IMPACTS OF THREE TYPES OF LASER REFRACTIVE SURGERIES ON BINOCULAR MATCHING METRICS AND BINOCULAR DEPTH-OF-FOCUS RANGES DERIVED COMPUTATIONALLY FROM HIGHER-ORDER-ABERRATIONS

A thesis presented to the graduate faculty of
New England College of Optometry in partial fulfillment
of the requirements for the degree of Master of Science

Jingyi (Alice) Tang

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Abstract

Research objective: As different types of corneal refractive surgeries have emerged and have been developed rapidly in recent years, visual performance post-operatively has been an important aspect to impact decision making for candidates. Previous studies focused on monocular factors, such as visual acuity, contrast sensitivity and aberrations, but little exploration was done to assess binocular visual outcomes in a systematic and comprehensive manner. This thesis aimed to study how binocular data derived from higher-order-aberrations (HOAs) change after three different types of refractive surgeries (i.e., photorefractive keratectomy or PRK, femtosecond Laser in-situ keratomileusis or LASIK and small incision lenticule extraction or SMILE). These data indicate the quality of binocular matching using metrics that correlate the retinal images of the two eyes, both when computations are done using larger 6 mm pupil sizes and more naturalistic 4 mm pupil sizes. An additional goal of this thesis was to compute binocular depth-of-focus (DOF) ranges using through-focus functions signifying retinal image quality at different focus levels.

Methods: We procured optical wavefront aberration data that included HOAs from 99 subjects that underwent PRK (n=26), LASIK (n=38) and SMILE (n=35). These data were used to derive computational metrics, and were assessed alongside empirical stereoacuity for 6 mm pupil sizes. Simulated retinal images were generated using HOAs and cross-correlations were performed on the left and the right eye images for each subject at each time point, and a horizontal (1-D) cross-correlation function was extracted. To quantify the interocular mismatches, four computational binocular metrics (signal width, signal height, signal-to-noise ratio, height-to-width ratio) were calculated and compared both longitudinally and across different surgery types. These analyses were done for both 6 mm and 4 mm pupil sizes. For DOF analyses, we obtained through-focus functions by calculating the image quality metric VSOTF (Visual Strehl ratio-based on the Optical Transfer Function) for different defocus levels, while keeping the same HOAs. Binocular DOF was obtained by summing the range at 20% drop from the peak of the through-focus functions of both eyes. Post-operative best focus positions and interocular differences in best focus positions were also compared for all surgery types. Based on the distribution of our data, non-parametric statistical comparisons were performed on the longitudinal data and comparisons at each time point across different surgery types. Spearman's rank correlations were obtained between stereoacuity and each binocular metric for 6 mm pupils.

Results: Of the four binocular metrics, height-to-width ratio showed the strongest correlation with stereoacuity ($r_s(97)=-0.77$). With both 6 mm or 4 mm pupil sizes, SMILE refractive surgery was better, displaying more optimal binocular performance than PRK or LASIK at all post-operative time points ($p<0.001$ in the majority of comparisons), but there was no difference between PRK and LASIK ($p>0.05$ in the majority of comparisons). With all three types of refractive surgeries, computationally derived binocular metrics for 6 mm and 4 mm pupils and stereo acuity (6 mm pupils) showed the pattern of immediate worsening post-operatively

($p<0.001$) in the majority of comparisons of pre-operative data with 1-week post-operative data. This was followed by a recovery period ($p<0.001$ or $p<0.01$) in the majority of comparisons of 1-week post-operative with 6-month post-operative time points. PRK and LASIK surgeries showed a clearer recovery trend than SMILE, and this was more obvious for 6 mm pupils compared to 4 mm pupils. Binocular DOF ranges, absolute values of best focus positions and interocular differences of best focus positions increased post-operatively for all surgery types ($p<0.01$ for PRK, LASIK and SMILE), except for the interocular differences of best focus positions of SMILE ($p>0.05$). For each of these parameters, there was a significant difference between PRK and SMILE groups ($p<0.01$), and between LASIK and SMILE groups ($p<0.001$), but not between PRK and LASIK groups ($p>0.05$).

Conclusion: Regardless of the two pupil sizes examined in these investigations, SMILE refractive surgery provided better overall binocular performance evident from the most optimal data for the four binocular metrics (6 mm and 4 mm pupils), stereoacuity (6 mm pupils), absolute value of post-operative best focus position and interocular differences of best focus positions; however, this superior binocular performance was accompanied by a smaller binocular DOF. PRK and LASIK introduced interocular aberration mismatches that worsened binocular matching and stereo acuity, but increased binocular DOF that could be beneficial following presbyopia onset. Smaller pupil sizes led to less deterioration of image quality by HOAs and reduced HOA mismatches post-operatively.

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General Introduction

Depth perception is a critical element in everyday life. Good depth perception allows us to perceive three-dimensional (3-D) shapes, estimate dimensions of objects and distances. While monocular cues such as visual angle of objects, overlay and parallax help us appreciate depth and distances, we rely on binocular vision for fine stereoscopic depth perception to perform certain daily activities and achieve a good vision-related quality of life. Stereoscopic depth perception is possible because we have two eyes that are frontally placed, and separated horizontally from each other. An object in front of the two eyes is seen by each eye from a different perspective, resulting in slightly different images of the same object on the two retinas based on the spatial orientation of the objects. This difference in perspective is known as retinal image disparity. Our brain combines and processes these two different perspectives from the two eyes via complex neurological processes to eventually give us depth information.

Stereo acuity is the smallest detectable depth difference using binocular vision. It is a clinical parameter that represents the resolution of an individual's stereoscopic depth perception. Stereo acuity can be measured using several different techniques. Titmus, Frisby, and TNO are projected depth stereo acuity tests that are frequently used in the clinic, and do not completely eliminate monocular depth cues that could arise from accommodation, perspective, shadows and motion parallax. Béla Julesz's invention of random dot stereograms (RDS) in 1959 excludes these confounding variables and provides more reliable and accurate estimates of stereo acuity. [1] In our study, we used computerized random dot stereograms to measure stereo acuity. Random dot stereograms consist of two two-dimensional monocular fields of randomly scattered dots. The images viewed by each eye are exactly the same except for a small subset of dots that are offset horizontally in each of the monocular images to generate 'horizontal disparity'. When the two eyes' images are combined by the brain, the relative horizontal binocular disparity elicits the perception of depth. The direction of relative horizontal displacement of the subset of dots determines the depth direction, i.e., whether they appear farther or nearer than the rest of the random dots, and the amount of relative horizontal displacement determines the depth magnitude. [2] Stereo acuity is the smallest relative binocular disparity that yields a perception of depth. The screening norm for stereo acuity in people aged 19-38 is 40 arc sec and slightly poorer for younger children, [3] and a widely accepted clinical norm is 20 arc sec.

Optimal visual perception of the surrounding 3D world requires clear retinal images formed on corresponding locations in each eye that are well-matched, leading to binocular single vision with stereoscopic depth perception. Stereoscopic depth perception could be hampered by several non-optical and optical factors that each cause mismatched in the retinal images. Non-optical factors stem from motor or neural defects, for instance, (1) strabismus, which refers to a misalignment of one or both eyes, causes an object to be imaged on non-corresponding locations on the retina leading to diplopia or double images, and (2) strabismic suppression, where the brain ignores conflicting or mismatched information from the corresponding region of the misaligned eye to promote single vision at the expense of lost binocularity. Optical

factors that cause the loss of stereoscopic depth perception stem from interocular optical mismatches that lead to mismatched retinal images on corresponding locations on the retina. Optical factors will be the subject of this thesis and are described in greater detail below.

Optical factors that cause interocular mismatches of retinal images arise from two broad categories: (1) monochromatic aberrations and (2) aniseikonia. The first factor, monochromatic optical aberrations, refers to imperfections of an optical system such as the eye, that prevent light rays from a point object from forming a faithful representation in a point image, and instead spread light in the image that is usually perceived and described as ‘blur’. Optical aberrations will be the subject of this thesis and will be described in greater detail subsequently. The second factor, optical aniseikonia, refers to differences in perceived image sizes between the eyes and could be induced by spectacle correction of anisometropia, and will not be further discussed in this thesis.

Mismatched retinal images can result from interocular mismatches of aberrations. In 1934, optical physicist Frits Zernike provided orthogonal circle polynomials to describe aberrations and polynomials could be arranged so that different radial orders are in different rows in the form of a Zernike pyramid. [4] Lower-order aberrations (LOAs) include the first six polynomials, or first three rows of polynomials and are correctable with spherocylindrical spectacle lenses. LOAs include defocus, i.e., myopia and hyperopia, and astigmatism that are common refractive errors in human eyes, and are correctable with spectacle lenses. Higher-order aberrations (HOAs), on the other hand, include all the polynomials after the first six that are more subtle and complex, and by definition are not correctable by spectacle lenses. HOA magnitude is often quantitatively assessed using the higher order root mean squared (HORMS) value, and this can be minimized using certain contact lens (CL) corrections. Both LOAs and HOAs are common in human eyes, and it is well known that in general, increased amounts of either type of aberration deteriorates visual image quality. LOAs largely vary among individuals with healthy eyes but most are correctable with optical aids. HOAs, on the other hand, are usually relatively minor in normal eyes of a healthy person. Large magnitudes of HOAs are usually pathologic or induced by injuries/surgeries that affect the optical components of the eye and lead to decreased retinal image quality. For example, patients with keratoconus experience significant increases of both monocular LOAs and HOAs. [5, 6] Significantly increased magnitudes of monocular HOAs are also seen in eyes with corneal pathologies like Pellucid marginal degeneration (PMD) [7], or those have had corneal injuries/surgeries, e.g., refractive surgeries. [8]

Apart from monocular visual performance issues, mismatched aberrations lead to binocular or stereo acuity losses. LOA mismatches between the two eyes or anisometropia induced by increasing monocular blur to one eye, have long been known to decrease stereo acuity. [9] Increasing amounts of cylinder power in the horizontal, vertical or oblique meridians monocularly would also decrease stereo acuity. [10] In terms of HOAs, in people with healthy eyes, the amount of HOAs are not only small but also fairly symmetrical, and thus have little impact on binocularity. [11, 12] However, when amounts of HOAs increase due to pathology or corneal injury/surgery, mismatches of aberrations between the eyes also increase and

impact binocularity. Previous studies have found that HOAs that are increased and mismatched in keratoconus [5, 6, 13] and following refractive surgeries [14-16] also cause poor stereo acuity.

We were interested in refractive surgeries as they are commonly performed procedures to correct LOAs, but might lead to increased monocular HOAs [17-19] and interocular differences in HOAs, hampering stereo acuity. [14, 16] Three generations of refractive surgeries to reshape the cornea for myopia correction, namely, PhotoRefractive Keratectomy (PRK), Femtosecond Laser-Assisted In situ Keratomileusis (FS-LASIK, that in the rest of this thesis is abbreviated as LASIK) and Small-Incision Lenticule Extraction (SMILE) were the subject of our investigations. In the PRK procedure, the corneal epithelium is removed mechanically, and part of corneal stroma is ablated by excimer laser. During FS-LASIK, the epithelium is not removed, but is made into a flap by a femtosecond laser. Excimer laser is then applied to the underlying corneal stroma, and finally the flap put back to its original position. In the SMILE procedure, a calculated intrastromal lenticule is created by femtosecond laser and extracted through a small incision on the side of cornea. [8, 20, 21] Each subsequent generation surgery has evolved to be less invasive; however, they are all still widely performed, and show differences in the corneal irregularities introduced. [16]

All three types of refractive surgeries are safe and provide efficacious refractive error correction and overall long-term visual outcomes. [22-24] Comparisons of the visual outcomes such as contrast sensitivity between different types of refractive surgeries resulting from induced corneal aberrations are not straightforward to assess across studies. For instance, one study shows LASIK and SMILE outcomes are not statistically significantly different in terms of contrast sensitivity, total aberrations and higher-order aberrations both short-term and long-term. [25] Another report suggests that SMILE gives better contrast sensitivity than PRK [26], and other studies have found that PRK introduces less HOA than LASIK. [27] Most previous studies used data from one eye of an individual and measured monocular visual outcomes, very few studies assessed binocular outcomes, and even fewer explored how resultant aberrations impact stereo perception. A more recent study compared post-operative wavefront aberrations, optical quality and stereo acuity after PRK, LASIK and SMILE, and found that SMILE provides significantly better visual outcomes from all these perspectives. [16] In addition, their longitudinal analysis suggested that for PRK and LASIK, all parameters including HORMS values, visual acuity and stereo acuity showed immediate worsening post-operatively followed by a recovery period, while for SMILE, only HORMS showed similar trend but all other parameters did not follow the pattern.

Previous studies have thus documented HOAs, monocular image quality impacts of HOAs and stereo acuities following refractive surgeries. We were interested in further investigating the differences among the three procedures in terms of their binocular impacts, and in particular, the optical contributions of the induced HOAs to disparity processing. Based upon a previous study in which cross-correlation analyses and binocular metrics were used to study the contributions of interocular optical mismatches to the stereo losses in keratoconus [13], we modeled the optical contributions of induced HOA to disparity visibility and binocular metrics

at different time points after PRK, LASIK, and SMILE refractive surgeries and compared them to the baseline measurements. All analyses were performed using a subset of the data from the study by Sarkar et al. [16] These analyses may pave the way to estimate binocular outcomes based on the two eyes' optical properties.

This thesis project had four specific aims. The first aim was to compute binocular metrics from wavefront aberration data and explore the correlation between the computed binocular metrics and empirical stereo acuity for 6 mm pupils. We hypothesized that if the optical mismatches following refractive surgery were responsible for changes in empirical stereo acuity, they would cause the computed binocular metrics and empirical stereo acuity to co-vary strongly. This could serve as a quantitative indicator of the contribution of optical changes to binocular visual performance. Our next aim was to observe changes in binocular metrics derived from aberrations longitudinally from pre-operative to different post-operative time points, and to compare across the three different types of refractive surgeries with 6 mm pupils. We expected to see deterioration in the short-term followed by recovery period for each parameter after each of the refractive surgeries. We hypothesized that SMILE would lead to less immediate post-operative disturbance in HOAs mismatches based on the data from Sarkar et al, 2020. We combined the first two aims in Chapter 1 for organization purposes, since they pertain to 6 mm pupils for which we had access to both empirical and computational data. Third, we reassessed binocular metrics after recalculating the HOAs from 6 mm to 4 mm pupils. Binocular metrics were computed using exactly the same steps as we did for 6 mm pupils in chapter 1, with the only exception that we could not correlate them with empirical stereo acuity data that were unavailable for 4 mm pupils. Resizing to a smaller pupil size provides a more realistic understanding of performance in day-to-day situations, and we expected smaller changes, but a similar trend for 4 mm pupils as we saw for 6 mm pupils longitudinally and in comparisons among the three surgery types. Fourth, we compared binocular depth of focus (DOF) ranges and interocular differences in best focus positions seen six months after refractive surgery with the pre-operative baseline for the three surgery types. Given that increased magnitudes of HOA can lead to expanded DOF monocularly, we hypothesized that surgical procedures which induced larger HOAs might also lead to wider ranges of binocular DOFs that combined the monocular DOF ranges from each eye. As we expected larger interocular differences in best focus positions after surgeries that led to higher HOAs, we examined whether there would be a potential benefit in the form of a wider DOF range if such HOA-inducing refractive surgeries were recommended based on individual need or availability.

General methods

We used a subset of optical and psychophysical data collected at the in LV Prasad Eye Institute, Hyderabad, India by Sarkar et al (2020). [16] All refractive surgeries were performed at this institution by two ophthalmologists (authors PKV/JR of Sarkar et al, 2020) with 6.5 mm optic zones, and empirical data described below was collected by one optometrist (first author SS of Sarkar et al, 2020). Information about recruitment, surgical procedures, post-operative care, inclusion and exclusion criteria for the research subject population are available in greater detail from Sarkar et al., 2020, and abridged relevant details are presented here.

Empirical methods

Subjects

The current study utilized optical and psychophysical data collected from patients that underwent PRK (n=26), LASIK and SMILE refractive surgeries (n=40 each for LASIK and SMILE, where ultimately n=38 for LASIK and n=35 for SMILE were available for analyses due to loss of subjects during follow-ups) during the 1-year study recruitment period by Sarkar et al, 2020. Our sample comprised a total of 99 patients due to missing data from two participants in the LASIK group and five from the SMILE group. Study participants were pre-presbyopic adults ≥18 years of age having stable refraction of -2.00 to -10.00 D, free from anisometropia ≥2D or astigmatism ≥1.5D, with normal corneal thickness and topography. The age distribution of subjects across the three refractive surgery types was similar. The recruited participants were also free from any other ocular pathology or monocular or binocular issues that would confound our results.

Wavefront aberration, refractive error and stereo acuity data

The study was designed to study the influence of HOAs on binocular matching and stereo acuity following three refractive surgeries (PRK, LASIK and SMILE). Data were collected prior to surgery and at discrete timepoints after surgery, resulting in five data collection sessions: pre-operative baseline, and after refractive surgery at 1-week and 1-, 3-, and 6-month post-operative time points. Empirical data collected from all participants and at all timepoints included wavefront aberrations and refractive error for both eyes, and stereo acuity following cycloplegia with 1% cyclopentolate to minimize any influence of focus fluctuations due to accommodation. The cycloplegia also implies dilated pupils, allowing the pupil diameter to be controlled (1) by using artificial apertures for empirical data obtained from all participants, and (2) by scaling computationally for comparisons.

Data collection procedures are detailed in Sarkar et al (2020). [16] Briefly, wavefront aberrations were measured unaided by optical corrections using the irx3 wavefront aberrometer (Imagine Eyes, Orsay, France). Three measurements of wavefront aberrations described by Zernike polynomials were obtained following cycloplegia and straight after one

or two blinks. Polynomials up to the sixth order were scaled to 6 mm-diameter pupils, averaged and used for further computational analyses.

Refractive error was measured by retinoscopy and if subjects were not emmetropic, residual power was fully corrected for all psychophysical measurements where subjects also self-regulated blinks to maintain optical clarity. Stereo acuity was measured using a custom program that presented stimuli and collected responses via MATLAB's (Mathworks Inc., Natick, MA, USA) Psychophysics Toolbox. [28, 29] Participants viewed a 7°×7° random-dot (RD) field through a mirror stereoscope that fully compensated for the optical vergence of the 40 cm testing distance They were asked to identify the orientation of a rectangular bar displayed in crossed disparity. Disparity was changed adaptively in 10% steps using a one-up one-down staircase set to terminate after 11 reversals, and the average of the last 8 reversals estimated the stereo acuity thresholds. All psychophysical measurements were performed in an otherwise dark room with 6 mm artificial pupil apertures placed in the spectacle plane.

Chapter 1.

Comparisons of the Longitudinal Impacts of Three Generations of Laser Refractive Surgeries on Binocular Matching Metrics Derived Computationally from Higher Order Aberrations for 6 mm Pupils

1.1 Introduction

Advances in the technologies and procedures for laser refractive surgeries have ensured significant success in achieving their primary goal of minimizing refractive errors to optimize distance visual acuities without the use of optical corrections. However, they are being scrutinized by the vision science community to examine the side effects of particular interest to us, namely the introduction of iatrogenic higher order aberrations (HOAs) and interocular mismatches of HOAs that could lead to binocular vision issues. Sarkar et al (2020) analyzed monocular visual outcomes such as spherical equivalent refractive error, HORMS, high-contrast visual acuities and modulation transfer functions based on the HOA profiles introduced after the three different types/ generations of refractive surgeries. Their goal was to document not only the changes in monocular optical quality and spatial vision but also stereo acuity brought about by the surgeries. They found that PRK gave rise to the largest increase in amount of HOAs, as measured by HORMS, and SMILE resulted in the least increase. The post-operative interocular difference in HOAs was also the smallest in the SMILE group, when compared to PRK and LASIK. In addition, their longitudinal analysis suggested that post-operative HOAs remained stable for most of the subjects, with the only exception of between 1 month and 3 months in SMILE group. They also studied the relationship between stereo acuity and average and interocular difference in HOAs, and came to a conclusion that average and interocular difference in HOAs explained approximately 74% and 43% of the variance in stereo acuity data. [16] However, monocular HORMS is a single summarizing parameter to evaluate the total amount of aberrations. It lacks spatial information on how different types of contributing aberrations lead to deterioration or deformation of image quality. In other words, it lacks information about the effects of individual aberrations on retinal image quality, and masks the fact that wildly different individual aberrations with different effects on retinal image quality may have the same RMS value. It may also not reveal the actual differences of monocular image quality when the RMS data changes (or does not change) between subsequent post-operative time points for the same refractive surgery. Furthermore, and more importantly, interocular differences in HORMS are too simple to

convey comprehensive details from a binocular stand point, which would be more relevant to stereo acuity.

In our study, we wanted to use the same patient data, and take the analyses a further step by computing binocular metrics from monocular optical parameters to better understand the relationship between monocular optical irregularities, binocular combination and empirical stereo acuity. We wanted to quantify how much, if at all, the mismatched HOAs induced by refractive surgeries contributed to the deterioration of stereo acuity measured following refractive surgery, and to compare across the three types of refractive surgeries as well as longitudinally assess the difference at different post-operative timepoints. A previous study by Metlapally et al looked at the relationship between stereo acuity and HOAs in keratoconus patients using a computational cross-correlation process. [13] Their goal was to understand if and how HOAs have an impact on the significant loss of stereo acuity in keratoconus patients. Their model and analyses used random dot images to simulate the retinal images of the two eyes, and mimic the process the brain might use to match the retinal images using a cross-correlation process to reach a peak cross-correlation product. By using this model, more detailed monocular image quality information and minor interocular differences would be taken into consideration, because the deterioration of image quality in the 2-Dimentional (2-D) monocular space of one eye would be fully utilized in the computational analysis, and assessed for a match with a 2-D patch of the deteriorated image in the other eye to more closely mimic the matching process performed by our neurology. Cross-correlation is considerably different and provides richer information than a monocular averaging or summing parameter such as the HORMS, or comparing interocular averages or differences of the HORMS parameter. Using this model Metlapally et al were able to find that both interocular contrast differences and differential phase shifts from HOAs contributed to the stereo acuity losses. Since our study was focused on how mismatches of HOAs induced after refractive surgery contributed to stereo acuity losses, and how this compared across the three types of refractive surgery, we utilized this model, analysis and the binocular metrics derived from this analysis for our study and comparisons.

1.2 Methods

The General methods section describes research subjects and empirical data collection, and computational methods are described below.

1.2.1 Computational methods

The impact of HOAs on disparity visibility following PRK, LASIK and SMILE refractive surgeries was assessed using computational cross-correlation analyses using general analysis procedures that have been described in greater detail in Metlapally et al, 2019. [13] Similar to this previous study, we assessed binocular matching and the quality of the disparity signal using custom MATLAB (Mathworks Inc., Natick, MA, USA) programs.

Briefly, given our interest in the binocular impact of HOAs induced by refractive surgeries, the LOA terms of defocus and astigmatism (Z_2^{-2}, Z_2^0, and Z_2^2) were set to 0 μm for all conditions. HOAs from each eye of subjects at specific time points were used to compute point-spread functions (PSFs) as depicted for a representative subject and time-point in Figure 1A and 1B. A 600x600-pixel RD image was convolved with the HOA-derived PSFs obtained for the left and right eyes to generate a corresponding pair of retinal images (Figure 1C, 1D).

A horizontal (1-D) cross-correlation function was extracted from the two-dimensional (2-D) normalized cross correlation of the left and right image pairs that were computed using an algorithm that closely followed the formula from Lewis (1995) on MATLAB. [30] We built-in relaxation of the epipolar constraint. [31] Four binocular cross-correlation metrics that we will hereafter refer to simply as “binocular metrics”, namely, (1) signal width, (2) signal height, (3) signal-to-noise ratio, and (4) height-to-width ratio were used to evaluate the quality of matches between the retinal images of the two eyes (also see Metlapally et al, 2019). [13] We define signal width as the full-width-at-half-maximum, or the range of disparities over which cross-correlation signal was greater than 50% of its maximum value. As HOAs increase, the image degradation causes the PSF of each eye to be less compact, meaning that there might be a greater disparity range over which reasonable cross-correlation matches are obtained around the best matched position. Thus, a greater spread of the energy in the monocular domain might generate “disparity blur” in the binocular domain, and a narrower signal width would represent better disparity signal quality. Signal height represents the strength of the disparity signal at the location where the images of the left and right eyes are best matched, and better strength is a signal height closer to the peak normalized value of one. Large noise peaks are generated by false matches. We picked the highest noise peak to represent noise that might interfere with the detection of the disparity signal, and computed a signal-to-noise ratio, where a higher ratio might represent better ability of the system to find the best matched position. Finally, since the combination of a greater signal height and a narrower signal width indicate better disparity signal quality, and vice versa, we computed the height-to-width ratio to take both parameters into account to estimate the disparity resolution.

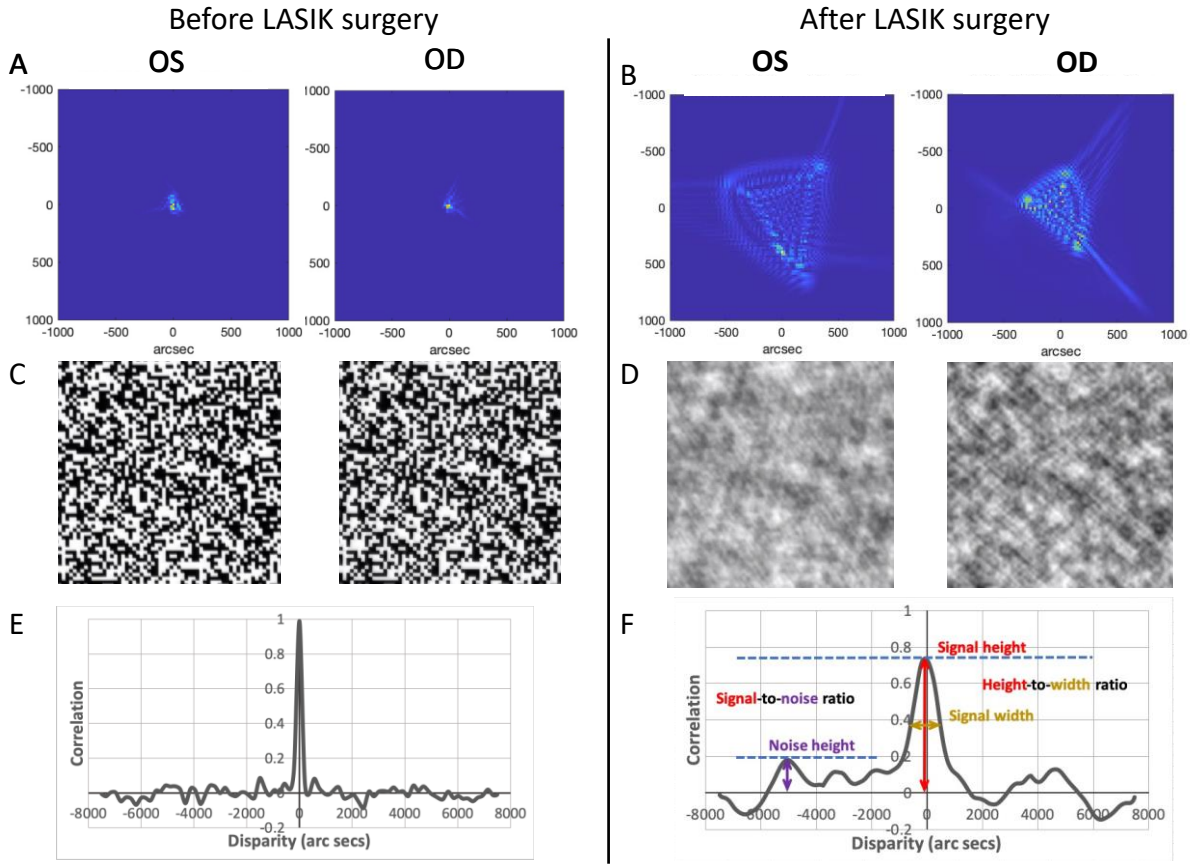


Figure 1: The higher-order aberrations (HOAs) of the left and right eyes of a subject were used to derive point-spread functions (PSFs) prior to LASIK refractive surgery (A) and after LASIK refractive surgery (B). Random-dot retinal image pairs were generated by convolution with the PSFs representing retinal image quality due to HOAs prior to LASIK (C) and following LASIK (D). One-dimensional (horizontal) cross-correlations were performed for left- and right-eye retinal images thus obtained for all subjects at baseline (e.g., E) and at all time points (e.g., F, shown here is one week time point after LASIK), for all refractive surgeries. We assessed the disparity noise and any changes in the quality of the disparity signal induced by the optical quality losses using cross-correlation metrics shown here (F) and described in the text. Shown here is a case where optical quality losses and interocular mismatches after LASIK caused a lowered peak, an increased spread (or width) of the signal peak, and increased height of the noise peaks in the cross-correlation function.

1.2.2 Statistical analyses

All empirical and computational data were organized and analyzed using Microsoft® Excel (Microsoft Corp, Redmond, WA, USA) and IBM SPSS Statistics for Mac version 27 (IBM Corp, Armonk, NY, USA). Since Shapiro-Wilk tests indicated that data were not normally distributed and common data transformations failed to give us normalized dataset, we performed non-parametric statistical tests for all our analyses. To investigate the relationships between

binocular metrics derived computationally from optical data and empirical stereo acuity, Spearman's rank correlations were performed between each of the binocular metrics and the measured stereo acuity for all three groups at the 6-month post-operative time point. To explore and compare the longitudinal changes in stereo acuity and all computational metrics, the pairwise Wilcoxon *post hoc* test (Wilcoxon signed-rank test) was performed. For comparisons between the refractive surgery groups, we selected the first 26 subjects of LASIK and SMILE groups in alphabetical order in order to equate sample sizes. In order to assess the binocular impacts of the three refractive surgeries across the post-operative time points, at each time point we performed Wilcoxon test separately for each of the derived binocular metrics and the empirical stereo acuity. Graphs were generated using Microsoft® Excel (Microsoft Corp, Redmond, WA, USA).

1.3 Results

According to the results of the Shapiro-Wilk test, 41.3% (31 of 75) of our data groups (including the stereo acuity and all computational metrics for each refractive surgery type at each timepoint) were not normally distributed [$p<0.05$, Wilcoxon test]. Some common data transformation methods, such as the Box Cox transformation, did not normalize the data, so we performed non-parametric tests for our study.

1.3.1 Relationships between binocular metrics computed from optical data and empirical stereo acuity over a 6 mm pupil

One of our main goals was to determine whether the increased and mismatched HOAs induced due to refractive surgeries contributed to the stereo acuity degradation measured following refractive surgery, and if they did, to quantify the contribution of optical mismatches to strength of binocular matches. We performed Spearman's rank correlation analyses between each of the four HOA-derived binocular metrics and stereo acuity at the 6-month post-operative time point (the longest-term follow up in our study) to assess the strength and direction of these relationships (Figure 2, A-D).

We found that signal width was positively correlated with empirical stereo acuity (Figure 2A) while signal height (Figure 2B), signal-to-noise ratio (Figure 2C) and height-to-width ratio (Figure 2D) had a negative correlation value with empirical stereo acuity. Spearman's rank correlations of each of the binocular metrics with empirical stereo acuity were statistically significant, with correlation coefficients $r_s(97) = 0.75$ for signal width, $r_s(97) = -0.65$ for signal height, $r_s(97) = -0.74$ for signal-to-noise ratio, and $r_s(97) = -0.77$ for height-to-width ratio [$p<0.001$ for all metrics, Wilcoxon test]. These data indicate that there are relatively strong monotonic relationships between the HOA-derived binocular metrics and empirical stereo

acuity. The height-to-width ratio showed the strongest correlation value (Figure 2D). Ranked HOA-derived binocular cross-correlation metrics and stereoacuities shared 65-77% of the variation.

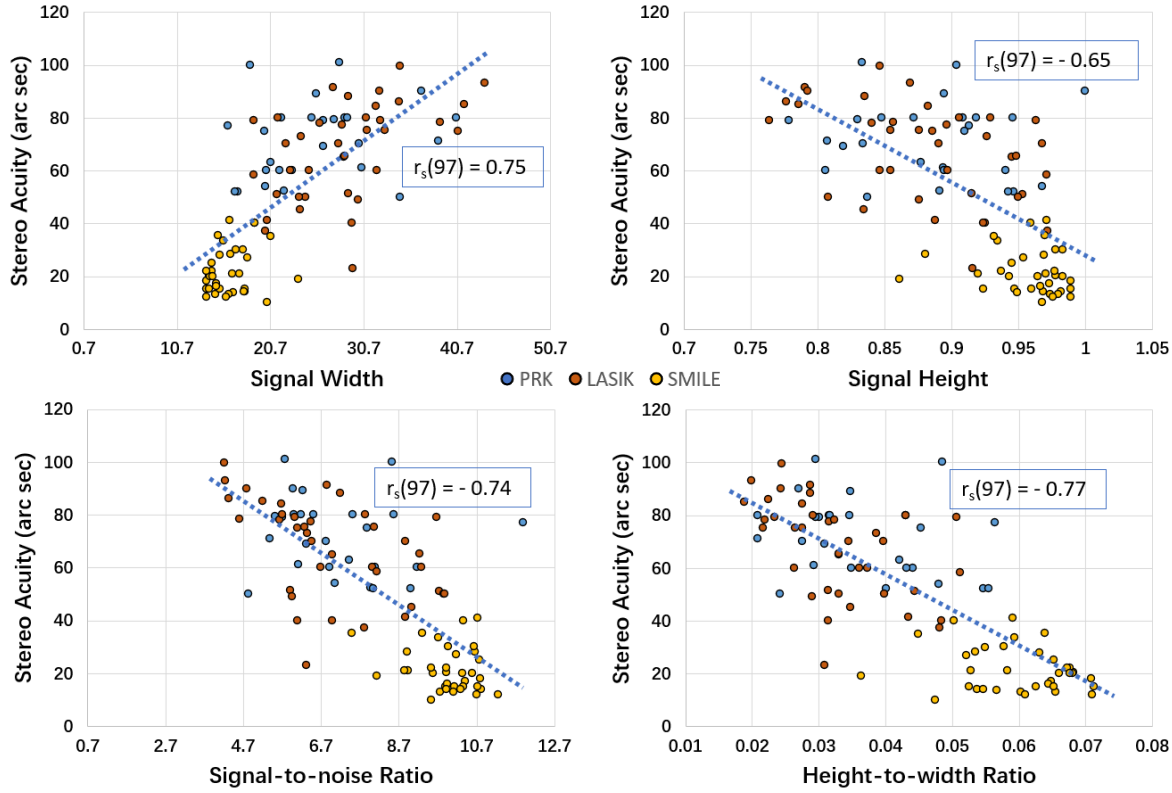


Figure 2. The correlation between each of the four HOA-derived binocular cross-correlation metrics and empirical stereo acuity at the 6-month post operative time point. Empirical stereo acuity co-varied strongly with signal width ($r_s(97)=0.75$, A), signal height ($r_s(97)=-0.65$, B), signal-to-noise ratio ($r_s(97)=-0.74$, C) and height-to-width ratio ($r_s(97)=-0.77$, D) [$p<0.001$ for Spearman rank correlations between each of the metrics and stereo acuity].

1.3.2 Longitudinal changes in each of the four computed binocular metrics and empirical stereo acuity, and comparisons of each of these outcome variables over time for each refractive surgery type with 6 mm pupils

The pre-operative value of all four binocular metrics and stereo acuity was not significantly different between the three refractive surgery types [$p>0.05$, Wilcoxon test]. We analyzed the longitudinal changes in the HOA-derived binocular metrics and empirical stereo acuity over time. At the one-week time point following surgery, it is evident that all four HOA-derived

binocular metrics changed for the worse for PRK and LASIK [p<0.001, Wilcoxon test], and SMILE [p<0.01, Wilcoxon test] (Figure 3), and subsequently trended towards the baseline during later post-operative visits. A general trend seen from the graph was that the largest recovery towards baseline was observed between the 1-week and the 1-month post-operative time points. Between the 3-month to 6-month post-operative time points, not many of the groups showed statistically significant improvement. For all three types of refractive surgery at the longest follow up time point (6-month post-operatively) in our study, all four computed binocular metrics did not recover to the corresponding pre-operative level [p<0.001 for PRK and LASIK, p<0.01, p<0.001 for SMILE, Wilcoxon test], with the only exception of signal height in the SMILE group. In general, PRK and LASIK showed greater worsening of all computed binocular metrics compared to SMILE at the 1-week time point and a larger “recovery” towards baseline over time. At the 6-month post-operative time point, PRK and LASIK were much different than their respective pre-operative values compared to SMILE. While empirical stereo acuity also worsened at the 1-week time point for the PRK and LASIK groups [p<0.001, Wilcoxon test], it improved significantly for the SMILE group, and continued to get significantly better at every subsequent visit [p<0.05 between any adjacent time points, Wilcoxon test] as described by Sarkar et al (2020). [16] Smaller improvements of stereo acuity during the post-operative visits were also seen for PRK and LASIK patients, as noted by Sarkar et al (2020). [16]

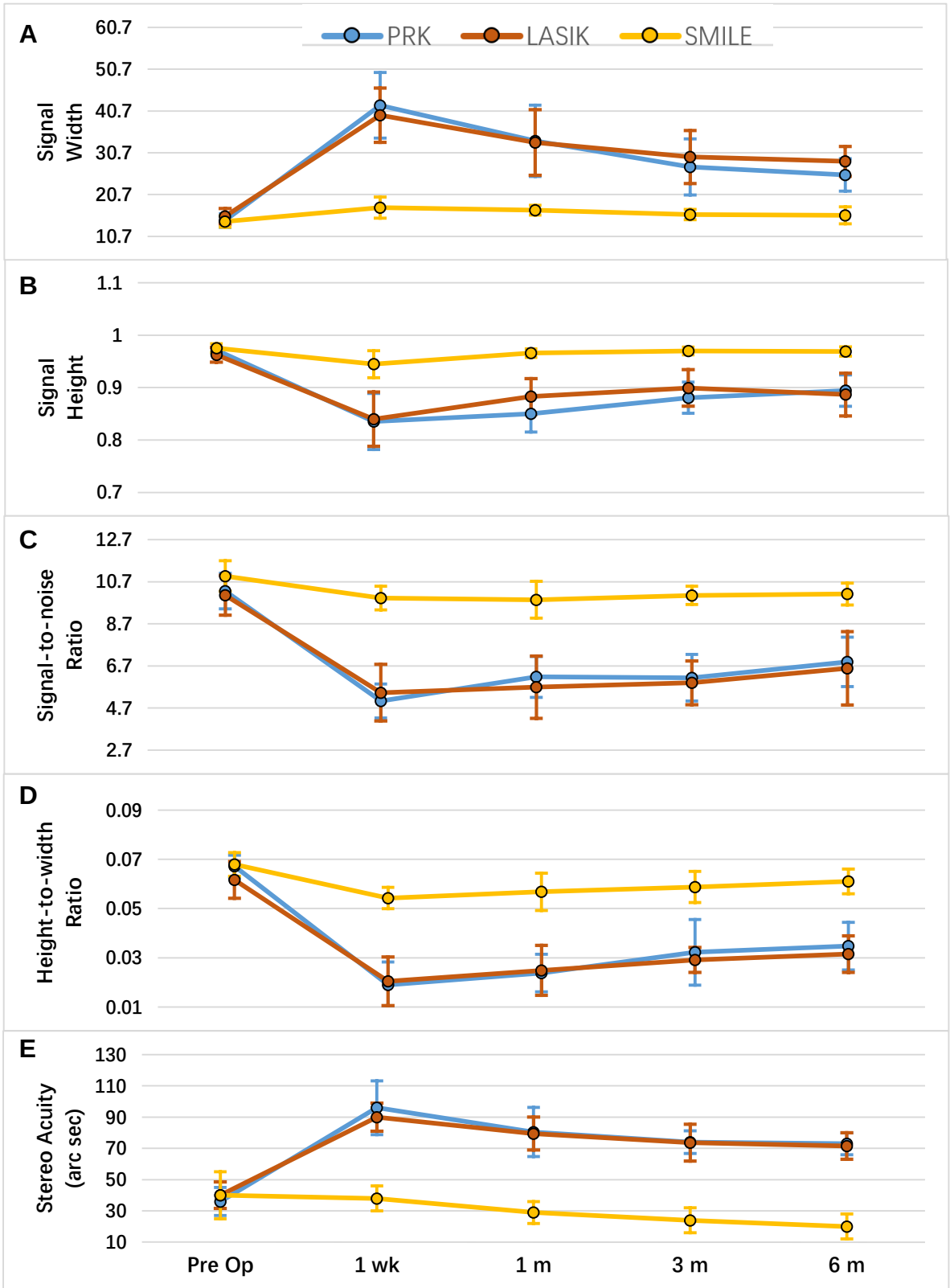


Figure 3. Comparisons of the four HOA-derived binocular cross-correlation metrics (panels A-D) and empirical stereo acuity (panel E) across the three types of refractive surgeries at different time points, i.e., pre-operative (Pre Op), 1-week (1 wk), 1-month (1 m), 3-months (3 m) and 6-months (6 m) after refractive surgery. Colored circles represent the median in each group and the error bars represent the 25th and 75th percentiles of the data distribution. See Appendix for Box-Whisker plots for each individual data group.

	p value	Pre vs. 1 wk	Pre vs. 1 m	Pre vs. 3 m	Pre vs. 6 m	1 wk vs. 1 m	1 wk vs. 3 m	1 wk vs 6 m	1 m vs. 3 m	1 m vs. 6 m	3 m vs. 6 m
PRK	Signal Width	<0.001 ***	<0.001 ***	<0.001 ***	<0.001 ***	0.022 *	<0.001 ***	<0.001 ***	0.003 **	<0.001 ***	0.151
	Signal Height	<0.001 ***	<0.001 ***	<0.001 ***	<0.001 ***	0.381	0.006 **	0.025 *	0.055	0.014 *	0.551
	Signal-to-noise	<0.001 ***	<0.001 ***	<0.001 ***	<0.001 ***	<0.001 ***	0.009 **	<0.001 ***	0.638	0.008 **	0.011 *
	Height-to-width	<0.001 ***	<0.001 ***	<0.001 ***	<0.001 ***	0.012 *	<0.001 ***	<0.001 ***	0.002 **	<0.001 ***	0.191
	Stereo acuity	<0.001 ***	<0.001 ***	<0.001 ***	<0.001 ***	<0.001 ***	<0.001 ***	<0.001 ***	<0.001 ***	<0.001 ***	<0.001 ***
LASIK	Signal Width	<0.001 ***	<0.001 ***	<0.001 ***	<0.001 ***	<0.001 ***	<0.001 ***	<0.001 ***	0.078	0.002 **	0.039 *
	Signal Height	<0.001 ***	<0.001 ***	<0.001 ***	<0.001 ***	0.054	<0.001 ***	<0.001 ***	0.015 *	0.119	0.777
	Signal-to-noise	<0.001 ***	<0.001 ***	<0.001 ***	<0.001 ***	0.464	0.175	<0.001 ***	0.500	0.001 **	0.003 **
	Height-to-width	<0.001 ***	<0.001 ***	<0.001 ***	<0.001 ***	0.007 **	<0.001 ***	<0.001 ***	0.069	0.022 *	0.091
	Stereo acuity	<0.001 ***	<0.001 ***	<0.001 ***	<0.001 ***	<0.001 ***	<0.001 ***	<0.001 ***	<0.001 ***	<0.001 ***	<0.001 ***
SMILE	Signal Width	<0.001 ***	<0.001 ***	0.003 **	0.002 **	0.044 *	0.002 **	0.002 **	0.057	0.023 *	0.812
	Signal Height	<0.001 ***	<0.001 ***	0.047 *	0.064	0.098	0.002 **	0.004 **	0.635	0.566	0.351
	Signal-to-noise	0.001 ***	0.002 **	0.002 **	0.003 **	0.731	0.622	0.422	0.870	0.658	0.238
	Height-to-width	<0.001 ***	<0.001 ***	0.002 **	<0.001 ***	0.003 **	<0.001 ***	0.001 **	0.074	0.032 *	0.731
	Stereo acuity	0.002 **	<0.001 ***	<0.001 ***	<0.001 ***	<0.001 ***	<0.001 ***	<0.001 ***	<0.001 ***	<0.001 ***	<0.001 ***

Table 1. Longitudinal analysis of the binocular impacts of PRK, LASIK and SMILE refractive surgery. Within each refractive surgery category, the binocular metrics computed from optical data, namely, signal width, signal height, signal-to-noise ratio, height-to-width ratio and also empirical stereo acuity were compared between pairs of time points as indicated in the column titles, i.e., pre-operative (Pre), 1-week (1 wk), 1-month (1 m), 3-months (3 m) and 6-months (6 m) after refractive surgery. *p≤0.05, ** p≤0.01, *** p≤0.001, Wilcoxon test

1.3.3 Comparisons of binocular metric and stereo acuity outcomes between the three refractive surgeries at each of the time points for 6 mm pupils

The pre-operative values of each of the four binocular metrics and of stereo acuity were not significantly different between the three refractive surgery types (20 out of 20 comparisons, 100%) [p>0.05, Wilcoxon test]. We found that the binocular metrics and stereo acuity were not statistically significantly different between PRK and LASIK across all time points [p>0.05, Wilcoxon test] with the 3-month and 6-month timepoints for height-to-width ratio being the only significant exceptions [p<0.05, Wilcoxon test]. SMILE had better binocular outcomes than PRK

and LASIK, as indicated by the computed binocular metrics and stereo acuity at each of the time points (20 out of 20 comparisons, 100%) [p<0.001, Wilcoxon test] (Table 2, Figure 3).

		p value (PRK vs. LASIK)	p value (PRK vs. SMILE)	p value (LASIK vs. SMILE)
Signal Width	1 wk	0.829	<0.001 ***	<0.001 ***
	1 m	0.657	<0.001 ***	<0.001 ***
	3 m	0.218	<0.001 ***	<0.001 ***
	6 m	0.159	<0.001 ***	<0.001 ***
Signal Height	1 wk	0.424	<0.001 ***	<0.001 ***
	1 m	0.124	<0.001 ***	<0.001 ***
	3 m	0.409	<0.001 ***	<0.001 ***
	6 m	0.770	<0.001 ***	<0.001 ***
Signal-to-noise Ratio	1 wk	0.248	<0.001 ***	<0.001 ***
	1 m	0.603	<0.001 ***	<0.001 ***
	3 m	0.790	<0.001 ***	<0.001 ***
	6 m	0.909	<0.001 ***	<0.001 ***
Height-to-width Ratio	1 wk	0.990	<0.001 ***	<0.001 ***
	1 m	0.849	<0.001 ***	<0.001 ***
	3 m	0.041 *	<0.001 ***	<0.001 ***
	6 m	0.034 *	0.002 **	<0.001 ***
Stereo acuity	1 wk	0.084	<0.001 ***	<0.001 ***
	1 m	0.067	<0.001 ***	<0.001 ***
	3 m	0.099	<0.001 ***	<0.001 ***
	6 m	0.206	<0.001 ***	<0.001 ***

Table 2. Comparisons of the binocular outcomes between pairs of refractive surgeries at each post-operative time point for 6 mm pupils. *p≤0.05, ** p≤0.01, *** p≤0.001, Wilcoxon test

In summary, PRK and LASIK showed a greater worsening of binocular outcomes at the 1-week time point for all metrics compared to SMILE. At the 6-month post-operative time point when cornea might have settled after the surgery, binocular outcomes for PRK and LASIK were still poor, and not comparable to SMILE (Figure 3, Table 2).

1.4 Discussion

Laser refractive surgeries might introduce significant interocular mismatches of HOAs. [16-18, 32] These optical mismatches lead to significant binocular detriment, of which stereo acuity is

a sensitive indicator. The current study investigates the contribution of the optical mismatches to the stereo losses experienced by these subjects. We describe how interocular HOA mismatches following three different laser refractive surgeries affect disparity signal quality by modeling the binocular matching process through horizontal cross-correlation of simulated retinal images blurred by induced HOAs. We derived binocular computational metrics with aberration data collected prior to surgery, and at various time points after surgery, and assessed their relationships with stereo acuity as done previously. [13]

The four HOA-derived binocular metrics that we used to quantify disparity matches and disparity signal quality were in good agreement with empirical stereo acuity. Specifically, Spearman's rank correlation values (r_s) with stereo acuity were strong [-0.77 for height-to-width ratio, 0.75 for signal width, -0.74 for signal-to-noise ratio, and -0.65 for signal height, listed here in descending order of r_s]. We would thus predict better empirical stereo acuity outcomes with a narrower signal width, greater signal height, greater signal-to-noise and height-to-width ratio of the cross-correlation function. This is in line with Metlapally et al (2019)'s findings of strong to very strong monotonic relationships between HOA-derived binocular metrics and empirical stereo acuity in keratoconus subjects. [13] All in all, the strength of the relationships between computational binocular metrics and empirical stereo acuity data emphasizes the usefulness of this method to assess the contributions of deteriorated optics to stereo (in)sensitivity.

We were interested in the short-term and longer term longitudinal optical changes as the two operated corneas settled after refractive surgery, and how these new alterations affected patients' binocular viewing. The patients in our study likely have seen small progressive changes in their refractive error, i.e., LOAs over a span of several years, and relative stability of refractive error is a necessary criterion leading up to refractive surgeries. A reasonable assumption with backing from baseline HOA data from Sarkar et al (2020) is that HOA profile distributions were within normative population ranges for our subjects' ages and refractive error, and remained symmetric between the two eyes. [11, 12, 16] However, shortly after PRK and LASIK refractive surgery, HOAs were elevated compared to baseline and interocular asymmetries had been introduced. [16], and at the six-month timepoint, these changes persisted. Unsurprisingly, all HOA-derived binocular metrics for PRK and LASIK group showed a significant worsening immediately after the surgery (1 week) when corneal optical profiles had been iatrogencially and dramatically altered over a short period of time. Most metrics had significantly improved at the 1-month compared to the 1-week timepoint in the lead up to the significant recovery at six months. The sub-optimal HOA-derived binocular metrics suggest that interocular optical mismatches introduced following refractive surgeries cause short-term and longer-term contrast and phase irregularities that parallel the empirical stereo acuity changes over time.

Dry eye is the most common complication after refractive surgeries and might deteriorate the optical quality by altering the surface of the cornea. Longitudinally, all three refractive surgeries lead to dry eye immediately after the procedure, which seems to return to pre-operative levels over time. SMILE affords the fastest dry eye recovery time among the three, and over the

longer term (after 6 months), there is no significant change in tear break up time (TBUT) and tear production (as measured by Schirmer's I test) compared with pre-operative levels for PRK and SMILE; however, for LASIK, most studies show that the recovery time is generally longer. This is thought to be due to the disruption of corneal nerves during flap generation procedure in LASIK. [33-35] The literature often compares the dry eye outcomes of two out of three surgeries of interest and there is a dearth of studies comparing dry eye assessments at the same post-operative time points across the three types of refractive surgeries perhaps due to these surgeries representing three different generations. There are no statistical differences in frequency and severity of dry eye symptoms at different post-operative time points between LASIK and PRK, and at some time points SMILE shows better results of TBUT, tear meniscus height and Ocular Surface Disease Index (OSDI) compared to LASIK. [34, 36, 37] There is also a lack of studies that compare SMILE and conventional PRK directly at the same post-operative time point. Overall, when we compare the HOAs and resulting binocular metrics at the same time points, different levels of dry eye could potentially contribute to differences in the optics. [38-40] Wavefront aberration measurements we used were collected straight after 1-2 blinks and psychophysical stereo acuity tests were performed with subjects' self-regulated blinks, as reported by Sarkar et al. [16]While dry eye caused by LASIK might have impacted our data, we believe that barring some variability introduced, the data may still be largely immune from its impacts due to the way in which data were collected. The correlations between the extent of dry eye and visual acuity and contrast sensitivity (monocular parameters) are available in the literature, but its impacts on stereo acuity remains to be explored, and additional follow ups at longer term (for example, 12 months) might also be valuable to explore these impacts further.

In addition to dry eye, refractive surgeries might also cause changes in vergence and vergence eye movements, which could also contribute to the stereo acuity changes. Retinal blur from LOAs, more specifically, defocus, affects vergence eye movements and results in heterophoria changes. [41] Also, heterophoria, especially esophoria, negatively impacts stereo acuity. [42, 43] Prism induced esophoria temporarily leads to deteriorated stereo acuity but after about nine minutes, stereo acuity could return to near baseline level due to vergence adaptation. [44] There is evidence that laser refractive surgeries lead to changes in fusional vergence amplitudes in moderate myopia patients. Han et al found that convergence amplitude at near decreased immediately (1-week and 1-month) after surgery, but gradually recovered back to near pre-operative level at 3-month post-operatively. [45] Other studies have found that the accommodative convergence/ accommodation (AC/A) ratio decreases initially after refractive surgeries, but increases after 1 month post-operatively, and stabilizes further on after 3 months. In our study, we did not account for phoria/ vergence criteria for recruitment nor the changes or impacts in these due to refractive surgeries and this requires more research. There is lack of studies that explore the correlation between HOAs and vergence, and it is still unknown if retinal blur caused by HOAs would induce vergence changes. Even if it does, further investigation will be needed to determine if refractive surgery introduces vergence changes that in turn affect stereo acuity, or just directly altering stereo acuity by changing the optics. We assume that vergence status of participants would have been within population norms, and any impacts of refractive surgeries on vergence might be

random as clear patterns are not evident from the literature. It is possible that the effects of phoria in larger populations than our sample might be less of concern with variable impacts on different phoria ranges canceling out.

In addition to the corneal irregularity caused by refractive surgery leading to HOAs, it is also known to cause subjective visual disturbances due to intraocular scattering in the form of haloes and starbursts after LASIK surgery (please cite papers). Whether the HOAs cause intraocular scattering or if the two are different issues stemming from corneal irregularity is unclear. Scattering could reduce contrast additionally, but data were collected without any disturbances from straylight sources and high-contrast targets stereo acuity targets were used to minimize any impacts of lowered contrast.

Six months might seem like a relatively short time period. Although at the 6-month post-operative time point, the binocular metrics show incomplete recovery toward pre-operative level, one can speculate that cornea might be able to continue recovering, potentially resulting in a restoration of its optical quality. Indeed, the converse fact that some complications, like post-LASIK ectasia, can happen after many years post-surgery might somehow lead to this speculation. In the few studies that take stabilization of total aberrations or HOAs post-operatively into account, the focus is often on comparison of aberrations with their pre-operative levels. There were, however, a few studies that showed that for PRK and LASIK, corneal HOAs stabilize at around 3 months after surgery, and remain stable from then on, but never come back to the pre-operative level. [18, 46, 47] Similar outcomes are observed in our study, where most of the binocular metrics for PRK and LASIK group reveal no statistically significant difference between 3-month and 6-month time point. For SMILE, previous research indicates that total corneal aberrations remain stable from pre-operative level to up to 7 years post-operatively [48], and corneal HOAs show significant improvement between 1-month and 3-month post-operative time points, and remain stable from the third up to six months after surgery. [16] In our study, some binocular metrics perhaps reveal the corneal recovery process between 1-week and 3-month period, but no significant improvement was observed after the 3-month time point. The choice of tracking these changes up to six months for the study was based on evidence from previous literature, and the recovery seems largely complete upon visual examination the slopes of our graphs that show a slowing down or plateauing of changes after about the 3-month time point.

The SMILE group was different in that although all the four cross-correlation metrics showed a significant worsening [$p<0.05$, Wilcoxon test] from the pre-operative baseline to the 1-week post-operative time point, empirical stereo acuity showed a significant improvement [$p<0.05$, Wilcoxon test]. This discrepancy might be explained by the significantly better optical outcomes for SMILE compared to PRK and LASIK, and learning effects of the subjective stereo acuity test. While similar learning effects are plausible in the PRK and LASIK groups, they were perhaps counterbalanced by greater detrimental effects of the increased magnitudes and interocular mismatches of HOAs seen in these groups.

Last but not least, we wanted to see based on our findings, if we could predict, and if so to what extent we could predict post-operative binocular visual performance based on pre-operative optical profiles, i.e., uncorrected LOAs, for a candidate who wants to undergo some type of refractive surgery. At this time, based on the data, we can only qualitatively estimate the immediate worsening of binocular outcomes for PRK and LASIK post-operatively, with a gradual recovery period up to six months. We could also educate patients about possible related subjective binocular visual disturbances associated with slightly reduced depth perception. We could also report to the wider optometry and vision science community about the likelihood of better binocular performance with SMILE when compared to LASIK or PRK. Due to the complexity of all factors discussed above, and a wider range of factors (such as availability, cost of the procedure and insurance coverage) that lead to a choice of PRK vs LASIK vs SMILE surgeries, we would have to await more data for more specific customized advice about the choice of the specific refractive surgery type that optimizes monocular and binocular outcomes for each patient.

Chapter 2.

Comparisons of the Longitudinal Impacts of Three Generations of Laser Refractive Surgeries on Binocular Matching Metrics Derived Computationally from Higher-order Aberrations for 4 mm Pupils, and Comparison with 6 mm Pupils

2.1 Introduction

The size of the pupil is an important determinant of optical quality. Large pupils hamper retinal image quality by increasing the influence of optical aberrations. Previous studies have found that pupil size can affect aberrations and monocular visual outcomes. HOAs, as quantified by RMS, become significantly higher as pupil size increases from 3 mm to 6.5 mm. [49] Image quality, as quantified by the visual strehl ratio and VSOTF (visual strehl ratio-based optical transfer function) was also found to become worse with increase in pupil size. [50, 51] In addition, monocular contrast sensitivity also decreases with larger pupil sizes. [52] The first chapter of this thesis focused on estimating the binocular outcomes of optical changes induced following refractive surgery using optical and psychophysical data gathered following cycloplegia at a constant pupil size of 6 mm for each subject, for each individual, each surgery and timepoint. This ensured that our estimates across subjects, times and refractive surgery conditions were well-controlled for the effects of the dynamic changes induced by accommodation and for the influence of the size of the pupil on optical quality.

Pupil sizes, in turn, are influenced by multiple factors. They can be very different from person to person just by individual biological variance. Besides, pupil size is not static, and is altered quickly by changes in ambient lighting or accommodation. Age can also contribute to changes in pupil size, with children exhibiting larger pupil sizes than much older adults. Thus, for pre-presbyopic adults (as used in our studies) in the most common lighting environments, and under realistic binocular conditions, we might not expect the computations performed with the 6-mm pupil in chapter 1 to be fully representative of their experience or performance.

While much is known about factors that affect pupil size and its impact on monocular image quality, it is not clear how pupil sizes impact binocular visual performance and stereo acuity in particular, due to lack of previous studies. The most relevant study might be one by Lovasik et al in 1985, which explored how stereo acuity changes with pupil sizes. [9] They found that

stereo acuity measured by Randot and Titmus methods was not affected by pupil size changes when the pupil size was greater than 2.5 mm (Randot) and 1.5 mm (Titmus). Under normal conditions, a healthy individual, whether young or old, rarely has pupil sizes smaller than 2.5 mm, even with strong illuminance. [53] So, we thought it was important to investigate the optical contribution to stereo acuity at a more nominal and naturalistic pupil size.

In this chapter, we rescaled the aberrations from 6 mm to 4 mm pupils. We expected a lower HORMS at 6-month post-operative time point for 4 mm pupil compared with 6 mm pupil. [16] We used the same methods to perform computational cross-correlation using the rescaled Zernike data as we did in chapter 1, to study any changes in the binocular metrics (signal width, signal height, signal-to-noise ratio and height-to-width ratio). We investigated whether the differences among the three different refractive surgeries were still significant with a smaller pupil size, and whether the recovery trend we observed for a 6 mm pupil size was still present. We also compared the absolute values of differences between the pre-operative time point to 6-month post-operative time point seen with 4 mm pupil sizes with the 6 mm pupil data set.

2.2 Methods

2.2.1 Computational methods

We used a debugged version of a Matlab program originally written by Campbell (2003) to recalculate the Zernike polynomials for 4 mm pupils based on the Zernike polynomials collected over 6 mm pupils. The HORMS was calculated as the square root of the sum of squares of the recalculated Zernike aberrations from the third order and above. Binocular cross-correlation analyses were performed as described in chapter 1, but using the Zernike aberrations recalculated over 4 mm pupils. Briefly, from the raw aberration data for each eye of each subject, the LOA terms (Z_2^{-2}, Z_2^0, and Z_2^2) were nulled given that our study only focused on HOAs. The HOAs were used to compute point-spread functions (PSFs) for a specific subject and time-point (refer to Figure 1A and 1B). Subsequently, the HOA-derived PSFs were used to convolve a 600x600-pixel random dot image to generate a corresponding pair of retinal images for the left and right eyes (refer to Figure 1C, 1D). A horizontal cross-correlation function was generated following an algorithm from Lewis (1995). [30] Four binocular metrics, namely (1) signal width, (2) signal height, (3) signal-to-noise ratio, and (4) height-to-width ratio were used to evaluate the quality of binocular matches between the retinal images of the two eyes now estimated using 4 mm pupils as before (also see Metlapally et al, 2019). [13]

2.2.2 Statistical analyses

All empirical and computational data were organized and analyzed using Microsoft® Excel (Microsoft Corp, Redmond, WA, USA) and IBM SPSS Statistics for Mac version 27 (IBM Corp, Armonk, NY, USA). Non-parametric tests were done for all analyses because of the non-normative nature of the data set, following the same steps as described in chapter 1. Briefly, to investigate the longitudinal changes in all binocular metrics, the Wilcoxon signed-rank test was performed. For comparisons between the refractive surgery groups, the first 26 subjects of LASIK and SMILE groups in alphabetical order were selected to equate sample sizes, and at each time point we performed Wilcoxon test separately for each of our binocular metrics. Wilcoxon signed-rank tests were performed to evaluate whether the changes from pre-operative time point to 6-month post-operative time point were significantly different for 4 mm pupil compared with 6 mm pupil. Graphs were generated using Microsoft® Excel (Microsoft Corp, Redmond, WA, USA).

2.3 Results

2.3.1 Monocular HORMS comparisons between 4 mm and 6 mm pupils

HORMS values derived for aberrations recalculated over 4 mm pupils of both eyes of all individuals at six-month post-operative time point had median values of 0.14 µm, 0.15 µm, and 0.10 µm, respectively, for PRK, LASIK and SMILE. From an eye practitioner's perspective, the HOAs measured using 4 mm pupils cause equivalent defocus blurs of 0.06, 0.07 and 0.04 D respectively (based on the formula from Thibos et al). [54] At the six-month time point, the median values of HORMS for 6 mm pupils were 0.67 µm, 0.58 µm, and 0.28 µm respectively for PRK, LASIK and SMILE, which were calculated using data from Sarkar et al (2020). In dioptric terms, these values would represent the equivalent defocus imposed by lenses of 0.13, 0.11 and 0.05 D respectively. The HORMS values and the equivalent defocus values at the six-month time point for 4 mm pupils were significantly reduced ($p<0.05$) compared to that of 6 mm pupils showing improved optical quality and reduced optical blur from the HOAs as expected.

2.3.2 Longitudinal changes in each of the four computed binocular metrics and empirical stereo acuity, and comparisons of each of these outcome variables over time for each refractive surgery type with 4 mm pupils

The pre-operative values for all four computed binocular metrics were not significantly different for all three refractive surgery types [$p>0.05$, Wilcoxon test]. When only looking at the 4 mm pupil analysis over time, the data showed a similar trend as seen for 6 mm pupils. At the one-week time point following surgery, all four binocular metrics for the three types of refractive surgeries revealed worse binocular outcomes [$p<0.001$, Wilcoxon test]; thereafter, they trended towards the pre-operative level during following post-operative visits (Figure 4, Table 3). Between 1-week and 1-month post-operative time point, the change in most of the binocular metrics (all four metrics for PRK, two metrics for LASIK and three metrics for SMILE) were not statistically significant [$p>0.05$, Wilcoxon test], indicating the short-term recovery trend was not as clear. The recovery was more evident when differences were analyzed over longer time intervals, as indicated by the columns comparing 1-week and 3-month, or 1-week and 6-month time points. The recovery was smaller when comparing the 3-month to 6-month post-operative time point, not many of the groups showed statistically significant recovery [$p>0.05$, Wilcoxon test], with the exception of two metrics in LASIK group [$p<0.05$, Wilcoxon test]. At the longest follow up (6-month time point), all binocular metrics in all refractive surgeries did not improve to pre-operative level [$p<0.001$ and $p<0.01$, Wilcoxon test], with only one exception of signal height in SMILE group, which indicated a non-significant difference [$p>0.05$, Wilcoxon test].

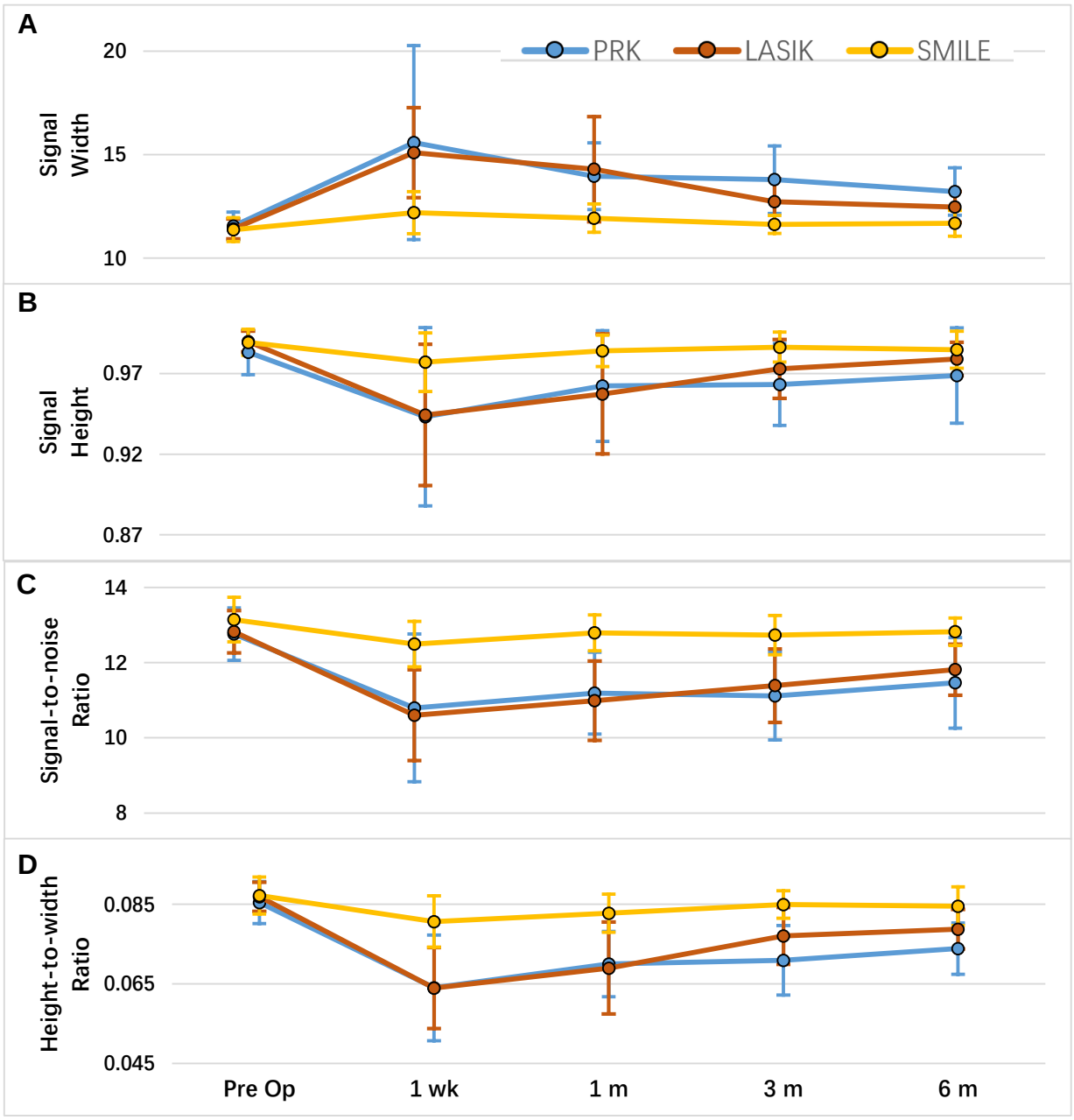


Figure 4. Comparisons of the four HOA-derived binocular cross-correlation metrics (panels A-D) across the three types of refractive surgeries (PRK, LASIK, SMILE) at different time points, i.e., pre-operative (Pre Op), 1-week (1 wk), 1-month (1 m), 3-months (3 m) and 6-months (6 m) after refractive surgery. Colored circles represent the median in each group and the error bars represent the 25th and 75th percentiles of the data distribution. See Appendix for Box-Whisker plot for each individual data group.

	p value	Pre vs. 1 wk	Pre vs. 1 m	Pre vs. 3 m	Pre vs. 6 m	1 wk vs. 1 m	1 wk vs. 3 m	1 wk vs. 6 m	1 m vs. 3 m	1 m vs. 6 m	3 m vs. 6 m
PRK	Signal Width	<0.001 ***	<0.001 ***	<0.001 ***	<0.001 ***	0.258	<0.001 ***	<0.001 ***	0.002 **	<0.001 ***	0.162
	Signal Height	<0.001 ***	<0.001 ***	<0.001 ***	<0.001 ***	0.228	0.001 **	<0.001 ***	0.124	0.008 **	0.182
	Signal-to-noise	<0.001 ***	<0.001 ***	<0.001 ***	<0.001 ***	0.322	<0.001 ***	<0.001 ***	0.218	0.012 *	0.137
	Height-to-width	<0.001 ***	<0.001 ***	<0.001 ***	<0.001 ***	0.112	<0.001 ***	<0.001 ***	0.001 **	<0.001 ***	0.107
LASIK	Signal Width	<0.001 ***	<0.001 ***	<0.001 ***	<0.001 ***	0.007 **	0.012 *	<0.001 ***	0.396	0.016 *	0.045 *
	Signal Height	<0.001 ***	<0.001 ***	<0.001 ***	0.008 **	0.130	0.130	0.01 **	0.971	0.335	0.280
	Signal-to-noise	<0.001 ***	<0.001 ***	<0.001 ***	<0.001 ***	0.380	0.722	0.261	0.925	0.097	0.220
	Height-to-width	<0.001 ***	<0.001 ***	<0.001 ***	<0.001 ***	0.008 **	0.006 **	<0.001 ***	0.421	0.029 *	0.034 *
SMILE	Signal Width	<0.001 ***	<0.001 ***	0.044 *	0.025 *	0.080	<0.001 ***	0.003 **	0.036 *	0.024 *	0.922
	Signal Height	<0.001 ***	0.057	0.064	0.120	0.124	0.01 **	0.088	0.385	0.954	0.694
	Signal-to-noise	<0.001 ***	0.005 **	0.005 **	0.004 **	0.044 *	0.055	0.017 *	0.793	0.941	0.461
	Height-to-width	<0.001 ***	<0.001 ***	0.029 *	0.018 *	0.088	<0.001 ***	0.002 **	0.035 *	0.027 *	0.987

Table 3. Longitudinal analysis for 4 mm pupil for PRK, LASIK and SMILE. Within each refractive surgery category, the computed binocular metrics of signal width, signal height, signal-to-noise ratio and height-to-width ratio data for pairs of time points as indicated in the column titles, i.e., pre-operative (Pre), 1-week (1 wk), 1-month (1 m), 3-months (3 m) and 6-months (6 m) were compared and tabulated. *p≤0.05, ** p≤0.01, *** p≤0.001, Wilcoxon test

2.3.3 Comparisons of binocular metric and stereo acuity outcomes between the three refractive surgeries at each of the time points for 4 mm pupils

Similar to analyses over 6 mm pupils, we found that the binocular metrics were not statistically significantly different between PRK and LASIK [p>0.05, Wilcoxon test across all time points with the only exception of 3-month and 6-month timepoint for height-to-width ratio (12 out of 16 comparisons, 75%) [p<0.05, Wilcoxon test]. SMILE had better binocular visual outcomes than PRK and LASIK at each of the time points, as indicated by the binocular metrics and stereo acuity (16 out of 16 comparisons, 100%) [p<0.001, Wilcoxon test] (Table 4, Figure 4). Many conclusions made for computations and analyses we performed with optical data gathered over 6 mm pupils hold for 4 mm pupils, with PRK and LASIK showing greater short-term deterioration in all binocular metrics than SMILE. Over the longer term (6-month post-

operative time point), the binocular outcomes for PRK and LASIK were still significantly worse than SMILE (Figure 4, Table 4).

		p value (PRK vs. LASIK)	p value (PRK vs. SMILE)	p value (LASIK vs. SMILE)
Signal Width	1 wk	0.869	<0.001 ***	<0.001 ***
	1 m	0.889	<0.001 ***	<0.001 ***
	3 m	0.041 *	<0.001 ***	<0.001 ***
	6 m	0.018 *	0.002 **	<0.001 ***
Signal Height	1 wk	0.675	<0.001 ***	<0.001 ***
	1 m	0.694	0.001 ***	0.001 ***
	3 m	0.159	0.001 ***	<0.001 ***
	6 m	0.638	0.052	0.002 **
Signal-to-noise Ratio	1 wk	0.280	<0.001 ***	<0.001 ***
	1 m	0.585	<0.001 ***	<0.001 ***
	3 m	0.603	<0.001 ***	<0.001 ***
	6 m	0.485	<0.001 ***	<0.001 ***
Height-to-width Ratio	1 wk	0.990	<0.001 ***	<0.001 ***
	1 m	0.849	<0.001 ***	<0.001 ***
	3 m	0.041 *	<0.001 ***	<0.001 ***
	6 m	0.034 *	0.002 **	<0.001 ***

Table 4. Comparison of the binocular outcomes between pairs of refractive surgeries at each post-operative time point for 4 mm pupils. *p≤0.05, ** p≤0.01, *** p≤0.001, Wilcoxon test

2.3.4 Comparisons between binocular metrics derived from 4 mm and 6 mm pupils

Estimates of the binocular metrics computed from optical data rescaled to 4 mm pupils were compared with the estimates for the 6 mm pupil analyses from Chapter 1. Graphs with same Y-axis scale as 6 mm pupil analyses (Figure 5) are shown for better visualization of comparison with 6 mm pupil results. The changes between the 6-month post-operative time point and pre-operative time point for 4 mm pupils were significantly smaller than those for 6 mm pupils for all the binocular metrics [p<0.001, Wilcoxon signed-rank test]. In general, the changes seen in each of the metrics over time were smaller than those seen with 6 mm pupils (Figure 5). We found some comparisons, e.g., PRK versus LASIK at 3-month post-operative time points for signal width that did not show statistically significance for 6 mm pupils (p=0.22)

were statistically significant (p=0.04) when for 4 mm pupils. In addition, some statistically significant differences seen between different post-operative time points for binocular metric computations using 6 mm pupils were not statistically significant for metrics computed using 4 mm pupil data. For example, from 1-week to 1-month post-operative time points, 7 of 12 binocular metrics (three from PRK, two from LASIK and two from SMILE) showed significant recovery towards the baseline preoperative data for 6 mm pupils, but only 3 of 12 (zero of PRK, two of LASIK and one from SMILE) indicated significant recovery for metrics computed over 4 mm pupils (Table 3, Table 4). Thus, the recovery trends were not as clear with 4 mm pupils as they were with 6 mm pupils.

We tabulated and compared the data for the two pupil sizes for longer-term changes. Specifically, we compared differences between pre-operative and six-month time points in the median values for both raw binocular metrics and percentage changes in all the binocular metrics in Table 5. Compared with 6 mm pupils, the changes of all metrics from pre-operative to six-month post-operative time points were significantly smaller ($p<0.05$) for 4 mm pupils, with the only exception of signal height of SMILE (p=0.21) (Wilcoxon signed-rank test). In the majority of cases, the changes in raw values and percentages of metrics for 4 mm pupils were one-third or less than the changes seen for 6 mm pupils (9 out of 12 comparisons for both raw values and percentages).

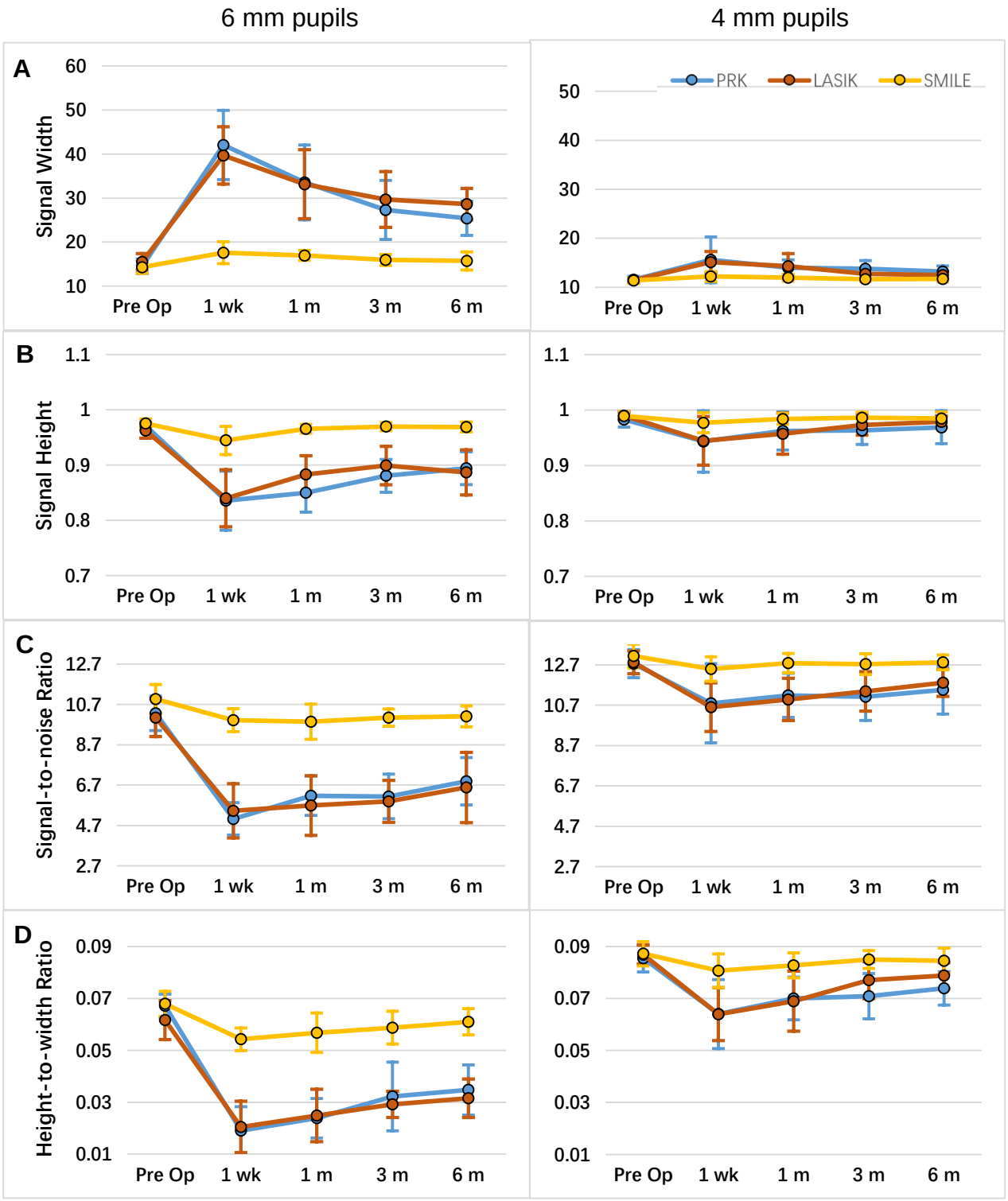


Figure 5. Binocular metrics obtained using HOA data over 6 mm pupils (left column) vs 4 mm pupils (right column) with the same y axis scale to compare. A) Signal Width; B) Signal Height; C) Signal-to-noise Ratio; D) Height-to-width Ratio. Colored circles represent the median in each group and the error bars represent 25th and 75th percentiles of the distributions.

		Pre-Operative		6 m		Difference (6 m – Pre-Operative)		Change in %	
Surgery	Binocular metrics	6 mm	4 mm	6 mm	4 mm	6 mm	4 mm	6 mm	4 mm
PRK	Signal Width	15.11	11.41	25.70	12.48	10.59	1.06	70.06	9.30
	Signal Height	0.96	0.99	0.89	0.98	-0.08	-0.01	-8.13	-1.1
	Signal-to-noise	10.18	12.82	7.14	11.81	-3.03	-1.01	-29.81	-7.86
	Height-to-width	0.07	0.09	0.04	0.08	-0.03	-0.01	-43.20	-9.34
	Stereo acuity	41.85	---	71.71	---	29.87	---	71.37	---
LASIK	Signal Width	15.95	11.55	28.42	13.22	12.47	1.67	78.21	14.42
	Signal Height	0.92	0.98	0.88	0.97	-0.04	-0.01	-4.30	-1.43
	Signal-to-noise	9.91	12.76	6.99	11.46	-2.92	-1.30	-29.45	-10.18
	Height-to-width	0.06	0.09	0.03	0.07	-0.03	-0.01	-44.84	-13.55
	Stereo acuity	42.81	---	67.20	---	24.39	---	56.98	---
SMILE	Signal Width	14.80	11.37	16.27	11.69	1.47	0.31	9.91	2.73
	Signal Height	0.97	0.99	0.96	0.99	-0.01	-0.01	-1.03	-0.47
	Signal-to-noise	10.63	13.14	9.98	12.82	-0.65	-0.32	-6.12	-2.46
	Height-to-width	0.07	0.09	0.06	0.09	-0.01	-0.00	-10.52	-3.08
	Stereo acuity	50.58	---	21.46	---	-29.12	---	-57.57	---

Table 5. Median values for each of the binocular metrics at the pre-operative and six-month (6 m) time points for 6 mm vs 4 mm pupils. Also shown are the changes of each of these values at six months after surgery compared to the pre-operative time points as raw metric value differences and percentage differences.

2.4 Discussion

All aberration measurements and stereo acuity tests reported by Sarkar et al, 2020 were based on 6 mm pupils following dilation from cycloplegia to eliminate the variability from the dominant effects of different pupil sizes on the optics; however, natural photopic and mesopic pupil sizes are likely much smaller, and would have significant impacts on naturalistic viewing. Our previous study (Chapter 1) shows that the HOAs induced by LASIK and PRK were significantly higher with the larger 6 mm pupil size. In order to estimate the optical contribution of HOAs to binocular outcomes for a pupil size more likely for this population in most everyday lighting and binocular conditions, we re-analyzed all the computational binocular metrics for 4 mm-pupil size and compared outcomes between the three different types of refractive surgeries and also longitudinally. We did not assess relationships between computed binocular metrics and stereo acuity, as stereo acuity was measured psychophysically using 6 mm artificial pupils.

Our results show that the HORMS for 4 mm pupils is significantly smaller than the HORMS for 6 mm pupils. The HORMS, however, is one all-encompassing number, and does not represent the image quality effects of individual HOAs nor how interocular differences between individual

HOAs might affect binocular combination. Would we get more information if we investigated individual aberrations or perhaps individual orders of Zernike aberrations? We anticipated very little benefit-to-cost for analyzing the impacts of the reductions of individual aberrations or RMS aberrations for each Zernike order, or their interocular differences for the 4 mm pupil size. Our study therefore did not assess the separate impacts of the reductions of individual aberrations or groups of aberrations between 6 mm and 4 mm pupils.

In addition, we expected that when the aberration data was recalculated for 4 mm pupils, the variability of each of the computed binocular metrics, irrespective of the different time-points or different refractive surgery types, would reduce. We also anticipated that the change at the six-month time point compared to baseline would also be minimized with the 4 mm pupil as would the magnitude of changes seen with every subsequent time point. These are evident from two right columns of Table 5 and the more “compact” data set (Figure 5), where we found some comparisons between some pairs of time points changed from significant to insignificant (Table 1 in chapter 1, Table 3 in chapter 2) after resizing the pupil size from 6 mm to 4 mm. This indicates that with a smaller pupil size, both the amount and variability of the distribution of HOAs decreases.

In this chapter where we analyzed data for 4 mm pupils, we only had access to the computational data derived from aberrations, and did not have empirical stereo acuity data. When comparing the change in percentage for 6 mm and 4 mm pupils in Table 5, we observed that our data for 6 mm pupils showed big differences in percentage from baseline to 6 months for all binocular metrics and stereo acuity, and from Chapter 1 it is evident that there are significant strong relationships between binocular metrics derived from HOAs and stereo acuity. So, given we found that the percentage changes in binocular metrics of 4 mm pupils were much smaller (i.e., one-third or less in the majority of cases) compared to those of 6 mm pupils, we explored the possibility of a corresponding improvement in stereo acuity in literature reporting relationships between pupil size and stereo acuity. Previous research indicates that stereo acuity does not change much with the change in pupil sizes for pupils >2.5 mm. [9] Conclusions in this study were based on data from normal individuals with normal HOAs; however, our study subjects had generally elevated HOAs, and may have a stereo acuity benefit over the smaller pupil size compared to the larger pupil size. Improving the optics of both eyes to be better than the optics of normal human eyes does not improve stereo acuity. [55] Vlaskamp et al (2011) hypothesized that small eye movements during fixation in normal well-focused eyes might be more detrimental to stereo acuity than visual resolution, [55] and it is yet unclear how much resolution loss due to HOAs needs to occur before it starts to affect stereo acuity. It would be an important next step to explore when HOA magnitudes exceed this tipping point and at what stage the interrelationships between HOAs and pupil sizes might become a significant factor that impacts stereo acuity.

In summary, naturalistic 4 mm pupils would provide unequivocally better optical quality, which is evident from the HORMS, and better binocular combination, as seen from the binocular metrics. [16] This would result in better vision, i.e., improved visual acuity and/ or contrast sensitivity; however, it is yet unclear if this would translate to better stereo acuity. We believe

that the two possibilities are still open: one possibility is that stereo acuity could be marginally better, or second, that there will not be a benefit from smaller pupils for stereo acuity given a variety of complex optical and neurological factors that govern it.

Chapter 3.

Computational Estimates of Binocular Depth of Focus and Interocular Differences of Dioptric Best Focus due to Higher-order Aberrations Six Months after PRK, LASIK and SMILE

3.1 Introduction

Young normal human subjects that are optimally corrected for refractive errors at far and are exerting the appropriate amount of accommodation at near achieve peak retinal image quality over a wide range of distances from far to near. In terms of monocular image quality, higher amounts of higher-order aberrations (HOAs) cause poorer image quality even at best focus, as light encounters the increased irregularities on the optical surfaces and cannot form a clear image on the retina. This is seen in young subjects that had increased HOAs induced following refractive surgery (Sarkar et al, 2020). Previous studies have found that apart from a decrease of peak monocular image quality seen with the increase in monocular HOAs, there is also a wider range of viewing distances with “reasonable” (not optimal) retinal image quality, i.e., the monocular depth of focus (DOF) expands. [56, 57] This has also been referred to by the term “pseudoaccommodation” . [58]

With the decreased ability or inability to accommodate such as with the onset of presbyopia or the insertion of an intraocular lens after cataract extraction, an increased DOF might prove beneficial, allowing reasonable visual functionality over certain viewing distances. Clinically, this concept of increased DOF or multifocality has already been widely applied to manage presbyopia, in the form of multifocal contact lenses (CLs) and multifocal intraocular lenses (IOLs). The general idea with these interventions is to split light into several foci to create superposed images from different distances simultaneously. [59-62] While a more conventional design of multifocal CL or IOL has separate optical zones that generate distinct focal points, a more recent design of extended-depth-of-focus (EDOF) design was introduced in both CL and IOL forms, with a continuum of foci. [63, 64] In all cases, the DOF is extended by compromising the peak image quality to allow adequate visual functionality when reasonable visual quality is desired over a range of viewing distances for presbyopic, pseudophakic or aphakic patients.

Although the concept that increases in HOAs lead to a larger DOF seems to be well understood and utilized in the clinic, there is not much literature focused on the changes of

DOF after refractive surgeries. The most relevant study for this thesis is from Sarkar et al [56], who found an extended monocular DOF after PRK and LASIK, compared to SMILE, which are all refractive surgeries of interest investigated in the previous chapters. To quantify image quality, they generated through-focus functions by plotting defocus against the logarithm of the image quality metric VSOTF (Visual Strehl ratio-based on the Optical Transfer Function). VSOTF is a Strehl ratio based image quality metric that represents the loss of image quality induced by the optical transfer function of the eye, mathematically weighted by the neural contrast sensitivity function. [65] VSOTF has been shown to have good correlation with empirical visual acuity. [65] Sarkar et al (2022) added defocus in 0.01D steps between -2.5D and +2.5D to the aberration data for each eye of subjects at pre-operative and 6-month post-operative time points, to create through-focus functions. They defined DOF as the range of defocus values over which image quality exceeded 80% of peak image quality as seen in their computed through-focus functions. In comparing across the three types of refractive surgeries, they found that DOF after PRK and LASIK was larger than the pre-operative level, and in comparison to SMILE .[56]

However, Sarkar et al focused on monocular analyses of DOF changes, by averaging the left and right eye data for each subject, and ignored any interocular differences for each subject. If the interocular mismatches of aberrations were taken into consideration, we might expect there to be more variation in the peak image quality achieved in each eye, the dioptric vergence value of the distance where the peak image quality is achieved, i.e., the best focus position, and the DOF ranges between the eyes. More specifically with regards to DOF, the width of the ranges and the distances over which reasonable image quality is maintained might be different in the two eyes, and the overlap between the two eyes may vary in every case. If so, there might be a potential benefit to the interocular mismatches, as it might lead to a greater extension of the range of distances over which reasonable image quality is maintained as the subjects would have access to the DOF ranges of each eye while viewing binocularly.

Chapters 1 and 2 of this thesis provide evidence for suboptimal binocular visual quality due to the HOAs induced by refractive surgeries both for large and more naturalistic pupil sizes. In this chapter, any patterns in the DOF interactions between the two eyes, i.e., the binocular DOF ranges were investigated. The hypothesis was that greater interocular mismatches would lead to a larger binocular DOF range and be a benefit to these subjects when they encountered presbyopia a few years later. First, we evaluated whether the interocular mismatches of aberrations caused the dioptric location of peak image quality in each eye to be different in the two eyes, i.e., cause an interocular difference of “refractive error” that would cause poor binocularity. Second, we investigated whether the two eyes collectively provided an extended DOF binocularly, which would be an added visual benefit for these patients upon presbyopia onset. For example, if the dioptric range with reasonable image quality (defined as >=80% of peak value) was different between the left and right eyes of a subject, we wanted to study the extent of their overlap by quantifying the differences of peak image quality of the two eyes. Smaller differences of peak image quality would represent smaller interocular differences and thus suggest better binocular vision. Patterns of interocular differences seen across the different refractive surgeries are unknown and would be informative. In addition, we explored

the total dioptric range where at least one eye could achieve >=80% of peak image quality at the 6-month post-operative time point after each refractive surgery. For the two retinal images formed by the two eyes, the human brain would weigh the image with better quality more and pay less attention to the one with less clarity, with the potential loss of stereo acuity. So, a larger total DOF range would mean a binocular optical system with a better ability to see reasonably well over a wide range of viewing distances with similar implications as monovision for the correction of presbyopia.

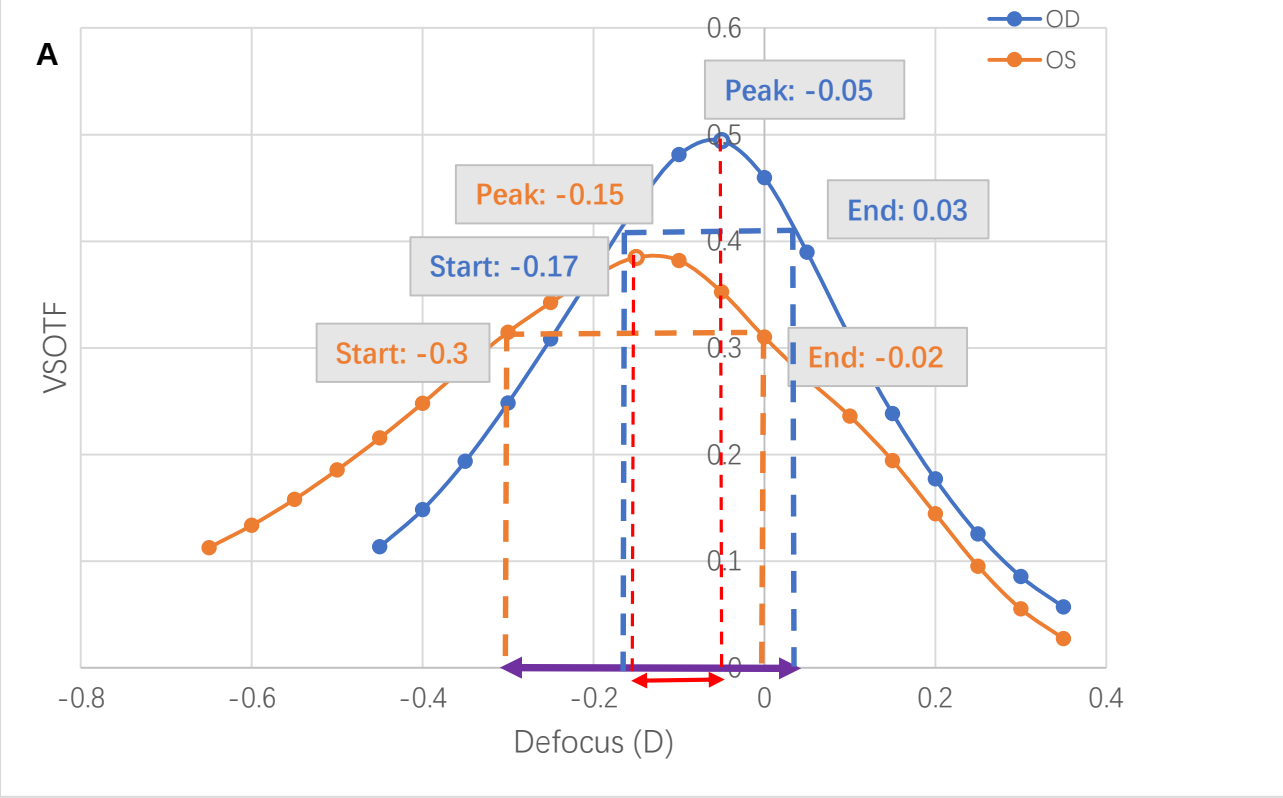
3.2 Methods

3.2.1 Computational methods

All computational procedures were done using MATLAB (Mathworks Inc., Natick, MA, USA) and Microsoft® Excel (Microsoft Corp, Redmond, WA, USA). We describe the procedure for the acquisition of wavefront aberrations, represented by Zernike polynomials up to sixth order for 6 mm-diameter pupils using an aberrometer in the General Methods section of this thesis. We picked the pre-operative and 6-month post-operative time points to study only the longer-term effects induced by the three different types of refractive surgeries. Zernike coefficients Z_1^1, Z_1^{-1}, Z_2^0, Z_2^2 and Z_2^{-2} of each eye were set to zero to null the impact of LOAs. We simulated the predominant effects of an eye stepping through a range of distances by altering the value of the defocus term (Z_2^0) in 0.05D intervals from –3.00D (hyperopia) to +3.00D (myopia) while all other Zernike terms were left unchanged. Image quality for each of these simulated defocus conditions was quantified using VSOTF much like Sarkar et al. [56] A larger VSOTF value signifies better image quality. A through-focus curve was generated with the logarithm of the image quality metric VSOTF as the y-axis and the different defocus values as the x-axis. The peak of the curve indicates the highest image quality possible given the simulated defocus value and the HOAs, with the x-axis position corresponding to the peak image quality representing the best focus position to achieve the peak image quality. We documented the best focus position (dioptric value on the X axis) of the peaks and how far away the x-axis value of the peak was from 0, and this by design represented the residual myopia or hyperopia due to HOAs alone pre- and post-operatively. They were averaged for each refractive surgery as a parameter that allows us to assess and compare the extent of variability of the post-operative visual results for each refractive surgery type based only on the residual HOAs induced.

We defined the depth-of-focus (DOF) as the dioptric range where the image quality remained above 80% of peak of the original VSOTF function. This is an arbitrary choice, and similar analyses in the literature have been done with a 50% drop from the peak. Our decision was to make a similar choice to Sarkar et al, 2022 whose data subset was made available to us.

To calculate the DOF, the left and right parts of the through-focus curve from the peak were separately fitted with quadratic equations to calculate the location on the curve that signified a 20% drop in image quality from the peak VSOTF value. The ranges selected to fit the quadratic were manually selected for each eye of each subject by visualization of the curve shape to exclude outliers or data points that fell on plateaus sometimes seen on the through-focus functions, in order to more accurately estimate the range of defocus values (abscissa) at which image quality was at least 80% of the peak or higher. The two ranges from quadratic fits to the left and right parts of the function were then added to get a total monocular span of the DOF. Then the total DOF of each eye for the same subject was put together to obtain the total binocular dioptric range where at least one eye had >=80% image quality. When the DOF of the two eyes had an overlap (occurs when the interocular peak difference is small), the total binocular span of reasonable image quality was represented by the difference between the more positive of the right boundaries and the more negative value of the left boundaries (Figure 6 A). When there was no overlap between the DOF of each eye (occurs when the peak values are very different between the eyes), the total binocular DOF range was calculated simply by adding the monocular DOF ranges (Figure 6 B). In both cases, we defined the resultant value in this chapter as the “binocular DOF range”（denoted by double-headed purple arrows along the abscissa)



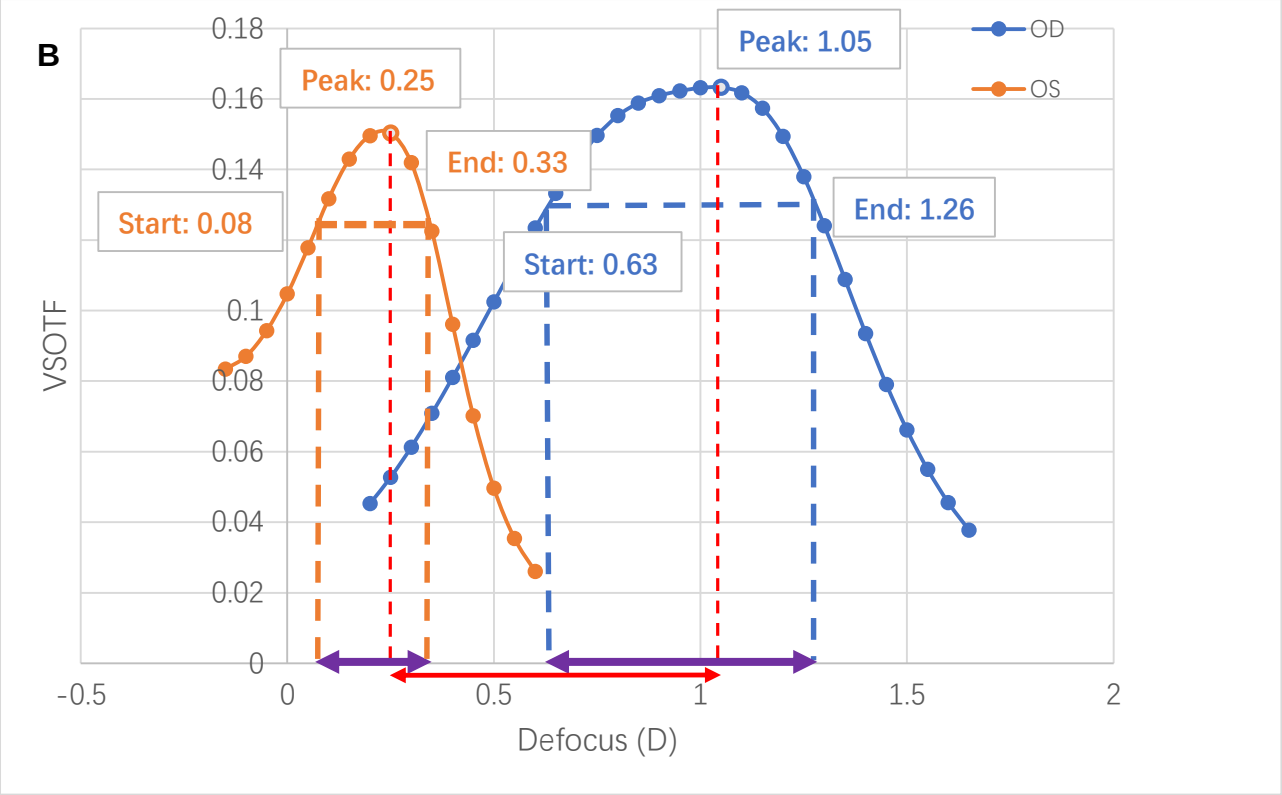


Figure 6. Examples of through-focus VSOTF graphs where we obtained the binocular DOF range under two different circumstances, (A) when there was an overlap between the DOF for the left and right eyes, or (B) when no overlap occurred. Monocular DOF ranges with 20% drop were annotated with dashed lines of correspondent colors. Binocular DOF range with 20% drop from the peak was annotated using double-headed purple arrows and interocular difference in best focus position was annotated using double-headed red arrows on the x-axes of both graphs.

When the through-focus curve was not a smooth bell-shaped function as seen in Figure 6, ranges to select for the quadratic fit were modified manually by visualizing the shape of the function. Several examples of through-focus functions that did not appear bell-shaped and were analyzed in this manner have been included in an appendix.

In addition to the binocular DOF range, the dioptric location of the peak value of the through-focus function on the abscissa was also recorded for the two eyes of an individual. This represents the defocus value needed to achieve the best image quality and will be termed the “best focus” or “best focus position”. The differences between the best focus positions of the left and right eyes were obtained as an additional measure to evaluate binocularity (denoted by the double-headed red arrows along the abscissa in Figure 6). Larger interocular differences in the best focus values represent larger interocular image quality differences brought about by HOAs, and thus were considered to represent worse binocularity in a given subject.

3.2.2 Statistical methods

All computational data was analyzed using Microsoft® Excel (Microsoft Corp, Redmond, WA, USA) and IBM SPSS Statistics for Mac version 27 (IBM Corp, Armonk, NY, USA). For both the binocular DOF range comparison and the peak difference evaluation, Wilcoxon signed-rank tests were performed to determine if there were changes in binocular DOF range when comparing pre-operative values with 6-month post-operative values, for each of the refractive surgery types. Wilcoxon test was performed to explore whether such changes were significantly different between refractive surgery groups.

3.3 Results

First of all, we look at the data from a monocular perspective to assess and compare the variation of the visual image quality outcomes after the three refractive surgeries. We found that patients who had PRK, LASIK and SMILE on average showed increases ($p<0.001$, $p<0.001$, $p<0.001$) in the distance of the peak image quality from the zero position, i.e., their best focus position signified greater refractive error due to the HOAs induced after surgery (Figure 7). The HOAs induced after refractive surgery caused the through-focus peak or best focus locations in absolute (unsigned) value to move from pre-operative averages of 0.17, 0.19, and 0.19 D to 0.55, 0.68, and 0.22 D six-months post-operatively, for PRK, LASIK and SMILE respectively. At the 6-month post-operative time point, there was a significant difference between PRK and SMILE groups ($p<0.001$), and between LASIK and SMILE groups ($p<0.001$), but not between PRK and LASIK groups ($p=0.468$). As a result, we observed that the absolute value of peak position of each eye increased significantly for the PRK and LASIK groups suggesting worse HOA induced outcomes, but such deterioration was much less with SMILE.

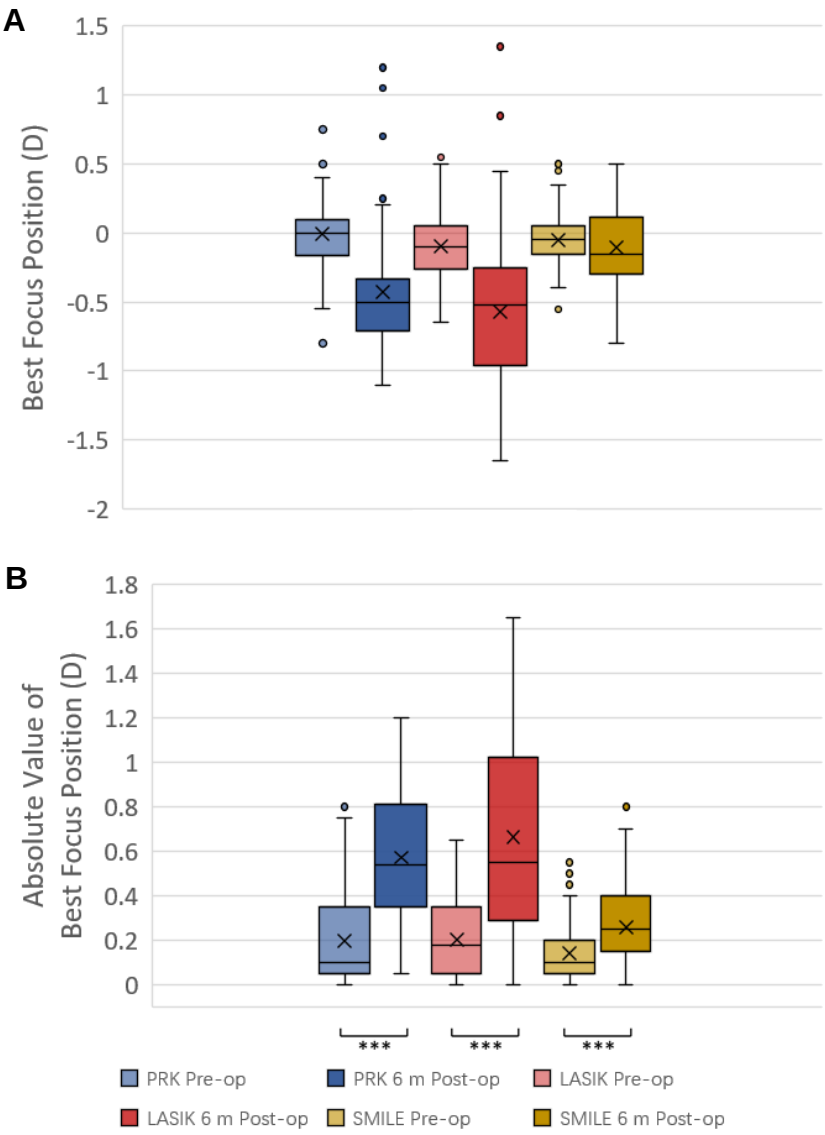


Figure 7. Box and Whisker plots of changes from pre-operative time points to 6 m post-operative time points for all three types of refractive surgeries PRK, LASIK and SMILE in best focus position (A), or absolute (unsigned) value of best focus position (B). The horizontal line within the boxes signifies the location of the median and the "X" symbol within the boxes signify the mean. Top and Bottom border of the box signify the 75th and 25th percentiles of the data set. Filled circles represent outliers that lie 1.5 times the length of the box (known as the interquartile range) from either end of the box, and the error bars signify the local minimum and maximum of the dataset without the outliers. *p≤0.05, ** p≤0.01, *** p≤0.001, Wilcoxon signed-rank test.

More interestingly, in evaluating the data for any binocular benefit of the induced HOAs, we found that the total binocular DOF range was significantly increased from pre-operative time point to the six-month post-operative time point for PRK (p=0.005), LASIK (p<0.001) and

SMILE (p=0.002) (Figure 8A**,** *post hoc* Wilcoxon signed-rank test). Since there were no significant differences among the three types of refractive surgeries at the pre-operative time point (p>0.05), binocular DOF ranges at the six-month post-operative time point were directly compared across the surgery types using *post hoc* Wilcoxon test. There were significant differences between the PRK and SMILE groups (p=0.02), and between the LASIK and SMILE groups (p<0.001), but not between the PRK and LASIK groups (p=0.340) (Figure 9A).

Similar tests were done to analyze the interocular differences in the location of the peak of the through-focus function or best focus or in other words, refractive error induced by HOAs. Again, there were no significant differences among the three refractive surgery groups pre-operatively. *Post hoc* Wilcoxon signed-rank test showed that the interocular differences in best focus positions were significantly increased from the pre-operative time point to the six-month post-operative time points for PRK (p=0.002), LASIK (p=0.003), but not for SMILE (p=0.122) (Figure 8B). In addition, there was a significant difference between PRK and SMILE groups (p=0.002), and between LASIK and SMILE groups (p=0.003), but not between PRK and LASIK groups (p=0.824), when comparing data at six-month post-op time point (Figure 9B).

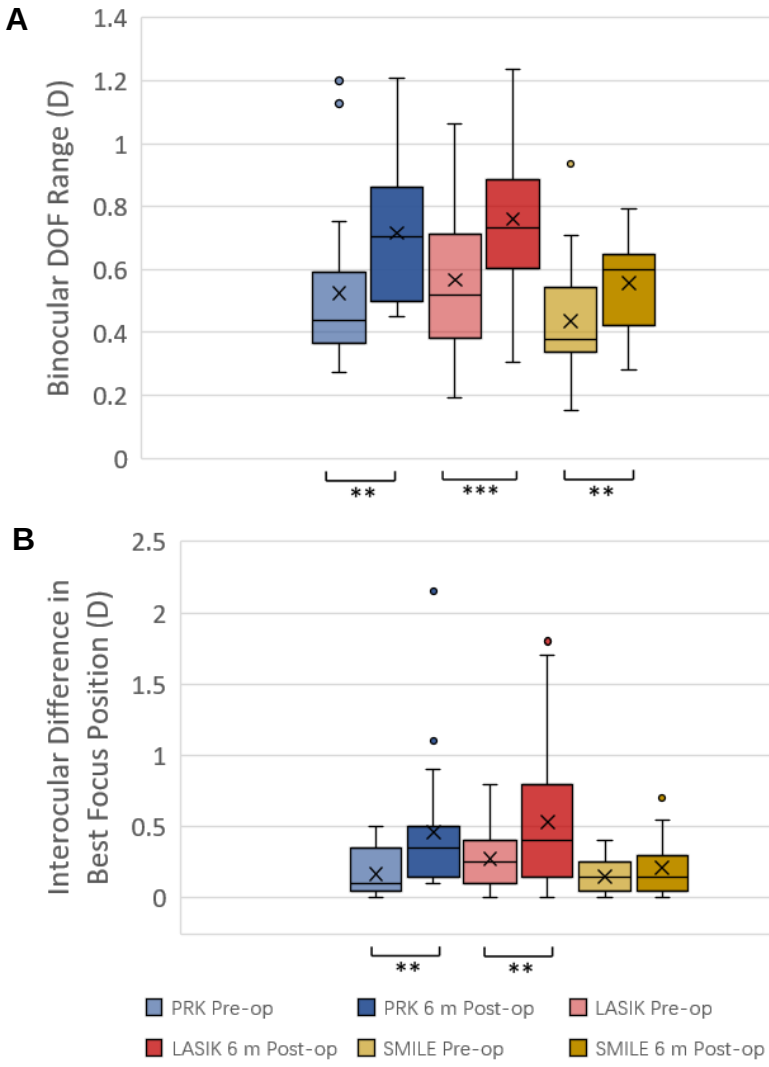


Figure 8. Box and Whisker plots comparing changes from pre-operative time points to 6 m post-operative time points for PRK, LASIK and SMILE in binocular DOF ranges (A), or interocular differences in best focus position (B). The horizontal line within the boxes signifies the location of the median and the "X" symbol within the boxes signifies the mean. Top and Bottom border of the box signify the 75th and 25th percentiles of the data set. Filled circles represent outliers that lie 1.5 times the length of the box (known as the interquartile range) from either end of the box, and the error bars signify the local minimum and maximum of the dataset without the outliers. *p≤0.05, ** p≤0.01, *** p≤0.001, Wilcoxon signed-rank test

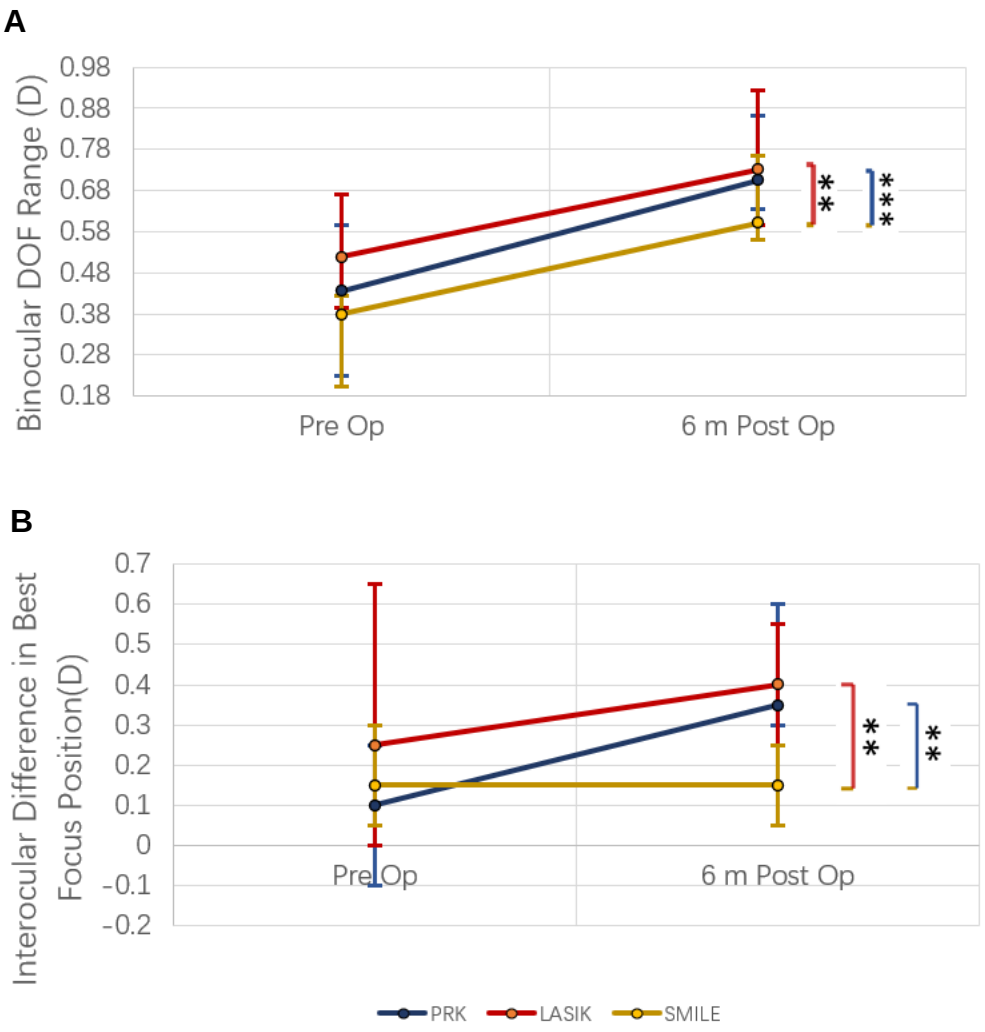


Figure 9. An alternative visualization of the graphs in Figure 9 depicting binocular DOF range changes (A) and interocular peak difference changes (B) from pre-operative to six-month post-operative time points for all three surgery types. The median, 25th percentile (negative error bars) and 75th percentile (positive error bars) were displayed. Presence of significant difference at the six-month post-operative time point was annotated (*p≤0.05, ** p≤0.01, *** p≤0.001, Wilcoxon test) with the span of the brackets and their colors indicating which pairs were significant (10A **PRK vs. SMILE, ***LASIK vs. SMILE; 10B **PRK vs. SMILE, **LASIK vs. SMILE. No significant differences were found between PRK and LASIK in both panels).

3.4 Discussion

The goals of this investigation were to evaluate (1) whether the interocular mismatches of aberrations caused dioptric location of peak image quality in each eye to be different from each other, i.e., cause an interocular difference of “refractive error” that would cause poor binocularity, and (2) whether the two eyes collectively provided an extended DOF binocularly, which would be an added visual benefit for these patients upon presbyopia onset.

From a monocular perspective, PRK and LASIK caused the best focus position as determined by HOAs to vary significantly. This monocular variation is problematic as it suggests that the HOAs cause the peak image quality to be located away from zero, suggesting a HOA-induced blur induced akin to refractive error. This monocular variation likely also contributes to a more random location of the ranges of reasonable image quality in each eye, thereby often increasing the binocular DOF ranges for PRK and LASIK group post-operatively.

We were more interested in the binocular perspective and a potential binocular benefit of the induced HOAs. Data from Sarkar et al, 2022 focused on monocular DOF and the potential binocular benefit was not available for our assessment. The motivation for our study was to add further information regarding the binocular benefit. If induced HOAs increased the binocular DOF, this could serve as a potential benefit of these refractive surgeries when these young normal subjects become presbyopic a few years after their refractive surgeries.

We found trends of an association between large binocular DOF and larger interocular differences of best focus positions when performing the analysis. In cases where the shape or the width of the peaks were similar, and when the interocular difference of best focus positions was larger, it was more likely that there would be no overlap between the DOF ranges of the left and right eye. The binocular DOF would be the sum of the two monocular DOF ranges, and therefore larger. When the interocular difference of best focus positions was small, the overlapped regions of the monocular DOF ranges caused a smaller binocular DOF range (see Figure 6). Peaks that are farther apart indicate larger interocular differences in HOAs and may cause worse binocularity simply by interocular contrast differences, but we found that it was associated with a larger binocular DOF range. We see interocular difference in the optics of the eye as an unintended consequence of surgery that we demonstrated in chapters 1 and 2 to cause a binocular detriment. The increased binocular DOF we found in chapter 3 potentially is a positive outcome arising from the mismatched aberration patterns between the eyes. This scenario is analogous to the deliberate use of monovision optical corrections for presbyopia where peak image quality is modulated for far vision in one eye, and near vision in the other (generally non-dominant eye) to increase the range of distances over which peak image quality is maintained, but to the detriment of stereo acuity/ binocularity.

Optical image quality computed from aberrations is an objective measure and will likely remain unchanged over time, as will the computed DOF derived from aberrations. However, human subjective performance in processing the optical information could vary among individuals, and could be altered over time by neural adaptation. [66] In other words, besides optical aspects, neural factors such as blur sensitivity and defocus adaptation may play an important role during the recovery period after the refractive surgeries. [67-70] Researchers have found that after long, sustained periods of exposure to blur, objective visual resolution increased and subjective visual disturbances decreased. [70-72] Adaptation might vary across individuals, and this may lead to differences in post-operative recovery of subjective performance and end results. However, there are limited studies that investigate the effects of neural adaptation on binocular DOF changes and tolerance to such changes. This adds another layer of complexity

when comparing the longer-term effects (6 month post-operatively, in our study) between the groups.

There are also some limitations of the current study. First, the height of the peak of each eye of each subject was frequently different, and thus the 20% drop from the peak signified different absolute values of VSOTF that signifies retinal image quality. Would it be reasonable, for example, to add the monocular DOF ranges, when the absolute values representing 20% drop was different between the two eyes? Further, is it meaningful to compare between different subjects when the 20% drop cut-off is not made at the same absolute value? Might it make sense to split the difference and choose the average peak value of each eye of each subject, and choose a DOF range 20% below the average value and make it the standard absolute value for each subject? Our final analysis choice was pragmatic, since peak values vary a lot among individuals and in many cases, the DOF obtained at a universal cut-off value would not make any sense on its own. There is currently a lack of literature in how such comparisons should be addressed. Sarkar et al in their original paper used the method of calculating the 20% drop for individual eyes, and we followed a similar method to assess ranges at which each eye achieved about 80% or greater performance compared to the peak performance in the same eye.

Second, there were many through-focus curves that were not smooth or bell-shaped. The most common shape is shown in Figure 10, where it was asymmetric when comparing the myopic and hyperopic sides of the function, with a smooth and sharp slope on one side and an abrupt change of slope with a “plateau” on the other side. The plateau was equally likely on either side of the peak, but often did not occur on both sides on the same curve. This shape caused the width of the function near the top and bottom to be dramatically different. As a result, the decision to measure the DOF range at a 20% drop from the peak might have made it narrower or wider for different eyes and different subjects depending on the shape of curve, creating variation. A decision to measure the DOF range at a larger drop from peak image quality (for example, 50% drop) might have resulted in less variation and different data or interocular differences for our comparisons. Given we did not have access to subjective measures of performance on a DOF task, it is not possible to know which choice would have been a closer representation of the naturalistic performance of individuals.

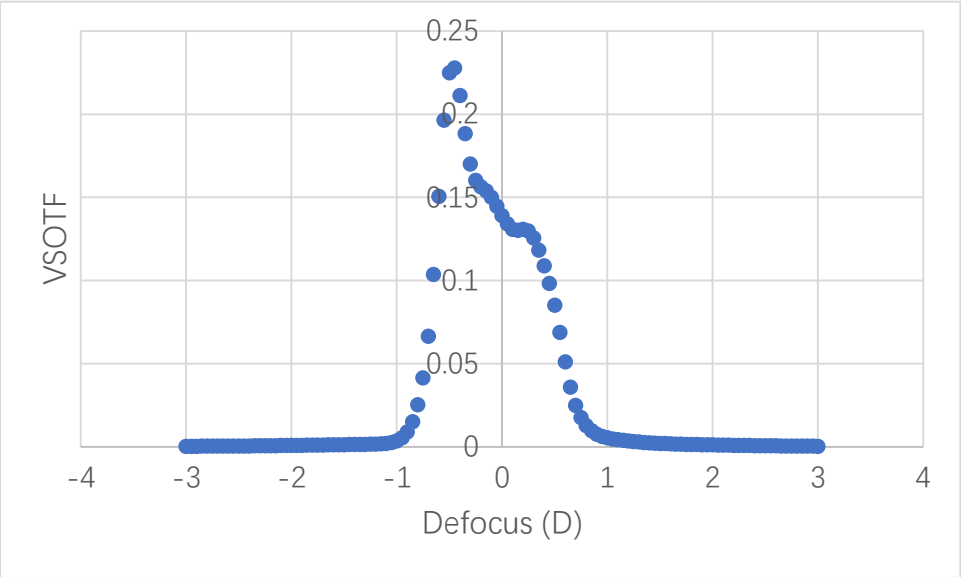


Figure 10. One representative through-focus function with an asymmetry on the myopic and hyperopic sides of the peak, with variation of slopes on either side of the peak, and showing a narrower width of the function near the top compared to the bottom. This was the left eye of subject #23 six months following PRK.

Third, the variations in the shapes of the through-focus functions, and the existence of double peaks, or triple peaks in some rare cases, remains unclear. The variation of the peak image quality signified by VSOTF and the best focus positions might come from the interactions between different Zernike aberrations, as they are not completely independent from each other. For example, spherical aberration (Z_4^0) interacts with defocus (Z_2^0) and thus might result in the formation of a second peak on the through-focus curve. Our simulations removed the effects of native LOAs, and introduced artificial defocus over a wide-range of values between -3 D and +3 D and the shapes might be attributable to these manipulations as well. Finally, we nulled the LOAs in our study to focus only on the impacts of HOAs induced during refractive surgeries. However, in reality, the impact of LOAs cannot be eliminated, and residual LOAs would interact with the HOAs, which adds another layer of complexity to the estimated binocular DOF ranges.

While it is near impossible to simulate the true subjective experiences of individuals to understand the impacts of variations in their optical profiles, these modeling attempts are very useful to predict and reveal a great amount of detail about the potential disadvantages and advantages of a variety of optical manipulations performed routinely in the clinic and in refractive surgeries.

General Conclusions, Implications, and Future Directions

This thesis utilizes monocular optical data to provide binocular perspectives by quantifying the binocular impacts of higher-order aberration (HOA) increases and mismatches after three types of refractive surgeries, i.e., PRK, LASIK and SMILE. The investigations described here generated computational binocular metrics, and also dioptric positions of best focus and binocular depth of focus (DOF) ranges based entirely on monocular optical aberration data from the two eyes of refractive surgery patients for the first time. Previous studies suggest similar monocular visual outcomes for all three surgery types; [22-24] however, studies described in this thesis indicate that altered optics in the two eyes alter the binocular outcomes for the three surgeries. Optical changes following SMILE refractive surgery resulted in the most optimal binocular combination as indicated by the computed binocular metrics, and the smallest change in interocular best focus position differences. On the other hand, while the HOA increases and mismatches following PRK and LASIK refractive surgeries resulted in poorer binocular outcomes, they gave rise to potentially beneficial extended binocular DOF ranges.

The results from our investigations would serve to help educate the vision research community and refractive surgery candidates on expected changes of binocular visual performance post-operatively. In addition to expected post-operative monocular LOA outcomes (i.e., residual refractive error and monocular unaided high-contrast visual acuity), the binocular aspects of HOA-changes following refractive surgery in terms of (1) binocular combination predicted by the optics that affects stereo outcomes and (2) binocular DOF ranges, would be informative to individuals working different occupations. For example, it might be valuable for some young adults to know that PRK and LASIK might induce larger magnitudes of HOAs and differences between the two eyes' HOAs that are both known to worsen stereo acuity or fine depth perception in the most productive part of their lives. At the same time, doctors could inform patients interested in PRK or LASIK that these surgeries could have a potential benefit a few years down the line, of a wider range of distances with acceptable image quality without glasses when they begin to lose accommodation due to presbyopia, compared with people who never had refractive surgeries or even those that had SMILE.

In addition, in circumstances where a certain type of refractive surgery is indicated or the only option available, we would be able to educate patients about pros and cons, not only in terms of monocular outcomes, but also binocular visual performance outcomes. For example, since SMILE is newly approved by FDA, many military laser centers are not yet equipped with SMILE technology, and PRK is still indicated for soldiers in active duty to avoid potential flap related complications that are caused by LASIK. According to data provided by the Department of Defense, more than 75% of all refractive procedures performed on military personnel are PRK procedures. [73] The military personnel who undergo PRK could be informed about the greater increases in monocular HOAs compared with other surgery types

and the associated symptoms, and the potential benefit of increased binocular DOF ranges, i.e., a wider range of distances over which they might be able to see with acceptable image quality upon presbyopia onset.

HOAs in the human optical system arise not only from refractive surgeries, but also a variety of causes, like pathology, trauma or surgical procedures on any part of the optical system (especially the cornea or the lens), and should always be taken into consideration. Refractive surgeries are now an iatrogenic cause for increased monocular HOAs and interocular HOA mismatches. With the improved technology and increased number of successful cases, there is increased trust and appreciation of corneal refractive surgeries, and increasingly, young individuals consider them to become independent from spectacles or CLs for a period of time in their lives. As a result, large amounts of non-naturalistic HOAs and HOA mismatches have become common in a much larger population compared with decades ago, which makes HOAs an even more relevant topic clinically. Unfortunately, induced HOAs are not generally taken into consideration when analyzing visual functions in the clinic following refractive surgery or any other surgical procedures that disrupt natural human optical system, and monocular refractive error measures and high-contrast visual acuities do not tell the full story. The world is dominated by lower contrast information, and HOAs hamper vision in low contrast environments. [74, 75] Increased HOAs when pupils are wide would impact low luminance vision (mesopic or scotopic), leading to deteriorated contrast sensitivity. [76, 77] A common complaint following refractive surgeries is increased night glare, and while this may be related to HOAs, a relationship between the two has not yet been demonstrated unequivocally. [77] HOAs and the mismatch of HOAs are objectively measurable, undoubtedly play an important role in subjective visual performance and thus should not be ignored.

There are several possible future directions from the studies performed in this thesis. First, for 6 mm pupils, we had both empirical data (stereo acuity) and computational data (the binocular metrics), but for 4 mm pupils, we did not have stereo acuity data to compare with the computational data we generated. It would be interesting to collect stereo acuity data for 4 mm pupils and compare with that of 6 mm pupils to see if there is any more information about the relationship between the stereo acuity and binocular metrics. In addition, given previous studies have used a clinically available tests that bracket stereo thresholds at set levels, we could map out the relationship between pupil sizes and stereo acuity measured psychophysically in the laboratory in individuals with HOAs within the norms of the population. This may expose the non-linearities of the relationships between optical and neural determinants of stereo acuity. A natural second step could be to investigate the relationship between pupil sizes and stereo acuity when large amounts of HOAs are present. These data would provide important and interesting information to estimate stereo acuity changes when the pupil sizes fluctuate due to change in ambient luminance or accommodation level in the young-adult population following refractive surgeries and as their pupil sizes decrease with age.

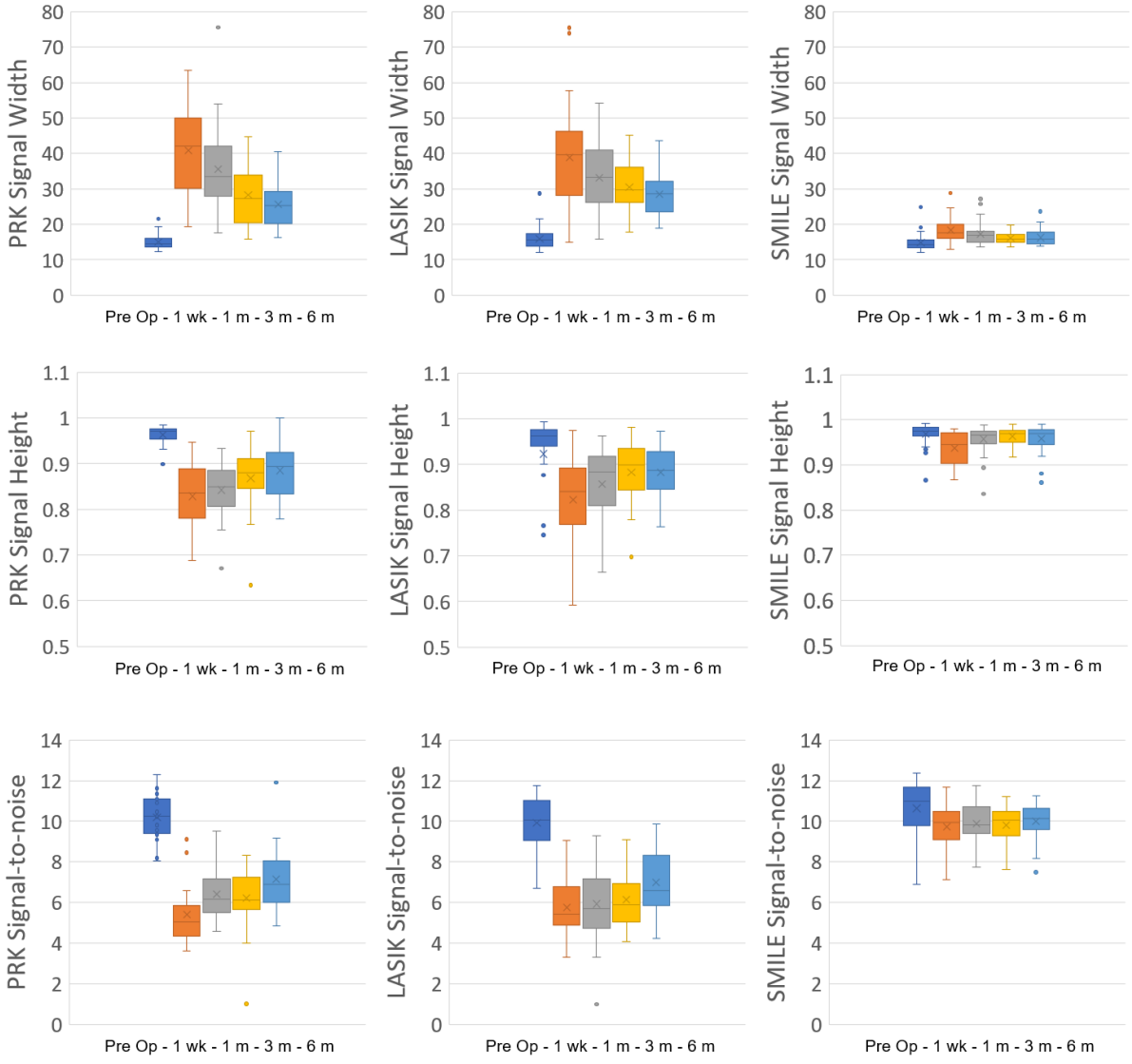
In addition, as mentioned in the discussion section of Chapter 3, the mapping of depth of focus (DOF) at a 20% drop from the peak of the through-focus function is somewhat arbitrary and

selecting another cut-off value (for example, 50%) would give us different results. It may therefore be worthwhile to perform studies that inform us as to a reasonable choice for the cut-off to use in computational studies based on subjective performance of human subjects in a through-focus task. Still, a subjective through-focus task may be prone to the impact of the definition used for the DOF, and the criteria used to determine how much reduction in performance is reasonable.

In the longer-term, a bigger picture goal would be to continue studies of the impacts of optical aberrations on binocular, rather than monocular visual performance, as naturalistic vision is binocular. It would also be beneficial for the vision research community to utilize objective measurements based on aberration data to model and estimate subjective visual performance, and evaluate the impacts of any new optical or refractive surgery procedures as they emerge.

Appendix 1:

The changes in the distribution of each of the four computed binocular metrics and empirical stereo acuity over time are shown in much greater detail as box and whisker plots below. Visualization of the comparisons between each of these variable distributions over time, and between the different refractive surgery types were summarized in Figure 3 (Chapter 1) and Figure 4 (Chapter 2). Chapters 1 and 2 pertain to binocular metrics computed for 6 mm and 4 mm pupils and descriptions of the results are available in sections 1.3.2 and 2.3.2 respectively.



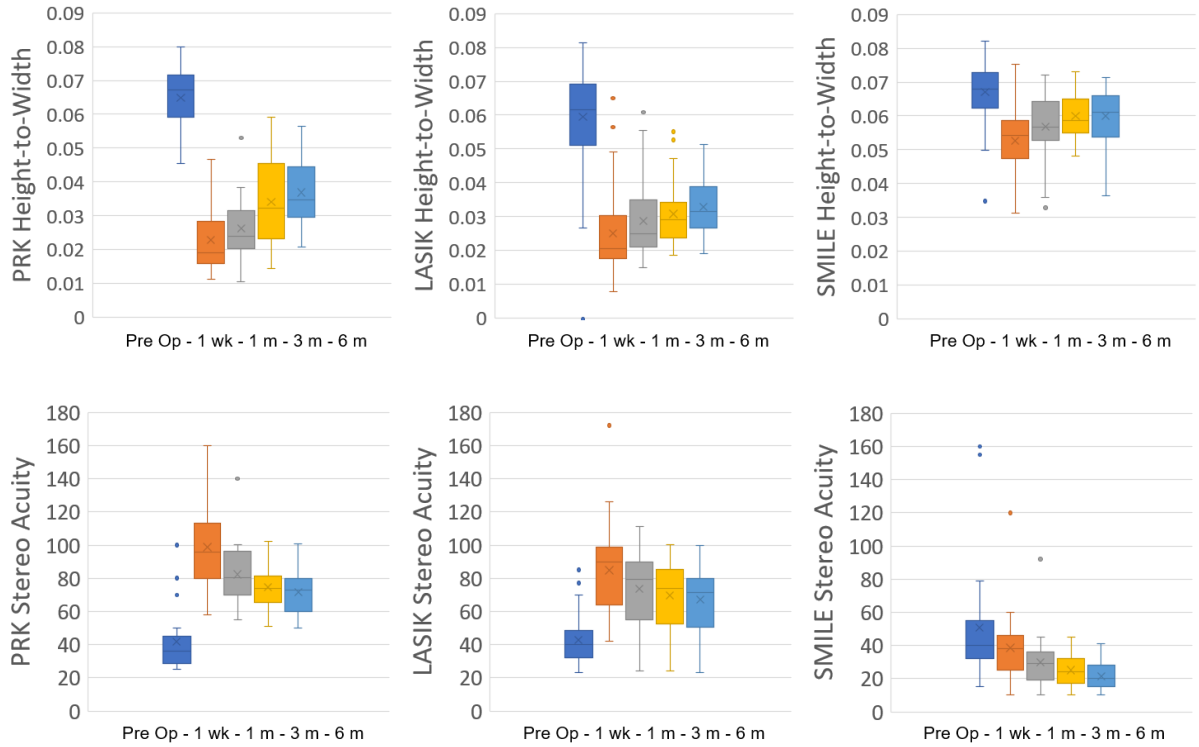


Figure 11. Comparisons of the four HOA-derived binocular cross-correlation metrics derived for 6 mm pupils (rows 1-4) and empirical stereo acuity for 6 mm pupils (row 5) for PRK (left), LASIK (middle) and SMILE (right) at different time points, i.e., pre-operative (Pre Op), 1-week (1 wk), 1-month (1 m), 3-months (3 m) and 6-months (6 m) after refractive surgery. The horizontal line within the boxes signifies the location of the median and the “X” symbol within the boxes signifies the mean. Top and Bottom border of the box signify the 75th and 25th percentiles of the data set. Filled circles represent outliers that lie 1.5 times the length of the box (known as the interquartile range) from either end of the box, and the error bars signify the local minimum and maximum of the dataset without the outliers.

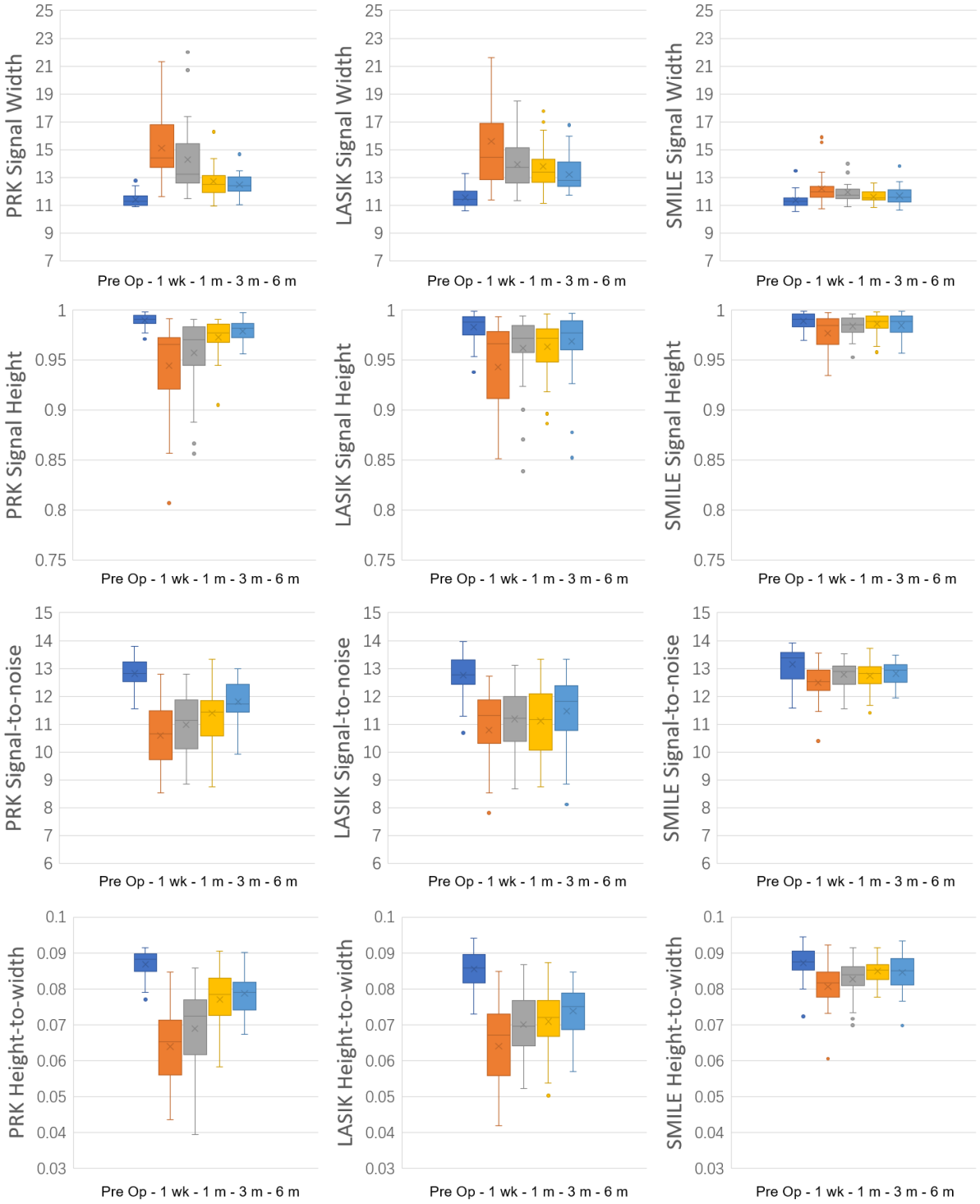


Figure 12. Comparisons of the four HOA-derived binocular cross-correlation metrics derived for 4 mm pupils (rows 1-4) and empirical stereo acuity for 4 mm pupils (row 5) for PRK (left), LASIK (middle) and SMILE (right) at different time points, i.e., pre-operative (Pre Op), 1-week (1 wk), 1-month (1 m), 3-months (3 m) and 6-months (6 m) after refractive surgery. The horizontal line within the boxes signifies the location of the median and the "X" symbol within the boxes signifies the mean. Top and Bottom border of the box signify the 75th and 25th percentiles of the data set. Filled circles represent outliers that lie 1.5 times the length of the box (known as the interquartile range) from either end of the box, and the error bars signify the local minimum and maximum of the dataset without the outliers.

Appendix 2:

There were several examples of abnormal shapes (Figure 13) of curves among the computed data from refractive surgery subjects that could have led to inaccurate quadratic fitting if done programmatically, which might have given inaccurate DOF ranges. Due to the non-bell-shaped functions, automatic quadratic fits give inaccurate results. The ranges of data points for quadratic fits were therefore selected manually by the investigator. In Figure 13 the sections highlighted in orange on each curve indicate the approximate ranges selected based on the visualization. In order to add an extra checkpoint and minimize errors, all the dioptric values corresponding to the start and end point of the DOF range (along the x-axis) output by Matlab were visualized on the original through-focus VSOTF curve by the investigator to ensure that the VSOTF (y values) correspondent to the x-values were approximately a 20% drop from the peak VSOTF value.

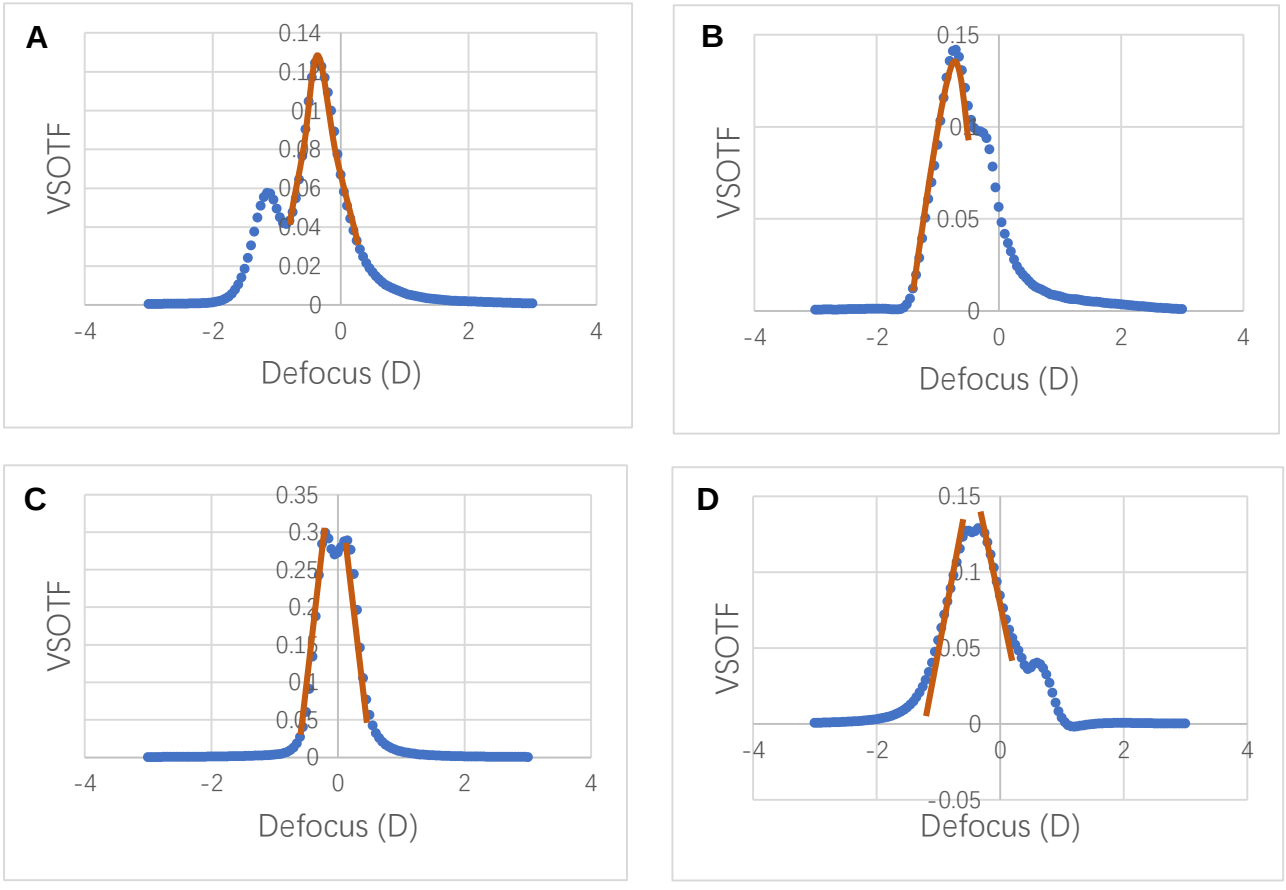


Figure 13. Examples of various shapes of through-focus functions, with highlighted sections of the curves (in orange) selected for quadratic fit. A) Right eye of subject #6 six months after PRK where we see an abrupt change in the sign of the slope and a second smaller peak. B) Right eye of subject #5 six months after PRK with a small plateau of the function seen on the right side of the curve C) and D). Double peaks seen pre-operatively in functions estimated for the right eyes of subject #6 in PRK group and subject #3 in LASIK group, respectively. Note that in C) and D), the data points in between the double peaks were not selected for quadratic fit.

In rare cases where the through-focus functions had abnormal shapes that could not be fit with a quadratic, or analyzed, for example, due to ambiguities in the presence of multiple salient peaks or two salient peaks away from each other with deep valleys (Figure 14), we excluded them from further statistical analysis (three from PRK group and three from LASIK group).

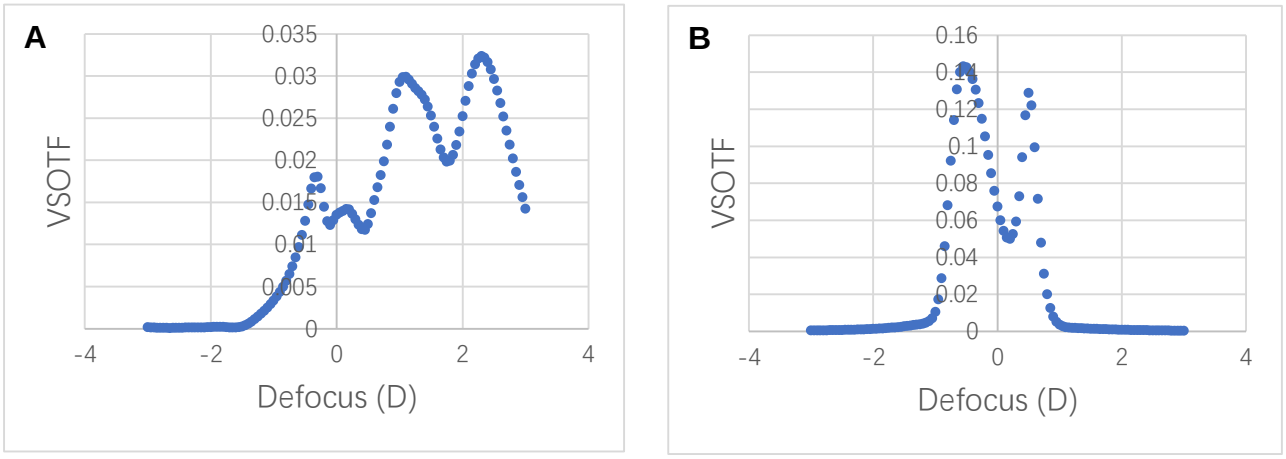


Figure 14. Examples of through-focus functions where the location of the function to fit a quadratic was ambiguous A) Left eye of subject #21six months following PRK. B) Right eye of subject #12 in PRK group estimated from pre-operative data

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