Inattention to Nonsuperimposable Midline Symmetry Causes Wavefront Analysis Error

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Background: The nonsuperimposable mirror-image symmetry of the body (enantiomorphism) is reflected in the wavefront error maps of eyes. Averaging the wavefront errors of right and left eyes has the potential to adversely affect correlations made between wavefront error and visual acuity or other factors. Not only are the results of past studies using Zernike terms suspected of being invalid, there is concern about possible errors in the algorithms used to create customized corneal ablations.

Objective: To compare the results of analysis with and without correction for enantiomorphism.

Methods: Fourteen TMS-1 corneal topographic maps from 7 patients having with-the-rule astigmatism in both corneas were selected for Zernike decomposition to 45 terms. The maps were distributed among 3 groups: 7 right eye maps, 7 left eye maps, and 7 left eye maps in which the topography was transposed about the vertical axial to correct for enantiomorphism (left eye–corrected). The wavefront error difference between the right and left eyes was compared with the difference between the right eye vs left eye–corrected category. The left eye wavefront error was then compared with the left eye wavefront error after correction (left eye vs left eye–corrected).

Results: Correcting for enantiomorphism produced a statistically significant difference in the first 5 radial orders of Zernike terms ($P = .02$). Of the 45 Zernike terms analyzed, 7 terms were significantly different at the $P < .05$ level in the right eye vs left eye category, compared with 4 terms in the right eye vs left eye–corrected category. Eleven terms were significantly different at the $P < .05$ level in the left eye vs left eye–corrected category.

Conclusions: Correcting for enantiomorphism makes the Zernike terms in right and left eyes appear more similar. Failure to correct for enantiomorphism causes certain terms to cancel each other when averaged across right and left eyes. Wavefront error studies that do not consider enantiomorphism, including those used to adjust laser surgical nomograms, will introduce significant errors to certain Zernike terms.

MATERIALS AND METHODS

Videokeratographs (TMS-1; Tomey Corp, Waltham, Mass) were obtained from patient records at the LSU Eye Center, New Orleans. Videokeratographic recording of patients has institutional review board approval, informed consent is obtained from clinical patients undergoing videokeratography, and the study conforms to the Declaration of Helsinki concerning ethical research. We selected 7 patients who exhibited similar patterns of with-the-rule astigmatism in both the right and left corneas and who had no prior report of ocular surgery, disease, or contact lens wear. The pairs of fellow eye maps were separated into 7 right eye maps and 7 left eye maps. Copies were made of all left eye TMS-1 files. The original left eye files were not altered; the copies were modified by replacing the RAD and DIO files with new files in which the topographic data were flipped about the vertical axis to correct for enantiomorphism. We used a software program written specifically for flipping left eye topographic data to a right eye presentation. None of the TMS-1 files for the right eye maps were altered. Thus, we had 3 categories for comparison: right eye, left eye, and left eye-corrected (ie, flipped).

All maps in each category were analyzed using CTView 3.0 (Server & Associates, Inc, Merritt Island, Fla). The CTView 3.0 preferences were set to report corneal wavefront error data for a 3-mm pupil using 45 Zernike terms (0-44; 0 through eighth radial orders). To help the reader, a diagram depicting the Zernike term indexing notation is provided in Figure 2. The pyramid is based on the radial order and angular frequency (sine and cosine phases) of the Zernike basis functions. Several standards exist for specifying Zernike terms. The method we chose uses a single number index that begins with the Zernike term 0 at the top of the pyramid and continues numbering from left to right along each subsequent row. For example, row 2 specifies Zernike terms 1 and 2, while row 3 specifies terms 3, 4, and 5, and so forth.

The value of the Zernike term, which is also commonly referred to as the “Zernike coefficient,” is the magnitude of wavefront error described in units of wavelengths of light (“waves”) or converted to other distance units such as micrometers. In the CTView 3.0 system, the default wavelength is given as 0.555 µm. Hyperopic errors are negative and myopic errors are positive. In CTView 3.0, negative error is coded in hot colors (red and pink) and positive error in cold colors (blue). Note that, in Figure 2, the flat keratometric meridian along axis 20-200 for a case of with-the-rule corneal astigmatism is aligned with the pinkish colors of the wavefront error scale. Because of the limitations of controlling the color scale in CTView 3.0, zero error is not aligned with the color green in the color scale in Figure 2, but it is aligned in all of the other figures. We encourage those using such maps to align zero error with the color green to aid in interpretation. Interpretation of wavefront maps is arguably more complex than evaluation of topographic maps, in part because of the lack of display standards at this time.

The extracted Zernike terms were imported into SigmaStat 2.03 (SPSS Science, Chicago, III) to calculate the mean and SEM for each Zernike term in each category. These data were used for preparing graphic plots in SigmaPlot 2001 (SPSS Science). The raw data were also used to generate t tests or Wilson signed rank tests to compare the differences in Zernike terms within the following comparisons: right eye vs left eye; right eye vs left eye-corrected; and left eye vs left eye-corrected.

RESULTS

Table 1 lists the Zernike terms that showed a statistically significant difference in at least 1 of the 3 test comparisons. Nonsignificant results (P > .05) are not reported. Figure 3A shows the mean difference between the right eye and uncorrected left eye corneal wavefronts for all 45 Zernike terms. Figure 3B shows the Zernike term mean difference between the right eye and the corrected left eye corneal wavefronts. Figure 3C shows the mean difference between the uncorrected and corrected left eye corneal wavefronts.
Zernike data, which is equivalent to the difference between Figures 3A and B. Figure 3D shows the results of Figure 3C normalized relative to the uncorrected left eye Zernike values. The mean values for Zernike terms 0 to 14 were plotted for all right eyes (Figure 4A), all left eyes (Figure 4B), and the mean of the means of the right and left eyes combined (Figure 4C).

As given in Table 1, 7 Zernike terms showed a significant difference between the right and left eyes. Six of these terms were within or below the fifth radial order (Figure 2). When the left eye was corrected for enantiomorphism (right vs left eye–corrected), the total number of significantly different Zernike terms dropped to 4, and only 1 of these terms (Zernike term 5; a second radial order term for astigmatism) was within the 0 to fifth radial order terms. A McNemar contingency test was used to compare the right eye vs the left eye group to the right eye vs the left eye–corrected group for the 0 to fifth radial orders, and the results were statistically significantly different (P = .025). Clearly, correcting for enantiomorphism had an effect on the left eyes that made them more similar to the right eyes with respect to their Zernike term values, at least for the lower-order terms.

When the uncorrected left eyes were compared with the corrected left eyes, the number of significant differences rose to 11, with 8 of the affected terms being lower-order terms. This result agrees with expectations because this comparison emphasizes the detrimental effects of enantiomorphism on Zernike term averaging, while minimizing the variance associated with comparing different eyes.

The significant differences seen in the higher-order terms for the 3 test categories (Zernike terms 36 or higher, Table 1) may be the result of finely scaled wavefront variations that are perhaps more likely caused by shape differences unrelated to enantiomorphism among the corneal wavefronts. We suspect that intereye variability, wavefront noise, and inaccuracies in fitting the Zernike polynomial terms become more predominant factors when higher-order aberrations are considered.

The Zernike terms that should not be affected by enantiomorphism are the radially symmetrical terms with a zero angular frequency (eg, defocus and spherical aberration), and the vertically oriented terms that are symmetrical only with respect to the vertical axis. The Zernike
terms predicted to be most affected by enantiomorphism are the terms shown in the gray boxes in Figure 2. Note that the affected terms alternate between positive and negative frequencies (cosine and sine phases) with respect to the radial order.

Figure 3C and D shows that, as predicted, some Zernike terms are largely unaffected by enantiomorphism, but other terms are greatly affected and show a large relative change in their Zernike term value. As expected, the terms that are radially symmetrical—such as terms 0, 4, 12, and 24—are largely unaffected by flipping the left eye data. Term 40, another radially symmetrical term, is totally unaffected in the left eye vs left eye–corrected comparison, but shows a significant difference for the right eye vs left eye and the right eye vs left eye–corrected comparisons (Table 1). Thus, Zernike term 40 probably shows a true right vs left eye difference that is not picked up by the left eye vs left eye–corrected test. Because a radially symmetrical term should be unaffected by the process of flipping, the significance for the right eye vs the left eye and the right eye vs the left eye–corrected comparisons should be identical for term 40, which is confirmed by the results. Although many terms are unaffected by enantiomorphism, in general, the process of flipping the corneal topographies of the left eyes prior to wavefront error analysis resulted in a significantly reduced difference between the right and left eye Zernike terms (compare Figure 3A with Figure 3B).

Table 1. Probability of Statistically Significant Difference in Zernike Terms for 7 Patients Having With-the-Rule Astigmatism in Both Corneas

<table>
<thead>
<tr>
<th>Zernike Term</th>
<th>OD vs OS</th>
<th>OD vs OS-Corrected</th>
<th>OS vs OS-Corrected</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>0.041*</td>
<td>0.602</td>
<td>0.268</td>
</tr>
<tr>
<td>3</td>
<td>0.031†</td>
<td>0.597</td>
<td>0.040*</td>
</tr>
<tr>
<td>5</td>
<td>0.016†</td>
<td>0.016*</td>
<td>0.040*</td>
</tr>
<tr>
<td>7</td>
<td>0.141</td>
<td>0.155</td>
<td>0.037*</td>
</tr>
<tr>
<td>8</td>
<td>0.010*</td>
<td>0.996</td>
<td>0.037*</td>
</tr>
<tr>
<td>10</td>
<td>0.004*</td>
<td>0.543</td>
<td>0.007*</td>
</tr>
<tr>
<td>14</td>
<td>0.529</td>
<td>0.758</td>
<td>0.007*</td>
</tr>
<tr>
<td>17</td>
<td>0.218</td>
<td>0.264</td>
<td>0.022</td>
</tr>
<tr>
<td>18</td>
<td>&lt;0.001*</td>
<td>0.538</td>
<td>0.023*</td>
</tr>
<tr>
<td>36</td>
<td>0.430</td>
<td>0.015*</td>
<td>0.002*</td>
</tr>
<tr>
<td>39</td>
<td>0.979</td>
<td>0.009*</td>
<td>0.063</td>
</tr>
<tr>
<td>40</td>
<td>0.047†</td>
<td>0.047†</td>
<td>1.000</td>
</tr>
<tr>
<td>41</td>
<td>0.681</td>
<td>0.633</td>
<td>0.047*</td>
</tr>
<tr>
<td>44</td>
<td>0.688</td>
<td>0.380</td>
<td>0.002*</td>
</tr>
</tbody>
</table>

*Value is calculated using the t test.
†Value is calculated using the Wilson signed rank test.
The standard notation for ocular cylinder axis orientation does not depend on angular frequency and, therefore, cylinder axis orientation (Figure 2). To complicate matters, the standard axis notation is applied identically in both the right and left eyes, with the 0°- to 180°-axis oriented horizontally and the 90°- to 270°-axis oriented vertically. Zero degrees is located to the examiner’s right at the 3-o’clock position for both the right and left eyes, with 90° in the 12-o’clock position. Because of the way axis orientation is defined in eyes, certain Zernike terms will tend to have coefficient values with opposite signs in the right and left eyes, and, thus, have the potential to cancel each other out when averaged.

Many of the affected higher-order terms appear to be clinically insignificant when plotted on the same scale as the lower-order terms, but they are statistically significant. We do not know the upper limit to the number of significant terms that might be produced by Zernike decomposition, and we do not yet know which individual or combinations of higher-order terms may be clinically significant for various ocular disorders.

Comparing Figure 4A with Figure 4B is an effective way to visualize the Zernike term differences for the low-order terms. Unfortunately, the low magnitude of the higher-order terms makes the difference impossible to see in this scale. However, by comparing Figure 4C with both Figure 4A and Figure 4B, it is easy to see in the low-order terms that averaging certain terms either has no effect, or has the unfortunate effect of making the term very much unlike that of either the right eye or the left eye.

Most Zernike basis functions are, by definition, dependent on angular frequency and, therefore, cylinder axis orientation (Figure 2). To complicate matters, the standard notation for ocular cylinder axis orientation does not consider the midline mirror-image symmetry of the body. The standard axis notation is applied identically in both the right and left eyes, with the 0°- to 180°-axis oriented horizontally and the 90°- to 270°-axis oriented vertically. Notice the marked difference in the uncorrected average map and the corrected average map, in which the left eye corneal waveform was flipped before averaging with the right eye corneal waveform.

In Figure 6, we illustrate a simpler model of right and left eye wavefronts composed of only 2 Zernike terms, 3 and 5, which define astigmatism. Note that averaging the right and left eyes causes Zernike term 3 to cancel out completely. Meanwhile, Zernike term 5 does not change when averaged because it is identical in both eyes. Thus, the net result of averaging the right and left eyes...
in this model is equal to the Zernike term 5 component of either one of the eyes, a result that may be unexpected to someone unfamiliar with the operation of Zernike analysis.

By flipping the topographic map of the left eye before processing, however, the left eye waveform acquires the same general shape as the right eye waveform and thus the right and left waveforms become superimposable and the shapes can be averaged without a loss of information (Figure 5). At first this may not seem to be the correct way to analyze these data. We are accustomed to thinking that because right and left eye images are combined into a single sensory image, we should also average right and left eye data in the same manner, but to do so is to throw away or distort useful data. There is no reason to believe that averaging Zernike terms without considering enantiomorphism is in any way equivalent to neural averaging. We know of no way to measure or translate into Zernike terms what aberrations the brain actually perceives in fused binocular images. More to the point, most experimental testing of vision for correlation to ocular aberrations is performed monocularly.

To avoid the problems of averaging Zernike terms, data collected from right and left eyes can be analyzed separately and applied separately to a specific question. This is not always practical, and is probably unnecessary if one waveform is flipped with respect to the other before combining them into one data set. We believe we

Figure 5. Two methods of averaging wavefront error maps. A and B, Right (OD) and left (OS) corneal wavefront error maps for a patient with a similar level of keratoconus expressed in both eyes. C, Averaging the wavefront error of the OD and OS maps without correcting for enantiomorphism generates a map that lacks essential characteristics of the original wavefronts. D, Averaging after correcting for enantiomorphism in the left eye wavefront generates a map that can be displayed in either the OD presentation (shown here) or transposed into an OS presentation, if needed. Careful examination of the map in part D confirms that it has the averaged characteristics of the OD and flipped OS maps.
can justify this approach because some factors such as age or sex are not specific to right or left eyes. The justification is slightly more ambiguous with visual performance measures such as high-contrast visual acuity and contrast sensitivity. Whereas current vision testing methods are certainly sensitive to blur caused by aberrations, the methods are probably not highly specific as to the orientation of the aberration.

For example, we ordinarily do not note for a given patient whether certain letters on eye charts are consistently easier to read compared with others, even though theoretically some letters (or parts of letters) should be more sensitive to specific directional aberrations that may be present in the eye being tested. Nor do we present mirror-reversed eye charts to left and right eyes, although one could argue that if letter-specific directional aberrations exist, then the orientation of the test letter does matter. Some vision tests do rotate letters such as E and C to various orientations, but this is not done to counteract the effects of enantiomorphism. Furthermore, reading eye charts involves recognition and not simply resolution of the image, so the use of letters may be inadequate for separating out the effects of different aberrations on visual acuity.

We believe that flipping the left eye waveform so that it has the same general shape as the right eye waveform will be beneficial in many correlation studies, because it eliminates the averaging error created by enantiomorphism and it allows combining any number of right and left eyes into one data set, which has practical benefits in designing studies and randomizing eyes. Alternatively, one could use a mathematical approach to correct for enantiomorphism during the decomposition process provided one has access to the algorithm. Details of

Figure 6. A simple model of nonsuperimposable mirror-image astigmatism in right (OD) and left (OS) eyes. In this example, astigmatism is defined only by Zernike term 3 (N3) and Zernike term 5 (N5) in each eye. A. The Zernike term 3 astigmatism component for right and left eyes averages to 0. B. The Zernike term 5 astigmatism component is identical in right and left eyes and so the average is unchanged from the original value of either eye. C. The averaged wavefront indicates with-the-rule astigmatism even though both the right and left eyes had highly oblique astigmatism.
this corrective procedure have not been well described in the literature, but the following equations can be used to determine what terms to correct for enantiomorphism, where equation 1 is for the Zernike double index scheme and equation 2 for the single index scheme.

\[
Z_n^m = \begin{cases} 
-Z_n^m & \text{for } m = 1, 3, \ldots, n \\
-Z_n^m & \text{for } m = -n, \ldots, -4, -2 \\
Z_n^m & \text{otherwise}
\end{cases}
\]

\[
Z_j = \begin{cases} 
-Z_j & \text{for } j = \frac{n (n + 2) + m}{2}, \\
& n = 1, 3, \ldots, m = 1, 3, \ldots n \\
-Z_j & \text{for } j = \frac{n (n + 2) + m}{2}, \\
& n = 2, 4, \ldots, m = -n, \ldots, -4, -2 \\
Z_j & \text{otherwise}
\end{cases}
\]

Equation 1 requires a change of sign for the positive \(m\) values when the orders \(n\) are odd numbered and for the negative \(m\) values when the orders \(n\) are even. For example, to transpose the Zernike expansion about the vertical axis through the 10th order, we would change the sign of the coefficients listed in Table 2.

Manually reversing the sign of selected Zernike coefficients after decomposition can be used to correct for nonsuperimposable symmetry, but such manipulation of these data will be more prone to error than an automated process. An incorrect sign of even 1 term can significantly alter the wavefront error.

A less obvious but no less important concern is that some manufacturers of laser systems for refractive surgery may be using Zernike terms averaged from historical records of right and left eye waveforms to fine-tune their tracking and ablation routines to perform optimally on average eyes. Even if the data set is composed largely of normal eyes, if enantiomorphism was not corrected in their data, the laser systems may be introducing new aberrations or not fully correcting the aberrations that are present. We are unsure what laser manufacturers are doing specifically in terms of generating surgical nomograms, but we believe that clinicians will want assurance that the nomograms compensate correctly for nonsuperimposable symmetry errors. Laser manufacturers should be strongly encouraged to review their research and development procedures for instances in which right and left eyes have been combined to generate input data about the optics of the eye. Manufacturers may wish to generate separate routines for right and left eyes or to generate a single database of corrected wavefront data that can be transposed back and forth from right to left eye versions, as needed.

We suggest that manufacturers of wavefront measurement systems and vision scientists consider adopting a standardized approach to correcting the effects of mirror-image symmetry by either mathematically correcting the problem or always flipping the left eye wavefront to appear in the same orientation as the right eye. It is critical to maintain accurate records as to whether a wavefront has been flipped or the sign of terms changed on a previous occasion. Manufacturers who develop wavefront analysis systems can aid their customers by incorporating a flip or sign change routine into their software and developing a systematic method of encoding such information into the data file.

### CONCLUSIONS

We have measured the effects of combining wavefront error data from right and left corneas that have with-the-rule astigmatism and found that certain Zernike terms are significantly different in the 2 eyes. The effect was shown to be caused by enantiomorphism because the differences in the right and left eyes were significantly minimized by flipping the left eye corneal surface data about a vertical axis before analysis. Averaging uncorrected right and left eye data reduces or distorts Zernike term values depending on the proportion of right and left eyes in the data set and the range of waveform shapes in the data set. Although we measured corneal wavefront Zernike terms, the same effect is present in whole eye ocular wavefront error maps. We strongly discourage averaging right and left eye wavefronts without correcting for the effects of enantiomorphism. Reasonable solutions are to
always analyze right and left eyes separately, standardize flipping the left eye wavefront before averaging, or to apply a sign change correction.

Submitted for publication July 16, 2001; final revision received October 25, 2001; accepted November 16, 2001.

This investigation was supported in part by Public Health Service grants R01EY03311 (Dr Klyce) and P30EY02377 (department Core grant) from the National Eye Institute, National Institutes of Health, Bethesda, Md.

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REFERENCES


We stumped you last month! The correct answer to our December challenge was multiple myeloma. For a complete discussion of this case, see the Clinicopathologic Reports, Case Reports, and Small Case Series section in the January Archives (Tranos PG, Andreou PS, Wickremasinghe SS, Brazier JD. Pseudohypon as a feature of multiple myeloma. Arch Ophthalmol. 2002;120:87-88).

Be sure to visit the Archives of Ophthalmology World Wide Web site (http://www.archophthalmol.com) and try your hand at our Clinical Challenge Interactive Quiz. We invite visitors to make a diagnosis based on selected information from a case report or other feature scheduled to be published in the following month's print edition of the ARCHIVES. The first visitor to e-mail our Web editors with the correct answer will be recognized in the print journal and on our Web site and will also receive a free copy of the Clinical Eye Atlas, published by AMA Press.