Suprathreshold contrast perception of resolvable high spatial frequencies remain intact in keratoconus

Preetam Kumar Bopt[1,2,3], Pravin Krishna Vaddavalli MS[4], Peter Campbell PhD[1], Christopher C. Hull PhD[1] and Shrikant R. Bharadwaj PhD[2,3]

Author affiliations:

[1]Department of Optometry and Visual Science, School of Health and Psychological Sciences, City, University of London, Northampton Square, London – EC1V 0HB, United Kingdom.

[2]Brien Holden Institute of Optometry and Vision Sciences, L V Prasad Eye Institute, Road no. 2, Banjara Hills, Hyderabad – 500034, Telangana, INDIA.

[3]Prof. Brien Holden Eye Research Centre, Hyderabad Eye Research Foundation, L V Prasad Eye Institute, Road no. 2, Banjara Hills, Hyderabad – 500034, Telangana, INDIA.

[4]The Cornea Institute, L V Prasad Eye Institute, Road no. 2, Banjara Hills, Hyderabad – 500034, Telangana, INDIA.

Corresponding author: Shrikant R. Bharadwaj

Brien Holden Institute of Optometry and Vision Sciences, L V Prasad Eye Institute, Road no. 2, Banjara Hills, Hyderabad – 500034 Telangana, INDIA.

bharadwaj@lvpei.org

Running title: Suprathreshold contrast perception in keratoconus

Number of figures in manuscript: 6

Number of tables in manuscript: 3

Word count in abstract: 250

Word count in the original manuscript: 6200

Word count in the revised manuscript: 7139

Date of original submission: 25th March 2023

Date of submission of revised manuscript: 4th June 2023

Abstract

Contrast detection thresholds are elevated with optical quality loss in keratoconus. This study hypothesized that suprathreshold contrast perception is also impaired in keratoconus, with the impairment being predictable from the pattern of loss in threshold-level performance. Contrast detection thresholds were determined across a range of spatial frequencies in 12 cases with mild to severe keratoconus and 12 age-similar controls. These values were used to predict the contrast needed to achieve perceptual matches between reference and test spatial frequency pairs (peak of CSF Vs. 0.3x, 0.5x, 2x or 3x spatial frequency from the peak) for stimuli at 10% and 50% suprathreshold contrast. Contrast thresholds predicted a 1.5 to 6.7-fold increase in the test pattern's contrast to obtain a perceptual match with the reference pattern in keratoconus, relative to controls. Contrary to predictions, the empirical data of contrast matches between test and reference patterns were similar for higher than peak spatial frequencies at both contrast levels. However, as predicted, test patterns required higher contrast than the reference pattern for a perceptual match for lower than peak spatial frequencies. These results were similar to controls and invariant of disease severity, interocular asymmetry and short-term changes in optical quality. Unlike thresholds, suprathreshold contrast perception of resolvable high spatial frequencies appears immune to optical quality losses in keratoconus. These results are discussed in the context of the prevailing models of contrast constancy in healthy humans. Breakdown of contrast constancy at lower than peak spatial frequencies may reflect the properties of the testing paradigm employed here.

Keywords: Contrast sensitivity; Contact lens; Contrast matching; Image quality; Keratoconus; Spatial vision

Deterioration of threshold-level visual performance with optical quality loss is well-established in keratoconus [e.g., visual acuity and contrast sensitivity (Devi, Kumar, Marella & Bharadwaj, 2022, Nilagiri, Metlapally, Kalaiselvan, Schor & Bharadwaj, 2018, Nilagiri, Metlapally, Schor & Bharadwaj, 2020, Shneor, Pinero & Doron, 2021)]. However, these measures do not provide a complete description of the patient's vision because the bulk of humans' visual experience occurs at suprathreshold levels (Haun & Peli, 2013, Jarvis, Triantaphillidou & Gupta, 2022, To, Gilchrist, Troscianko & Tolhurst, 2011). For instance, the perception of a naturalistic scene involves processing contrasts that are significantly higher than detection thresholds and at spatial frequencies that are significantly lower than the acuity limit (Haun & Peli, 2013, Jarvis et al., 2022). Perceived contrast matches at suprathreshold levels occur at similar physical contrast levels in humans with normal vision even though their contrast detection thresholds vary by several orders of magnitude across spatial frequencies (Brady & Field, 1995, Georgeson & Sullivan, 1975, Kulikowski, 1976, Smith, 2015). This "contrast constancy" might reflect an active normalization of suprathreshold visual inputs to compensate for threshold-level losses in performance (Georgeson & Sullivan, 1975). Alternatively, contrast constancy may also reflect uniform gains across spatial frequency channels, with sensitivity losses occurring due to a reduction in signal-to-noise ratio at threshold (Brady & Field, 1995). Irrespective of the model, threshold-level losses in contrast perception across spatial frequencies may not manifest as deficiencies at suprathreshold levels in visually healthy human observers.

It is well-known that contrast sensitivity progressively degrades with increasing disease severity in keratoconus (Devi et al., 2022, Kumar, Bandela & Bharadwaj, 2020) and that these losses primarily arise from the underlying loss of retinal image quality from increased wavefront aberrations of the distorted cornea (Devi, Kumar & Bharadwaj, 2023, Metlapally, Bharadwaj, Roorda, Nilagiri, Yu & Schor, 2019, Nilagiri et al., 2020). However, very little is known about the status of suprathreshold contrast perception in keratoconus. It is important to address this issue for two reasons: first, it will determine if the loss of spatial vision in keratoconus is restricted only to the detection of fine details and threshold levels of contrast or whether the losses extend to stimuli typically encountered in day-to-day living. The latter may have an impact on the patient's quality of life beyond what is predicted from the deficit in visual acuity and contrast sensitivity. Second, losses in suprathreshold contrast perception may indicate that, like threshold level performance, the neural outputs of the different spatial frequency channels are also impacted at suprathreshold levels by the optical quality losses in keratoconus. Conversely, contrast constancy at suprathreshold may reflect recalibration of neural

gains across spatial frequency channels to account for the exaggerated loss of contrast sensitivity in this disease condition (Georgeson & Sullivan, 1975). It could also reinforce the hypothesis that suprathreshold contrast gains are uniform across spatial frequency channels, regardless of the increased threshold level noise from optical degradation in the keratoconic visual system (Brady & Field, 1995).

The primary aim of this study was to test the status of suprathreshold contrast perception in different severities of keratoconus, relative to age-similar controls. The well-established contrast matching paradigm that was employed to demonstrate the phenomenon of contrast constancy in visual healthy humans (Georgeson & Sullivan, 1975) was employed to evaluate suprathreshold contrast perception in this study (Experiment 1). The study tested the hypothesis that, unlike controls, contrast constancy will be impaired owing to the exaggerated loss of optical quality in keratoconus and that the deficiency may be predicted from the corresponding threshold-level losses in contrast sensitivity. As a corollary, the study also hypothesized that the quantum of loss in contrast constancy will be directly proportional to the severity of keratoconus. Figure 1 illustrates these predictions using data of a representative control and three keratoconic cases that participated in the present study. Relative to the control, the contrast threshold function of cases showed an overall constriction arising from an increase in contrast detection thresholds across all spatial frequencies and a shift in the trough of the contrast threshold function towards lower spatial frequencies (Figure 1A). The fold-change in contrast required to achieve a suprathreshold perceptual match between the test and reference stimuli was calculated from these curves by dividing the threshold contrast of the test stimuli by that of the reference stimulus (Figure 1B). Contrast constancy is absent if the empirical data from contrast matches yield the same fold-change as predicted from this figure *– i.e., at a given suprathreshold level, the test stimulus required the same proportion of increased contrast as seen at threshold for a perceptual match with the reference stimulus.* Conversely, contrast constancy is complete if the empirical fold-change was unity – *i.e., a perceptual match was obtained between the test and reference stimuli at the same physical contrast level, indicating complete compensation for the lower contrast sensitivity of the test stimuli at threshold* (Figure 1B). Ng et al (2022) recently observed contrast constancy for spatial frequencies that are habitually experienced by keratoconic eyes. However, contrast constancy was not present for frequencies artificially made visible through adaptive optics manipulation (Ng et al., 2022). *Based on this observation, the study hypothesized that contrast constancy will be present for spatial frequencies within the contrast sensitivity function in*

keratoconic eyes. A complete breakdown in contrast constancy was deemed as the null hypothesis of the study. It is worth to acknowledge that, given the robustness of this phenomenon, the chance of accepting the null hypothesis was rather remote.

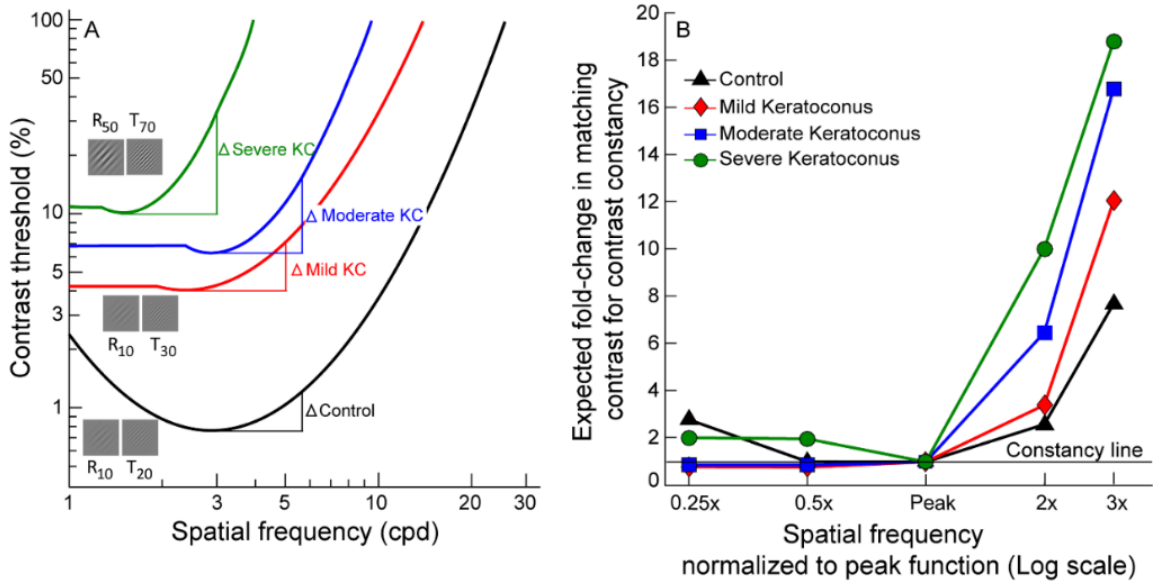

Figure 1: *Panel A) Representative contrast threshold function for a control subject and three cases with mild, moderate, and severe keratoconus that participated in this study. Representative pairs of the test (T) and reference (R) grating patterns used in the contrast matching paradigm of this study are shown in this figure (see also Methods). Panel B) Fold-change in suprathreshold matching contrast expected from the contrast threshold functions for the different spatial frequencies tested in this study. The abscissa plots $\log_{10}$ values of spatial frequency, normalized to the peak values of the subject.*

This study also evaluated two additional aspects of suprathreshold contrast perception that are relevant for the everyday visual experience of patients with keratoconus. Experiment 2 addressed variations in suprathreshold contrast perception in bilaterally asymmetric keratoconus. *This study hypothesized that contrast constancy will be impaired to a greater extent in the optically worse eye relative to the better eye and that the pattern of binocular contrast constancy will be dominated by the pattern observed in the better eye (Devi et al., 2022, Marella, Conway, Suttle & Bharadwaj, 2021). Information about the suppressed stimulus appears to impact information processing in the higher cortical areas, potentially impacting contrast processing at suprathreshold levels in these eyes (Tong, Meng & Blake, 2006).* Experiment 3 determined changes in contrast constancy when the viewing experience of patients with keratoconus changes from habitual contact lens wear to spectacle lens wear. While retinal image quality and threshold-level visual performance are known to be superior with rigid contact lens wear than spectacles in keratoconus (Devi et al., 2022, Nilagiri et al., 2018), equivalent changes in suprathreshold contrast perception have remained unexplored. This study

hypothesized that the pattern of contrast constancy observed in a subject may be established over extended time periods for a relatively uniform viewing experience. Any sudden alteration to this viewing experience, such as the degradation of image quality induced by switching from contact lenses to spectacles in keratoconus, or its restoration with contact lens wear within a short period of time, may lead to a break-down of contrast constancy.

Methodology

Subjects

The study was conducted at the L V Prasad Eye Institute (LVPEI), Hyderabad, India. Ethics committee approval was obtained from the Institute's internal review board. The study protocol was in accordance with the Declaration of Helsinki and all subjects had the study explained to them before signing written consent forms. Twelve cases (age range: 20 – 32 years; 8 males and 4 females) with a confirmed diagnosis of bilateral keratoconus, using clinical signs (e.g., Vogt's striae, Fleischer's ring) and corneal tomography data (e.g., superior-inferior asymmetry in corneal curvature and elevation, asymmetric bow-tie pattern, relative corneal thinning etc.) were recruited from the patient pool of LVPEI. Patients with corneal scar, retinal pathology or any other ocular co-morbidity that can affect contrast perception were excluded. Twelve age-similar controls (23 – 27 years; 7 males and 5 females) were recruited from the post graduate students and staff pool at LVPEI.

Assessment of the corneal structure

An assessment of the corneal structure of cases and controls was performed using a Scheimpflug imaging technique (WaveLight Oculyzer II®, Alcon, Fort Worth, USA) (Kanellopoulos & Asimellis, 2012). The Belin-Ambrósio enhanced ectasia display map, derived from the tomography data, was used to obtain the D-index for all cases and controls (Duncan, Belin & Borgstrom, 2016, Shajari, Steinwender, Herrmann, Kubiak, Pavlovic, Plawetzki, Schmack & Kohnen, 2019). This index includes deviations of front and back surface elevations of the cornea, pachymetric progression, thinnest corneal point and deviation of Ambrósio relational thickness maximum. The D-index is considered to be the most comprehensive measure of corneal shape and has been found to have good reliability in diagnosis keratoconus and determining its severity/progression over time (Shajari et al., 2019). For keratoconus, higher D-index values indicate greater disease severity. The D-index was obtained from both eyes of each subject. For those with similar disease severity in the two eyes, one eye was randomly allocated for psychophysical measurements. For those with interocular asymmetry in

disease severity, the eye with greater disease severity was considered for the psychophysical measurements. This strategy ensured that a wide range of disease severities were included to test the study hypothesis. Unlike some previous studies, visual acuity was not considered for grading disease severity (Kanellopoulos & Asimellis, 2012).

Psychophysical measurements

All psychophysical measurements were carried out with the subject's best-corrected spectacles (cases and controls) or rigid contact lenses (only cases) in a dimly-lit room with their natural pupils. Keratoconic cases wore conventional tri-curve rigid gas permeable contact lenses (Purecon McAsfeer, Silver line laboratory Pvt ltd, India) whose fitting was deemed appropriate by an experienced optometrist. Subjects were provided with sufficient breaks during the psychophysical procedures to avoid fatigue and boredom.

Assessment of threshold-level performance

Monocular and binocular high contrast logMAR acuity was determined with best corrected spectacles and contact lenses at 3m viewing distance using COMPlog® (Clinical Vision Measurement Systems Ltd, UK) (Laidlaw, Tailor, Shah, Atamian & Harcourt, 2008). For each level of vision, five Sloan letters, selected randomly from the complete Sloan optotype set, were displayed on an LCD screen (1680 × 1050 pixels) at 80cd/m^2 luminance. The acuity was determined by decreasing the angular height of the letter using a staircase thresholding algorithm until three out of five letters were incorrectly identified. Visual acuity was calculated by the software as the cumulative number of letters that were read correctly during optotype presentation, with a value of 0.02 logMAR units allotted per optotype (Laidlaw et al., 2008).

Monocular and binocular contrast sensitivity functions (CSF) were measured using a modified version of the quick CSF program, executed using Psychotoolbox-3® in Matlab® (Mathworks Inc, Natick, MA) (Brainard, 1997, Lesmes, Lu, Baek & Albright, 2010, Pelli, 1997, Rosen, Lundstrom, Venkataraman, Winter & Unsbo, 2014). In this task, a Gabor stimulus, orientated in one of two oblique directions (45° and 135°), was presented on a CRT monitor (1280 × 1024 pixels; 85 cd/m^2) with a spatial frequency ranging between 1 and 50cpd. Calibration of the CRT monitor was performed using a LS-110 luminance meter (Konica Minolta, Inc, Tokyo, Japan). The Bits# stimulus processor (Cambridge Research System Ltd, Kent, UK) was synchronized with the psychophysics toolbox to enhance the bit-

depth of the stimulus display on the CRT monitor, facilitating finer contrast measurements during the experiment. The stimulus subtended an angle of $4^{\circ} \times 4^{\circ}$ at the subject's ocular plane. Subjects judged the orientation of the Gabor stimulus in a 2AFC procedure from 1m viewing distance. The grating spatial frequency and contrast were varied in an adaptive thresholding manner, which included a one-step-ahead search algorithm to evaluate the next trial's possible results. This allows the threshold for the visible range of spatial frequencies to be estimated within 100 trials. The contrast sensitivity was summarised using three parameters: area under the curve, cut-off spatial frequency, and the contrast sensitivity at the peak of the CSF (Lesmes et al., 2010, Rosen et al., 2014).

Assessment of suprathreshold contrast matching

The contrast matching paradigm, implemented using Psychotoolbox-3®, was adapted from the previous work of Georgeson and Sullivan (Georgeson & Sullivan, 1975). For each trial, reference and test Gabor stimuli of different spatial frequencies were presented sequentially at the centre of the screen, each for 500ms duration. The reference grating had a spatial frequency corresponding to the peak of the CSF (R in Figure 1A) whereas the test grating, whose contrast changed during the procedure, had a spatial frequency set to a multiple of the spatial frequency of the reference grating (T in Figure 1A). Unlike the previous studies, where the spatial frequency of the reference grating was fixed (Brady & Field, 1995, Georgeson & Sullivan, 1975), this parameter was varied in this study to correspond to the peak spatial frequency of the CSF of each individual participant. The reference grating was manipulated in this study according to the threshold performance. This ensured that the reference and test gratings were resolvable by the subject, especially for cases with keratoconus. A fixation cross appeared at the centre of the screen during the exchange of stimuli to retain the attention of the subject. The order of presentation of the reference and test patterns were randomized across trials. Similarly, the orientation of the grating pattern was also randomized between 45° and 135° orientations across trials. The subject reported which of the two patterns was perceived with greater contrast after both presentations. Like previous literature on the measurement of contrast constancy (Georgeson & Sullivan, 1975), subjects were specifically instructed to base their judgment on the contrast of the stimulus and avoid other confounding cues such as brightness and sharpness of the grating pattern. Based on the response after each trial, the contrast of the test grating was increased or decreased using a 2-alternate forced choice 2-down 1-up adaptive staircase procedure. The initial assignment of physical contrast of the test pattern was randomized and a given staircase was terminated after the completion of 8 reversals. The matching

contrast for that test pattern, in comparison to the reference pattern, was calculated as the average contrast of the last 5 reversals.

Contrast matching in Experiment 1 was assessed at 10% and 50% contrast for spatial frequencies that were 0.25x, 0.5x, 2x and 3x that of the reference pattern's spatial frequency (Figure 1B). For each set of contrast matching trials, the spatial frequency of the test pattern and the suprathreshold contrast level of the reference pattern (10% or 50%) were randomly allocated and kept constant until the end of the trial. All contrast matching trials were also repeated twice on each subject. Thus, an entire session of data collection on a given subject contained 16 contrast matching trials (4 spatial frequency combinations x 2 suprathreshold contrasts x 2 repetitions = 16). These measurements were all made monocularly for each eye of the participant while the fellow eye was occluded. In two cases with advanced keratoconus, the contrast threshold at the peak of the CSF was close to 10%. In such cases, the contrast matches were obtained at 20% and 50% supra-threshold contrast levels. One keratoconic subject could not perform the task at the 20% contrast level and hence the experiment was conducted only at 50% contrast.

The expected fold-change in contrast match for the 10% and 50% suprathreshold stimulus was calculated for each participant from their contrast threshold function by dividing the threshold contrast of the test spatial frequencies by that of the reference spatial frequency. For instance, for the representative case shown in Figure 1A with moderate keratoconus, the test stimulus at 2x of peak spatial frequency is predicted to be 6-times higher in contrast to achieve perceptual match with the standard stimulus (Figure 1B). This resulted in an expected fold-change in contrast match of 6x for that spatial frequency, relative to the standard stimulus. *The observed fold-change in contrast match was defined as the ratio of the physical contrasts of the reference and test stimulus at which a perceptual match was observed psychophysically. The observed and expected fold-changes were then compared to determine the presence/absence of contrast constancy.* If the observed and expected fold-change in contrast matches were equal, it signalled the absence of contrast constancy. An observed fold-change in contrast match of unity signalled intact contrast constancy. *Subjects will not be able to achieve a perceptual match for certain combinations of test and reference stimulus that required a large fold-change in the expected contrast match, in the event of a complete failure of contrast constancy. For instance, in the example given above, if the expected fold-change for a given test-reference stimulus combination was 6x, the test stimulus had to be presented at 300%*

contrast to achieve a perceptual match with the reference stimulus at the 50% suprathreshold contrast level. Since this is not physically possible, the subject would not be able to make a perceptual match for this combination of test and reference stimuli.

Data for Experiment 2 were obtained by repeating the contrast matching paradigm on a subset of 5 subjects (20 – 32yrs; 2 males and 3 females) who participated in Experiment 1. These subjects had bilaterally asymmetric keratoconus determined from the D-index values. The eye with the higher of the two D-index values was designated the worse eye in these participants. Experiment 3 repeated the contrast matching paradigm on a subset of 3 subjects (23 – 26yrs; 2 males and 1 female) who had previously participated in Experiment 1. Data were obtained monocularly (right eye) at four different time points: with their habitual contact lens correction (data included in the analysis of main experiment), immediately after switching from contact lenses to spectacles, after one week of spectacle lens wear and after two weeks of spectacle lens wear. During this 2-week period, subjects did not use their habitual contact lenses.

Data analysis

Data analyses were performed using Matlab® R2016a and IBM SPSS statistics v20.0® (SPSS, Chicago, IL, USA). The Shapiro-Wilk test was used to determine normality and then data from cases and controls were compared using appropriate parametric or non-parametric tests. The impact of three independent factors – spatial frequency of the test pattern, suprathreshold contrast level and cohort type – on this fold-change in matching contrast was analysed using 3-factor repeated measures analysis of variance (RM-ANOVA). Spatial frequency of the test pattern and suprathreshold contrast level of the reference pattern were considered as independent factors to determine if, like previous studies (Brady & Field, 1995, Georgeson & Sullivan, 1975, Smith, 2015), their experimental manipulation produced predictable changes in the contrast constancy results in cases and controls. The cohort type was considered as an independent factor to determine if the pattern of contrast constancy differentially varied in subjects with and without the disease condition. Lack of statistical significance in this factor would indicate that contrast constancy is independent of the disease status. Post-hoc tests with Bonferroni correction for multiple comparisons were performed to determine the statistical significance of the pairwise differences in fold-change of matching contrast across different spatial frequencies. $P \leq 0.05$ was considered statistically significant. Effect size was quantified using the partial Eta-squared (η_p^2) statistic (Lakens, 2013). Since only a small number of

subjects participated in Experiments 2 and 3, their data were not subjected to any formal statistical analysis but described qualitatively, instead.

Results

Demographic details

The demographic details for the keratoconic subjects are shown in Table 1. Age and gender distribution were comparable to the controls that participated in this study. As expected, the corneal tomographic features such as the steeper and flatter keratometry values and the D-index was significantly higher in cases compared to controls ($p<0.001$) (Table 1). The D-index ranged from 1.3 to 6.9 in the better eye and from 9.1 to 33.3 in the worse eye of this cohort. For sphero-cylindrical refraction, the spherical equivalent (M) in power vector terminology (Thibos, Wheeler & Horner, 1997) was significantly higher in cases than in controls ($p<0.001$) while the regular (J0) and oblique astigmatism (J45) components were not statistically different between the cohorts ($p=0.4$ and $p=0.7$, respectively) (Table 1).

Experiment 1 - Visual acuity and contrast sensitivity

The mean spectacle-corrected high contrast logMAR visual acuity of cases was significantly poorer than the controls ($p<0.001$) (Table 1). Figure 2 shows representative data of the contrast threshold function and contrast matches obtained for the 10% and 50% stimuli from one control participant (panel A) and individual keratoconic case with mild, moderate, and severe disease (panels B – D). Contrast sensitivity was overall attenuated in cases, relative to controls, with this attenuation progressively increasing with the disease severity (Figures 1 and 2A – D). Table 1 shows three parameters of the contrast sensitivity function for cases and controls that participated in this study. All the parameters showed significant deterioration compared to controls ($p<0.001$). The area under the CSF parameter showed a significantly negative correlation with the D-index ($r=-0.84$; $p=0.001$) (Table 1, Figures 2B - D).

Table 1: *Demographic and clinical details of study participants. Cases are presented individually while control data is represented as mean±1SD of the outcome variable. All cases participated in Experiment 1, cases P4, P7, P9, P11 and P12 participated in Experiment 2 and cases P3, P6 and P8 participated in Experiment 3. For participants in Experiment 2, data from each eye and from both eyes are noted in the table. The M, J0 and J45 terms represent the sphero-cylindrical refractive error in power vectors, wherein M = spherical equivalent of refraction and J0 and J45 represent the regular and oblique astigmatic components of refraction (Thibos et al., 1997). M: F = Male: Female; HCVA= spectacle corrected high contrast visual acuity; Cpd = cycles per degree; AUCSF = Area under curve of contrast sensitivity function.*

Cohort	Age| Gender	Eye	Keratometry (D)		D-index (unitless)	Refraction (D)			HCVA (logMAR)	Contrast sensitivity function		
			Steep K	Flat K		M	J0	J45		Peak CS	Cut off SF (Cpd)	AUCSF (unit area)
P1	25 | M	LE	50.3	45.1	5.2	-3.0	-1.1	1.9	0.32	1.4	6.9	1.5
P2	26 | F	RE	50.6	47.9	9.4	-6.6	-0.9	-0.7	0.22	1.8	18.4	1.9
P3	23 | F	RE	53.9	49.7	8.0	-5.5	0.4	-1.9	0.14	1.4	15.4	1.3
P4	24 | F	RE	72.6	61.2	17.4	-18.0	0	0	0.68	1.1	9.1	0.8
		LE	48.8	48	5.1	-6.5	0	0	0.06	1.9	16.9	1.8
		Bino	N/A						0.1	2.2	17.5	2.0
P5	25 | M	LE	58.2	55.6	12.3	-19.3	-0.2	1.2	0.38	1.7	7.8	1.1
P6	24 | M	RE	64.6	56	19.2	-2.0	-2.0	0	0.66	1.4	9.1	0.9
P7	24 | M	RE	42.4	40.9	2.9	-0.5	0	0	0.0	1.5	18.2	1.5
		LE	50.5	46.3	9.1	-5.0	-1.5	1.3	0.22	1.0	6.9	0.8
		Bino	N/A						0.0	1.7	17.2	1.7
P8	25 | M	RE	41.6	40	2.9	-2.1	-0.6	0	0.14	1.8	14.7	1.8
P9	28 | M	RE	51	47.7	11.9	-1.5	1.4	-0.5	0.52	1.1	12.1	0.9
		LE	43.8	43.5	1.25	0	0	0	0.0	2.4	29.8	2.7
		Bino	N/A						0.0	2.4	36.6	2.8
P10	22 | M	RE	55.4	52.2	13.3	-2.8	0.5	-0.8	0.5	1.2	5.2	0.6
P11	21 | M	RE	45.8	45.1	2.9	-0.3	-0.2	-0.1	0.0	2.4	25.3	2.4
		LE	70.4	65.8	28.9	-9.0	0.5	2.9	0.8	1.8	7.4	0.5
		Bino	N/A						0.02	2.4	25.8	2.5
P12	32 | M	RE	49	46.6	6.9	-4.4	-0.4	0.8	0.1	1.9	15.3	1.8
		LE	74.0	70.7	33.3	-11.3	0.3	1.5	0.9	0.9	3.4	0.4
		Bino	N/A						0.08	1.8	15.5	1.7
Controls	24.8±2.2 7 M | 5 F	n=12	43.4±1.2	42.7±1.2	0.55±0.2	-1.6±3.7	-0.1±0.4	0.04±0.08	-0.03±0.04	2.3±0.2	25.9±4.6	2.4±0.2

Experiment 1 - Suprathreshold contrast matching

The fold-change for 10% and 50% contrast stimuli were close to unity for spatial frequencies higher than the peak but greater than unity for spatial frequencies lower than the peak (Figure 2A – D). The main effects of spatial frequency and suprathreshold contrast on the fold-change in contrast match was statistically significant for cases and controls (Table 2, Figure 2E and F). The interaction between the two main factors were also statistically significant for cases and controls (Table 2, Figure 2E and F). Fold-changes of matching contrasts in controls and cases were significantly higher and farther away from the unity value for the 10% contrast than for the 50% contrast, indicating lower magnitude

of contrast constancy for the former than latter stimuli (Figure 2E and F). Fold-changes were also significantly larger for the lower two spatial frequencies than the higher two spatial frequencies for both cases and controls (Table 2, Figure 2E and F). The fold-change for 0.25x spatial frequency was significantly greater the 0.5x spatial frequency, more so for the 10% than 50% contrast (Table 2, Figure 2E and F). Fold-changes for the 2x and 3x spatial frequencies were not significantly different from each other (Table 2, Figure 2E and F).

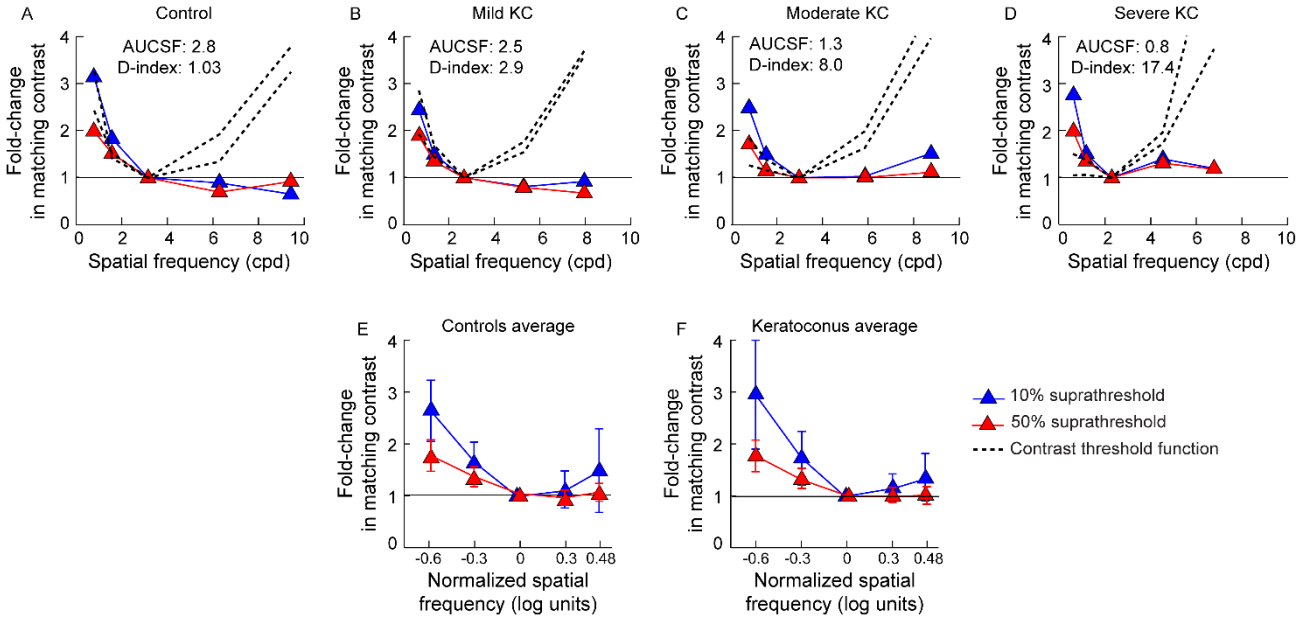

Figure 2: *Panels A – D: Fold-change in contrast of test grating required to match the perceived contrast of the reference grating for one representative control subject (panel A) and three representative cases with different severities of keratoconus (panels B – D; these panels correspond to cases P11, P3 and P4 in Table 1, respectively). Threshold and suprathreshold data in all panels are normalized to the peak spatial frequency of that participant. Dashed curves indicate ±95% confidence interval of the fold-change for contrast detection thresholds. The area under the contrast sensitivity function (AUCSF) derived from the threshold function and the D-index of the participant as a measure of disease severity are also noted. Panels E and F: Average (±1 SD) fold-change across all study participants in the controls and cases, respectively.*

Table 3 shows the mean (±1SD) expected fold-change from the contrast threshold function and the observed fold-change in contrast match for all test spatial frequencies in controls and cases. The P-values from t-tests performed to compare expected versus observed values are also included. The observed fold-change was similar to or higher than the expected fold-change for lower than peak spatial frequencies, relative to higher than peak spatial frequencies. This pattern was exaggerated for the 10% than 50% contrast (Table 3). The observed fold-change in contrast match across spatial frequencies was poorly correlated with D-index (Pearson's correlation coefficient for 10% contrast: $r=0.19$; $p\geq0.38$, 50% contrast: $r=0.3$; $p\geq0.15$) (Figure 3).

Table 2: *Outcomes of the 3-factor RM-ANOVA and post-hoc Bonferroni test performed to evaluate the statistical significance of the fold-change in contrast match with test spatial frequency and suprathreshold contrast in controls and cases.*

	F-value	P-value	η_p^2
Spatial frequency	F(4, 11) = 46.5	<0.001	0.81
Suprathreshold contrast	F(2, 11) = 41.9	<0.001	0.79
Cohort	F(2, 11) = 0.84	0.38	0.07
Spatial frequency x Cohort	F(4, 11) = 1.22	0.32	0.09
Spatial frequency x Suprathreshold contrast x	F(4, 11) = 14.5	<0.001	0.57
Suprathreshold contrast x Cohort	F(2, 11) = 0.81	0.38	0.07
Cohort x Suprathreshold contrast x Spatial frequency	F(2, 11) = 1.65	0.19	0.13
Post-hoc tests for spatial frequency			
0.25x – 0.5x	-	<0.001	-
0.25x – 2x	-	<0.001	-
0.25x – 3x	-	<0.001	-
0.5x – 2x	-	0.001	-
0.5x – 3x	-	0.12	-
2x – 3x	-	0.1	-

Table 3: *Mean (±1SD) expected and observed fold-change in contrast matching and the P-value of the corresponding paired T-tests for the 10% and 50% suprathreshold contrast in controls and cases.*

Suprathreshold contrast level	Spatial frequency	Expected fold-change	Observed fold-change	P-value	Expected fold-change	Observed fold-change	P-value
		Controls			Cases		
10%	**0.25x**	2.32 (0.9)	2.73 (0.6)	0.13	1.69 (1.0)	3.28 (1.3)	0.003
	0.5x	1.53 (0.3)	1.69 (0.3)	0.29	1.52 (0.9)	1.89 (0.6)	0.03
	2x	1.92 (0.4)	1.13 (0.4)	<0.001	2.16 (0.7)	1.15 (0.3)	0.001
	3x	5.09 (2.7)	1.53 (0.8)	0.001	6.67 (3.7)	1.35 (0.6)	<0.001
50%	**0.25x**	2.32 (0.9)	1.81 (0.3)	0.05	1.69 (1.0)	1.80 (0.2)	0.71
	0.5x	1.53 (0.3)	1.34 (0.2)	0.11	1.52 (0.9)	1.39 (0.3)	0.62
	2x	1.92 (0.4)	0.93 (0.1)	<0.001	2.16 (0.7)	0.95 (0.1)	<0.001
	3x	5.09 (2.7)	1.06 (0.2)	<0.001	6.67 (3.7)	1.02 (0.3)	<0.001

Experiment 2 – Suprathreshold contrast matching in bilaterally asymmetric keratoconus

As intended, significant disease asymmetry was noted in the five subjects that participated in the Experiment 2 (cases P4, P7, P9, P11 and P12 Table 1). Their D-index values ranged from 1.25 to 6.9 units in the better eye and 9.1 to 33.3 units in the worse eye (Table 1). The contrast threshold function for the two representative participants of this experiment showed a clear difference in performance between the worse eye and the better eye – the data showed a relatively more attenuated contrast threshold function in the worse eye, relative to the better eye (Figures 4A and B). Interestingly, the binocular contrast threshold function always matched or was slightly superior to the better eye in all cases (Figures 4A and B). The area under the contrast threshold function was lower for the worse eye (ranged from 0.4 to 0.8 units) compared to the better eye (ranged from 1.5

to 2.7 units) (Table 1). All other threshold parameters of contrast and spectacle corrected high contrast visual acuity in the worse eye was prominently reduced compared to the better eye performances (Table 1).

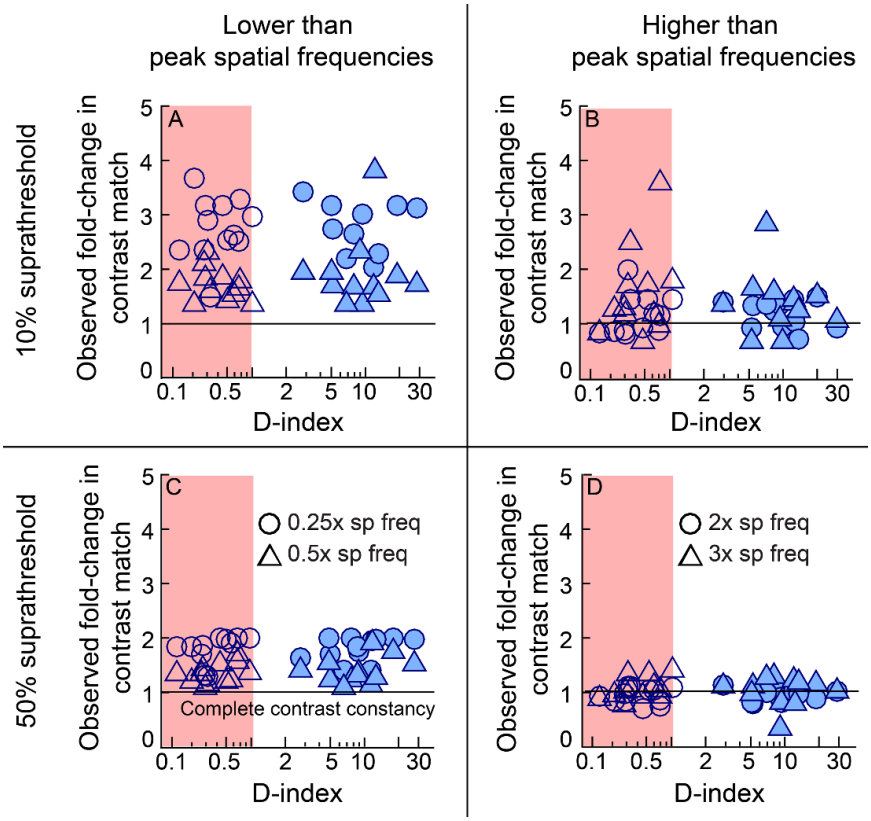

Figure 3: *Scatter diagram of the fold-change in suprathreshold contrast match plotted as a function of the D-index for all controls (open symbols within the red band) and cases (filled symbols) that participated in the study. Panels A and B show data for 10% contrast while Panels C and D show data for 50% contrast.*

Figures 4C and D shows a scatter diagram of the fold-change in contrast required for achieving a match between reference and test stimuli at the 10% and 50% suprathreshold levels while using the worse eye or under binocular viewing against the corresponding fold-change when using the better eye. The contrast matches obtained with the worse eye or under binocular viewing were similar to those obtained with the better eye, independent of the test spatial frequency (Figure 4). The data points for spatial frequencies higher than the peak were closer to the unity fold-change, relative to those lower than the peak (Figures 4C and D). This effect was more pronounced for the 50% contrast than the 10% contrast (Figures 4C and D).

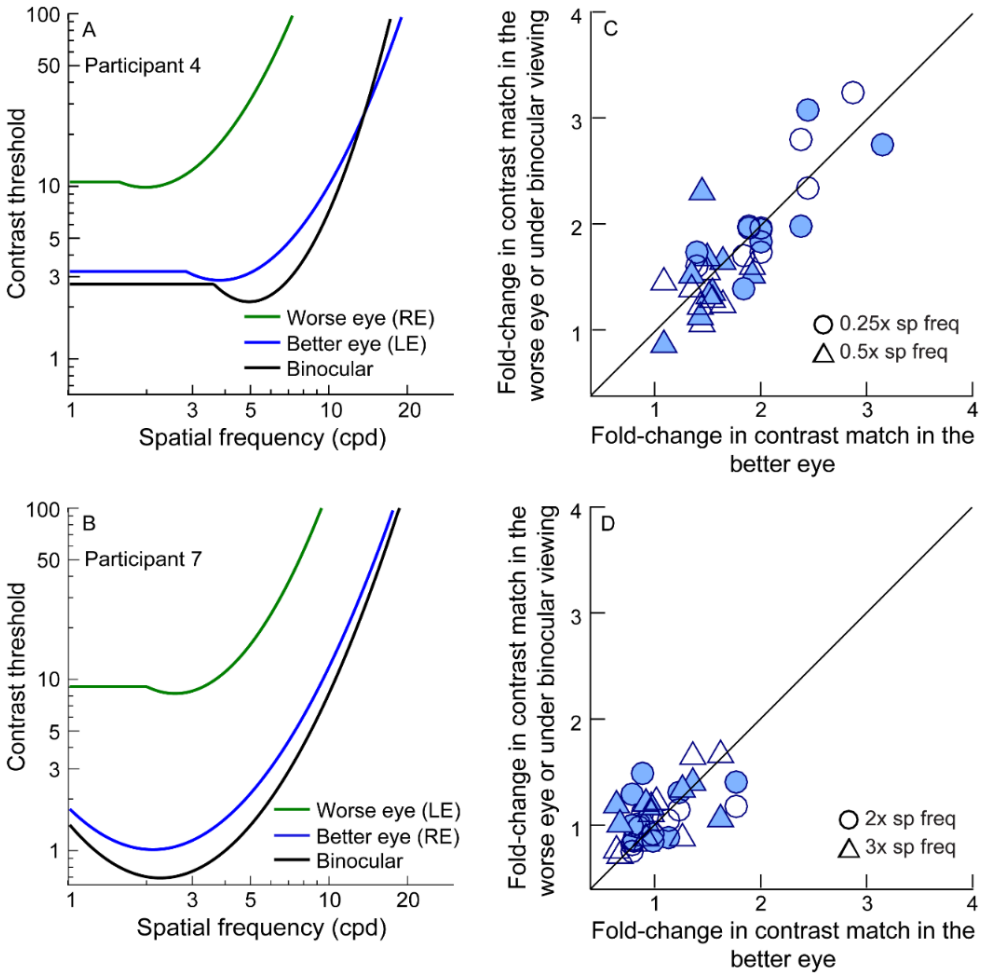

Figure 4: *Panels A and B show contrast threshold functions of the worse eye, better eye and binocular viewing of two representative cases with keratoconus (out of 5 cases) that participated in Experiment 2. Both these participants had large interocular asymmetry in their disease severity [right eye was worse than left eye in Participant 4 and left eye was worse than right eye in Participant 7 (Table 1)]. Panels C and D show scatter diagram of the fold-change in suprathreshold contrast match observed for the worse eye viewing (filled symbols) or binocular viewing (open symbols) plotted against the corresponding fold-change obtained for the better eye viewing in five participants with bilateral asymmetry in keratoconus. Panels C and D represent data for spatial frequencies lower than the peak and higher than the peak, respectively. Given the similarity in data trends for the 10% and 50% suprathreshold contrast levels, both sets of data are plotted together, without identifying them separately, in these two panels. The diagonal 1:1 line indicates equal contrast matching performance in the test conditions in these two panels.*

Experiment 3 – Changes in suprathreshold contrast matching with short-term changes in the eye's optical quality

The individual trend of the contrast threshold function with RGP contact lens as well as with the spectacles during the different visits are shown in Figures 5A – C for the three keratoconic cases that participated in Experiment 3 (cases P3, P6 and P8 in Table 1). All the three contrast sensitivity function parameters with the RGP contact lenses were significantly better compared to spectacles wear for all participants. Interestingly, an improvement in the threshold performance with the best

corrected spectacles was noted during the last visit (second week after lens removal) and this trend was most prominent for Participant 8 in this study (Figure 5C), relative to participants 3 and 6. Notably, the severity of keratoconus was least in participant 8, relative to the other two participants (Table 1). However, the performance did not reach the level of contact lens wear in any of the participants (Figure 5A – C).

Figure 5 plots the longitudinal data of each participant for all four spatial frequencies tested at the 10% and 50% suprathreshold contrast levels. As seen in previous results, the contrast matching data of all three subjects was close to the unity line for the 50% (Figures 5B, D and F) than for the 10% (Figures 5A, C and E) suprathreshold contrast level. The higher two spatial frequencies (2x and 3x) did not show any significant trends in the contrast matching fold-change values across the four visits for both suprathreshold stimuli (Figure 5). The lower two spatial frequencies (0.25x and 0.5x) did show a pattern of the fold-change in contrast match tending towards unity values in the second and third participants, but not in the first participant (Figure 5). These trends were more apparent for the 10% than for the 50% suprathreshold contrast stimuli (Figure 5). However, the hypothesized pattern of an increase in the fold-change immediately after switching from contact lenses to spectacles was not observed in any participant, for any spatial frequency or contrast level (Figure 5).

Discussion

Summary of results

While losses in visual acuity and contrast sensitivity are well-known in keratoconus (Kumar et al., 2020, Shneor et al., 2021, Xian, Sun, Ye, Zhang, Zhao, Shen, Lu, Zhou & Zhao, 2023), an assessment of suprathreshold performance in this disease condition has received little attention (Ng et al., 2022). The phenomenon of contrast constancy was used as a paradigm to address this issue in the present study. The results were overwhelmingly similar across the three experiments conducted here and between keratoconic cases and controls in the study. Stimuli at higher levels of suprathreshold contrast showed better contrast constancy than those at lower levels of suprathreshold contrast (Figures 2 and 3 and Tables 2 and 3). Similarly, stimuli with spatial frequencies higher than the peak of the CSF showed better contrast constancy than those lower than the peak of the CSF (Figures 2 and 3 and Tables 2 and 3). All these trends were independent of disease severity (Figure 3), its interocular symmetry (Figure 4) and short-term changes in the quality of threshold-level viewing experience (i.e., contact lens Vs. spectacles) (Figure 5). These results match well with the recent

observation of intact contrast constancy for spatial frequencies that are habitually experienced by keratoconic eyes (Ng et al., 2022).

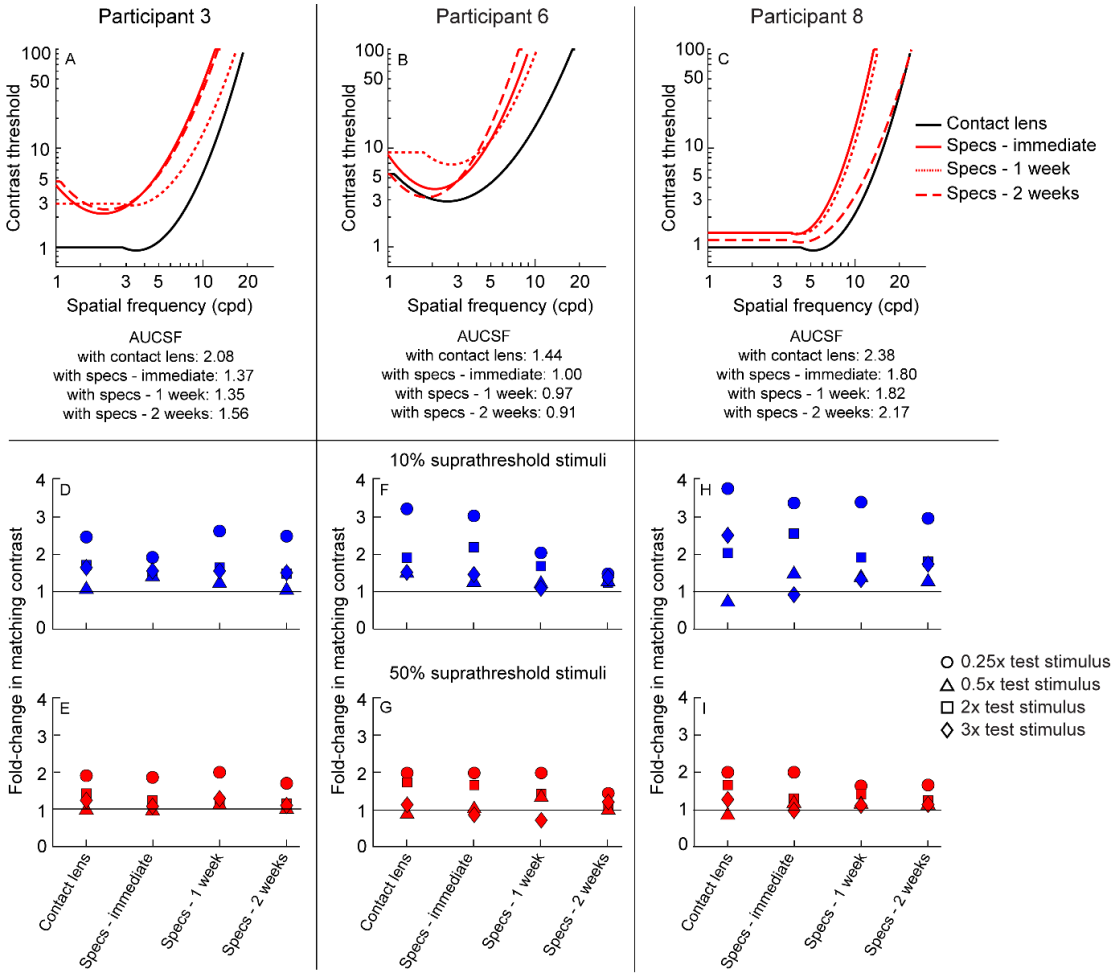

Figure 5: *Panels A – C show the monocular contrast threshold functions of the three cases with keratoconus that participated in Experiment 3 (corresponding to Participants 3, 6 and 8 in Table 1). Contrast threshold curves are plotted for contact lens wear and with their best-corrected spectacle correction immediately after switching from contact lens wear (Specs - immediate), one week of spectacle wear (Specs – 1 week) and two weeks of spectacle wear (Specs – 2 weeks) for each participant. The area under the CSF obtained for each viewing condition and each participant is also noted in this figure. Panels D – I show fold-change in suprathreshold contrast match for three participants across the four viewing conditions tested in this experiment. Panels D, F and H show data for 10% suprathreshold contrast stimuli while Panels E, G and I show data for the 50% suprathreshold contrast stimuli.*

Implication of results for contrast perception in keratoconus

The study outcomes have three important implications for contrast perception in keratoconus. First, the optical degradation in keratoconus progressively constricts the "visible" region of spatial vision in keratoconus (Figure 1A) (Kumar et al., 2020, Nilagiri et al., 2020, Shneor et al., 2021). The present results suggest that the perception of relative contrasts across different high spatial frequency stimuli

may remain intact within this visible region (i.e., for spatial frequencies between the peak and cut-off value of the CSF) across a range of keratoconus disease severities (Figures 2 and 3). Patients with keratoconus may thus not experience any local contrast variation across high spatial frequency components of natural scenes in their suprathreshold viewing experience. Variations in contrast perception across spatial frequencies may start becoming apparent as the target approaches threshold levels of contrast, as suggested by the relatively weaker pattern of contrast constancy for 10% than for 50% suprathreshold contrast stimuli in this study (Figures 2 – 4, Table 2). However, the observed fold-change in matching contrast for the 10% suprathreshold stimuli in keratoconus was still several orders of magnitude smaller than the expected fold-change based on the contrast threshold function (Table 3). This suggests that any variations in contrast perception of high spatial frequencies may be minor for patients with keratoconus under low suprathreshold contrast viewing conditions. Second, the pattern of contrast constancy for high spatial frequencies was similar for spectacles and contact lenses in this study (Figure 5), suggesting that correcting the optics of the keratoconic eye primarily serves to expand the region of visibility for spatial vision, as determined by the CSF, without having any significant impact on suprathreshold contrast perception. A natural scene with broad spatial frequency content may, however, appear sharper and crisper with these contact lenses owing to the overall expansion of the region of visibility to include higher spatial frequencies (Devi et al., 2022, Kumar et al., 2020, Lim & Lim, 2020, Marta, Marques, Almeida, Jose & Barbosa, 2021). Interestingly, Ng et al recently observed that contrast constancy fails for spatial frequencies that are not within the habitual visual experience of the keratoconic visual system (Ng et al., 2022). This implies that keratoconic patients who are habitual spectacle wearers and potentially adapted to a low-pass filtered retinal image may experience variations in contrast perception for high spatial frequencies soon after they switch to contact lenses. Contrast processing in the visual system eventually adjusts to the expanded range of spatial frequencies, as suggested from the lack of difference in results between spectacles and contract lenses in the seasoned contact lens wearers of the present study (Figure 5). The time course of such an adaptation needs further investigation. Describing other aspects of object appearance in the suprathreshold space (e.g., sharpness, clarity, etc) is beyond the scope of this study and also needs further investigation. Third, the pattern of contrast constancy across high spatial frequencies was remarkably similar in the two eyes of patients with bilaterally asymmetric keratoconus (Figure 4). This observation suggests that the perceived contrast of high spatial frequencies at suprathreshold levels may be largely similar in the two eyes of these patients even while their optical quality and threshold-level performance may show significant

interocular asymmetry. Expectedly, the contrast constancy pattern under binocular viewing conditions was similar to monocular viewing in these subjects (Figure 4). This observation leads to a prediction that keratoconic patients with bilaterally asymmetric disease severity may remain binocular for tasks involving suprathreshold judgments, while their threshold-level performance may be dictated by the performance of the better eye, leading to severe compromise in binocularity (Marella et al., 2021, Metlapally et al., 2019, Nilagiri et al., 2018). This prediction may be tested using appropriate paradigms in the future.

In addition to the steep drop in the contrast sensitivity for higher spatial frequencies, the CSF of keratoconic cases also showed an overall loss of sensitivity, all relative to controls (Figure 1). This overall loss was greater for eyes with more severe keratoconus (Figures 1, 4A and B) and for eyes with spectacles than contact lens correction (Figure 5A – C). The present study only assessed the relative perception of contrast across spatial frequencies for suprathreshold stimuli (essentially, the impact of the steep drop in the contrast sensitivity for higher spatial frequencies). The study did not address the impact of the absolute loss of contrast sensitivity at any given spatial frequency for suprathreshold stimuli. This issue is equally important to determine whether patients with keratoconus experience the suprathreshold visual scene with the same perceived contrast as healthy observers or are there deficiencies in the perception of absolute contrast with this disease condition. Such an intactness or deficiency in absolute contrast perception will provide insights on any normalization of neural activity within a given spatial frequency channel to optimize suprathreshold visual experience, especially with disease progression in the two eyes or in the presence of asymmetric disease severities in the two eyes. The experimental paradigm needed to study this question is, however, not trivial and needs to be investigated in a separate study.

Comparison of results with previous literature

The observation of near-complete contrast constancy for higher than peak spatial frequencies across the two different cohorts in the present study match well with the previous studies on this topic, albeit for the normal subjects (Figure 6) (Brady & Field, 1995, Georgeson & Sullivan, 1975). Contrary to the observations at high spatial frequencies, contrast constancy appears to fail for the two low spatial frequency stimuli tested in this study, more so lower than higher suprathreshold contrast stimuli (Figures 2 – 5). The pattern of contrast matches observed in keratoconic subjects for lower than peak spatial frequencies were very similar to those observed in healthy controls (Figures 2E and

F). These results indicate that keratoconic patients as well as the control subjects may perceive suprathreshold low spatial frequency stimuli to have lower contrast than their higher frequency counterparts. These results are partially at odds with the previous literature (Figure 6) (Brady & Field, 1995, Georgeson & Sullivan, 1975, Kulikowski, 1976). Like the present results, the data of Georgeson and Sullivan (1975) and, to a lesser extent, Brady and Field (1975) also showed poorer contrast constancy for lower than peak spatial frequencies, more so for lower than higher suprathreshold contrast stimuli (Figures 6A and C). The magnitude of the deviation was, however, not as much as what was observed in the present study (Figure 6). These differences may arise from the differences in the methodology employed to measure contrast constancy in these studies. First, the spatial frequencies of the reference pattern varied based on the threshold function of the subject in the present study while it was held constant across subjects in the previous studies (Brady & Field, 1995, Georgeson & Sullivan, 1975, Kulikowski, 1976). Second, the perceptual matches in suprathreshold contrast were achieved using an adaptive staircase method in this study while they were obtained using the method-of-adjustment in the previous studies, the reference and test stimuli were presented sequentially for 500ms each in the present study while they were presented simultaneously with a spatial separation between the two stimuli in the computer screen for as long as the subject required to complete the matching task in previous studies (Georgeson & Sullivan, 1975). Third, the stimulus size was fixed at 4° for all spatial frequencies in the present study while it was scaled to accommodate equal number of sine wave cycles in the previous studies (Brady & Field, 1995, Georgeson & Sullivan, 1975, Kulikowski, 1976). This posed a unique challenge to the subjects as some of them did actually report difficulty in performing the matching task for lower spatial frequencies as only a limited number of cycles of the grating stimulus was present for them to veridically judge the contrast. This was reflected in the increased number of trials during testing before obtaining the desired number of reversals in the staircase procedure and in the relatively larger inter-subject variability of the suprathreshold contrast match obtained for these spatial frequencies in controls and cases with keratoconus (Figures 2E and F). Fourth, in contrast to all the previous methodologies, the study by Smith used a rather unique experimental paradigm to test this phenomenon. Instead of the reference pattern having a fixed spatial frequency, suprathreshold contrast matches were tested for adjacent pairs of spatial frequencies spanning entire region of visibility (Smith, 2015). This paradigm enabled the stimulation of the same spatial frequency channel for the reference and test stimuli. However, the perception of contrast at suprathreshold appears to be a robust system to be influenced by his methodological difference as shown by the alignment of

their result with the present study (Figure 6). Taken together, we conclude that the present results may not necessarily reflect selective deficiencies of contrast processing in keratoconus but a uniqueness of the study methodology that may have led subjects to perceive suprathreshold low spatial frequency test patterns to have lower contrast than the reference pattern. The similarity in results of these experiments indicates that, unlike low spatial frequencies, contrast constancy for high spatial frequencies is robust enough to withstand the methodological differences encountered across studies (Figure 6).

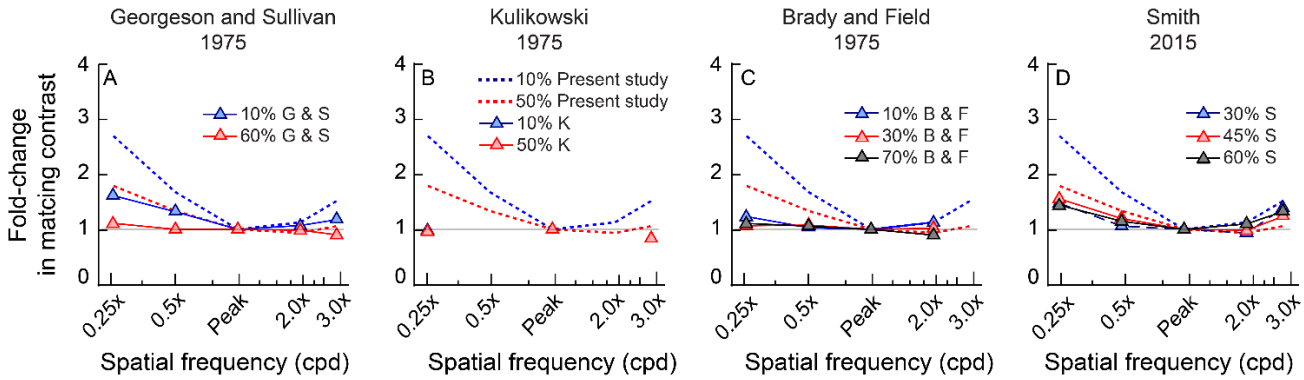

Figure 6: *Comparative analysis of the present study results with those of previous studies investigating the contrast constancy phenomenon. The organization of this figure is similar to that of Figures 2E and F. The fold-change value from the previous literature (solid lines with symbols) was calculated from the physical contrast of the reference stimulus and the matched contrast of the test stimulus, in line with the methodology used in the present study. From the spectrum of spatial frequency and suprathreshold contrast level tested in these studies, only those closer to the ones used in the present study are plotted here. The results of the present study are shown as dashed coloured lines in all figure panels.*

Interpretation of results in the context of the prevalent models of contrast constancy

The results obtained for the higher than peak spatial frequencies of the present study may be interpreted in the context of two prominent models of contrast constancy reported in the literature. Georgeson and Sullivan (1975) model this phenomenon as a normalization process involving active gain control of the different spatial frequency channels mediating contrast perception in the visual system. The extent of normalization required to achieve contrast constancy may be readily derived from the contrast threshold function, as performed in this study (Figure 1). There is a higher demand on the contrast gain control mechanism in keratoconus to achieve constancy for suprathreshold stimuli, relative to controls, as evident from the predictions shown in Figure 1B. That the pattern of contrast constancy was remarkably similar for cases and controls, despite the increased demand in the former cohort, indicates that the operating range for such a gain control mechanism is larger than what has been observed in controls previously (Figures 1B – 3). This normalization process also

appears to have a short time course of implementation (matter of several minutes) (Figure 5) and mediated by monocular contrast processing channels (Figure 4), as suggested from the second and third experiments of this study. This gain control model inherently operates across different spatial frequency channels, unable to normalize contrast threshold differences occurring within a single channel (Georgeson & Sullivan, 1975). The methodological issues described in the previous section notwithstanding, this could be a plausible neurophysiology explanation for why contrast constancy was not observed for the lower than peak spatial frequencies in this study. The visual system inherently possesses the ability to dynamically recalibrate the neural processing of blur to optimize spatial vision (Webster, Georgeson & Webster, 2002). For instance, the perceived sharpness of an image can be systematically biased within minutes of exposure to the same or related images that are synthetically blurred or over-sharpened by altering their amplitude spectrum (Webster et al., 2002). The perception of optimal focus of an image also seems to be inherently calibrated to the eye's own optical quality such that images corrected for all optical defects are adjudged not to be in best focus (Artal, Chen, Fernandez, Singer, Manzanera & Williams, 2004, Sawides, de Gracia, Dorronsoro, Webster & Marcos, 2011). Such re-adjustments are also possible in the presence of interocular differences in blur, but with the binocular percept biased by the sharper of the two eyes' retinal images (Kompaniez, Sawides, Marcos & Webster, 2013). The perceived focus of an image may also be optimized through a long-term form of adaptation with age-related losses in optical quality due to cataracts (Parkosadze, Kalmakhelidze, Tolmacheva, Chichua, Kezeli, Webster & Werner, 2013). Such mechanisms of "blur adaptation" may also be at play in diseases like keratoconus and, perhaps, the maintenance of contrast constancy observed in this study and by Ng et al (Ng et al., 2022) are reflections of this underlying ability.

Brady and Field (1995) explain this phenomenon through a contrast-response gain function that remains constant across the spatial frequency channels. Suprathreshold contrast matching across spatial frequencies is determined only by the signal strength of the stimulus, independent of threshold level performance. Contrast threshold, on the other hand, is determined by the noise level in the visual system that scales with spatial frequency, resulting in a progressive reduction in the signal-to-noise ratio (Brady & Field, 1995). Threshold-level losses in keratoconus may be explained by increased noise in the visual system arising from the degraded optical quality of the eye, even while the contrast-response gain function of the different spatial frequency channels remain unaltered in this disease condition. Thus, unlike the Georgeson and Sullivan model, there is no need for

recalibration or re-normalization of neural inputs for suprathreshold contrast perception in keratoconus. Differentiating the two models of contrast constancy in keratoconus is outside the scope of the present study.

The present study assumed that the perceived contrast of the test and reference stimuli used for the matching experiment was linearly related to the physical contrasts of the stimuli presented on the computer monitor. That this assumption is too simplistic is suggested from evidence of a Weber's law type compressive non-linear transducer present in the internal representation of the contrast, using which judgments about contrast discrimination and contrast difference scaling may be made by the visual system (Shooner & Mullen, 2022). Given Weber's law, as the suprathreshold contrast level increases, the delta contrast needed for discrimination must also go up since the perceived contrast has been compressed in the process of transduction from image to percept (Shooner & Mullen, 2022). This will result in the expected fold-change in contrast matching shown in Figure 1B to vary non-linearly with the suprathreshold contrast level of the reference stimulus, in the absence of contrast constancy. The present study acknowledges this as a limitation of the present model and suggest that future studies of contrast constancy explore the impact of this non-linear transformation from physical stimulus to perception in greater detail. That the results of the cases and controls were identical in this study suggests that the pattern of this non-linearity remains unaltered in keratoconus, vis-à-vis, controls (Figures 2E and F). The present results on keratoconus may thus not be differentially impacted by the simplistic model that was used here to calculate the expected fold-change in contrast matches.

Implications of study results for other forms of optical degradations in the human eye

Apart from keratoconus, the human eye experiences chronic degradation of retinal image quality from distorted optics due to aging, disease or iatrogeny. For instance, the optical quality of the eye degrades due to increased wavefront aberrations following sculpting of the cornea to correct myopia/hyperopia in different forms of LASER refractive surgery for myopia (Sarkar, Bharadwaj, Reddy & Vaddavalli, 2020, Sarkar, Devi, Vaddavalli, Reddy & Bharadwaj, 2022). While, unlike keratoconus, the eye's wavefront aberrations do not progressively increase over time following such surgeries, they do not also reduce over time, resulting in chronic losses of retinal image quality in these patients (Benito, Redondo & Artal, 2011). A second example involves patients who undergo corneal transplantation to surgically replace their opaque cornea with a healthy and transparent donor cornea (Bandela, Satgunam, Garg & Bharadwaj, 2016, Chamberlain, Omid, Lin, Farid, Gaster &

Steinert, 2012). The transplanted eye experiences increased magnitudes of higher-order aberrations and irregular astigmatism, both of which significantly and chronically degrade its optical quality (Bandela et al., 2016). If this procedure is performed uniocularly, then the visual system has to contend with widely dissimilar retinal image qualities arising from the two eyes – good retinal image from the native eye and degraded retinal image from the transplanted eye (Bandela et al., 2016). A third example are of individuals who are fitted with multifocal contact lenses or intraocular lenses for correction of presbyopia. By design, these optical interventions widen the depth of focus of the presbyopic eye by introducing selected higher-order wavefront aberrations, which, in turn degrade retinal image quality at any given focal plane (Greenstein & Pineda, 2017, Ravikumar, Bradley, Bharadwaj & Thibos, 2016). The image quality loss experienced herein also stays for as long as the individual wears these optical interventions. While threshold level losses in visual acuity and contrast sensitivity are well-documented in these cases (Devi et al., 2022), suprathreshold contrast perception remains largely unknown. The increase in higher-order wavefront aberrations in all these examples and, thus, the loss of retinal image quality is certainly higher than age-similar controls but not as much as what is experienced in a keratoconic eye (Devi et al., 2022). The phenomenon of contrast constancy reflects fundamental mechanisms driving the optimization of suprathreshold spatial vision. The similarity in the pattern of contrast constancy between cases and controls indicates that this optimization process remains unaltered despite significant disease-driven deterioration in the eye's optics. In this context, keratoconus may be viewed only as a disease model to study the limits of such an optimization process and that the results of the present study may be extrapolated to the other forms of front-end limitations of the eye, as described above. It may be hypothesized that, like keratoconus, the suprathreshold contrast perception may also remain largely unaffected in all these cases. Activities of daily living within the visible space may therefore remain uninterrupted even while visual resolution may be comprised in all these cases. Direct evidence for this needs to be sought in the future by replicating the present protocol on different patient cohorts.

Conclusions

The ability to retain the perceived invariance of contrast across spatial scale in keratoconus is remarkably similar to controls and extends across a range of disease severity, interocular asymmetry and short-term changes in optical quality and threshold-level visual experience. Correction strategies aimed at improving the optical quality in keratoconus may therefore function primarily to expand the

region of visibility and resolution acuity in this disease condition, with only a limited influence on the contrast perception of suprathreshold objects.

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) and by the Hyderabad Eye Research Foundation, L V Prasad Eye Institute.

References

Artal, P., Chen, L., Fernandez, E.J., Singer, B., Manzanera, S., & Williams, D.R. (2004). Neural compensation for the eye's optical aberrations. *J Vis, 4* (4), 281-287.

Bandela, P.K., Satgunam, P., Garg, P., & Bharadwaj, S.R. (2016). Corneal Transplantation in Disease Affecting Only One Eye: Does It Make a Difference to Habitual Binocular Viewing? *PLoS One, 11* (3), e0150118.

Benito, A., Redondo, M., & Artal, P. (2011). Temporal evolution of ocular aberrations following laser in situ keratomileusis. *Ophthalmic Physiol Opt, 31* (4), 421-428.

Brady, N., & Field, D.J. (1995). What's constant in contrast constancy? The effects of scaling on the perceived contrast of bandpass patterns. *Vision Res, 35* (6), 739-756.

Brainard, D.H. (1997). The Psychophysics Toolbox. *Spat Vis, 10* (4), 433-436.

Chamberlain, W., Omid, N., Lin, A., Farid, M., Gaster, R.N., & Steinert, R.F. (2012). Comparison of corneal surface higher-order aberrations after endothelial keratoplasty, femtosecond laser-assisted keratoplasty, and conventional penetrating keratoplasty. *Cornea, 31* (1), 6-13.

Devi, P., Kumar, P., & Bharadwaj, S.R. (2023). Computational analysis of retinal image quality with different contact lens designs in keratoconus. *Cont Lens Anterior Eye, 46* (2), 101794.

Devi, P., Kumar, P., Marella, B.L., & Bharadwaj, S.R. (2022). Impact of Degraded Optics on Monocular and Binocular Vision: Lessons from Recent Advances in Highly-Aberrated Eyes. *Semin Ophthalmol, 37* (7-8), 869-886.

Duncan, J.K., Belin, M.W., & Borgstrom, M. (2016). Assessing progression of keratoconus: novel tomographic determinants. *Eye Vis (Lond), 3*, 6.

Georgeson, M.A., & Sullivan, G.D. (1975). Contrast constancy: deblurring in human vision by spatial frequency channels. *J Physiol, 252* (3), 627-656.

Greenstein, S., & Pineda, R., 2nd (2017). The Quest for Spectacle Independence: A Comparison of Multifocal Intraocular Lens Implants and Pseudophakic Monovision for Patients with Presbyopia. *Semin Ophthalmol, 32* (1), 111-115.

Haun, A.M., & Peli, E. (2013). Perceived contrast in complex images. *J Vis, 13* (13), 3.

Jarvis, J., Triantaphillidou, S., & Gupta, G. (2022). Contrast discrimination in images of natural scenes. *J Opt Soc Am A Opt Image Sci Vis, 39* (6), B50-B64.

Kanellopoulos, A.J., & Asimellis, G. (2012). Correlation between central corneal thickness, anterior chamber depth, and corneal keratometry as measured by Oculyzer II and WaveLight OB820 in preoperative cataract surgery patients. *J Refract Surg, 28* (12), 895-900.

Kompaniez, E., Sawides, L., Marcos, S., & Webster, M.A. (2013). Adaptation to interocular differences in blur. *J Vis, 13* (6), 19.

Kulikowski, J.J. (1976). Effective contrast constancy and linearity of contrast sensation. *Vision Res, 16* (12), 1419-1431.

738 Kumar, P., Bandela, P.K., & Bharadwaj, S.R. (2020). Do visual performance and optical quality vary
739 across different contact lens correction modalities in keratoconus? *Cont Lens Anterior Eye, 43* (6), 568-
740 576.
741 Laidlaw, D.A., Tailor, V., Shah, N., Atamian, S., & Harcourt, C. (2008). Validation of a computerised
742 logMAR visual acuity measurement system (COMPlog): comparison with ETDRS and the electronic
743 ETDRS testing algorithm in adults and amblyopic children. *Br J Ophthalmol, 92* (2), 241-244.
744 Lakens, D. (2013). Calculating and reporting effect sizes to facilitate cumulative science: a practical
745 primer for t-tests and ANOVAs. *Front Psychol, 4*, 863.
746 Lesmes, L.A., Lu, Z.L., Baek, J., & Albright, T.D. (2010). Bayesian adaptive estimation of the contrast
747 sensitivity function: the quick CSF method. *J Vis, 10* (3), 17 11-21.
748 Lim, L., & Lim, E.W.L. (2020). Current perspectives in the management of keratoconus with contact
749 lenses. *Eye (Lond), 34* (12), 2175-2196.
750 Marella, B.L., Conway, M.L., Suttle, C., & Bharadwaj, S.R. (2021). Contrast Rivalry Paradigm Reveals
751 Suppression of Monocular Input in Keratoconus. *Invest Ophthalmol Vis Sci, 62* (2), 15.
752 Marta, A., Marques, J.H., Almeida, D., Jose, D., & Barbosa, I. (2021). Keratoconus and Visual
753 Performance with Different Contact Lenses. *Clin Ophthalmol, 15*, 4697-4705.
754 Metlapally, S., Bharadwaj, S.R., Roorda, A., Nilagiri, V.K., Yu, T.T., & Schor, C.M. (2019). Binocular cross-
755 correlation analyses of the effects of high-order aberrations on the stereoacuity of eyes with
756 keratoconus. *J Vis, 19* (6), 12.
757 Ng, C.J., Sabesan, R., Barbot, A., Banks, M.S., & Yoon, G. (2022). Suprathreshold Contrast Perception
758 Is Altered by Long-term Adaptation to Habitual Optical Blur. *Invest Ophthalmol Vis Sci, 63* (11), 6.
759 Nilagiri, V.K., Metlapally, S., Kalaiselvan, P., Schor, C.M., & Bharadwaj, S.R. (2018). LogMAR and
760 Stereoacuity in Keratoconus Corrected with Spectacles and Rigid Gas-permeable Contact Lenses.
761 *Optom Vis Sci, 95* (4), 391-398.
762 Nilagiri, V.K., Metlapally, S., Schor, C.M., & Bharadwaj, S.R. (2020). A computational analysis of retinal
763 image quality in eyes with keratoconus. *Sci Rep, 10* (1), 1321.
764 Parkosadze, K., Kalmakhelidze, T., Tolmacheva, M., Chichua, G., Kezeli, A., Webster, M.A., & Werner,
765 J.S. (2013). Persistent biases in subjective image focus following cataract surgery. *Vision Res, 89*, 10-
766 17.
767 Pelli, D.G. (1997). The VideoToolbox software for visual psychophysics: transforming numbers into
768 movies. *Spat Vis, 10* (4), 437-442.
769 Ravikumar, S., Bradley, A., Bharadwaj, S., & Thibos, L.N. (2016). Expanding binocular depth of focus by
770 combining monovision with diffractive bifocal intraocular lenses. *J Cataract Refract Surg, 42* (9), 1288-
771 1296.
772 Rosen, R., Lundstrom, L., Venkataraman, A.P., Winter, S., & Unsbo, P. (2014). Quick contrast sensitivity
773 measurements in the periphery. *J Vis, 14* (8), 3.
774 Sarkar, S., Bharadwaj, S.R., Reddy, J.C., & Vaddavalli, P.K. (2020). Longitudinal Changes in Optical
775 Quality, Spatial Vision, and Depth Vision after Laser Refractive Surgery for Myopia. *Optom Vis Sci, 97*
776 (5), 360-369.
777 Sarkar, S., Devi, P., Vaddavalli, P.K., Reddy, J.C., & Bharadwaj, S.R. (2022). Differences in Image Quality
778 after Three Laser Keratorefractive Procedures for Myopia. *Optom Vis Sci, 99* (2), 137-149.
779 Sawides, L., de Gracia, P., Dorronsoro, C., Webster, M.A., & Marcos, S. (2011). Vision is adapted to the
780 natural level of blur present in the retinal image. *PLoS One, 6* (11), e27031.
781 Shajari, M., Steinwender, G., Herrmann, K., Kubiak, K.B., Pavlovic, I., Plawetzki, E., Schmack, I., &
782 Kohnen, T. (2019). Evaluation of keratoconus progression. *Br J Ophthalmol, 103* (4), 551-557.
783 Shneor, E., Pinero, D.P., & Doron, R. (2021). Contrast sensitivity and higher-order aberrations in
784 Keratoconus subjects. *Sci Rep, 11* (1), 12971.
785 Shooner, C., & Mullen, K.T. (2022). Linking perceived to physical contrast: Comparing results from
786 discrimination and difference-scaling experiments. *J Vis, 22* (1), 13.
787 Smith, W.S. (2015). Contrast constancy revisited: the perceived contrast of sinusoidal gratings above
788 threshold. *Q J Exp Psychol (Hove), 68* (2), 363-380.

Thibos, L.N., Wheeler, W., & Horner, D. (1997). Power vectors: an application of Fourier analysis to the description and statistical analysis of refractive error. *Optom Vis Sci, 74* (6), 367-375.
To, M.P., Gilchrist, I.D., Troscianko, T., & Tolhurst, D.J. (2011). Discrimination of natural scenes in central and peripheral vision. *Vision Res, 51* (14), 1686-1698.
Tong, F., Meng, M., & Blake, R. (2006). Neural bases of binocular rivalry. *Trends Cogn Sci, 10* (11), 502-511.
Webster, M.A., Georgeson, M.A., & Webster, S.M. (2002). Neural adjustments to image blur. *Nat Neurosci, 5* (9), 839-840.
Xian, Y., Sun, L., Ye, Y., Zhang, X., Zhao, W., Shen, Y., Lu, Z.L., Zhou, X., & Zhao, J. (2023). The Characteristics of Quick Contrast Sensitivity Function in Keratoconus and Its Correlation with Corneal Topography. *Ophthalmol Ther, 12* (1), 293-305.