Binocular benefits of optical treatment in anisometropic amblyopia

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In this study, we investigated the effect of optical treatment on sensory eye balance in anisometropic amblyopia. Fourteen individuals (age: 13.7 ± 8.4 years old) with previously untreated anisometropic amblyopia were enrolled in the study. The average magnitude of their anisometropia (spherical equivalent) was 4.02 ± 1.19 DS. Their best corrected monocular visual acuity and sensory eye balance were measured before and after a 2-month period of full refractive correction (i.e., our optical treatment). Spectacle-corrected distance visual acuity (at 5 m) was measured monocularly using the Tumbling E Chart. Sensory eye balance was quantitatively assessed using a binocular phase-combination paradigm to determine the interocular contrast ratio at which the two eyes were balanced in binocular sensory combination (i.e., the balance point). We found that both interocular contrast ratio at the balance point (p = 0.006) and visual acuity of the ambyopic eye (p < 0.001) were significantly improved after 2 months of optical treatment, often referred to as refractive adaptation. We conclude that sustained optical treatment improves interocular sensory balance in anisometropic amblyopia as well as monocular acuity. Optical treatment is a passive form of binocular therapy and a necessary first step in treating the binocular dysfunction that characterizes amblyopia.

Introduction

Amblyopia is a common condition that results from abnormal visual experience, such as strabismus, anisometropia, or form deprivation during visual development. A large portion of amblyopia (37%) is caused by uncorrected anisometropia (Pediatric Eye Disease Investigator Group, 2002). Several studies have shown that individuals with amblyopia have not only poor monococular visual function—e.g., visual acuity (Levi & Klein, 1982; Simmers et al., 1999), contrast sensitivity (Bradley & Freeman, 1981; Hess & Howell, 1977), and spatial distortion (Bedell & Flom, 1981; Sireteanu, Lagreze, & Constantinescu, 1993)—but also binocular visual deficits—e.g., binocular summation (Baker, Meese, Mansouri, & Hess, 2007; Huang, Zhou, Lu, & Zhou, 2011), interocular suppression (Harrad & Hess, 1992; Levi, Harwerth, & Smith, 1980), and stereopsis (Walraven &
Table 1. Clinical characteristics of participants with amblyopia. Notes: VA = visual acuity; M = male; F = female; DS = diopter spherical; DC = diopter cylindrical; RDS = random dot stereogram.

<table>
<thead>
<tr>
<th>Participant</th>
<th>Age (years) /sex</th>
<th>Cycloplegic refractive error</th>
<th>Amblyopic eye</th>
<th>Fellow eye</th>
<th>Amblyopic eye</th>
<th>Fellow eye</th>
<th>Pre</th>
<th>Post</th>
<th>Pre</th>
<th>Post</th>
<th>Balance point</th>
<th>Stereoacuity-RDS (arcsec) at 40 cm</th>
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<tbody>
<tr>
<td>S1</td>
<td>6/M</td>
<td>+5.00 DS</td>
<td>+1.50 DS</td>
<td>0.68</td>
<td>0.07</td>
<td>0.47</td>
<td>0.07</td>
<td>0.16</td>
<td>0.29</td>
<td>&gt;3,000</td>
<td>400</td>
<td></td>
</tr>
<tr>
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<td>7/F</td>
<td>+2.00 DS</td>
<td>Plano</td>
<td>0.98</td>
<td>−0.03</td>
<td>0.85</td>
<td>−0.03</td>
<td>0.23</td>
<td>0.29</td>
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<td>&gt;3,000</td>
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<tr>
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<td>+4.00 DS</td>
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<td>0.55</td>
<td>−0.03</td>
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<td>&gt;3,000</td>
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<tr>
<td>S5</td>
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<td>+4.50 DS</td>
<td>Plano</td>
<td>0.57</td>
<td>0.07</td>
<td>0.47</td>
<td>0.07</td>
<td>0.14</td>
<td>0.33</td>
<td>400</td>
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<tr>
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<td>11/F</td>
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<td>Plano</td>
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<td>0.18</td>
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<td>−0.03</td>
<td>0.47</td>
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<td>0.18</td>
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<td>0.45</td>
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<td>−2.50 DS</td>
<td>0.95</td>
<td>−0.03</td>
<td>0.95</td>
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<td>35/M</td>
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<td>−0.03</td>
<td>0.15</td>
<td>0.30</td>
<td>800</td>
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</table>

Janzen, 1993; Wood, Fox, & Stephenson, 1978); for reviews, see Lee & Isenberg, 2003 and Hess, Thompson, & Baker, 2014. It has also been shown that binocular summation is normal in individuals with amblyopia when the contrast of the fellow eye’s input is selectively reduced (Baker et al., 2007; Huang et al., 2011), suggesting a link between interocular suppression and amblyopia. Furthermore, there is evidence that stronger interocular suppression is associated with poorer stereoaucity and poorer amblyopic-eye visual acuity (Li et al., 2011), which also supports the important role that interocular suppression in amblyopia.

Previous studies have shown that a period of refractive correction (sustained optical correction of the amblyopic eye) can significantly improve visual acuity in most types of amblyopia and is recommended before other treatments such as penalization or occlusion (Cotter et al., 2007; Harvey, Dobson, Miller, & Clifford-Donaldson, 2008; Stewart, Moseley, Fielder, Stephens, & the MOTAS Cooperative, 2004). This is commonly referred to as optical treatment (Moseley, Fielder, & Stewart, 2009), and is a distinct component of the treatment for amblyopia.

Recently, we have shown that individuals with nonamblyopic anisometropia (with an interocular spherical difference of 1.50 D or larger) who wore optical correction for at least 16 weeks had more balanced sensory eye balance than those whose anisometropia was not corrected (Zhou, Feng, Lin, & Hess, 2016). In this study we raise a further question: Can the sensory eye balance of individuals with anisometropic amblyopia also be restored by this form of optical treatment (i.e., full refractive correction)? To answer this question, we quantitatively assessed the sensory eye balance in a group of 14 newly diagnosed patients with anisometropic amblyopia before and after 2 months of optical treatment.

Materials and methods

Participants

Fourteen individuals with anisometropic amblyopia, ages 6–35 (13.7 ± 8.4 years old), were enrolled in the study. The average magnitude of their anisometropia (spherical equivalent) was 4.02 ± 0.85, which also supports the important role that interocular suppression in amblyopia.

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All participants received a complete initial ophthalmological examination, including cycloplegic refraction, best corrected visual acuity at distance (5 m) for each eye, eye alignment by cover testing, slit-lamp biomicroscopy for anterior segment examination, and dilated fundus examination. Exclusion criteria included history of prior treatment with spectacles, history of occlusion or penalization therapy, presence of strabismus (including monofixation or any movements in the cover/uncover test), corneal opacity, cataract, glaucoma, ocular pathology, and previous eye surgery.

Objective streak retinoscopy was done after instillation of cycloplegic eye drops (1% tropicamide, six drops at 5-min intervals to relax ciliaris sufficiently, the last drop being provided at 30 min before the refraction measurement). Note that unlike previous studies that used cyclopentolate for the refraction (Harvey et al., 2008), here tropicamide was used, as it is the preferred medication when used in the dose application just described. This dosage regimen stems from some previous reports on the cycloplegic effects of tropicamide (Lin et al., 1998; Manny et al., 2001), in which people used two drops of 1% tropicamide at 5-min intervals and showed that it is an effective cycloplegic agent. There are also studies using three drops of 1% tropicamide, given every 5 min (Lai, Hsu, Wang, Chang, & Wu, 2009). Here, six drops were given every 5 min to provide adequate cycloplegia.

All patients were prescribed spectacles by author LF based on the cycloplegic refraction performed on the initial visit. Optical treatment was conducted by using the following prescriptions: Myopic and astigmatic refractive errors were fully corrected. Hyperopic refractive errors were corrected within 1.00 D of the full correction, while anisometropia was corrected to less than 1.00 D. All patients were asked to wear spectacles all day long, and compliance was determined by self- or parent report. At the follow-up visit, patients and/or their parents were asked how long the spectacles were worn on each day. Only patients with good reported all-day compliance (i.e., all waking hours) were included in the study.

Baseline performance (include the best corrected visual acuity at distance, sensory eye balance, and stereopsis) was measured after at least 6 hr of optical treatment (usually after 1 or 2 days of optical treatment). This enabled patients to adapt to the new spectacles—e.g., the minification caused by myopic shifts in refractive correction and magnification caused by hyperopic shifts (Applegate & Howland, 1993).

The study protocol was approved by the institutional review boards of Anhui Medical University, McGill University, and Wenzhou Medical University. Written informed consent was obtained from each participant or a parent or legal guardian (for participants younger than 18) after explanation of the nature and possible consequences of the study. The methods and data collection were carried out in accordance with approved guidelines.

**Apparatus**

Participants’ best spectacle-corrected visual acuity was measured monocularly using the full Tumbling E Chart (Mou, 1966) at 5 m. Patients were asked to read the optotypes one after another and were stopped when they could not respond within 10 s. The amblyopic eye was always examined first during the experiment. Visual acuity was defined as the score associated with 75% correct judgments. This was achieved by measuring participants’ percentage correct at different lines and using linear interpolation to calculate the score associated with 75% correct judgments.

Sensory eye balance was measured with custom-built programs using MATLAB (MathWorks, Natick, MA) and PsychToolBox 3.0.9 extensions (Brainard, 1997; Pelli, 1997). The stimuli were displayed on a gamma-corrected LG D2342PY 3D LED screen (LG Life Science, Seoul, South Korea) with a 1,920 × 1,080 resolution and a 60-Hz refresh rate. Participants were asked to wear their prescribed spectacles with the polarized glasses to view the display dichoptically in a dimly lit room at a viewing distance of 136 cm. The background luminance was 46.2 cd/m² on the screen and 18.8 cd/m² through the polarized glasses. A chin and forehead rest was used to minimize head movements during the experiment.

**Design**

Participants’ monocular best corrected visual acuity and sensory eye balance were measured before and after 2 months of optical treatment. All the visual-acyuity tests were conducted by the same nurse, who was uninformed as to the purpose of this study, and all the sensory eye-dominance measures were conducted by author JW.

The experimental design and procedure for measuring sensory eye balance were similar to what we used in our previous studies (Feng, Zhou, Chen, & Hess, 2015; Zhou, Huang, & Hess, 2013), in which we quantitatively assessed the sensory eye balance of individuals with anisometropic amblyopia using a binocular phase-combination paradigm. In this measure, two monococular horizontal sine-wave gratings of different contrast and with phase-shifts in opposite directions (upward or downward 22.5° relative to the center of the screen, respectively) were dichoptically presented through polarized glasses. Binocularly, one stimulus is seen, and its perceived phase was measured for a 100% fixed
contrast in the amblyopic eye and a variable contrast (0, 10%, 20%, 40%, 80%, and 100%) for the grating seen by the fellow eye. These data defined the relationship of phase versus interocular contrast ratio (Huang et al., 2011) and allowed the derivation of the specific interocular contrast ratio at which the binocular perceived phase was 0°—in other words, the point at which the two eyes contributed equally to the binocular phase combination. This specific interocular contrast ratio, which we refer to as the effective contrast ratio at balance point (or balance point for short).

Figure 1. An illustration of the binocular phase-combination paradigm. Two monocular horizontal sine-wave gratings with different contrast and phase shifts in opposite directions were dichoptically presented to the two eyes; the two eyes were balanced when the binocular perceived phase was 0°. The interocular contrast ratio where the two eyes were balanced indicated the sensory eye balance and was termed the effective contrast ratio at balance point (or balance point for short).

Statistical methods

For statistical analysis, participants who had no stereopsis (>3,000 arcsec) were assigned a stereoacuity of 3,000 arcsec. Visual acuity was defined as the score associated with 75% correct judgments and converted to logMAR. The normality of the data sets was tested using a one-sample Kolmogorov–Smirnov test. The measures before and after optical treatment were compared using paired-samples t-tests. And the difference between children (≤11 years) and adults (≥17 years) was compared using independent-samples t-tests. The relationship between age and the restoration of sensory eye balance (or visual acuity) was evaluated using Spearman’s correlation analysis; the relationship between the magnitude of anisometropia and the restoration of sensory eye balance (or visual acuity) was evaluated using Pearson’s correlation analysis. For all of these statistical analyses, SPSS 24.0 (IBM Corp., Armonk, NY) was used.

Results

Change in sensory eye balance

As plotted in Figure 2, the mean effective contrast ratio at the balance point was 0.22 ± 0.11 (M ± SD) before optical treatment, and it significantly increased to 0.31 ± 0.09 after 2 months of spectacle wearing, \( t(13) = 3.289, p = 0.006 \) (Figure 2). The mean difference of post- and pre- sensory eye balance was 0.08, and the 95% confidence interval of the difference was [0.03, 0.14].

Change in visual acuity

The mean visual acuity (in logMAR) of the amblyopic eyes before optical treatment was 0.59 ± 0.26, and it significantly improved to 0.44 ± 0.25 after 2 months of spectacle wearing, \( t(13) = −5.940, p < 0.001 \) (Figure 3), indicating that the poor visual acuity of the amblyopic eye could also be improved by optical treatment alone, something that has been noted in a number of clinical studies (Cotter et al., 2006; Stewart et al., 2004). The mean difference of post- and pre-visual acuity was −0.14, and the 95% confidence interval of the difference was [−0.19, −0.09].

Change in stereopsis

The mean stereopsis of the participants at baseline was 1,670 ± 1,399 arcsec before optical treatment, and
it significantly improved to $947 \pm 1351$ arcsec after 2 months of spectacle wearing, $t(13) = -2.362, p = 0.034$.

The effect of age on visual outcomes from optical treatment

In the current study, our participants had ages that ranged from 6 to 35 years, which was not normally distributed ($p = 0.007$, one-sample Kolmogorov–Smirnov test). All other parameters—improvement of visual acuity, improvement of balance point, magnitude of anisometropia—were normally distributed ($p > 0.05$). One relevant question is whether the visual outcomes from optical treatment that we observed here are age dependent, as would be expected from clinical experience. First, we conducted a Spearman’s correlation analysis and found that the correlation between age and improvement of visual acuity was not significant ($\rho = -0.435, p = 0.12$). The relationship between age and improvement of balance point was also not significant ($\rho = -0.06, p = 0.84$). Since nine participants were $\leq 11$ years old and five were $\geq 17$, we also compared the treatment outcomes for these two subgroups. We found that there was no significant difference between these two subgroups in improvement of visual acuity, $t(4.728) = 1.655, p = 0.162$, or improvement of balance point, $t(12) = 1.165, p = 0.266$. In this case, the improvements of visual acuity as well as binocular balance measures were not different for these two groups. These results suggest that the visual improvements from optical treatment are comparable in children and adults with amblyopia. Our sample size is small, and this conclusion needs to be confirmed with a larger sample of participants (Figure 4).

The effect of the magnitude of anisometropia on visual outcomes from optical treatment

To investigate the effect of the magnitude of anisometropia on the visual benefits from the 2 months of optical treatment, we first conducted a Pearson’s correlation analysis, and found that the relationship between magnitude of anisometropia and visual-acuity improvement was significant, $r = -0.732, p = 0.003$; the
The relationship between magnitude of anisometropia and improvement of balance point was not significant, $r = 0.214$, $p = 0.463$ (Figure 5b). According to the Spearman's correlation analysis, age significantly correlated with magnitude of anisometropia ($\rho = 0.662$, $p = 0.010$). Thus, to better understand whether these anisometropia-related improvements in visual acuity were due to the magnitude of anisometropia per se or were driven by the covariation between age and magnitude of anisometropia, we undertook a partial correlation analysis (with age as a partial factor). We found that the correlation between magnitude of anisometropia and improvement of visual acuity was not significant, $r = -0.462$, $p = 0.112$ (Figure 5a), once the correlation between age and anisometropia was factored out. Again, it should be noted that our sample size is small.

**Discussion**

In the present study, we quantitatively assessed the visual acuity and sensory eye balance of 14 individuals newly diagnosed with anisometropic amblyopia before and after 2 months of optical treatment. We show that their sensory eye balance could be significantly improved by optical treatment alone and that the restoration of a healthier sensory eye balance was accompanied by an improvement of visual acuity in the amblyopic eye after 2 months of optical treatment (approximately 0.15 logMAR).

To the best of our knowledge, no study has quantitatively assessed the change of sensory eye balance by optical treatment alone in anisometropic amblyopia. One technical concern is whether our main observation (i.e., the change of sensory eye balance) was simply due to repeated testing (i.e., participants were more familiar with the procedures in the posttest). We do not believe this is the case, as our design in assessing sensory eye balance took into consideration the influence of the potential positional bias by using a two phase strategy across trials—the phase shift of the grating was $22.5^\circ$ in the amblyopic eye and $-22.5^\circ$ in the fellow eye in some trials and vice versa in other trials. Therefore, there is no way for participants to use the phase-shift direction as a cue to the task. Thus, the improvement we report is unlikely to be due to bias and repeated testing per se. This is confirmed by our reanalysis of our original test data before the optical treatment, in which we divided the data from the eight repetitions into two parts and calculated two balance points for each subject from the first four repetitions (test1) and the last four repetitions (test2). The balance points derived from these two tests were similar: $0.24 \pm 0.10$ (test1) versus $0.22 \pm 0.13$ (test2), $t(13) = 0.64$, $p = 0.53$ (two-tailed paired-samples $t$ test).
The restoration of better sensory eye balance from optical treatment is consistent with a recent study (Zhou et al., 2016) which showed in a cross-sectional cohort study that the two eyes of individuals with uncorrected anisometropia (but without amblyopia) were more imbalanced compared to those of individuals with anisometropia who have worn their spectacles for 16 weeks or more. Both studies suggest that optical correction plays an important role in rebalancing the contribution from each eye to the binocular sum. A relevant question is: To what extent are the changes in sensory eye balance a consequence of the changes in visual acuity? Since individuals with non-amblyopic anisometropia exhibit comparable changes in sensory eye balance after optical correction (Zhou et al., 2016), it would seem that these two benefits of optical treatment (sensory eye balance and visual acuity) are independent. Comparing the two studies, the sensory balance in individuals with anisometropia and amblyopia is worse than in those without amblyopia (0.22 compared with 0.5), and the improvement obtained by optical treatment is also smaller in the amblyopic group (0.1 compared with 0.2). This suggests that amblyopia per se makes a contribution to eye imbalance that is different from that of the anisometropia, and the interocular imbalance is more severe and less responsive to optical treatment in anisometropic amblyopia than it is in anisometropia without amblyopia. This lesser responsiveness could also be dependent on the duration (i.e., 2 months) of optical treatment used in this study. It will be interesting to see whether greater binocular benefits are achieved with longer-term optical treatment.

After optical treatment, stereopsis also improved in participants with anisometropic amblyopia, consistent with previous studies (Richardson, Wright, Hrisos, Buck, & Clarke, 2005; Stewart, Wallace, Stephens, Fielder, & Moseley, 2013). We did not analyze the relationship between improvement in sensory eye balance and in stereopsis, as we believed that the clinical stereopsis measure we used is too coarse (Hess et al., 2016) and may not be precise enough in reflecting the real improvement after optical treatment compared with the precise measure of sensory eye balance that we made here. In fact, some participants did not have measurable stereovision with this clinical test before optical treatment (i.e., those marked as >3,000 arcsec). In addition, the measurement of sensory eye balance was conducted at a low spatial frequency (1 c/deg), while the stereopsis measurement using the clinical book was conducted with broadband stimuli. As both stereopsis (Reynaud, Zhou, & Hess, 2013) and sensory eye balance (Ding, Klein, & Levi, 2013; Kwon, Wiecek, Dakin, & Bex, 2015) are spatial-frequency dependent,
our current study cannot provide a precise relationship between them. Optical treatment over a duration of 2 months improves not only visual acuity in the amblyopic eye but also sensory eye balance. Participants’ baseline performance was measured after at least 6 hr of optical treatment, to lessen the discomfort from the different spherical equivalents between the two eyes. We should note that this could miss some effects, in which case the optical treatment’s true effect could be slightly greater than we report here. It should be pointed out that tropicamide was used as the cycloplegic in our study, which may or may not be able to reveal the full amount of hyperopic refractive errors and thus could miss some effects.

Even though the correlation between visual outcomes from the 2 months of optical treatment and the age of the participants was not significant (within the limits and small sample size tested here), the magnitude of the correlation coefficients was relatively large (i.e., −0.06 for age and improvement in balance point, and −0.435 for age and improvement in visual acuity). This result may suggest that optical treatment could be more effective for children than adults with anisometropic amblyopia. However, because it is not easy to find adults who have been newly diagnosed with amblyopia and have never received any treatment, we had only four adults with amblyopia in the current study. A clear answer for the effect of optical treatment in adults with anisometropic amblyopia needs further study with larger samples.

It should be noted that we used the Tumbling E Chart rather than the standard methods of measuring visual acuity in individuals with amblyopia (e.g., ETDRS or HOTV charts; Cotter et al., 2007; Stewart et al., 2004), and thus the acuity measurements may not be as precise. This is because presently, the Tumbling E Chart is a common and standard visual-testing chart in China (Mou, 1966), where English is not the native language. To minimize the potential bias in the visual-acuity measure, a nurse who was uninformed as to the purpose of this study measured participants’ visual acuities at different visits. Furthermore, visual acuity was calculated as the score associated with 75% correct judgments. Even though visual acuity was not the main focus of this study, we confirm the conclusion reached by previous studies in terms of the effect of optical treatment (i.e., refractive adaptation) in improving the amblyopic eye’s visual acuity in anisometropic amblyopia (Cotter et al., 2006; Stewart et al., 2004).

On the other hand, the visual outcomes from the 2 months of optical treatment were not significantly correlated with the magnitude of anisometropia once we controlled for the correlation between age and anisometropia. This is probably due to a limitation of our sample, because all of our participants had a moderate magnitude of anisometropia (ranging from 2.00 to 6.625 D). We did not include individuals with amblyopia and a higher magnitude of anisometropia, as they typically have problems fusing the images of the two eyes (Campos & Enoch, 1980), and their aniseikonia would need to be corrected before we could measure sensory eye balance. More participants, taking these issues into account, are needed in future studies.

In summary, a sustained optical treatment (as short as 2 months) in individuals with anisometropic amblyopia achieves two independent benefits: better interocular sensory balance and improved monocular acuity. Optical treatment is an established first step in any amblyopia therapy. We see it as a passive form of binocular therapy, one that is consistent with more active binocular therapeutic approaches (Birch et al., 2015; Hess, Mansouri, & Thompson, 2011). In future studies, it will be interesting to see whether a longer term of optical treatment will produce greater binocular visual benefits.

Keywords: amblyopia, contrast gain, Refractive adaptation, binocular vision

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