 44 children aged 5 to 11 years: 10 with normal vision, 17 with anisometropia without amblyopia, and 17 with anisometropic amblyopia. The dominant eye was either fully or partially occluded. The difference in nondominant eye visual function between the full-and partial-occlusion conditions was termed the interaction index. The index of each visual function was compared between subject groups. A higher index indicates stronger inhibition of nondominant eye function with partial occlusion of the dominant eye. Amblyopic children had 6 months of therapy (refractive correction and occlusion), and the reduction in interocular difference in high-contrast acuity was regarded as the treatment outcome. The relationships of the interaction index with the degree of anisometropia, the severity of amblyopia, and the treatment outcomes were examined.

Results. The acuity interaction index was significantly higher in anisometropic children with amblyopia than in those without ($P = 0.003$). It was positively correlated with the degree of anisometropia ($r_s = 0.35$, $P = 0.042$) and the amblyopic treatment outcomes ($r_s = 0.54$, $P = 0.038$). No such difference or association was found between the contrast sensitivity or alignment sensitivity interaction index and anisometropic amblyopia.

Conclusions. Interocular interactions are associated with amblyopia, the degree of anisometropia, and amblyopia treatment outcomes, but these associations are visual function dependent. (*Invest Ophthalmol Vis Sci.* 2011;52:6849–6859) DOI:10.1167/iovs.10-6755

In the visual system, monocular signals interact in several ways during the processing that underpins sensory fusion. Interocular interaction of this kind can be classified broadly into two categories: excitatory and inhibitory. Studies have demonstrated that visual performance with two eyes exceeds that of the better eye when identical images are presented to each eye.[1,2] This phenomenon is termed binocular summation,[3] which is an example of an excitatory interaction. However, such apparent summation is not always obtained, particularly if the stimulation of each eye occurs at different times or differs in spatial detail.[4] When stimuli presented to each eye differ in luminance, chromatic, and/or spatial properties, perception may alternate between the two eyes (exclusive dominance), or may be a "patchwork" continuously changing over time (mosaic dominance), a phenomenon known as binocular rivalry,[5] and an example of inhibitory interaction. Independent stimulation of each eye is known as dichoptic stimulation (or dichoptic masking), and the resulting effects are underpinned by interocular interactions. Studies using dichoptic stimulation have shown that visual functions of one eye can be improved (e.g., summation) or reduced (e.g., rivalry) with a masking stimulus presented to the fellow eye.[6–10]

Uncorrected anisometropia causes blurred visual input to one eye in particular. During visual development, this may result in amblyopia, which occurs in approximately 3% of the adult population,[11] with deficits in a range of visual functions including optotype acuity, contrast sensitivity, vernier acuity, and binocularity.[12–15] In some types of anisometropia, such as spherical myopic anisometropia, monovision can be achieved, with the less ametropic eye used for distant vision, whereas the more ametropic eye is used for near vision. In these observers, neither eye is relatively disadvantaged (unless the more ametropic eye has extremely high refractive error), and amblyopia is unlikely to develop. It is possible, however, that binocularity is abnormal, and there may be a lack of interocular interaction, because the monocular images differ. In uncorrected hyperopic anisometropia, the less ametropic eye may be able to achieve a clear retinal image in distant vision, but the more ametropic eye receives relatively blurred input and may never have a sharp image focused on its retina. This is a form of dichoptic stimulation and may lead to inhibition of the more ametropic eye by the fellow eye and the development of amblyopia.

The severity of amblyopia correlates positively with the degree of anisometropia,[16] but exceptions have been reported.[17] Thus, there may be other factors that influence the development of anisometropic amblyopia, and these factors may be key to understanding this development. In normal visual systems, interocular interactions may differ with different amounts of monocular defocus. Binocular summation may occur with a fogging lens of equal to or less than +1.50 DS in front of one eye, but inhibition may occur at higher powers.[18,19] It is possible that these types of interaction also occur in uncorrected anisometropia, but whether there is a relationship between them and anisometropic amblyopia is unknown. Previous studies have found that interocular interactions differ between amblyopic and normal observers. However, high interindividual variation has been reported in these interactions in animals and humans with amblyopia.[8–9,20]

Thus, previous work has enhanced understanding of the way in which stimulation (or occlusion) of one eye may affect

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vision in the fellow eye in the normal visual system, and it has been established that interocular interactions are abnormal in amblyopia. The present study was conducted to improve understanding of the role (if any) of interactions in the development of anisometropic amblyopia, by examining (1) whether these interactions differ in children with normal vision and anisometropic children with or without amblyopia; (2) the relationship between these interactions, the degree of anisometropia, and the severity of amblyopia; and (3) the relationship between these interactions and the response to amblyopia therapy.

METHODS

Subjects

Subjects were aged 5 to 11 years, including 10 children with normal vision (mean age, 9.2 ± 1.5 [SD] years; 7 boys, 3 girls), 17 with anisometropia without amblyopia (mean age, 8.8 ± 0.9 years; 7 boys, 10 girls), and 17 with anisometropic amblyopia (mean age, 8.8 ± 1.2 years; 10 boys, 7 girls). All subjects were recruited through a school-based screening program in Huadu, China. Approval was obtained from the Human Research Ethics Committee of the University of New South Wales and the ethics committee of the Zhongshan Ophthalmic Centre. Written, informed consent was obtained from parents of all subjects after explanation of the nature of the study. Assent was obtained from each child. The study complied with the Declaration of Helsinki. Table 1 shows the clinical characteristics of the anisometropic children, with and without amblyopia.

One week before the visual function testing, a series of eye examinations were conducted during vision screening, including a clinical acuity test for distance (arithmetic scaled high-contrast E chart; the only type of chart available to us at the clinic), cover test for distance and near (with refractive correction, if needed), eccentric fixation test (direct ophthalmoscope), fundus examination, binocularity (Worth four-dot test at 6 m), stereopsis (Randot circles stereoacuity test at 40 cm), and a hole-in-the-hand ocular dominance test.[21] No ocular deviation or eccentric fixation was found in any of the subjects. Cycloplegic refraction (1% cyclopentolate) was performed on all anisometropic children with and without amblyopia. Correction was prescribed by one of the present authors (XJL) and applied throughout. Based on results from cycloplegic refraction, myopia, astigmatism, and anisometropia were fully corrected, and hyperopia was either fully corrected or symmetrically undercorrected by no more than 1.50 DS.

Subjects were included only if they had no history of ocular trauma and/or ocular pathology, no systemic disease (by self-report), no strabismus (based on cover test), no previous or current treatments of anisometropia and/or amblyopia (refractive correction or occlusion), and no eccentric fixation and met the following criteria:

Children with normal vision

Uncorrected acuity of 0.0 logMAR or better in each eye, with an interocular difference of less than 0.1 logMAR;

Spherical and cylindrical refractive error of 0.50 D or less for distance;

Stereopsis of equal to or better than 40 arc seconds (arcsec).

Anisometropic children

Best corrected acuity: a) for children without amblyopia, 0.3 logMAR or better in each eye, with an interocular difference of less than 0.1 logMAR; b) for children with amblyopia, 0.3 logMAR or worse in one eye and 0.3 logMAR or better in the other eye, with an interocular difference of 0.1 logMAR or more.

Refractive error: interocular difference in spherical refractive error of 0.75 DS or more for hyperopic children and 1.25 DS or more for myopic children; cylindrical refractive error of 1.00 DC or more for children with astigmatism (refractive errors were defined using negative cylinder).[16] Based on the refractive error, anisometropic children with and without amblyopia were combined and classified into four subgroups: spherical hyperopes, spherical myopes, cylindrical hyperopes, and cylindrical myopes (Table 1). Note that subjects with hyperopia in one eye and myopia in the fellow eye were classified on the basis of the higher absolute spherical refractive error. Subjects with hyperopia equal to or higher than the absolute cylindrical refractive error in their more ametropic eye were classified as cylindrical hyperopes; other subjects with astigmatism were classified as cylindrical myopes. Subjects with both spherical and cylindrical refractive errors were assigned to both subgroups.

Apparatus

Visual stimuli were generated with a graphics card (VSG 2/5; Cambridge Research Systems, Cambridge, UK) externally connected to a laptop (HP 8530P; Hewlett Packard, Palo Alto, CA) and were displayed on a gamma-corrected 21-in. cathode ray tube monitor (Trinitron GDM-F520; Sony, Tokyo, Japan). The refresh rate was 120 Hz. The stimuli were viewed through Ferro-electric shutter goggles (FE-1; Cambridge Research Systems). The goggles were worn using an elasticized strap and were held in place by an assistant to reduce their weight and to minimize discomfort. For anisometropic children with and without amblyopia, refractive error was always corrected using trial lenses. Three visual functions were measured: (1) low-contrast acuity (20% Weber contrast when viewing through the goggles); (2) contrast sensitivity; and (3) alignment sensitivity. The mean room illuminance was 4.78 ± 2.76 lux (Konica T-10 illuminance meter; Minolta, Tokyo, Japan).

Each visual function was measured in the full- and partial-occlusion conditions. In the full-occlusion (monocular) condition, an opaque eye patch was used to cover the nontested eye. In the partial-occlusion condition, a square central patch (78% Weber contrast) was used as a partial occluder (see below) presented at the center of the monitor and visible to the nontested eye only. The goggles were worn in both viewing conditions and were synchronized with the monitor so that alternate frames were presented to each eye (e.g., odd-numbered frames to right eye, even-numbered frames to left eye). Thus, each eye viewed the stimuli (or occlusion) at a refresh rate of 60 Hz. The background luminance of the monitor was fixed at 170 cd/m^2, and this level was reduced to approximately 21 cd/m^2 at each eye when viewing through the goggles.

Stimuli and Experimental Tasks

Acuity was measured using a single letter E constructed in a 5 × 5 grid, in which each stroke and gap was one fifth of the dimension of the square grid. The letter was presented to the tested eye only at one of four possible orientations on each trial (right, left, up, or down). The square partial occlusion was presented to the nontested eye in the partial occlusion condition only. A fusion lock (a ring target at 78% Weber contrast) with a width of 0.1° was constantly presented to both eyes to ensure that both eyes were in alignment in the partial-occlusion condition. In the full-occlusion condition, the fusion lock was visible by the tested eye only, because the fellow eye was occluded. Suppression markers were four lines, with two lines presented to each eye at a peripheral location (Table 2). They were used in the partial-occlusion condition only, to check for suppression of either eye.

Contrast sensitivity was measured with a modified temporal two-alternative, forced-choice method with a Gabor stimulus (vertical, at 6 cyc/deg). The circular Gabor patch subtended 3.5°, with the SD of the Gaussian envelope 0.65°. Alignment sensitivity was measured using three Gabor patches at 65% Michelson contrast (vertical, at 6 cyc/deg). The upper and lower Gabor patches were in vertical alignment. The central Gabor patch was displaced either to the left or right relative to this alignment on each trial. The square partial occlusion, the fusion lock, and the suppression markers were applied only in the partial-occlusion condition for the acuity, contrast, and alignment sensitivity

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TABLE 1. Clinical Characteristics of Anisometropic Children with and without Amblyopia

A. Anisometropic Children without Amblyopia

Subject	Sex	Age (y)	Prescription		BCVA (logMAR)		IDVA (logMAR)	Subject Subgroups	Stereoacuity (arcsec)
			Right Eye	Left Eye	DE	NDE			
1	M	7.1	−1.75	−1.75/−1.00 × 85	0	0	0	Cylindrical myope	40
2	F	7.2	0/−3.25 × 175	0/−2.25 × 5	0	0	0	Cylindrical myope	70
3	M	7.6	plano	+0.50/−3.50 × 155	0	0	0	Cylindrical myope	70
4	F	8.2	−1.00/−1.00 × 30	−3.75/−3.00 × 170	−0.2	−0.2	0	Spherical myope, cylindrical myope	30
5	F	8.3	−2.50	−2.75/−1.25 × 165	−0.1	−0.1	0	Cylindrical myope	40
6	M	8.4	+1.25/−1.25 × 175	+1.75/−4.00 × 175	0	0	0	Cylindrical myope	30
7	M	8.6	0/−0.50 × 170	−1.50	−0.1	−0.1	0	Spherical myope	40
8	F	8.8	−4.75/−0.50 × 180	−3.25/−0.50 × 170	0	0	0	Spherical myope	30
9	F	8.9	−0.25	−1.50	0	0	0	Spherical myope	30
10	M	9.0	−6.50	−4.75/−0.50 × 30	0	0	0	Spherical myope	30
11	F	9.3	−5.00/−1.50 × 35	−6.25/−2.00 × 150	0	0	0	Spherical myope	40
12	F	9.3	+1.00/−1.00 × 165	+2.00/−2.25 × 175	−0.2	−0.2	0	Cylindrical myope	140
13	M	9.5	−6.50/−1.00 × 95	−8.25/−4.00 × 150	0	0	0	Spherical myope, cylindrical myope	140
14	F	9.5	−2.25	−2.00/−1.00 × 115	0	0	0	Cylindrical myope	40
15	F	9.6	−12.50	−10.50	0	0	0	Spherical myope	30
16	F	9.8	+3.00/−0.75 × 180	−1.00/−0.50 × 175	0	0	0	Spherical hyperope	140
17	M	9.8	−3.75	−2.25/−0.75 × 160	0	0	0	Spherical myope	30

B. Anisometropic Amblyopic Children

Subject	Sex	Age (y)	Prescription		Before Therapy			After Therapy			Subject Subgroups	Stereoacuity (arcsec)
					BCVA (logMAR)		IDVA (logMAR)	BCVA (logMAR)		IDVA (logMAR)		
			Right Eye	Left Eye	DE	NDE		DE	NDE			
1	M	6.4	plano	+3.00	−0.2	0.1	0.3	−0.2	0.05	0.25	Spherical hyperope	50
2	M	6.5	+0.25	+6.50/−2.00 × 180	−0.1	0.5	0.6	−0.1	0.5	0.6	Spherical hyperope, cylindrical hyperope	400
3	M	7.4	+6.25	+7.00	0.1	0.3	0.2	0.1	0.3	0.2	Spherical hyperope	400
4	F	8.3	0/−1.75 × 95	−1.00	0	0.1	0.1	0	0.1	0.1	Cylindrical myope	30
5	F	8.4	+2.25/−0.50 × 170	+0.50/−1.00 × 10	−0.2	0.2	0.4	−0.2	0	0.2	Spherical hyperope	70
6	M	8.4	−4.00/−2.25 × 50	−2.50/−0.50 × 170	0	0.15	0.15	0	0.15	0.15	Spherical myope, cylindrical myope	50
7	F	8.5	+0.75/−0.50 × 130	+3.75	0	0.5	0.5	—	—	—	Spherical hyperope	100
8	F	8.6	+4.25/−0.50 × 155	+0.25/−0.50 × 15	−0.1	0.3	0.4	−0.1	0.3	0.4	Spherical hyperope	70
9	F	9.1	+4.50/−1.00 × 160	plano	−0.1	0.2	0.3	−0.1	0.2	0.3	Spherical hyperope, cylindrical hyperope	50
10	M	9.2	+0.50	+7.00/−2.00 × 45	−0.2	0.2	0.4	−0.2	0.2	0.4	Spherical hyperope, cylindrical hyperope	400
11	F	9.3	−4.50/−1.50 × 10	−1.25	−0.2	0.4	0.6	−0.2	0.4	0.6	Spherical myope, cylindrical myope	50
12	M	9.5	−3.25/−0.75 × 170	plano	0	0.15	0.15	0	0.15	0.15	Spherical myope	30
13	M	9.8	−6.00/−1.75 × 40	−4.25/−1.00 × 130	0	0.1	0.1	0	0.05	0.05	Spherical myope	40
14	M	9.8	plano	+6.00/−0.75 × 50	0	0.4	0.4	0	0.2	0.2	Spherical hyperope	400
15	M	10.1	+2.50/−2.50 × 180	+4.50/−2.50 × 180	0	1.0	1.0	0	1.0	1.0	Spherical hyperope	400
16	M	10.3	+1.25/−0.75 × 15	+3.50/−1.25 × 180	−0.2	0.2	0.4	—	—	—	Spherical hyperope	400
17	F	10.4	plano	+5.00/−0.50 × 175	−0.1	0.5	0.6	−0.1	0.7	0.8	Spherical hyperope	400

No monocular suppression or diplopia was reported in any of these subjects (Worth four-dot test). BCVA, best corrected acuity measured at the screening program and after amblyopia therapy (using a high-contrast E chart); IDVA, interocular difference in high contrast acuity; DE, dominant eye; NDE, nondominant eye; M, Male; F, Female; -, subjects had poor compliance with amblyopia therapy.

Table 2. Stimulus Parameters and Staircase Procedures Used in the Main Experiment

Test	Stimulus Parameters (deg)				Staircase Procedures				
	Partial Occlusion Size	Fusion Lock Size	Suppression Markers		Determination of Individual Start Levels		Determination of Thresholds		Step Size
			Location	Size	Staircase Rules	Termination Rules	Staircase Rules	Termination Rules	
Acuity test	2.3	4	6	0.3	1/1 Single staircase	4 Reversals	2/1 Double staircase	10 Reversals	0.08 logMAR
Contrast sensitivity test	3.5	8	10	2.5	1/1 Single staircase	4 Reversals	2/1 Double staircase	8 Reversals	3.5 dB
Alignment sensitivity test	9.5	15	19.5	1	1/1 Double staircase	4 Reversals	1/1 Double staircase	8 Reversals	1.5 arcmin

tests (see Table 2 for parameters in each visual function test). Figure 1 shows target and partial-occlusion stimuli for each visual function test.

The central target and the partial occlusion used in this study are a form of dichoptic stimulation, since different stimuli are presented to each eye. In the partial-occlusion condition, the square patch occluded the central visual field, but was not a conventional occluder. It is referred to as partial occlusion because only the central field is occluded and to distinguish from full occlusion with an opaque eye patch.

Since all subjects were naïve, a training session was conducted on each subject before the main experiments. The stimulus duration was 400 ms during training and was reduced to 140 ms for the main experiments to minimize the effects of eye movements.[22] However, the subjects were allowed to take their time to give responses after each trial. The experimental tasks were identical in the training and the main experiments. These tasks were (1) acuity: indicate by pointing the orientation of the E target; (2) contrast sensitivity: verbally report whether the Gabor patch was presented in interval one or two; and (3) alignment sensitivity: point to the offset direction (left or right) of the central Gabor patch. All responses were input to the program by the examiner (XJL). No feedback was given.

The viewing distance was 4, 2, and 1 m for acuity, contrast sensitivity, and alignment sensitivity tests, respectively. To maintain viewing distance, subjects were carefully monitored by observation, and a backrest was used. Subjects were instructed to hold their viewing distance during experiments and were reminded every time their position was observed to have changed.

Procedures

In the training session, the dominant eye of each subject was tested in all three visual functions in the partial-occlusion condition only. A two-down, one-up (2/1) single-staircase method was used in the acuity and contrast sensitivity tests, and a 1/1 double-staircase method was used in the alignment sensitivity test. Starting levels were based on previous findings,[8,9] to ensure that subjects could easily detect the stimuli, and the step sizes were sufficiently small to ensure that the stimuli were always suprathreshold during training. Square partial occlusion used for training subtended 3°, 5°, and 7° in the acuity, contrast sensitivity, and alignment sensitivity tests, respectively. Subjects who could give 10 consecutively correct answers were regarded as having passed the training.

The main experiments were conducted within 3 days of the training. Note that none of the subjects had undergone any treatment for anisometropia or amblyopia before these experiments. Each visual function was tested in the two viewing conditions in the nondominant eye only. This is because in pilot work, interocular interactions were slightly (though not significantly) stronger when the nondominant eye was tested, compared with when the dominant eye was tested. All tests were conducted in a pseudorandom order. For each subject, start levels were determined, and after a short rest, thresholds were measured (Table 2).

An unforced-choice method[23] (allowing "don't know" answers) was used in acuity and contrast sensitivity tests, since experimental duration was up to 8 minutes. This method enhanced subjects' cooperation and increased the likelihood of test completion.[23,24] Although subjects were not forced to give a response to each trial, they tended to give as many answers as they could, with an average of only one "don't know " answer given by each child during each test. An incorrect response was recorded for the "don't know " answers. A forced-choice method[25] was used in the alignment sensitivity test to reduce the variability of the subjects' judgment of alignment.

A gamelike atmosphere[26] was used. At the beginning of the experiments, the child was asked to add his or her name to a list of "challengers" posted on a wall and was told that he or she was going to play three games (three visual function tests) that day. Each game included two stages (two viewing conditions) and he or she was allowed to paste a little red flag after his or her name when he or she passed a stage of a game. The child who had more flags after his or her name at the end of each day would be the "champion of red flags. " Subjects were always tested in groups of two

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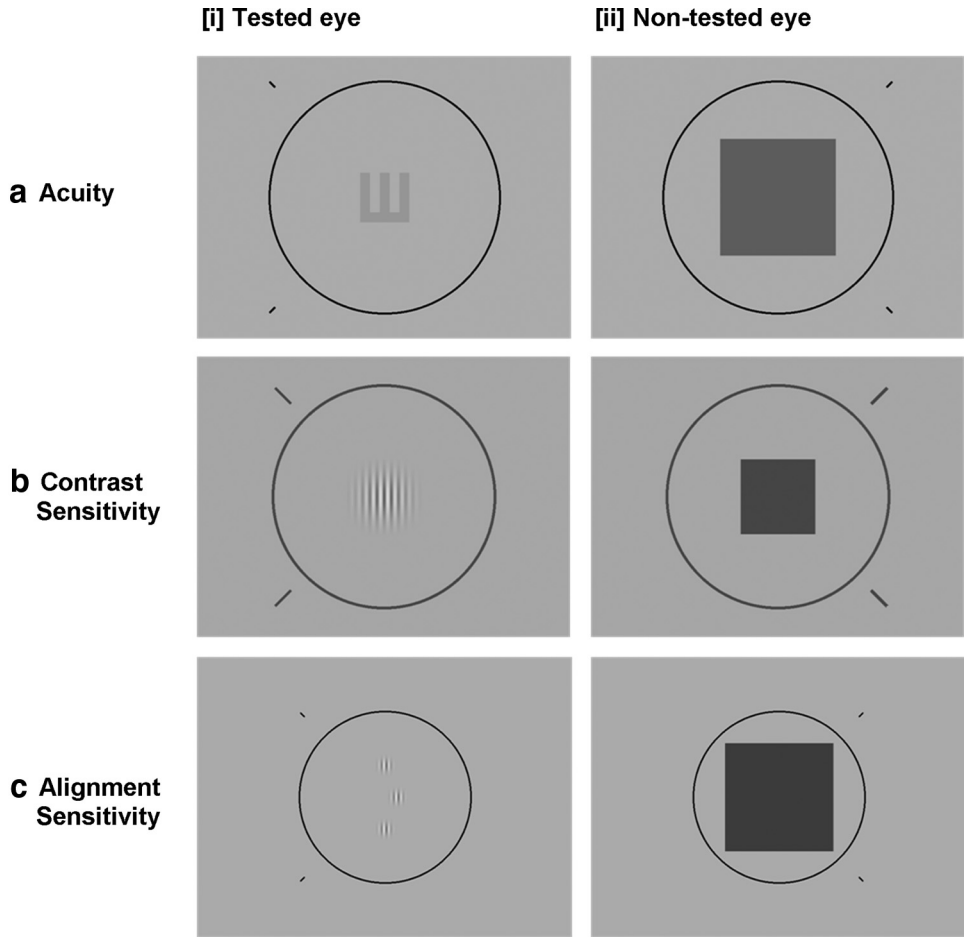

FIGURE 1. Examples of stimuli presented to the tested eye (i) and square partial occlusion presented to the nontested eye (ii) in the partial-occlusion condition for measurements of acuity (**a**), contrast sensitivity (central target at 4 cyc/deg is presented, actual target is at 6 cyc/deg) (**b**) and alignment sensitivity (central target at 2 cyc/deg is presented, actual target is at 6 cyc/deg) (**c**).

to four; thus, they were tested in turns, and breaks were given when they were not being tested. Words were carefully used in instructions of the experimental task to ensure that they were easily understood by the subjects. For example, the word "mountain" was used to describe the E target (because the E letter looks like a character meaning "mountain" in Mandarin); "the sun" was used to describe the fusion lock, and "ray" was used to describe the suppression markers. The examiner (XJL) frequently praised and encouraged the subjects throughout the experiments, and breaks were allowed on request.

Refractive correction (all waking hours) and occlusion therapy (6 hours per day) were prescribed simultaneously to all amblyopic children after the main experiments. After 6 months of therapy, best corrected acuity was remeasured using the high-contrast E chart in subjects who showed good compliance with treatments ($n = 15$). A reduction in the posttherapy interocular difference in high-contrast acuity compared with that before therapy was taken to indicate a response to the treatment. Compliance was assessed based on a checklist completed by parents and a questionnaire (Table 3) completed by parents as well as children independently without viewing the other's answers. Subjects satisfying the following criteria were deemed to have good compliance: (1) claimed to have worn the spectacles and the occluder as prescribed for 95% of the days during therapy; and (2) gave identical responses by parent and child to at least five items in the questionnaire.

Data Analysis

In the single- and double-staircase methods, trials up to the first reversal on each track were excluded. In the acuity and contrast sensitivity

TABLE 3. Questions for Compliance Check after 6 Months of Therapy

Number	Questions for Parents	Questions for Amblyopic Children
1	Does your child wear glasses at home or just at school?	Do you wear glasses at home or just at school?
2	Has your child complained to you about discomfort or inconvenience when wearing glasses?	Have you complained to your parents about discomfort or inconvenience when wearing glasses?
3	What time did your child usually start wearing the eye patch every day?	What time did you usually start wearing the eye patch every day?
4	Which eye did your child cover with the eye patch?	Which eye did you cover with the eye patch?
5	What did your child usually do when he/she was wearing the eye patch?	What did you usually do when you were wearing the eye patch?
6	Has your child complained to you about discomfort or inconvenience when wearing the eye patch?	Have you complained to your parents about discomfort or inconvenience when wearing the eye patch?

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tests, the mean of midpoints of peaks and valleys of the remaining reversals were taken to represent threshold. In the alignment sensitivity test, the SD of the midpoints was taken to represent the variability of a subject's judgment of alignment, thus the reciprocal of this was regarded as alignment sensitivity.

The difference in nondominant eye visual function between the full- and partial-occlusion conditions is termed here the "interaction index." As a threshold measure, the acuity interaction index was calculated by the following normalizing function:

$$\text{Interaction index} = \frac{\text{acuity}_{(\text{partial})} - \text{acuity}_{(\text{full})}}{|\text{acuity}_{(\text{partial})} + \text{acuity}_{(\text{full})}|}$$

As sensitivity measures, contrast and alignment sensitivity interaction indices were calculated as follows:

$$\text{Interaction index} = \frac{\text{sensitivity}_{(\text{full})} - \text{sensitivity}_{(\text{partial})}}{|\text{sensitivity}_{(\text{full})} + \text{sensitivity}_{(\text{partial})}|}$$

For each visual function, a positive interaction index indicates that the inhibition of nondominant eye visual function was stronger with partial relative to full occlusion of the dominant eye.

An exploratory data analysis[27] was performed on each set of data to test for normality of distribution. Full- and partial-occlusion conditions for each visual function were compared using the repeated-measures ANOVA for each subject group if data were sampled from a normal distribution and were compared using the Wilcoxon signed-rank test if data were not normally distributed. Each visual function and the interaction index of each visual function were compared between the three subject groups using the Kruskal-Wallis analysis of variance and the Mann-Whitney U test (because of unequal sample size between groups). All tests were corrected for multiple comparisons by using the Bonferroni correction.

The degree of anisometropia was indicated by the absolute value of interocular difference in refractive error in terms of spherical equivalent. The severity of amblyopia was indicated by the interocular difference in best corrected acuity measured using the high-contrast E chart (see the Subjects section). Correlation between the degree of anisometropia and the interaction indices was examined in anisometropic children (with and without amblyopia combined as a single group and the subgroups). Correlation between the severity of amblyopia and the interaction indices was examined in the anisometropic children with amblyopia and in the subgroups. Correlation between the response to therapy and the interaction indices was examined in the 15 amblyopic subjects who had good compliance with therapy. Correlations were not examined in the subgroups with small samples (fewer than five subjects; e.g., cylindrical hyperopes; Table 1). These correlations were examined for each visual function using the Pearson correlation (r) or the Spearman's correlation (r_s).

Results

Visual Functions

Acuity was found to be significantly poorer in the partial- than in the full-occlusion condition in all three subject groups, although this difference was slight in the children with normal vision and in the anisometropic children without amblyopia (Fig. 2; children with normal vision: $F_{1,9} = 8.159$, $P = 0.019$; anisometropic children without amblyopia: $F_{1,16} = 6.052$, $P = 0.026$; amblyopic children: $F_{1,16} = 8.373$, $P = 0.011$). Contrast sensitivity was significantly lower (worse) in the partial- than the full-occlusion condition in the children with normal vision ($F_{1,9} = 13.203$, $P = 0.005$) and the amblyopic children ($z = -2.817$, $P = 0.005$), but this difference was not found in the anisometropic children without amblyopia ($F_{1,16} = 0.700$, $P > 0.05$). Alignment sensitivity was not significantly different between the two viewing conditions in any subject group (children with normal vision: $z = -1.478$; anisometropic children without amblyopia: $F_{1,16} = 0.392$; amblyopic children: $F_{1,16} = 0.179$; $P > 0.05$).

Contrast sensitivity was significantly higher (better) in the children with normal vision (full: $\chi^2_2 = 19.946$, $U = 11.0$, $z = -3.716$; partial: $\chi^2_2 = 22.073$, $U = 14.0$, $z = -3.565$; $P < 0.001$) and the anisometropic children without amblyopia (full: $U = 33.0$, $z = -3.840$; partial: $U = 21.0$, $z = -4.254$; $P < 0.001$) than in the amblyopic children, but it was not significantly different between the children with normal vision and anisometropic children without amblyopia (full: $U = 77.5$, $z = -0.377$; partial: $U = 77.0$, $z = -0.402$; $P > 0.017$; note that $P < 0.017$ was the significance level corrected for multiple comparison). Surprisingly, neither acuity (full: $\chi^2_2 = 7.241$; partial: $\chi^2_2 = 7.942$; $P > 0.017$) nor alignment sensitivity (full: $\chi^2_2 = 2.468$; partial: $\chi^2_2 = 0.387$; $P > 0.017$) was significantly different between the three subject groups.

Interocular Interactions

Figure 3 shows the interaction index for each of the three visual functions tested. The acuity interaction index was found to be significantly higher in the anisometropic children with amblyopia than in those without ($\chi^2_2 = 10.287$, $P = 0.006$; $U = 57.0$, $z = -3.014$, $P = 0.003$), but it was not significantly different between the children with normal vision and the anisometropic children with ($U = 50.0$, $z = -1.758$) or without ($U = 55.0$, $z = -1.506$) amblyopia ($P > 0.017$). No significant difference was found in the interaction index of contrast ($\chi^2_2 = 6.764$, $P > 0.017$) or alignment ($\chi^2_2 = 0.866$, $P > 0.017$) sensitivity between any subject groups. Thus, the reduction in nondominant eye acuity with partial relative to full occlusion of the dominant eye was greater in the anisometropic children with amblyopia than in those without, but it did not differ between the children with normal vision and those with anisometropic amblyopia. In addition, the difference was found to be visual function dependent, occurring in acuity but not in contrast or alignment sensitivity.

When the anisometropic children with and without amblyopia were considered as a single group, the acuity interaction index showed a weak but significant positive correlation with the degree of anisometropia ($r_s = 0.35$, $P = 0.042$; Fig. 4). This finding suggests that the inhibitory impact on nondominant eye acuity with partial relative to full occlusion of the dominant eye was greater in the anisometropic children (with and without amblyopia) with higher anisometropia. However, when the subgroups were considered separately, a significant correlation was found only in spherical myopes ($r = 0.76$, $P = 0.003$; see Table 1, Fig. 4), but not in the other subgroups ($P > 0.05$), indicating that the correlation between the acuity interaction index and the degree of anisometropia may occur in this type of anisometropia only. The lack of correlation in other subgroups may also reflect the small samples included in these subgroups.

The response to amblyopia therapy was found to correlate positively with the acuity interaction index evaluated before treatment in the 15 amblyopic children (who showed good compliance with therapy; $r_s = 0.54$, $P = 0.038$, Fig. 5). Note, however, that while the correlation was significant, most of these subjects showed no response to the therapy.

Discussion

Visual Functions between Subject Groups

Consistent with previous studies, nondominant eye contrast sensitivity was found to be significantly poorer in the anisometropic amblyopic children than in the children with normal vision and the anisometropic children without amblyopia.[13,14] However,

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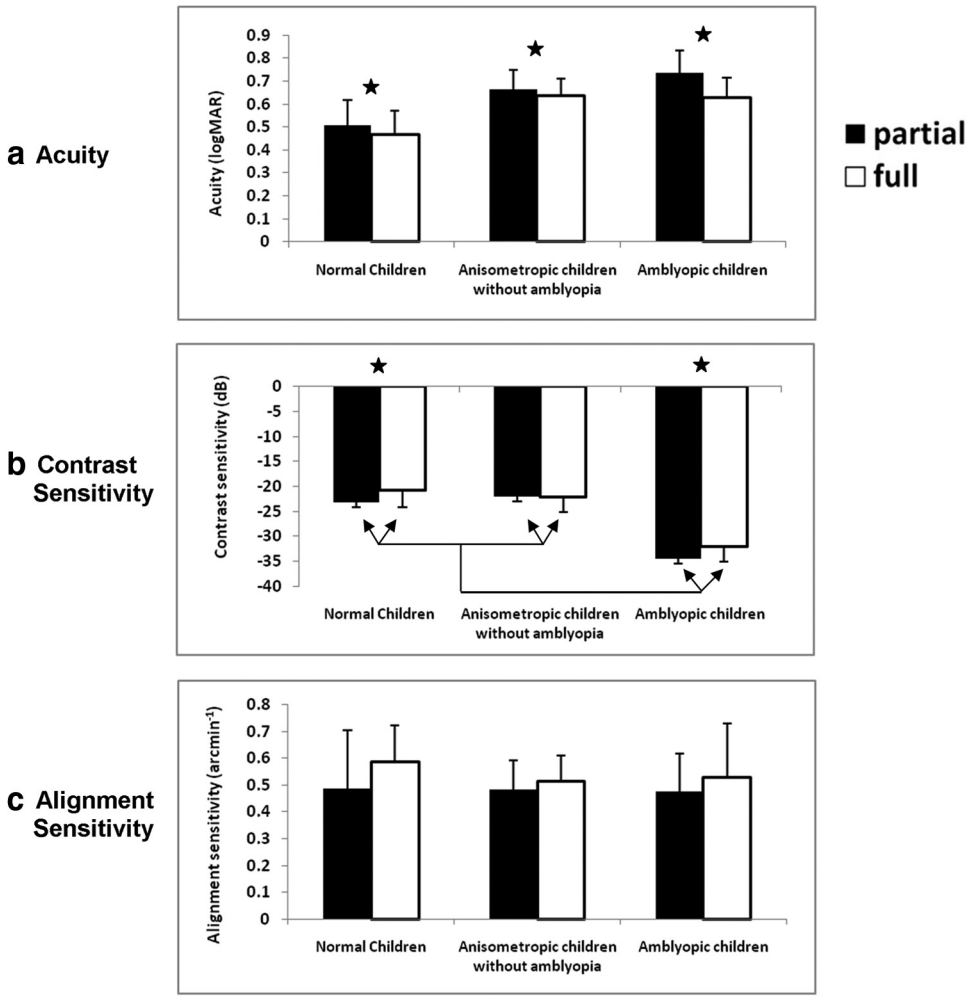

FIGURE 2. Acuity (logMAR) (**a**), contrast sensitivity (dB) (**b**), and alignment sensitivity (arcmin^{-1}) (**c**) measured in the nondominant eye of the children with normal vision and the anisometropic children with and without amblyopia in the full and partial occlusion conditions. Error bars, 95% CI. *Groups with visual function significantly different between the full- and partial-occlusion conditions ($P < 0.05$). *Arrows*: Contrast sensitivity was significantly lower (worse) in the amblyopic children than in children with normal vision and the anisometropic children without amblyopia in both viewing conditions ($P < 0.017$).

this difference was not found in acuity or alignment sensitivity. This lack of difference may be due to the reduction in luminance presented to each eye via the goggles, resulting in relatively poor acuity and alignment sensitivity. For example, previous work using acuity cards in room lighting found acuity to be 0.2 logMAR better than in the present study, using a similar contrast target, in children aged on average 4 years younger.[28]

In previous studies, alignment sensitivity was found to be reduced in amblyopic subjects.[15,29–31] The etiology of amblyopia (e.g., strabismus, anisometropia) plays a major role in determining its pattern of visual function deficits.[14,15] Although a range of deficits have been found in different types of amblyopia, major deficits were spatial uncertainty and distortion in strabismic amblyopia and reduced spatial resolution in anisometropic amblyopia.[29,32] Our finding of normal alignment sensitivity in our anisometropic amblyopic children may reflect this pattern. In addition, McKee et al.[14] classified levels of amblyopia in terms of acuity (e.g., resolution acuity and vernier acuity) and sensitivity (e.g., contrast sensitivity) of the amblyopic eye. They found moderate deficits in acuity and more severe deficits in sensitivity in anisometropic subjects, compared to strabismic subjects, consistent with findings of the present study.

Interocular Interactions with Full and Partial Occlusion

Acuity and contrast sensitivity were both found to be reduced in the partial- compared with the full-occlusion condition in children with normal vision and in those with anisometropic amblyopia, indicating greater inhibitory interactions (perhaps also weaker excitatory interactions) in the partial- compared to the full-occlusion condition. Although acuity was poorer in the partial- than the full-occlusion condition in anisometropic children without amblyopia, the difference was small (< 0.03 logMAR), and no such difference was found for contrast sensitivity in this group.

According to previous work,[18] acuity was improved when allowing light input to the nontested eye. This situation occurred in the partial-occlusion condition of the present study, but visual function was worse in this condition compared with full occlusion, indicating that in the partial-occlusion condition, signals generated by the nontested eye had a negative influence on those of the tested eye. This negative influence may be due to one or a combination of at least four factors:

First, perhaps the bright periphery produces an interocular inhibitory effect. Denny et al.[33] suggested that binocular summation (an excitatory effect) could reflect in part a suppressive influence from the occluded eye in monocular viewing. Optimal visual function could be achieved when tonic interocular suppression is removed from a dark-adapted eye by light adaptation. In our partial-occlusion condition, the bright periphery may have allowed light adaptation of the nontested eye, but visual function was reduced in this condition, indicating that any interocular interactions occurring here differ from those demonstrated by Denny et al.

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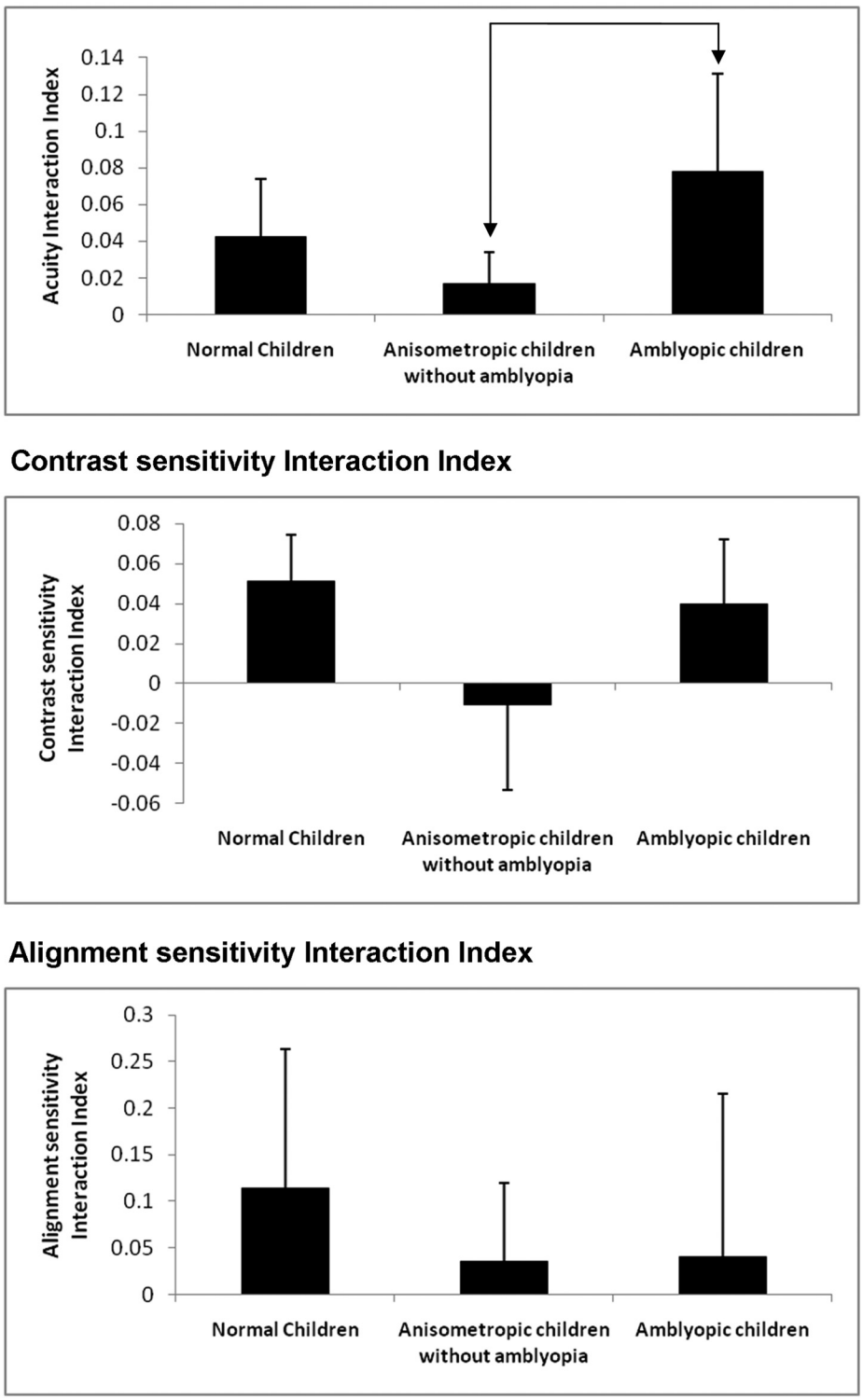

FIGURE 3. Acuity (**a**), contrast sensitivity (**b**), and alignment sensitivity (**c**) interaction indices in the children with normal vision and anisometropic children with and without amblyopia. Error bars, 95% CI. The index toward the positive *y*-axis represents stronger inhibitory impact on nondominant eye visual function with partial relative to full occlusion of the dominant eye. *Arrows*: the acuity interaction index is significantly higher in the anisometropic amblyopic children than in the anisometropic children without amblyopia ($P < 0.017$).

Second, the bright periphery may have enhanced an inhibitory effect of the central (partial) occlusion, thus raising the threshold for the tested eye. The size of the partial occlusion was determined based on a pilot experiment, in which stronger inhibition was achieved using 2° versus 4° occlusion. However, in that pilot experiment, the size of the light surround co-varied with the size of the occlusion, and the relative effects of the central dark and surrounding light regions were unclear.

Third, contour interaction[34] may have arisen from the presence of the partial-occlusion edge presented to the nontested eye around the target of the tested eye.[10] However, foveal contour interaction is limited in its spatial extent and in this study exceeded that limitation.[35,36] Moreover, Simmers et al.[37] found contour interaction with optotypes of high contrast, but not with those of low contrast, and thus it seems unlikely to have been a significant

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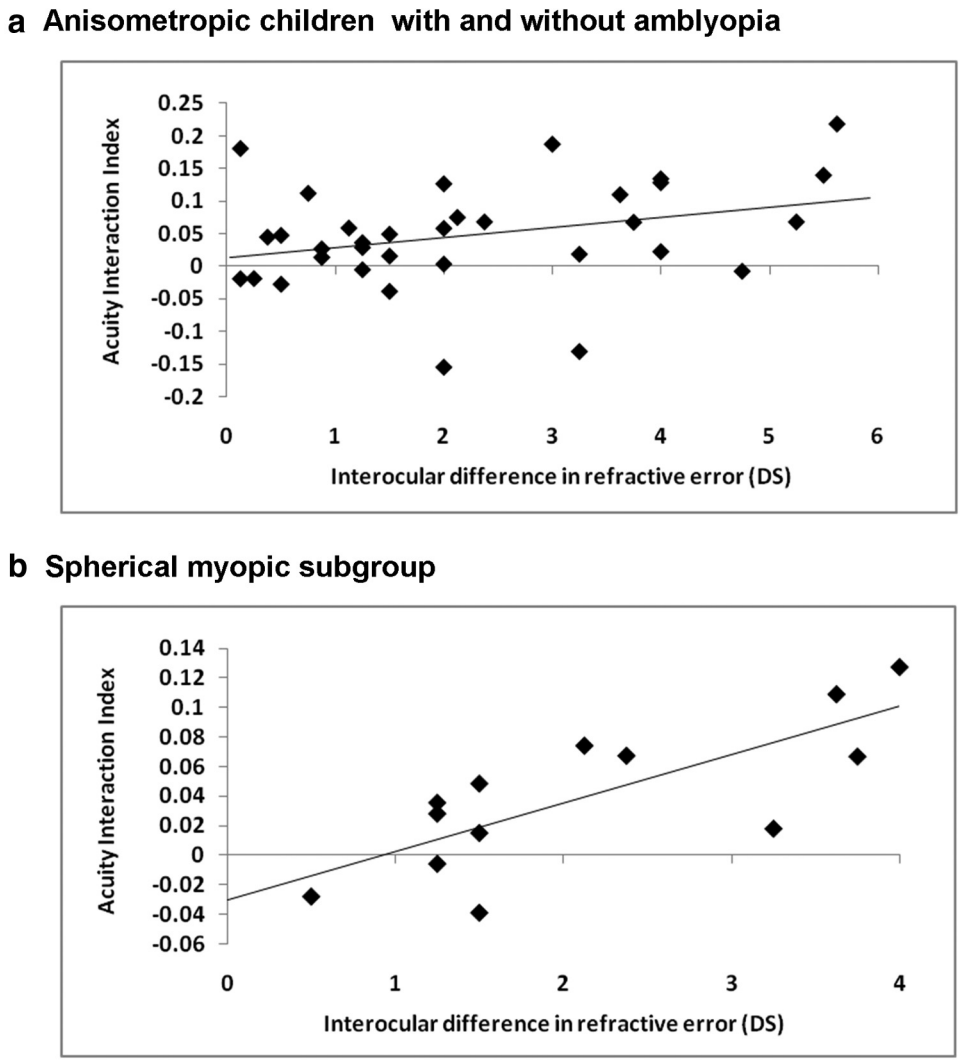

Figure 4. Acuity interaction index as a function of interocular difference in refractive error (DS) in the anisometropic children with and without amblyopia combined as a single group (**a**) and in the spherical myopic subgroup (**b**). Correlations indicate that the inhibitory impact on nondominant eye acuity with partial relative to full occlusion of the dominant eye is stronger in the anisometropic children with a higher degree of anisometropia.

influence on acuity in our study. However, contour interaction or a related form of suppression due to interocular stimulus difference may have played a role in the reduction in contrast sensitivity in the partial-occlusion condition.

Finally, a higher level function such as attention may be involved. The partial occlusion may raise visual attention in the nontested eye and increase the threshold of the tested eye, whereas this would not be expected to occur when the nontested eye is fully occluded.

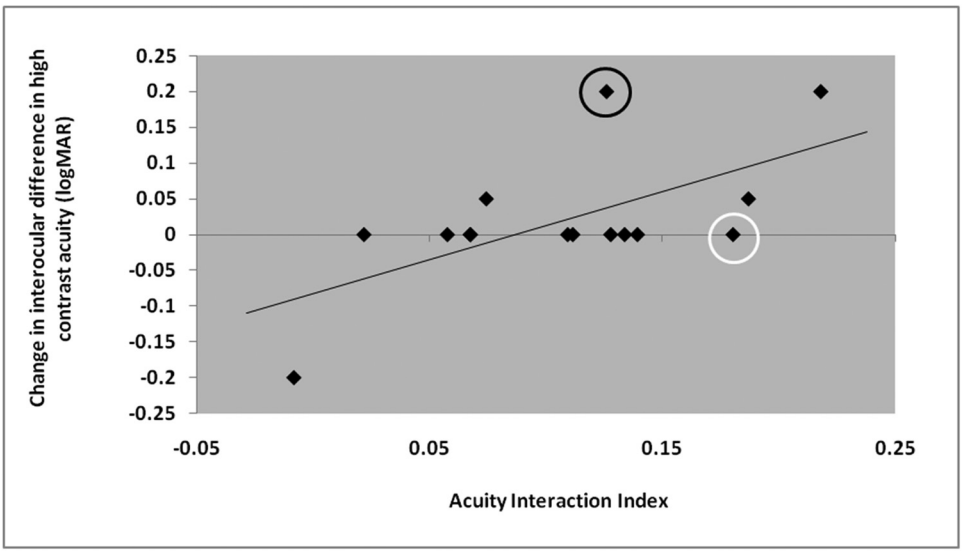

Figure 5. Reduction in interocular difference in high-contrast acuity after amblyopia therapy as a function of the acuity interaction index (before therapy) in the 15 anisometropic amblyopic children who had good compliance with therapy. Positive correlation indicates better amblyopic treatment outcomes in the anisometropic amblyopic children with higher acuity interaction indices before treatment. Note that one subject with moderate acuity interaction index before treatment had a very good response to amblyopia therapy (*black circle*) and one subject with high acuity interaction index before treatment had no response to amblyopia therapy (*white circle*).

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Interocular Interactions between Subject Groups

The interaction index indicated the level of interocular interactions in terms of the relative impact of full and partial occlusion of the dominant eye on function of the nondominant eye. Different values of the index indicated different levels of dichoptic masking effect engendered using the setup of the present study, which may suggest a difference in inhibitory (e.g., rivalry) or excitatory (e.g., summation) interaction. However, our experiment cannot determine whether a difference in interaction index between groups reflects enhanced inhibition or reduced excitation.

The results presented in Figure 3 indicated that the inhibition of the nondominant eye acuity due to partial occlusion of the dominant eye was stronger (or excitation was weaker) in anisometropic children with amblyopia than in those without. These differences between the subject groups in the full- and partial-occlusion conditions may reflect the differences in organization and function of the visual systems in these groups. For example, previous research has indicated that in the amblyopic visual system, the percept of the amblyopic eye is inhibited along with a reduction in binocular neurons and a shift of representation toward the dominant (nonamblyopic) eye.[20,38] Thus, signals from the nonamblyopic eye would dominate the resulting perception. If this were the case for the amblyopic visual system in the present study, the partial occluder presented to the nonamblyopic eye would dominate perception, at the expense of the target presented to the amblyopic eye. In the full-occlusion condition, input to the nonamblyopic eye was blocked with the opaque cover, and thus the target would be more easily detectable by the amblyopic eye, resulting in the difference in acuity between the two viewing conditions and the high acuity interaction index in this group of subjects. In the anisometropic children without amblyopia, however, instead of inhibition of the more ametropic eye, perhaps input from this eye was not inhibited or was weakly inhibited. This possibility is consistent with our finding of a low acuity interaction index in this group of subjects.

As shown in Figure 4, the acuity interaction index correlated positively with the degree of anisometropia. It is possible that subjects with lower degrees of anisometropia did not have a significant interocular difference in image quality, and hence binocular fusion was likely to be achieved. In contrast, subjects with higher degrees of anisometropia had greater interocular image differences which were less easily fused to yield a unified percept. Another consideration is that the image size difference in uncorrected anisometropia depends on whether the anisometropia is due to refractive or axial length differences between the two eyes.[39] Some subjects with similar degrees of anisometropia had widely varying acuity interaction indices (Fig. 4a). Perhaps some of those subjects had refractive and some axial anisometropia. When spherical myopes were analyzed separately, the correlation between the degree of anisometropia and the acuity interaction index was stronger (Fig. 4b), indicating that refractive error type also influenced interocular interaction.

Although we found a relationship between interactions and anisometropic amblyopia, the nature of this relationship is unknown, since amblyopia may result from or cause anisometropia.[40,41] In addition, the refractive history such as the period since age of onset was unclear in the subjects of the present study. This may be an important factor in the development of amblyopia and may affect interocular interactions. Further experiments on a larger sample with clear refractive and amblyopic history may improve understanding of the relationship between interocular interactions and anisometropic amblyopia.

The interaction indices of contrast sensitivity and alignment sensitivity did not differ between any of the subject groups. There are at least three possible explanations for this lack of difference. First, these tests were not familiar to the subjects, and the experimental tasks were relatively difficult to comprehend, contributing to the high interindividual variation of these functions (Fig. 2) and their interaction indices (Fig. 3). Second, these visual functions may not have reached maturity in the subjects recruited (Table 1), and the thresholds measured in both viewing conditions may be too low for any difference in the interaction indices between subject groups to be significant.[42–44] Moreover, the interactions in these visual functions may be immature in these children, and the interindividual variation in the maturation process may add to the high interindividual variation in the interaction index.[8] Third, the partial-occlusion configuration may have different impacts between acuity and these two aspects of visual functions.

The amblyopic children with a higher acuity interaction index before therapy tended to show a better treatment outcome (Fig. 5). Treatment outcome could be related to age, since the visual system has more plasticity during early than later childhood.[45] However, the four children who showed improvement in the present study were aged from 6 to 10 years, suggesting that age was not a factor. During occlusion therapy, vision of the nonamblyopic eye was blocked for 6 hours per day; thus, any inhibitory impact on the amblyopic eye due to dissimilar (sharp) images presented to the fellow eye may be reduced. For the amblyopic children with stronger inhibitory interaction before therapy, a reduction in this interaction may play an important role in the recovery from amblyopia. However, in some cases, the amblyopic children with moderate acuity interaction indices before therapy showed great improvement, and some of the subjects with high acuity interaction indices before therapy showed little or no improvement, suggesting that factors not controlled for, such as the age of onset and the severity of amblyopia, also play a role in the response to therapy. It is important to note that interaction may develop differently depending on intervention (refractive correction with and without occlusion, or no treatment). The relationship between interaction and types of intervention cannot be addressed here, because identical treatments were prescribed to all of the amblyopic children.

High-contrast acuity measures before and after treatments were based on a chart with unequal steps between lines and an unequal number of letters per line (see the Methods section). This discrepancy may be a confounding factor in our assessment of acuity improvement in the amblyopic children. In addition, only 4 of the 15 amblyopic children showed improvement in terms of a reduction in interocular difference in high-contrast acuity after therapy. This may be due to the age range of these subjects (mean age, 8.7 ± 1.2 years; eight subjects were older than 9 years), and perhaps reflects poorer compliance than that indicated on the checklist and questionnaire.

SUMMARY

Inhibition of nondominant eye acuity due to partial occlusion of the dominant eye was significantly stronger (or excitation was weaker) in anisometropic children with amblyopia than in those without. This effect correlated positively with the degree of anisometropia in anisometropic children (with and without amblyopia). Amblyopic subjects with stronger inhibition before therapy showed a better amblyopic treatment outcome. However, these differences and associations were found in acuity only, but not in contrast sensitivity or alignment sensitivity. A better understanding of the relationship between interocular interaction and anisometropic amblyopia may be

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achieved with a larger sample, as well as a comparison in this interaction before and after amblyopia therapy.

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