Contrast Sensitivity and Stereoacuity in Successfully Treated Refractive Amblyopia

Yu Jia, Qingqing Ye, Shenglan Zhang, Lei Feng, Jing Liu, Zixuan Xu, Yijing Zhuang, Yunsi He, Yusong Zhou, Xiaolan Chen, Ying Yao, Rengang Jiang, Benjamin Thompson, and Jinrong Li

1State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangzhou, China
2Centre for Eye and Vision Research, 17W Science Park, Hong Kong
3School of Optometry and Vision Science, University of Waterloo, Waterloo, Ontario, Canada
4Liggins Institute, The University of Auckland, Auckland, New Zealand

Correspondence: Jinrong Li, State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University, 54 Xianlie South Road, Guangzhou, China; lijirng3@mail.sysu.edu.cn.

Benjamin Thompson, School of Optometry and Vision Science, University of Waterloo, 200 Columbia Ave W, Waterloo, ON N2L3G1, Canada; ben.thompson@uwaterloo.ca.

YJ and QY contributed equally as co-first authors.

BT and JL contributed equally as co-last authors.

Received: October 20, 2021
Accepted: December 3, 2021
Published: January 6, 2022


Purpose. To assess whether monocular contrast sensitivity and stereoacuity impairments remain when visual acuity is fully recovered in children with refractive amblyopia.

Methods. A retrospective review of 487 patients diagnosed with refractive amblyopia whose visual acuity improved to 0.08 logMAR or better in both eyes following optical treatment was conducted. Measurements of monocular contrast sensitivity and stereoacuity had been made when visual acuity normalized. All patients had been treated with refractive correction for approximately 2 years following diagnosis. No other treatments were provided. Monocular contrast sensitivity was measured using the CSV-1000E chart for children 6 years of age or younger and a psychophysical technique called the quick contrast sensitivity function in older children. Stereoacuity was measured using the Randot Stereoacuity Test.

Results. Statistically significant interocular differences in contrast sensitivity were observed. These differences tended to occur at higher spatial frequencies (12 and 18 cycles per degree). Stereoacuity within the age-specific normal range was achieved by 47.4% of patients for the Random Dot Test and only 23.1% of patients for the Randot Stereoacuity Test.

Conclusions. Full recovery of visual acuity following treatment for refractive amblyopia does not equalize interocular contrast sensitivity or restore normal stereopsis. Alternative therapeutic approaches that target contrast sensitivity and/or binocular vision are required.

Keywords: amblyopia, treated, contrast sensitivity, stereoacuity

The success of amblyopia treatment is judged on amblyopic eye visual acuity (VA) improvement. However, in addition to impairing monocular high-contrast VA of the affected eye, amblyopia affects a broad range of monocular and binocular visual functions, including contrast sensitivity and stereopsis. The effect of amblyopia on binocular vision and stereopsis is particularly important because it contributes to visuomotor function deficits experienced by individuals with amblyopia. Therefore, when evaluating the functional significance of amblyopia treatment, it is important to consider whether improvements extend beyond amblyopic eye VA.

The gold-standard treatment for amblyopia in children involves correction of refractive error followed by occlusion or penalization of the fellow eye if necessary. It is well established that this treatment produces clinically significant improvements in amblyopic eye VA. However, contrast sensitivity and stereopsis deficits may remain. In follow-up studies of children randomized to either occlusion or atropine therapy at younger than age 7 years, the Pediatric Eye Disease Investigator Group (PEDIG) assessed monocular contrast sensitivity using the Pelli-Robson chart at age 10 years and stereoacuity using the Randot Preschool Test at ages 10 and 15 years. Contrast sensitivity was statistically significantly poorer for amblyopic eye versus fellow eye viewing, but the absolute difference was small. Stereopsis impairments were more pronounced with only 18% of children at age 10 years and 14% of children at age 15 years having stereopsis within the normal range for the Randot Preschool Test (60 arcsec or better). Most of the children followed up by PEDIG in these two studies had residual amblyopia, which may have influenced the stereoacuity outcomes. However, a larger follow-up study conducted by the same group revealed improved stereopsis in a subset of children and teens who had undergone therapy for anisometropic amblyopia even when the amblyopic eye VA deficit had mostly resolved.
The posttreatment deficits in amblyopic eye contrast sensitivity and stereopsis reported by PEDIG are consistent with other studies of posttreatment visual function in amblyopia. Amblyopic eye contrast sensitivity remains poorer than that of the fellow eye or control eyes and stereopsis tends to be impaired, although this is not always the case. Attenuated and delayed pattern reversal visually evoked potentials have also been reported for treated amblyopic eyes relative to fellow eyes, supporting the idea that treatment does not restore normal cortical processing of visual information in amblyopia.

In this study, we retrospectively evaluated contrast sensitivity and stereopsis in a large group of over 400 individuals with treated refractive amblyopia who no longer had a VA deficit. We hypothesized that contrast sensitivity and stereopsis deficits would be present even when the amblyopic eye VA deficit had fully resolved following standard treatment. We chose to focus on refractive amblyopia because strabismus can impair stereopsis independently from amblyopia, and very few patients with deprivation amblyopia within our patient database achieved normal distance VA in both eyes. The American Academy of Ophthalmology identifies two types of refractive amblyopia: unilateral (anisometropic amblyopia) and bilateral (isoametropic amblyopia). We included both types in our retrospective study.

**Methods**

This study followed the tenets of the Declaration of Helsinki and was approved by the Institutional Ethics Committee of Zhongshan Ophthalmic Center, Sun Yat-sen University.

The retrospective review used the Abnormal Binocular Function and Low Vision Rehabilitation Database at Zhongshan Ophthalmic Center, a major regional eye hospital. The database stores longitudinal measurements of visual function made at each clinical visit for all patients with amblyopia treated in the hospital. Standard operating procedures are followed for all measures to minimize intertester variability. Measurements include routine ocular examination, monocular tumbling E-Early Treatment Diabetic Retinopathy Study (E-ETDRS) distance best-corrected VA (BCVA), stereopsis, cycloplegic refraction, fixation assessment (central or eccentric), and monocular contrast sensitivity function (CSF) assessment. Data for all pediatric patients diagnosed with refractive amblyopia from January 2015 to April 2021 were exported from the database. In addition to clinical and vision measures, the age at first visit to Zhongshan Ophthalmic Center (i.e., the age at which refractive amblyopia was diagnosed) and age when VA had normalized (i.e., the age at which the patient’s VA met the study inclusion criteria) were extracted. Some patients may have received prior amblyopia diagnosis and treatment at another clinical site prior to their first visit at Zhongshan Ophthalmic Center.

Anisometropic and isoametropic amblyopia were defined according to the Preferred Practice Pattern from the American Academy of Ophthalmology. Specifically, anisometropic amblyopia required an interocular difference of >1.5 diopters (D) for sphere and/or >1 D for cylinder along with an interocular BCVA difference of at least 0.2 logMAR. Isoametropic amblyopia was defined as >3 D for sphere or >2 D for cylinder and BCVA worse than the age-specific cutoff values provided within the Preferred Practice Pattern. If both the anisometropia and isoametropia criteria were met, patients were classified as isoametropic.

The inclusion criteria for our retrospective review were (1) meeting the criteria for refractive amblyopia at the first visit to Zhongshan Ophthalmic Center, (2) ability to resolve an E on the 0 logMAR line of the E-ETDRS chart (i.e., 0.08 logMAR or better) for each eye following amblyopia treatment at Zhongshan Ophthalmic Center, and (3) ability to cooperate with and understand the CSF and stereocuity tests. Exclusion criteria were (1) the presence of any other eye disease, including constant, nonalternating, or unequally alternating tropias and visual deprivation; (2) history of previous eye surgery; (3) eccentric fixation; (4) opacity of refracting media; and (5) older than 18 years of age.

**Vision Assessment**

**Visual Acuity.** High-contrast (96.9 ± 0.83) logMAR best-corrected distance VA was measured using the ETDRS tumbling E Chart (WEHEN Vision, Guangzhou, Guangdong, China), viewed from a distance of 4 m at a luminance of 200 candels per square meter (cd/m²). The chart consisted of 5 optotypes per line for a total of 14 lines, decreasing from 1.0 to −0.3 logMAR. Visual acuity was scored per correct letter (/0.02 logMAR per letter).

**CSF.** Monocular CSF measurements were made using the CSV-1000E chart for children aged 6 years or younger and a computerized quick contrast sensitivity (qCSF) psychophysical test for those older than 6 years. The CSV-1000E chart (VectorVision, Dayton, OH, USA) provides an auto-light calibration to maintain a light level of 85 cd/m² for testing. The chart consists of four rows of grating aperture pairs. Grating spatial frequency varies by row (3, 6, 12, and 18 cycles per degree [cpd]) and contrast varies by column. Patients identify which aperture in a pair contains the grating. The qCSF measurement was performed and analyzed as described by Zheng et al. The qCSF measurement generated contrast thresholds at 19 spatial frequencies (equally spaced in log units) together with the cutoff spatial frequency. The area under the log contrast sensitivity function (AULCSF) was also calculated for both CSF measurement types. This was done by fitting a third-order polynomial to the threshold data for each spatial frequency.

**Stereocuity.** Near stereocuity was measured using the Random Dot Stere Acuity Test (Vision Assessment Corporation, Elk Grove Village, IL, USA), and distance stereocuity was measured using the Randot Stereocuity Test (Stereo Optical, Inc., Chicago, IL, USA). The tests were administered in accordance with the manufacturer’s instructions. For the near Random Dot Stere Acuity Test, patients were tested using sections B and C, which include contour-based circle and symbol targets with disparities ranging from 12.5 to 400 arcsec. Monocular cues are available. The distance Randot Stereocuity Test includes disparities ranging from 60 to 400 arcsec with no monocular cues. Each measurement was repeated twice. Age-normal performance was defined as meeting the third interquartile locations or the lower limit of published normative data for the relevant age group. For the Random Dot Stere Acuity Test, normal performance was considered ≤70° at 5 years, ≤50° at 6 and 7 years, ≤30° at 8 and 9 years, and ≤40° at 10 years and older. For the Randot Stereocuity Test, normal performance was defined as ≤200° at 5 years and ≤100° at 6 years and older.

**Fixation.** A direct ophthalmoscope YZ6E (66Vision, Tech, Suzhou, China) was used to screen for eccentric fixation.
**Statistical Analysis**

The eyes of patients with anisometropic amblyopia were labeled as the fellow eye (FE) and the amblyopic eye (AE). For isoametropic amblyopia, which is bilateral, the eyes were labeled fellow (Iso-FE) and amblyopic (Iso-AE) depending on which had the better BCVA. If there was no interocular difference in BCVA, then the eye with less refractive error was labeled Iso-FE. If there was no interocular difference in refractive error, the labels were assigned randomly (very few cases). Data sets were allocated to one of four groups for analysis according to amblyopia type (anisometropic versus isoametropic) and CSF measurement method (CSV-1000E chart versus qCSF).

Statistical analyses were performed using SPSS version 25 (SPSS, Inc., Chicago, IL, USA) and plots were produced using GraphPad Prism 9 (GraphPad Software, La Jolla, CA, USA). Descriptive statistics were used to summarize patient demographics. Categorical variables were expressed as frequencies (percentage) and continuous variables as mean and SD or median and quartiles depending on their distribution. No missing data were reported for age, sex, amblyopia type, BCVA, CSF, or refractive error. Comparisons between paired eyes (FE versus AE or Iso-FE versus Iso-AE) and paired subset groups (at first visit versus at normal VA) were made using the Wilcoxon signed-rank test. Comparisons of stereoacuity between the anisometropic group versus isoametropic group were made using Mann–Whitney U test. Differences were considered significant at $P < 0.05$.

| Table 1. Summary Demographics for the Anisometropic and Isoametropic Amblyopia Groups |
|------------------------------------|------------------------------------|------------------------------------|
| Characteristic                     | Anisometropic ($n = 269$)         | Isoametropic ($n = 218$)           | Total ($N = 487$)                  |
| Male                               | 155 (57.6)                        | 120 (55)                           | 275 (56.5)                        |
| Age at first visit                 | 6.2 (5.0, 7.9)                     | 5.6 (4.5, 7.1)                     | 6 (5.0, 7.5)                      |
| Age at normal VA                   | 7.6 (6.5, 9.3)                     | 7.9 (6.6, 9.0)                     | 7.7 (6.6, 9.2)                    |
| Hyperopia                          | 237 (88.1)                        | 201 (92.2)                         | 438 (90)                          |
| Myopia                             | 32 (11.9)                         | 17 (7.8)                           | 49 (10)                           |
| Spherical refractive error (x-axis) and cylindrical refractive error (y-axis) measured under cycloplegia at the first visit to Zhongshan Ophthalmic Center. | | | |

Data are presented as median (quartile 1, quartile 3) for age (years), otherwise as $n$ (%). First visit refers to the patient's first appointment at Zhongshan Ophthalmic Center.
Table 2. Contrast Sensitivity and Visual Acuity for Each Eye When Visual Acuity Had Normalized Following Amblyopia Treatment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FE</th>
<th>AE</th>
<th>P Value</th>
<th>Iso-FE</th>
<th>Iso-AE</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSV group</td>
<td>n = 104</td>
<td>n = 104</td>
<td>0.01*</td>
<td>n = 87</td>
<td>n = 87</td>
<td></td>
</tr>
<tr>
<td>CS-3 cpd</td>
<td>1.49 (1.34, 1.63)</td>
<td>1.49 (1.34, 1.63)</td>
<td>1.63 (1.49, 1.63)</td>
<td>1.49 (1.49, 1.63)</td>
<td>0.383</td>
<td></td>
</tr>
<tr>
<td>CS-6 cpd</td>
<td>1.84 (1.70, 1.84)</td>
<td>1.84 (1.70, 1.84)</td>
<td>1.84 (1.70, 1.84)</td>
<td>1.70 (1.70, 1.84)</td>
<td>0.108</td>
<td></td>
</tr>
<tr>
<td>CS-12 cpd</td>
<td>1.54 (1.40, 1.54)</td>
<td>1.54 (1.40, 1.54)</td>
<td>&lt;0.01*</td>
<td>1.40 (1.40, 1.54)</td>
<td>1.40 (1.40, 1.54)</td>
<td>0.06</td>
</tr>
<tr>
<td>CS-18 cpd</td>
<td>1.10 (0.96, 1.14)</td>
<td>0.96 (0.81, 1.10)</td>
<td>&lt;0.001*</td>
<td>0.96 (0.81, 1.10)</td>
<td>0.96 (0.81, 1.10)</td>
<td>0.079</td>
</tr>
<tr>
<td>Cutoff SF</td>
<td>1.28 (1.27, 1.29)</td>
<td>1.27 (1.26, 1.28)</td>
<td>&lt;0.001*</td>
<td>1.27 (1.26, 1.29)</td>
<td>1.27 (1.26, 1.28)</td>
<td>0.304</td>
</tr>
<tr>
<td>AULCSF</td>
<td>1.24 (1.19, 1.31)</td>
<td>1.20 (1.15, 1.28)</td>
<td>&lt;0.001*</td>
<td>1.25 (1.17, 1.35)</td>
<td>1.21 (1.14, 1.29)</td>
<td>0.008*</td>
</tr>
<tr>
<td>LogMAR BCVA</td>
<td>0.00 (0.00, 0.00)</td>
<td>0.02 (0.00, 0.04)</td>
<td>&lt;0.001*</td>
<td>0.00 (0.00, 0.02)</td>
<td>0.00 (0.00, 0.04)</td>
<td>0.007*</td>
</tr>
</tbody>
</table>

Data are presented as median (quartile, quartile 3). Comparisons between the FE versus AE and Iso-FE versus Iso-AE were made using the Wilcoxon signed-rank test. Data are split by amblyopia group (anisometropia [FE and AE] and isometropia [Iso-FE and Iso-AE]) as well as type of contrast sensitivity measurement: CVS-1000E (top) and qCSF (bottom). CS, contrast sensitivity; SF, spatial frequency.

*Statistically significant difference.

The Wilcoxon signed-rank test indicated a statistically significant difference in the distribution of signed ranks despite the median and interquartile ranges being the same for each eye.

RESULTS

The Abnormal Binocular Function and Low Vision Rehabilitation database contained data from 3677 patients with refractive amblyopia. Of these patients, 487 (269 anisometropic and 218 isometropic amblyopia) met the study inclusion criteria (Table 1). Thirty-five of these patients met the criteria for both anisometropic and isometropic amblyopia and were classified as isometropic. All included patients had been treated with refractive correction only since their first visit to Zhongshan Ophthalmic Center. Treatment duration was approximately 2 years. The range of refractive errors at the time of the first visit to Zhongshan Ophthalmic Center is shown in Figure. The anisometropic and isometropic groups did not differ significantly in the distribution of sex ($\chi^2 = 0.325, P = 0.569$) and age at normal VA ($\chi^2 = 0.271, P = 0.625$). Patients with isometropic amblyopia had a younger age at first visit than patients with anisometropic amblyopia ($\chi^2 = 0.33, P = 0.001$).

Near and distance stereoacuity measurements made when VA had normalized are shown in Table 3. Over 47% of patients had normal stereoacuity for the Random Dot Test (which includes monocular cues), whereas only 23% had normal distance stereoacuity for the Randot Stereotest. The distribution of stereoacuity scores did not differ significantly between the anisometropic and isometropic amblyopia groups for either test (near stereoacuity Random Dot Test, $z = -0.624, P = 0.533$; distance stereoacuity Randot Stereotest, $z = -0.524, P = 0.601$).

Stereotest data were available for a subset of patients at the time of first visit to Zhongshan Ophthalmic Center and when VA had normalized (Table 4). Near stereoacuity measured using the Random Dot Test improved significantly from first visit to when VA had normalized ($z = -4.555, P < 0.001$) and isometric ($z = -3.642, P < 0.001$) groups were considered separately. Distance stereopsis measured using the Randot Stereotest also improved significantly from first visit to when VA had normalized (all participants, $z = -5.551, P < 0.001$; anisometropia only, $z = -4.778, P < 0.001$; isometropia only, $z = -2.852, P = 0.004$), although the magnitude of

Table 3. Stereotest When Visual Acuity Had Normalized

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total</th>
<th>Anisometropic</th>
<th>Isoametropic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randot Stereotest Test</td>
<td>n = 464</td>
<td>n = 258</td>
<td>n = 206</td>
</tr>
<tr>
<td>Age-normal</td>
<td>220 (47.4)</td>
<td>118 (45.7)</td>
<td>102 (49.5)</td>
</tr>
<tr>
<td>Reduced for age</td>
<td>208 (44.8)</td>
<td>121 (46.9)</td>
<td>87 (42.2)</td>
</tr>
<tr>
<td>Unmeasurable</td>
<td>36 (7.8)</td>
<td>19 (7.4)</td>
<td>17 (8.3)</td>
</tr>
<tr>
<td>Randot Test</td>
<td>n = 468</td>
<td>n = 257</td>
<td>n = 211</td>
</tr>
<tr>
<td>Age-normal</td>
<td>108 (23.1)</td>
<td>60 (23.5)</td>
<td>48 (22.7)</td>
</tr>
<tr>
<td>Reduced for age</td>
<td>177 (37.8)</td>
<td>92 (35.8)</td>
<td>85 (40.3)</td>
</tr>
<tr>
<td>Unmeasurable</td>
<td>181 (39.1)</td>
<td>105 (40.9)</td>
<td>76 (37.0)</td>
</tr>
</tbody>
</table>

Data are presented as n (%). See main text for definitions of age-normal stereoacuity.
improvement was smaller (15.5% age-normal at first visit versus 26.5% when VA normalized).

Because our sample had a large age range, we reran our analyses including only patients who were 12 years or younger when their VA normalized (n = 460; 94.5% of the total sample). The pattern of results was the same as the original analysis (Supplementary Analysis).

**DISCUSSION**

Our retrospective review of a large group of patients with successfully treated refractive amblyopia revealed significant interocular differences in contrast sensitivity, particularly for high spatial frequencies, and prevalent stereoacuity deficits. In addition, no systematic differences in contrast sensitivity or stereoacuity outcomes were apparent for patients with successfully treated anisometropic amblyopia versus those with isoametropic amblyopia.

Our results are consistent with previous observations of residual deficits in monocular and binocular function despite recovery of normal VA following amblyopia treatment.20,29–31,39 Of these residual deficits, the persistent loss of binocular vision may be the most functionally significant as it contributes to motor function impairments that are, in turn, associated with reduced self-perception.41 Amblyopia treatments that directly target binocular vision and stereopsis have been developed, and promising initial results have been reported, including improvements in motor function.4 However, randomized clinical trial outcomes have been mixed for these new treatments, possibly due to adherence difficulties. The current results highlight the importance of continued research into amblyopia treatments that directly target binocular vision and stereopsis.

A large number of patients with refractive amblyopia met our conservative VA criterion for successful treatment (BCVA of 0.08 logMAR or better in each eye) following treatment with spectacles alone for a period of approximately 2 years. Refractive correction is an effective treatment for both anisometropic and isoametropic amblyopia, although the underlying mechanism is not known. It is also unknown whether the results of this study would have differed if the patients had been treated with additional therapies such as fellow eye occlusion. However, overall, the available data, including the present results, point to a dissociation between improvements in VA, contrast sensitivity, and stereopsis following treatment in both anisometropic and isoametropic amblyopia. Amblyopia is associated with changes in brain connectivity, white matter microstructure, and functional responses to visual stimuli at multiple stages of the visual pathway.48 It is possible that contrast sensitivity for high spatial frequencies and binocular visual function are more susceptible to these neurologic changes than high-contrast monocular letter acuity even when neural function is improved following treatment.

Our sample included similar numbers of patients with anisometropic and isoametropic amblyopia. Although anisometropic amblyopia is generally more common than isoametropic amblyopia, the difference in prevalence between the two types of amblyopia varies substantially across studies of different populations. Studies of children in China have reported prevalence rates ranging from 0.45% to 0.47% for unilateral anisometropic amblyopia and 0.24% to 0.65% for isoametropic amblyopia. Therefore, our sample likely reflects the similar prevalence of anisometropic and isoametropic amblyopia in children in China.

We observed a large difference in stereoacuity outcomes following treatment depending on the test. Stereoacuity was substantially better for the Random Dot Test than the Randot Stereoacuity Test. We attribute this difference to monocular cues that are present in the Random Dot Test but not the Randot Stereoacuity Test. Several new digital stereopsis tests are being developed for pediatric testing that may provide even more accurate stereoacuity estimates in future studies of amblyopia treatment.

In conclusion, we observed interocular differences in contrast sensitivity and a high risk of impaired stereopsis in a large group of successfully treated patients with refractive amblyopia. Given the importance of stereopsis for motor function, these results indicate the need for the continued development of treatments that directly target binocular vision.

**Acknowledgments**

Supported by National Key Research & Development Project (2020YFC2003905) and National Natural Science Foundation of China (81770954). B. Thompson is supported by the Hong Kong Special Administrative Region Government and InnoHK.

Disclosure: Y. Jia, None; Q. Ye, None; S. Zhang, None; L. Feng, None; J. Liu, None; Z. Xu, None; Y. Zhuang, None; Y. He, None;
Contrast Sensitivity and Stereacuity in Successfully Treated RA

Y. Zhou, None; X. Chen, None; Y. Yao, None; R. Jiang, None; B. Thompson, None; J. Li, None

References


