City Research Online

City, University of London Institutional Repository

Citation: Marella, B. L., Vaddavalli, P. K., Reddy, J. C., Conway, M. L., Suttle, C. M. & Bharadwaj, S. R. (2023). Interocular Contrast Balancing Partially Improves Stereoacuity in Keratoconus. Optometry and Vision Science, 100(4), pp. 239-247. doi: 10.1097/opx.0000000000002001

This is the accepted version of the paper.

This version of the publication may differ from the final published version.

Permanent repository link: https://openaccess.city.ac.uk/id/eprint/30515/

Link to published version: https://doi.org/10.1097/opx.0000000000002001

Copyright: City Research Online aims to make research outputs of City, University of London available to a wider audience. Copyright and Moral Rights remain with the author(s) and/or copyright holders. URLs from City Research Online may be freely distributed and linked to.

Reuse: Copies of full items can be used for personal research or study, educational, or not-for-profit purposes without prior permission or charge. Provided that the authors, title and full bibliographic details are credited, a hyperlink and/or URL is given for the original metadata page and the content is not changed in any way.

City Research Online: http://openaccess.city.ac.uk/ publications@city.ac.uk

Abstract

Significance: Stereoacuity in bilaterally asymmetric keratoconus may improve from baseline levels by balancing the contrast input to the two eyes.

Purpose: Interocular differences in image quality, characterized by dissimilar contrast loss and phase shifts, is implicated in stereoacuity loss in keratoconus. This study determined whether contrast balancing improves stereoacuity in this disease condition, and, if so, whether it is dependent on the baseline interocular contrast imbalance.

Methods: Interocular contrast imbalance and stereoacuity of 43 subjects (16-33years) with bilaterally asymmetric keratoconus were tested with spectacle correction as baseline using a binocular rivalry paradigm and random-dot stereograms, respectively. Stereoacuity measurements were repeated in a subset of 33 subjects at their contrast balance point (i.e., contrast level in stronger eye allowing balanced rivalry with 100% contrast in weaker eye) and with contrast levels biased in favor of stronger or weaker eye, all conditions in randomized order.

Results: Contrast imbalance level was significantly correlated with the subject's stereoacuity at baseline ($r=-0.47$, $p=0.002$). The median (25th-75th IQR) stereoacuity improved by 34.6% (19.0-65.1%) from baseline [748.8arc sec (261.3-1257.3arc sec)] to the contrast balanced condition [419.0arc sec (86.6-868.9arc sec)] ($p<0.001$), independent of their baseline stereoacuity or contrast imbalance levels ($r<0.2$, $p>0.26$ for both). Contrast bias in favor of weaker eye [881.3arc sec (239.6 to 1707.6arc sec)] worsened stereoacuity more than a bias towards stronger eye [502.6arc sec (181.9 to 1161.4arc sec)], both relative to the contrast balanced condition ($p<0.001$).

Conclusion: Interocular contrast balancing partially improves stereoacuity in bilaterally asymmetric keratoconus, independent of their baseline contrast imbalance level. Cyclopean viewing may be inherently biased towards the input from the stronger eye in keratoconus.

Keywords: Binocular rivalry; Contrast sensitivity; Contrast balance point; D-index; Interocular difference

Losses in monocular and binocular visual functions due to increased corneal distortions are well-known in keratoconus.[1-5] Of these, random-dot stereoacuity, an indicator of binocularity, *is impaired 10- to 12-folds* in unilateral and bilateral keratoconus, relative to age-similar controls.[2, 5] This loss is expectedly larger with spectacle than rigid contact lens wear in this disease condition.[2, 3, 5, 6] Stereoacuity losses have been hypothesized to arise from poor correspondence matching between the optically distorted monocular retinal images[6] and/or due to suppression of the weaker eye from interocular contrast imbalances in asymmetric keratoconus.[3] *This study specifically addressed the impact of interocular contrast imbalance on stereoacuity in cases with bilaterally asymmetric severity of keratoconus.*

Several psychophysical paradigms have been employed to quantify interocular contrast imbalance, primarily in the context of balancing monocular neural inputs in amblyopia.[7] These dichoptic paradigms include tasks of global motion coherence,[7, 8] letter acuity,[9] phase combination[10, 11] and contrast rivalry[3]. The present study used the contrast rivalry paradigm to quantify the extent of interocular contrast imbalance in keratoconus.[3] In this paradigm, the pattern of contrast rivalry switches between the monocular percepts is mapped while viewing orthogonally-oriented Gabor patches.[3] In baseline viewing, the percentage of time each eye's grating orientation was perceived (dwell time) is biased towards the eye with lesser disease severity (i.e., the stronger eye) in keratoconus.[3] This dwell time is balanced when this contrast imbalance is minimized by decreasing the stimulus contrast presented to the stronger eye.[3] The extent of contrast attenuation required in the stronger eye for a balanced dwell time is taken as a measure of the contrast imbalance in these cases. *This contrast "balance point" has been shown to shift closer to 0% contrast, signaling greater contrast imbalance with increasing interocular disease severity.*[3]

Several lines of evidence demonstrate a link between interocular contrast difference and impaired stereoacuity.[12] Individuals with habitual myopic anisometropia or presbyopes corrected using the monovision strategy have good spatial vision *at both distance and near fixation* but deteriorated stereoacuity owing to the interocular difference in retinal image contrast.[12] Stereoacuity loss in healthy human observers is typically greater when the contrast reduction is applied to only one eye than when applied to both eyes equally.[13-15] Cross-correlation of monocular retinal images that are dissimilarly blurred by point spread functions derived from asymmetric keratoconus produces higher rates of false correspondence matches and lower disparity signal-to-noise ratios, eventually leading to poor stereoacuity, relative to stereoacuity derived from similarly blurred point spread functions.[6] Stereoacuity is poorer in those with strong sensory eye dominance, relative to those with nearly equal dominance of the two eyes.[16] Stereoacuity of anisometropic and strabismic amblyopes is inversely related to the contrast imbalance in the two eyes and balancing the contrast inputs produces a commensurate improvement in stereoacuity.[17] All five observations indirectly suggest that the contrast imbalance between the two eyes may explain the stereoacuity loss in bilaterally asymmetric keratoconus.

Three specific objectives were tested in the present study. *The first objective was to determine the correlation between the keratoconic subject's stereoacuity against their interocular contrast imbalance using the paradigm described in Marella et al. (2021),[3] with the caveat that correlation does not indicate a causal relationship between the two variables.* This objective tested the hypothesis that stereoacuity will be inversely correlated with the extent of contrast difference between the two eyes in keratoconus. The second objective was to evaluate the subject's stereoacuity at baseline (i.e., with 100% stimulus contrast in both eyes) and at their contrast balance point to test whether stereoacuity in keratoconus is improved when monocular retinal image contrasts are equalized. This objective tested the hypothesis that stereoacuity *will be better* at the contrast balance point, *relative to baseline* and that this improvement will be greater for cases with poorer stereoacuity at baseline. The third objective was to determine whether a purposeful bias in the interocular stimulus contrast ratio either in favor of the stronger eye or in favor of the weaker eye will cause symmetric loss of stereoacuity in keratoconus, both relative to the stereoacuity at the contrast balance point. This objective tested the hypothesis that the stereoacuity will be equally poor in both biased viewing conditions.

Methods

Study participants

Forty-three cases (16 to 33 years; 26 males and 17 females) with bilaterally asymmetric keratoconus and 10 age-matched controls (21 to 33 years; 4 males and 6 females) were recruited for the study amongst the patient, staff and student pool of the *L V Prasad Eye Institute (LVPEI), Hyderabad, Telangana, India*. The study protocol was in accordance with the tenets of the Declaration of Helsinki and was approved by the institutional review boards of LVPEI and City, University of London. All adult cases signed a written informed consent form and assent was obtained from cases <18 years of age. The diagnosis of the keratoconus was confirmed through standard clinical and topographical findings.[18] Cases with visual acuity of 20/100 or better in the weaker eye were recruited to ensure that they were able to resolve the 5cpd grating stimulus used in the binocular rivalry task. Cases with corneal pathology associated with or independent of keratoconus, oculomotor dysfunction or co-morbidities that may unduly influence the study results were excluded. Ten cases were experienced contact lens wearers and they discontinued contact lens wear two weeks prior to the study. All other cases were habitual spectacle wearers. All the controls had logMAR visual acuity of 20/25 or better in both eyes and Randot stereoacuity of 40 sec of arc or better, and *did not have* any ocular pathology in the two eyes. The correlation between stereoacuity and contrast balance point (objective 1 of the study) was tested in all 43 cases while stereoacuity measurements at different interocular contrast combinations (objectives 2 and 3 of the study) were tested in a subset of 33 cases who consented to participate in additional experimental sessions of this study. Control subjects participated in a separate experiment that systematically determined the relation between stereoacuity and changes in stimulus contrast in one or both eyes simultaneously. *This experiment was intended to provide* the necessary reference data to compare the results obtained from cases in this study.

Estimation of contrast imbalance using the contrast rivalry paradigm

In accordance with the paradigm described in Marella et al.(2021),[3] cases dichoptically viewed orthogonally-oriented Gabor patches (right eye: 45° orientation and left eye: 135° orientation) with 5cpd carrier spatial frequency on a gamma calibrated LCD monitor (1680 × 1050 pixel resolution, 59Hz refresh rate) displayed and controlled using MATLAB (R2016a; The MathWorks, Natick, USA) with Psychtoolbox interface.[19] The task was performed at 50cm with the subject's best-corrected spectacle prescription incorporated in a trial frame and with their accommodation and pupils in natural state. The dichoptic stimuli were fused using a handheld stereo viewer with built-in periscopic mirrors to adjust for the subject's phoria and interpupillary distance (Screen-Vu Stereoscope, Portland, USA). Data collection began once the subject reported stable fusion of the bounding box and crosses around each Gabor patch through the stereo viewer (Figure 1).

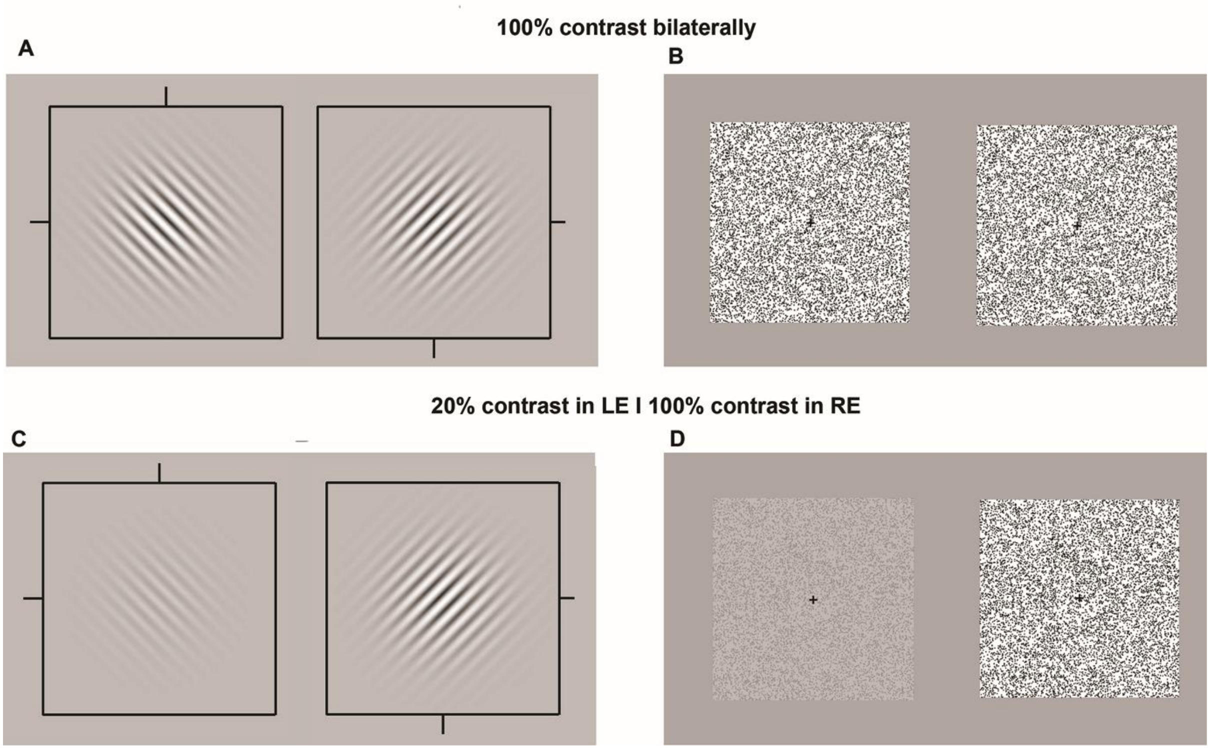

Figure 1: Examples of orthogonally oriented Gabor stimuli at baseline (panel A) and with 80% interocular difference in contrast (panel B) used for estimating the contrast balance point. Examples of random-dot stereograms with the same two contrast combinations for estimating stereoacuity at baseline (panel C) and with 80% interocular difference in contrast (panel D). Image pairs can be cross fused to appreciate contrast rivalry in panels A and B and stereo depth of a rectangular bar in panels C and D.

This task was performed with 100% contrast grating presented to each eye (baseline; Figure 1A) and with 6 levels of suprathreshold interocular contrast difference (2.5%, 5%, 10%, 20%, 40%, 80%; Figure 1B), presented in random order. The contrast difference was induced by attenuating the stimulus contrast to the stronger eye of cases while maintaining the weaker eye's contrast at 100%. Cases viewed the stimuli for 60sec and reported every instance of a complete switch in grating orientation using arrow keys on the keyboard. They were explicitly instructed to ignore periods of piece-meal rivalry during the task.[3] The dwell time on each grating orientation was calculated as the sum of the elapsed time between key presses over the 60sec duration.[3] The percent dwell time on the weaker eye's percept was then plotted as a function of stimulus contrast and a spline interpolation function was fit to these data to determine the percentage contrast in the weaker eye when the dwell time became equal in both eyes [see Figure 2B in Marella et al.(2021)[3]]. This percent contrast value was considered as the contrast balance point, the primary outcome measure of this test.

Measurement of random-dot stereoacuity

Cases viewed random dot stimuli of a rectangular bar oriented either with a leftward tilt or a rightward tilt in eso disparity on the same LCD monitor and using the same handheld stereo viewer at 50cm with their best-corrected spectacle correction (Figure 1C and D). Cases made 2-alternative forced-choice judgments of the bar tilt for every stimulus presentation while the retinal disparity varied in a 2-down and 1-up adaptive staircase for 11 reversals. The average of the last 8 reversals was recorded as the subject's stereoacuity in units of arc seconds as the primary outcome measure of this test.

Stereoacuity was estimated in the following four conditions on each case in random order: 1) at baseline with ~100% contrast of the random-dot pattern shown to both eyes, 2) at the estimated contrast balance point of the subject and 3) and 4) with 20% interocular contrast difference on either side of the contrast balance point. An interocular contrast difference of 20% higher than the balance point in the stronger eye effectively biased the viewing in favor of the stronger eye (third condition) and an interocular contrast difference of 20% lower than the balance point effectively biased the viewing in favor of the weaker eye (fourth condition). For cases with balance point <20% or >80%, the contrast bias was set to 10% on the either side of the balance point. The Michelson's contrast of the random dot stimuli was reduced by changing the luminance of black dots on the white background (Figure 1D). All cases undertook a sequence of learning trials before the actual test and frequent breaks were provided to avoid fatigue and boredom. In total, the duration of both paradigms was ~40-60min.

Measurement of visual acuity and corneal topography

In addition to binocular rivalry and stereoacuity, monocular high contrast visual acuity and corneal topography were also measured in each case using standard clinical protocols. Visual acuity was estimated using an electronic projection chart (COMPlog; Medisoft Inc., Leeds, UK) at a 3m using a protocol described in detail elsewhere.[3] Corneal topography scans were obtained using the Wavelight Oculyzer II (Pentacam HR Technology, Oculus, Arlington, USA). The eye with higher D-index (a unitless topographic measure of corneal distortions[20]) and poorer acuity was designated as the weaker eye. The severity of keratoconus was also graded into mild (<48D steepest keratometry value), moderate (48-53D), severe (53-58D) and advanced (>58D) categories based on the Amsler-Krumeich classification.[21] *Unlike Marella et al.(2021)*[3]*, most cases in the present study had an interocular difference in D-index ≤10 (except one subject with an interocular D-index difference of 14) to ensure that they did not exhibit suppression of the weaker eye and had measurable stereoacuity.*[3, 22]

Stereoacuity with contrast variations in controls

Stereoacuity was determined in the 10 control subjects by purposefully reducing stimulus contrast in the two eyes equally from 100% to 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10%, 5% and 2.5% or by changing only the dominant eye's contrast in the same range while fixing the non-dominant eye's contrast at 100%. *The latter manipulation created interocular difference in contrast of* 0%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% and 97.5%, respectively. Ocular sighting dominance was determined in all these subjects using the hole-in-the-card test. All the contrast combinations described above were tested in random order.

Data analysis

Data analysis was performed using SPSS version 21 (IBM SPSS, Chicago, USA) and Matlab R2016a. The Shapiro-Wilk test indicated that stereoacuity and contrast balance point – both *continuous outcome variables* – were non-normally distributed and, therefore, non-parametric tests were used for all analyses. The hypothesis of the first study objective was tested by determining the rank correlation coefficient between baseline stereoacuity and the contrast balance point using the Spearman's rank correlation coefficient. Visual inspection of the data revealed a monotonic relation between the two variables, satisfying the assumption required for deriving this correlation. The hypotheses of the second and third study objectives that stereoacuity will be significantly better in the contrast balanced condition, *relative to baseline*, and that the two contrast biased conditions will worsen stereoacuity, *relative to the contrast balanced condition*, were tested using the rank-based Friedman test. Similarly, the hypothesis that stereoacuity of controls will deteriorate with an equal or unequal reduction of stimulus contrast in the two eyes was also tested using the rank-based Friedman test. Both sets of data represented repeated measurements of a continuous variable obtained from the same cohort of cases or controls (4 conditions in cases and 12 conditions each for equal and unequal contrast reduction in controls), thus satisfying the assumptions for conducting the Friedman test. The *Wilcoxon Signed-rank test* was then used for pairwise comparison of stereoacuities between the different contrast combinations in cases and controls. Each comparison represented paired and continuously distributed stereoacuity values obtained from independent experiments of a given stimulus contrast combination, satisfying the assumptions for conducting the

Wilcoxon Signed-rank test. Bonferroni correction was subsequently applied to the output of each pairwise comparison to avoid increased risk of Type-I errors in the analysis.

Results

The 43 cases included 14 eyes with mild keratoconus, 18 with moderate and 11 with severe keratoconus in their weaker eye; 33 eyes with mild keratoconus and 10 eyes with moderate keratoconus in their stronger eye.[21] Cases had a wide range of D-indices and keratometry readings (Table 1), with interocular difference in D-index ranging from 0.25 to 14.74 and average keratometry ranging from 0.05D to 21D.

Correlation between stereoacuity and contrast balance point in cases (Study objective 1)

The baseline stereoacuity ranged from 24.39 – 2093.8 arc sec and the interocular contrast difference ranged from 0% – 91.4% across all 43 cases that participated in this study (Table 1). Baseline stereoacuity of cases was modestly negatively correlated with their contrast balance point [Spearman's rho (ρ)=-0.47, *P*=.002] (Figure 2). Three data points (open circles in Figure 2) show good stereoacuity irrespective of their moderate balance point. These were considered to be outliers, but their removal did not significantly alter the strength of the relation between variables (ρ=-0.53, *P*<.001). This result supports the hypothesis of the first study objective that stereoacuity in keratoconus is inversely related to the contrast balance point, albeit with the caveat that this relation is modest owing to significant intersubject variability.

Table 1: *Demographic, visual acuity, corneal topography and manifest refractive error of keratoconic cases in this study. All data shown here are median with 25th to 75th interquartile*

ranges. Refractive error was represented M (spherical equivalent), J0 and J45 are the cross-cylinder powers. M/F: male to female ratio.

Age (years)		21 (16 to 33)	
Gender (M/F)		26/17	
		Stronger eye	**Weaker eye**
Visual acuity (logMAR)		0.04 (0.00 to 0.08)	0.3 (0.2 to 0.4)
D index		5.7 (3.6 to 8.1)	9.5 (6.6 to 11.6)
Keratometry (D)	**Maximum**	47.2 (45.4 to 49.4)	51.3 (48.6 to 55.6)
	Minimum	44.4 (43.7 to 45.5)	46.9 (45.4 to 50.4)
Refractive error (D)	**M**	-2.3 (-3.1 to -1.3)	-3.6 (-5.9 to -1.6)
	J0	0.07 (-0.6 to 0.4)	-0.2 (-1.2 to 0.5)
	J45	0.0 (-0.3 to 0.8)	0 (-0.9 to 0.9)
Stereoacuity (arc sec)		667.9 (203.3 to 1245.5)	
Contrast balance point (%)		50 (21.8 to 68.8)	

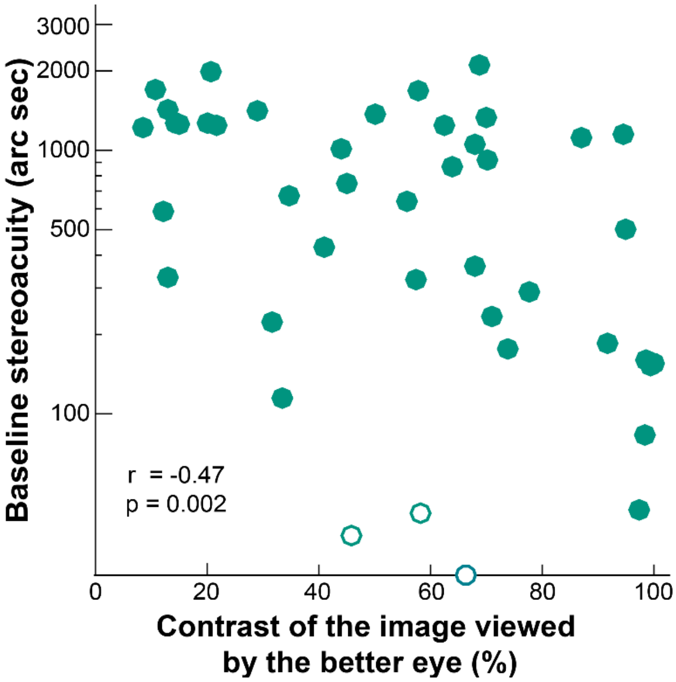

Figure 2: Baseline stereoacuity of cases plotted as a function of the image contrast viewed by better eye (i.e., contrast balance point).[3] Open circles in the figure represents outliers. The contrast balance point plotted along the abscissa represents the 1- interocular contrast imbalance, with 100% contrast balance point representing no interocular difference in contrast (Figure 1, panels A and C) and 20% contrast balance point representing 80% interocular difference in contrast (Figure 1, panels B and D).

Stereoacuity at baseline and at the contrast balance point in cases (Study objective 2)

Stereoacuity was re-tested in a subset of 33 cases at contrast balanced condition and on either side of the balance point. Figure 3 plots stereoacuity as a function of the interocular difference in stimulus contrast for three representative cases with different contrast balance points. In general, stereoacuity improved for all three cases at their respective contrast balance points, relative to baseline values (Figure 3). Amongst these cases, case 1 had the poorest stereoacuity at baseline (1423arc sec), followed by case 2 (641arc sec) and then case 3 (234arc sec) (Figure 3). The stereoacuity of all three cases improved at their respective contrast balance points, with the quantum of change being approximately similar in first two cases (28% and 35% in cases 1 and 2, respectively) while it was significantly larger (87%) and reached the level of controls in case 3 (Figure 3).

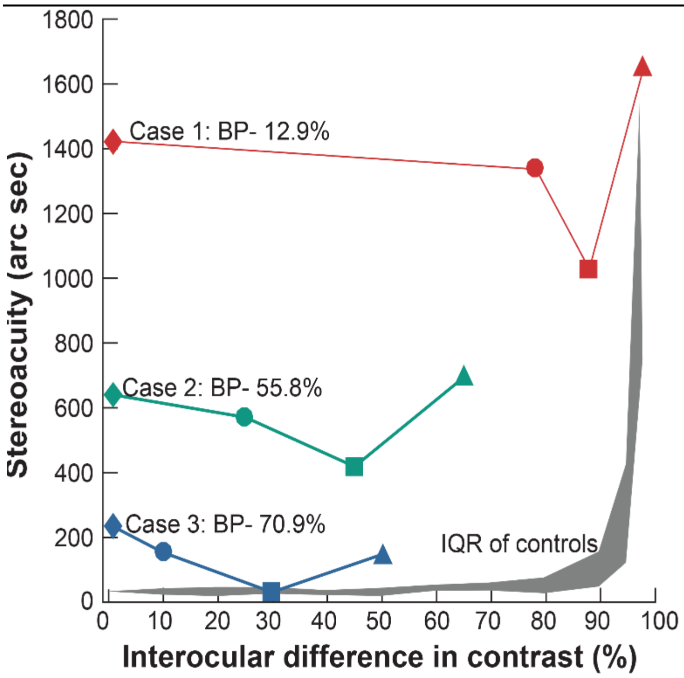

Figure 3: Stereoacuity plotted as a function of the interocular difference in stimuli contrast for three representative cases with different contrast balance points (BP). For each subject, the four data points represent the stereoacuity measured at baseline (i.e., 0% interocular difference in stimulus contrast) (diamond symbols in the figure), the stereoacuity measured at the individual's contrast balance point (square symbols in the figure) and stereoacuity measured for the conditions with contrast bias in favor of the stronger eye (20% above the balance point) (circle symbols in the figure) and contrast bias in favor of the weaker eye (20% below the balance point) (triangle symbols in the figure). The gray band shows 95% confidence interval of stereoacuity obtained from controls in this study (See section on Stereoacuity with induced interocular differences in contrast in controls for details).

Across the 33 cases, 28 showed an improvement in stereoacuity from baseline to the contrast balanced condition, while the remaining 5 cases showed no improvement or slight deterioration in stereoacuity at the contrast balanced condition. The median (25th to 75th IQR) stereoacuity of cases was 748.8arc sec (261.3 – 1257.3arc sec) at baseline and it improved to 419.0arc sec (86.6 to 868.9arc sec) at their respective contrast balance points (*Wilcoxon Signed-rank test*; Z=4.3; P<.001) (Figure 4A). This corresponded to a median improvement in stereoacuity of 34.6% (19.0 – 65.1%) from baseline to the contrast balanced condition (Figure 4A). The results of individual cases in the baseline and contrast balanced condition are shown in a scatter diagram in Figure 4B. Data points of majority of cases fell below the 1:1 line of equality in the contrast balanced condition, relative to baseline, indicating an improvement of stereoacuity in the former condition relative to latter (Figure 4B). The quantum of improvement in stereoacuity from baseline to the contrast balance point was however poorly correlated with the baseline stereoacuity (ρ=-0.19, P=.29) and with the subject's balance point

(ρ=0.2, P=.26). Taken together, these results only partially support the hypothesis of the second objective of the study in that contrast balancing improves the stereoacuity of cases, relative to their baseline, but this improvement is far from complete restoration to the level of controls. The hypothesis that the quantum of improvement in stereoacuity is inversely related to their corresponding baseline stereoacuity was not supported by the present data.

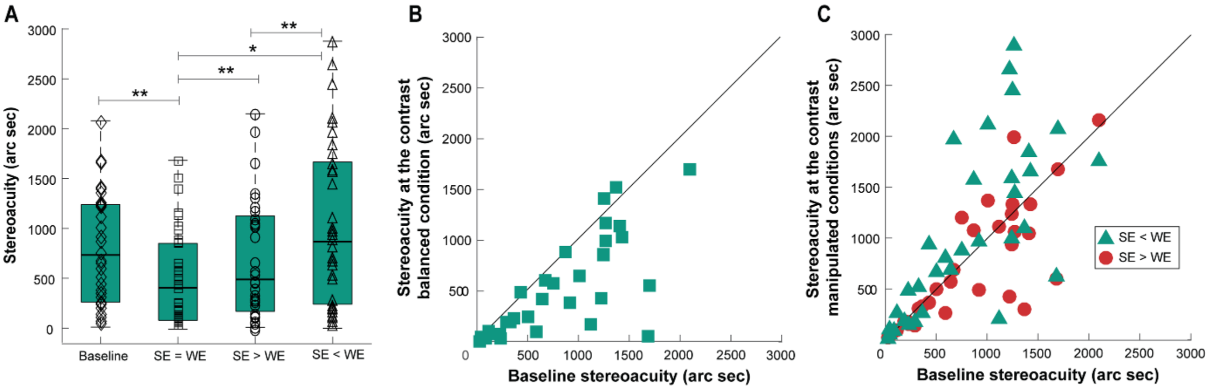

Figure 4: Box and Whisker plots of stereoacuity obtained at the four testing conditions in this study – baseline, at the subject's contrast balance point [Stronger eye (SE) = Weaker eye (WE)], at contrast of the stronger eye 20% above the contrast balance point (SE > WE) and at contrast of the stronger eye 20% below the contrast balance point (SE < WE) (Panel A). Single and double asterisks represent p<.01 and p<.001, respectively. Statistically non-significant differences amongst pairs are not shown here. The solid black line within the box represents the median value, lower and upper edges of the box indicate the 25th and 75th interquartile range and lower and upper whiskers indicate the 1st and 99th quartile. The gray square, circle and triangle symbols represent the individual data points at three contrast combinations (refer to figure 3 legend). Panel B shows scatter diagram of stereoacuities obtained at contrast balance condition plotted against baseline stereoacuity values. Panels C shows the stereoacuity in contrast biased conditions plotted as a function of baseline stereoacuity.

Stereoacuity with interocular contrast biases in cases (Study objective 3)

Representative data from the three cases in Figure 2 and the median data in Figure 4A clearly indicated that the stereoacuity in the two contrast biased conditions were significantly worse than the stereoacuity at the contrast balanced condition (*Wilcoxon Signed-rank test*; $Z \geq 3.61$; $P < .002$, for both). The stereoacuity values were however asymmetrically distributed around the contrast balance point, with the loss being significantly greater when the contrast was biased in favor of the weaker eye [881.3arc sec (239.6 – 1707.6arc sec)] than when it was biased in favor of the stronger eye [502.6arc sec (181.9 – 1161.4arc sec)] ($Z=3.29$, $P=.012$) (Figure 4A). The stereoacuities were comparable to baseline [748.8arc sec (261.3 – 1257.3arc sec)] when the contrast was biased in favor of the stronger eye ($Z=1.73$, $P=.08$) and the weaker eye ($Z=2.46$, $P=.09$) (Figure 4A). Figure 4C shows a scatter diagram of the stereoacuity of individual cases at the two contrast biased conditions in relation to the baseline stereoacuity. Stereoacuity of cases were *above the 1:1 line when the contrast was biased towards* the weaker eye, indicating worse stereoacuity compared to baseline condition. *On the other hand, the stereoacuity was comparable to the baseline with the data points closer to the 1:1 line when the contrast was biased towards the stronger eye.* These results only partially supported the hypothesis of the third study objective that biasing the contrasts of the two eyes in favor of the stronger or weaker eye causes a drop in stereoacuity, but this loss was asymmetric around the contrast balance point.

A secondary analysis was also performed to determine the association between interocular difference in visual acuity and D index with the balance point and stereoacuity in keratoconus. Larger interocular difference in logMAR visual acuity was associated with lower contrast balance point (ρ=-

0.54, *P*<.001) and poorer stereoacuity (ρ=0.37, *P*=.01). Interocular difference in D-index was, however, not significantly correlated with contrast balance point (ρ=-0.22, *P*=.16) or stereoacuity (ρ=0.17, *P*=.28).

Stereoacuity with contrast variations in controls

For equal reduction of stimulus contrast in the two eyes of controls, stereoacuity remained constant at a median (25th – 75th IQR) value of 29arc sec (14.4 – 43.2arc sec) up to 10% stimulus contrast (Z<1.58, *P>.11*) (Figure 5A). Beyond this level, stereoacuity decreased significantly to 85.6arc sec (51.6 – 122.3arc sec) and 97.2arc sec (68.1 – 258arc sec) for the 5% and 2.5% stimulus contrast, respectively (Z>2.8*, P<.005*, for both) (Figure 5A). For unequal reduction of contrast in the two eyes, controls showed a remarkably stable stereoacuity until 80% of interocular difference in contrast (25th to 75th IQR of stereoacuity: 14.4 – 43.2arc sec) *(P=.13*), beyond which there was a rapid deterioration of stereoacuity (745.3 – 1538.8arc sec for 97.5% interocular difference in contrast) (*P<.001*) (Figure 5B).

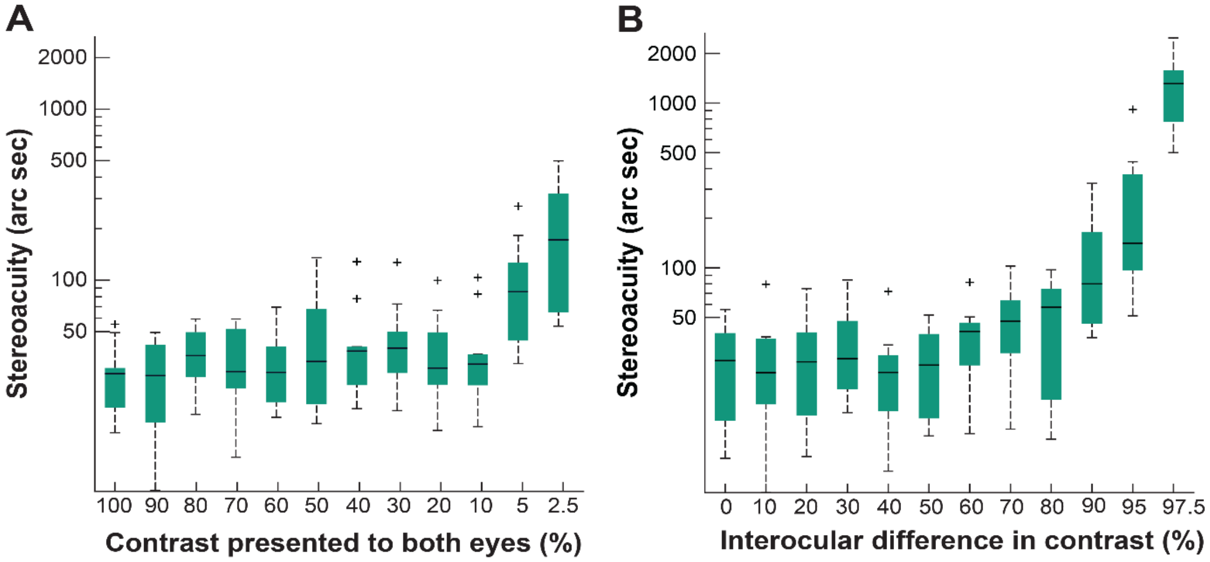

Figure 5: Box and Whisker plots of stereoacuity of controls as a function of equal reduction in stimulus contrast in both eyes (panel A) and interocular difference in contrast between the two eyes (panel B). The solid black line within the box represents the median value, lower and upper edges of the box indicate the 25th and 75th interquartile range and lower and upper whiskers indicate the 1st and 99th quartile. Plus symbols indicate outliers.

Discussion

Summary of findings

1. There was a modest but statistically significant negative correlation between interocular contrast balance and stereoacuity across all 43 subjects that participated in the study (Figure 2).
2. Stereoacuity measured at the contrast balance point improved between 19.0 – 65.1% in the subset of 33 cases, relative to baseline viewing (Figures 3 and 4A and B).
3. Biasing the stimulus contrast ratio of the two eyes either in favor of the stronger eye or the weaker eye resulted in predictable losses of stereoacuity, relative to the contrast balance point (Figure 4A and C).
4. The loss of stereoacuity in control subjects was greater for interocular differences in contrast than for equal reduction in contrast in both eyes (Figure 5), confirming earlier findings (Figure 5).[13-15]

Implications of results for depth perception in keratoconus

These results reiterate the importance of interocular differences in retinal image quality in defining the status of binocularity in bilaterally asymmetric keratoconus. Larger interocular differences in visual acuity and D-index were associated with larger interocular contrast imbalance and poorer stereoacuity in the present and previous study by *Marella et al.(2021).*[3] This association, however, did not reach statistical significance in the present cohort, potentially due to the recruitment of patients with a restricted range of keratoconus asymmetry. That the stereoacuity was intact up to an interocular contrast difference of 80% beyond which it started to deteriorate is not surprising because the modulation transfer functions for 0.50D to 1.00D spherical blur produces the contrast loss of at least 80%.[23] These results suggest that keratoconic patients who had contrast difference of 80% might be the ones who benefit the most from contrast balancing. While losses of stereoacuity in asymmetric keratoconus and their partial recovery with rigid contact lens wear have been demonstrated earlier,[2, 5] the present study provides the basis, at least partially, for such losses occurring in keratoconus. The highly compromised stereoacuity with spectacles and their partial improvement with RGP contact lenses in keratoconus may reflect the larger interocular contrast differences present *in spectacles than in contact lenses*,[2, 5] as can be interpreted from the corresponding patterns of higher-order wavefront aberrations and retinal image quality.[6] *Optical corrections for keratoconus should therefore not only aim to improve the overall optical quality in one eye but also minimize interocular difference in optical quality to optimize binocularity.* Similar clinical recommendations have been made for patients post keratorefractive procedures for myopia, albeit the effect being much smaller than in keratoconus.[24]

Reasons for partial improvement of stereoacuity with contrast balancing in keratoconus

Stereoacuity of cases should have improved by a median of 719arc sec to reach the level of controls [29.1arc sec (14.4 – 43.2 arc sec)] (Figure 1), but the observed improvement in stereoacuity was only a median of 330arc sec (19.0 – 65.1%) with contrast balancing (Figure 5A). Three factors might explain this partial improvement in stereoacuity. First, retinal image quality is determined by a combination of contrast loss and phase shifts, both of which increase with the magnitude of higher-order wavefront aberrations in the optical system *(~2- to 5-fold in keratoconus compared to controls*[4, 25]).[26, 27] The impact of contrast loss on retinal image quality and visual function is well-documented in keratoconus[27] but changes in the phase transfer function are yet to be systematically investigated in this disease condition.[26, 28] Metlapally et al. demonstrated that the cross-correlation of monocular retinal images for binocular disparity computation is significantly affected by phase shifts introduced by higher-order aberrations in keratoconus.[6] Indeed, a combination of contrast loss and phase shifts due to higher order aberrations explained the empirical loss of stereoacuity in keratoconus, more than each variable alone, in their study.[6] As a limitation, the present study did not address the impact of phase shifts or their correction on stereoacuity in keratoconus. This issue needs further investigation in future studies.

Second, the measure of contrast balance achieved in this study using the contrast rivalry paradigm may not fully reflect the balance point of inputs from the two eyes that optimizes random-dot stereoacuity. Stereoacuity was measured using random-dot stereograms *containing broadband spatial frequency spectra*[29] and requiring a fine level of correspondence matching to perceive stereo depth. Binocular contrast rivalry, on the other hand, was measured with Gabor patches containing single spatial frequency and single pair of orthogonal orientations. These two aspects of binocularity are mediated through different neural mechanisms that may have different sensitivities for interocular differences in stimulus properties.[30] This imperfect approach may also explain why only a modest negative correlation between the contrast balance point and stereoacuity was observed in this study (Figure 3) and why the percentage change in stereoacuity with contrast balancing was not correlated with the contrast balance point of the subject (Figure 5C). Stereoacuity could have also been measured using Gabor patches with spatial frequency matched to the contrast rivalry stimulus to address dissimilarities in stimulus properties between the two outcome measures.[13] Such an attempt was indeed made during the pilot phase of the project but the investigators were unsuccessful in creating a vivid sense of depth using these stimuli even in controls. Hence, the study was continued using random-dot stereograms that produced a strong sensation of depth. Other measures of contrast balance reported in the literature (e.g., dichoptic motion coherence) either suffer from the same limitation of stimulating different neural mechanisms,[31] or are simply unsuitable for the keratoconus cohort owing to the optics of the disease interfering with the stimuli used in these paradigms (e.g., dichoptic phase combination using sinewave gratings).[11] Therefore, the present study is limited by this imperfect approach and its results should be interpreted as a proof of concept for contrast balancing improving stereoacuity of cases with bilaterally asymmetric keratoconus. Should equivalent stimuli be used for measuring stereoacuity and contrast balance in the future, the stereoacuity improvement with contrast balancing may be greater and with better correlation than what is presently reported (Figures 3 and 5C).

Third, the keratoconic visual system may show neural insensitivities akin to meridional amblyopia, due to prolonged exposure to blur from partially-corrected astigmatism and higher order aberrations.[32] Indeed, Sabesan and Yoon demonstrated in a small cohort of keratoconics that their monocular high-contrast visual acuity remained poorer than that of age-similar healthy controls, even after both cohorts were rendered aberration-free in their adaptive-optics set-up.[33] The deleterious impact of neural insensitivity on stereoacuity of patients with developmental pathology like anisometropic amblyopia is well-known.[34] Although all of the patients included have passed beyond the critical age for amblyopia, more subtle cortical changes might still be possible. While a direct demonstration of such a relation is not available thus far for keratoconus, the present results in the two contrast biased conditions point to inherent biases of inputs from the two eyes in keratoconus (Figure 5A). That the stereoacuity deterioration was asymmetrical suggests that the signal from the stronger eye of keratoconus might be weighted more than the signal strength from the weaker eye. Even when the stimulus condition is biased to favor the weaker eye, the relative weakening of signal from the stronger eye may have resulted in the stereoacuity worsening much more than when the bias was in favor of the stronger eye.

Comparison of present results with previous literature on amblyopia

The present results are also in line with the previous evidence noted in amblyopia by Webber et al. who demonstrated partial improvement in stereoacuity when the contrast is balanced, albeit using a different paradigm for interocular contrast balancing from the present study and a different study group of cases with abnormal binocular vision development.[17] They also performed a similar experiment of reducing contrast in only one eye of their control cases using Bangerter filters and observed a significantly steeper drop in stereoacuity with interocular contrast difference than what was observed here (Figure 2).[17] Stereoacuity became nearly immeasurable (>3.0log arc sec) with only 40% interocular contrast difference in their study,[17] while it remained close to 1.5log arc sec with 97.5% interocular contrast difference (Figure 2). While exploring the reasons for the difference in results is beyond the scope of the present study (e.g., methodology used for creating interocular contrast difference and measuring stereoacuity or cohort-level differences), the results do suggest that contrast balancing may be beneficial for those even with smaller interocular differences in contrast that what was observed from the control cohort in the present study.

Conclusions

In conclusion, stereoacuity losses in bilaterally asymmetric keratoconus may be driven by contrast imbalances in the two monocular inputs. Stereoacuity may be partially restored in these patients by minimizing the contrast difference between the two eyes. Inherent biases may also exist in the way the monocular inputs from the two eyes are processed in keratoconus for cyclopean viewing which may determine the status of binocularity in these patients.

Acknowledgments

The authors thank all the participants of this study. This study was financially supported by a partnership grant from the Department of Biotechnology, Govt. of India to the L V Prasad Eye Institute (BT/PR32404/MED/30/2136/2019).

References:

1. Ferdi AC, Nguyen V, Gore DM, et al. Keratoconus Natural Progression: A Systematic Review and Meta-Analysis of 11 529 Eyes. Ophthalmology 2019;126:935-45.
2. Nilagiri VK, Metlapally S, Kalaiselvan P, et al. Logmar and Stereoacuity in Keratoconus Corrected with Spectacles and Rigid Gas-Permeable Contact Lenses. Optom Vis Sci 2018;95:391-8.
3. Marella BL, Conway ML, Suttle C, Bharadwaj SR. Contrast Rivalry Paradigm Reveals Suppression of Monocular Input in Keratoconus. Invest Ophthalmol Vis Sci 2021;62:15.
4. Nilagiri VK, Metlapally S, Schor CM, Bharadwaj SR. A Computational Analysis of Retinal Image Quality in Eyes with Keratoconus. Sci Rep 2020;10:1321.
5. Devi P, Kumar P, Marella BL, Bharadwaj SR. Impact of Degraded Optics on Monocular and Binocular Vision: Lessons from Recent Advances in Highly-Aberrated Eyes. Semin Ophthalmol 2022:1-18.
6. Metlapally S, Bharadwaj SR, Roorda A, et al. Binocular Cross-Correlation Analyses of the Effects of High-Order Aberrations on the Stereoacuity of Eyes with Keratoconus. J Vis 2019;19:12.
7. Mansouri B, Thompson B, Hess RF. Measurement of Suprathreshold Binocular Interactions in Amblyopia. Vision Res 2008;48:2775-84.
8. Li J, Hess RF, Chan LY, et al. Quantitative Measurement of Interocular Suppression in Anisometropic Amblyopia: A Case-Control Study. Ophthalmology 2013;120:1672-80.
9. Kwon M, Wiecek E, Dakin SC, Bex PJ. Spatial-Frequency Dependent Binocular Imbalance in Amblyopia. Sci Rep 2015;5:17181.
10. Huang CB, Zhou J, Lu ZL, et al. Binocular Combination in Anisometropic Amblyopia. J Vis 2009;9:17 1-6.
11. Kwon M, Lu ZL, Miller A, et al. Assessing Binocular Interaction in Amblyopia and Its Clinical Feasibility. PLoS One 2014;9:e100156.
12. Evans BJ. Monovision: A Review. Ophthalmic Physiol Opt 2007;27:417-39.
13. Schor C, Heckmann T. Interocular Differences in Contrast and Spatial Frequency: Effects on Stereopsis and Fusion. Vision Res 1989;29:837-47.
14. Legge GE, Gu YC. Stereopsis and Contrast. Vision Res 1989;29:989-1004.
15. Halpern DL, Blake RR. How Contrast Affects Stereoacuity. Perception 1988;17:483-95.
16. Han C, He ZJ, Ooi TL. On Sensory Eye Dominance Revealed by Binocular Integrative and Binocular Competitive Stimuli. Invest Ophthalmol Vis Sci 2018;59:5140-8.
17. Webber AL, Schmid KL, Baldwin AS, Hess RF. Suppression Rather Than Visual Acuity Loss Limits Stereoacuity in Amblyopia. Invest Ophthalmol Vis Sci 2020;61:50.
18. Romero-Jimenez M, Santodomingo-Rubido J, Wolffsohn JS. Keratoconus: A Review. Cont Lens Anterior Eye 2010;33:157-66; quiz 205.
19. Brainard DH. The Psychophysics Toolbox. Spat Vis 1997;10:433-6.
20. Duncan JK, Belin MW, Borgstrom M. Assessing Progression of Keratoconus: Novel Tomographic Determinants. Eye Vis (Lond) 2016;3:6.
21. Krumeich JH, Daniel J, Knulle A. Live-Epikeratophakia for Keratoconus. J Cataract Refract Surg 1998;24:456-63.

22. Antunes-Foschini RMS, Coutinho J, Rocha EM, Bicas HEA. Oculomotor Status, Binocular Vision, and Stereoacuity in a Series of Keratoconus Subjects. Invest Ophthalmol Vis Sci 2018;59:1869-77.
23. Hopkins HH. The Frequency Response of a Defocused Optical System. Proc R Soc A 1955;231:91-103.
24. Moreno-Barriuso E, Lloves JM, Marcos S, et al. Ocular Aberrations before and after Myopic Corneal Refractive Surgery: Lasik-Induced Changes Measured with Laser Ray Tracing. Invest Ophthalmol Vis Sci 2001;42:1396-403.
25. Kumar P, Bandela PK, Bharadwaj SR. Do Visual Performance and Optical Quality Vary across Different Contact Lens Correction Modalities in Keratoconus? Cont Lens Anterior Eye 2020;43:568-76.
26. Sarver EJ, Applegate RA. The Importance of the Phase Transfer Function to Visual Function and Visual Quality Metrics. J Refract Surg 2004;20:S504-7.
27. Ravikumar A, Marsack JD, Bedell HE, et al. Change in Visual Acuity Is Well Correlated with Change in Image-Quality Metrics for Both Normal and Keratoconic Wavefront Errors. J Vis 2013;13:28.
28. Ravikumar S, Bradley A, Thibos L. Phase Changes Induced by Optical Aberrations Degrade Letter and Face Acuity. J Vis 2010;10:18.
29. Field DJ, Brady N. Visual Sensitivity, Blur and the Sources of Variability in the Amplitude Spectra of Natural Scenes. Vision Res 1997;37:3367-83.
30. Cormack LK, Stevenson SB, Landers DD. Interactions of Spatial Frequency and Unequal Monocular Contrasts in Stereopsis. Perception 1997;26:1121-36.
31. Zhou J, Reynaud A, Yao Z, et al. Amblyopic Suppression: Passive Attenuation, Enhanced Dichoptic Masking by the Fellow Eye or Reduced Dichoptic Masking by the Amblyopic Eye? Invest Ophthalmol Vis Sci 2018;59:4190-7.
32. Harvey EM. Development and Treatment of Astigmatism-Related Amblyopia. Optom Vis Sci 2009;86:634-9.
33. Sabesan R, Yoon G. Visual Performance after Correcting Higher Order Aberrations in Keratoconic Eyes. J Vis 2009;9:6 1-10.
34. Levi DM, Knill DC, Bavelier D. Stereopsis and Amblyopia: A Mini-Review. Vision Res 2015;114:17-30.