

Effect of Disease Progression on the PRL Location in Patients With Bilateral Central Vision Loss

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Purpose: To investigate the effect of disease progression on the monocular preferred retinal locus (PRL) of the better eye (BE) and worse eye (WE) of patients with central vision loss.

Methods: Fifty-one patients with bilateral macular diseases were included. The monocular PRL was recorded for each eye ($N = 102$ eyes) with the MP-1 microperimeter in two visits that were 458 ± 249 days apart. For each eye and visit, the PRL distance from the former fovea, polar angle, and scotoma size were measured. The change in PRL location from visit 1 to visit 2 was evaluated with the differential map analysis.

Results: Scotoma size increased significantly in both eyes. The PRL distance from the former fovea increased significantly from visit 1 to visit 2 in the BE, but not in the WE. The polar angle was relatively stable in both visits for the BE. The change in PRL location in the BE was predicted only by the PRL distance from the former fovea in visits 1 and 2, but not by polar angle or scotoma size. For the WE, the change in PRL location depended on the change in PRL location in the BE, rather than on measurements made on that eye.

Conclusions: Disease progression affects monocular PRL location differently in the 2 eyes. The results suggest a recalibration of the oculomotor system with its reference at the PRL from the BE.

Translational Relevance: These findings are important for deciding the course of treatment and/or for developing rehabilitation techniques focusing on PRL relocation.

Introduction

Progressive macular diseases such as age-related macular degeneration (AMD) destroy central vision in both eyes, often asymmetrically.^{1,2} In the absence of the fovea, the visual system adapts by consistently using a preferred retinal locus (PRL) in the eccentric part of the retina for visual tasks^{3,4}; generally, the PRL becomes the new reference position of the oculomotor system.^{5,6} The location of the PRL is typically identified during a fixation task using imaging instruments such as the MP-1 or the MP-3 microperimeters (Nidek Technologies Srl., Padova, Italy) that incorporate an eye-tracking system capable of continuously registering the gaze position with respect to a retinal anatomical landmark. A fundus photograph is essen-

tial for determining the PRL location on the retina and this requirement has restricted investigators to studying the PRL during monocular viewing only, because binocular microperimeters do not yet exist. However, PRL locations during binocular viewing can be inferred in an experimental setting using a combination of the MP-1 microperimeter and a custom-made eye tracker.⁷

The relative change in PRL location with viewing condition can be identified with binocular eye-trackers. In a series of studies, our laboratory reported the following findings⁷⁻¹⁰: (1) during binocular viewing, fixational control is driven primarily by the better eye (BE) and the PRL in this eye does not change from monocular to binocular viewing, (2) the PRL in the worse eye (WE) can change location from monocular to binocular viewing to come in retinal

correspondence with that from the BE particularly in patients with large interocular differences and monocular PRLs in noncorresponding locations; in some cases, this can result in the fixation target to disappear into scotoma for the WE during binocular viewing; and (3) the PRL does not change with viewing distance.

We know very little about the impact of disease progression on PRL location. Using gaze-contingent techniques, it has been shown that the temporary PRL induced by a simulated scotoma imposed on a healthy visual system moves further into the periphery, but maintains the same meridian (i.e., same polar angle) when increasing the scotoma size.¹¹ This research was conducted in young healthy observers and the PRL was trained in several visits over a short time, using a simulated scotoma that had a regular shape and was centered on the fovea. However, AMD is fast or slow progressing and widely heterogeneous, producing asymmetric damage in the two eyes and scotomas of varying shapes and sizes.

It has been shown that, in Stargardt's disease, 1-year progression produced no change in PRL distance from the former fovea in a cohort of young patients.¹² Stargardt's disease typically affects both eyes symmetrically, it is slow progressing, and the PRL is located above the scotoma on the retina in about 70% of cases.^{13,14} In AMD, the change in PRL location with disease progression was examined using the Rodenstock scanning laser ophthalmoscope in a study that provided only a qualitative analysis of the PRL location relative to the scotoma, but that nevertheless revealed interesting characteristics of the oculomotor adaptation with the passage of time.² Notably, it was found that (1) when data from both eyes were available, if the monocular PRLs in both eyes were in corresponding positions at baseline they maintained correspondence at follow-up, (2) the PRL location relative to the scotoma remained largely in the same area (i.e., superior, inferior, temporal, or nasal) over time for most patients, and (3) the fixation stimulus fell on the scotoma, suggesting that no PRL was developed in a limited number of eyes. The Rodenstock scanning laser ophthalmoscope is no longer commercially available, but it has been shown that fixation stability and PRL location are comparable with those recorded with the MP-1 microperimeter in patients with macular diseases,^{15–17} despite the technological differences in data acquisition between the two instruments.¹⁵

Understanding how disease progression impacts the monocular PRL location in both eyes is important for deciding the course of treatment and/or for devising better rehabilitation techniques that focus on PRL relocation and fixation stability training, but

currently there is a lack of quantitative research on this issue in the field. Therefore, the purpose of this study was to investigate the effect of disease progression on the monocular PRL of the BE and the WE of patients with central vision loss. We hypothesized that, in the BE, the PRL distance from the former fovea increases with disease progression while maintaining the same polar angle. However, in the WE, the change in the PRL location may reflect the need for retinal correspondence with the PRL from the BE rather than the need to use a location on functional retina.

Methods

Participants

Our laboratory has collected a large amount of data on the PRLs of patients with central vision loss since 2006. For this retrospective research, patients for whom both eyes were examined with the MP-1 microperimeter in two visits an average of 1 year apart were identified from our 14-year research database. We included cases with complete sets of data (i.e., fixation examination for both eyes) for two visits that were at a minimum of several months apart. If more frequent datasets were available for one patient, we chose the examinations that were generally 1 year apart. Cases with unclear fundus photographs that did not permit reliable measurements for both eyes and visits were excluded. Patients with complete sets of data, but the two visits only within 3 months from each other were not included.

Fifty-one patients with bilateral central vision loss (26 females, 25 males; mean age at first visit of 77 ± 11 years) were included ($N = 102$ eyes). Most patients had AMD ($n = 46$), but there were also two cases of Stargardt's disease, two cases of cone dystrophy, and one case of myopic maculopathy. For a subgroup of 15 patients (8 females and 7 males; mean age at first visit 76 ± 10 years), data from 3 yearly visits were available. Patients had no other significant comorbid ocular pathologies with the exception of mild cataract and had no neurologic or cognitive impairments. There was no active bleeding from neovascular AMD at the time of testing. All patients were either under treatment or monitored for disease progression and were recruited from the Eye Clinic from the Toronto Western Hospital. They participated in various research studies that adhered to the tenets of the Declaration of Helsinki and for which informed consent was obtained.

The BE was identified as the eye with the smallest scotoma and best fixation stability (i.e., smallest

bivariate contour ellipse area provided in the MP-1 fixation examination output) or, in cases with equal damage to the two eyes, on best fixation stability and/or visual acuity if the information was available. The PRLs of the BE and the WE were recorded during two visits that were an average of 458 ± 249 days apart. The time intervals between the two visits were 137 to 299 days for 20% of cases, 300 to 499 days apart for 47% of cases, and more than 600 days apart for 33% of cases. For the subgroup whose data from three visits were available, the average time difference between visit 1 and 2 was 404 ± 245 days and between visit 2 and 3 was 521 ± 369 days.

Apparatus

The MP-1 microperimeter is a monocular instrument that records horizontal and vertical eye position during a fixation task at a sampling rate of 25 Hz. The point with coordinates defined by the average horizontal eye position and the average vertical eye position is the centroid of the fixation cluster and determines the location of the PRL; this point was estimated visually. Changes in PRL location can be examined in two ways: (1) by measuring changes in the PRL distance from the former fovea and in polar angle from one examination to another using the built-in grid of the MP-1, and (2) by using the differential map analysis module, which provides the Euclidean distance in degrees between the centroids of the fixation clusters of two examinations. These methods are described in second paragraph of the Procedure section.

Procedure

Fixation stability was recorded in a dark room for a duration of 15 to 30 seconds while the patients kept their gaze stable on a 3° red fixation cross projected on the carefully calibrated graphics screen of the MP-1. The mean recording time for BE was 28.3 ± 5.8 seconds in visit 1 and 25.3 ± 6.3 seconds in visit 2, whereas for the WE these values were 26.8 ± 5.4 seconds in visit 1 and 25.6 ± 6.2 seconds in visit 2. Occasionally, in cases with poorer vision, the cross was enlarged to facilitate visibility. A color fundus photograph was taken at the end of each examination.

For each eye and visit, the built-in grid of the MP-1 was used to obtain the following measurements: (1) PRL distance from the former fovea, (2) polar angle of the PRL, and (3) horizontal and vertical measurements of the scotoma. The grid's center was placed at the statistically average location of the former fovea at 15.5° horizontally and 1.3° below the middle of the optic disc; these coordinates were obtained from the

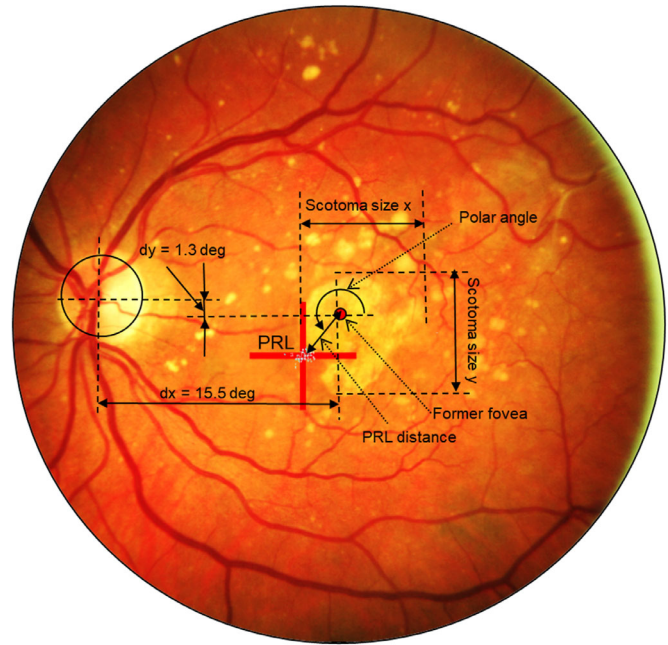


Figure 1. PRL location and scotoma measurements on fundus photograph. Former fovea is at $(15.5^\circ; -1.3^\circ)$ from the middle of the optic disc. PRL distance from the former fovea and the polar angle were measured with the built-in grid of the MP-1 that was centered at the fovea. For clarity, the built-in grid is not shown.

literature¹⁸ and represented the average fovea location of a group of participants with healthy vision.¹⁹ The middle of the optic disc was considered to be the point at the intersection of the disc's horizontal and vertical diameters. Once placed, the grid was used to measure the PRL distance from the fovea, its polar angle (i.e., the counterclockwise angle from the horizontal axis to the PRL), and the largest horizontal and vertical dimensions of the central lesion (i.e., scotoma size), as shown in Figure 1. The change in PRL location from visit 1 to visit 2 was also evaluated with the differential map analysis module of the MP-1. This procedure measures the distance between the centroids of two fixation clusters; that is, the distance between the PRL in visit 1 and PRL in visit 2. This measure does not give any indication about the direction in which the PRL has moved. All measurements were performed by an experienced experimenter (L.T.N.).

Data Analysis

The outcome measures for each eye and visit were (1) the PRL distance from the former fovea, (2) PRL location in polar coordinates, (3) differential map analysis of the PRL location, and (4) horizontal and vertical dimensions of the scotoma. Data were analyzed using paired-samples *t*-tests, correlations, and multiple regressions, using a critical *P* value of 0.05. For

Table. PRL Distance From the Former Fovea, Polar Angle, and Scotoma Size for the BE and WE in Visit 1 and Visit 2

| | BE | | WE | |
|--------------------------------|------------|------------|------------|------------|
| | Visit 1 | Visit 2 | Visit 1 | Visit 2 |
| PRL distance from former fovea | 3.8 ± 3.1 | 4.7 ± 3.7 | 5.1 ± 4.4 | 5.3 ± 4.0 |
| Range | 0–13 | 1–17 | 0–19 | 0.5–19 |
| PRL polar angle | 147 ± 92 | 150 ± 79 | 144 ± 92 | 158 ± 89 |
| Range | 0–335 | 0–335 | 0–345 | 15–350 |
| Scotoma size | 11.5 ± 6.8 | 12.7 ± 6.9 | 13.9 ± 5.6 | 15.2 ± 5.9 |
| Range | 0–27.5 | 0–28.0 | 5.5–30.0 | 6–32 |
| Differential map analysis | 3.5 ± 2.8 | | 4.9 ± 4.1 | |
| Range | 0.2–14.4 | | 0.5–20.9 | |

Values are mean ± standard deviation unless otherwise noted. Descriptive statistics are also shown for the differential map analysis of BE and WE.

the subgroup of patients for whom the data from three visits were available, the analysis was performed with a repeated-measures analysis of variance, using a Bonferroni approach to control for the multiple pairwise comparisons.

Results

Changes in PRL Distance From the Former Fovea

Separate paired-sample *t*-tests showed that for the BE, PRL distance from the former fovea increased significantly from $3.8 \pm 3.1^\circ$ in visit 1 to $4.7 \pm 3.7^\circ$ in visit 2, $t(50) = 2.23$, $P = 0.03$, whereas for the WE, this distance did not change significantly from visit 1 to visit 2. Table shows the means ± standard deviations and ranges of the PRL distance from the former fovea in visit 1 and visit 2 for BE and WE.

We computed the change in the PRL location from the former fovea between the two visits as follows:

$$\Delta \text{PRL distance} = \text{PRL distance}_{\text{visit 2}} - \text{PRL distance}_{\text{visit 1}}$$

A negative value of this variable indicates that the PRL moved to a nearer location from the former fovea in visit 2. A decrease in the PRL distance from the former fovea in visit 2 was observed in 39% cases ($n = 20$; range difference from -0.5° to -11.5°) for the WE and 24% cases ($n = 12$; range difference from -0.5° to -4.0°) for the BE. Although this finding may seem to be counterintuitive, an example is shown in Figure 2 where the PRL distance from the former fovea was shorter in visit 2 than in visit 1 for the WE, and the opposite was true for the BE. This case shows that, in visit 1, the PRL was located on an island of good vision

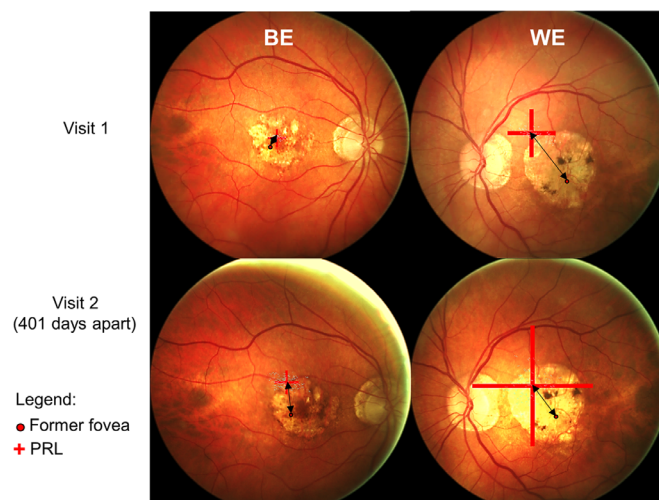


Figure 2. Example of change in PRL distance from the former fovea in the BE (left) and in the WE (right) during two visits that were 401 days apart. The small central red circle on each fundus photograph represents the former fovea.

that was in the proximity of the fovea (i.e., 3° distance) in the BE, whereas that in the WE was located at 10° eccentricity, on functional retina. In visit 2, the PRL in the BE moved to 6° eccentricity on the functional retina, suggesting that the disease progression engulfed all the central area while the PRL in the WE came into retinal correspondence with that from the BE, at a 7° distance from the former fovea. The PRL in the WE landed on the scotoma, but the arms of the 20° fixation cross fell on functional retina and facilitated the gaze stability recording. However, the cluster of fixations landing on the scotoma clearly indicates that no functional PRL was evident in the WE during visit 2, and that the reference of gaze position occurred at a location in retinal correspondence with the PRL from the BE, rather than the fovea.

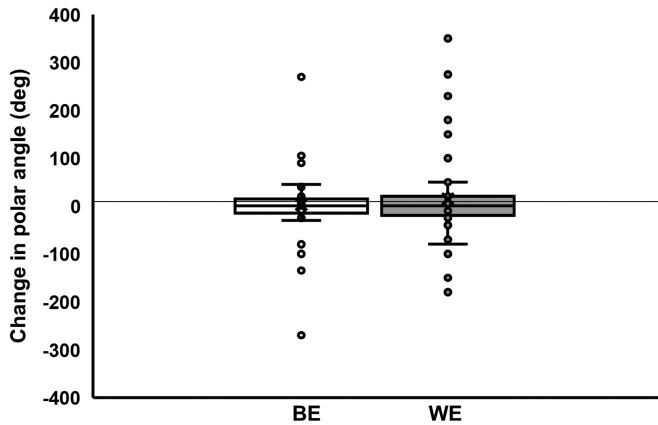


Figure 3. Box plots showing the change in the PRL's polar angle between visit 2 and visit 1 (i.e., Δ PRL polar angle), for the BE and for the WE.

The Δ PRL distance correlated significantly with the number of days between the two visits for the BE, $r(49) = 0.41$, $P = 0.003$, and for the WE, $r(49) = 0.38$, $P = 0.006$. The absolute values of the Δ PRL distance were $1.4 \pm 1.7^\circ$ for the BE and $1.9 \pm 2.4^\circ$ for the WE.

The PRL distance from the former fovea in the subgroup for whom data from three visits were available was analyzed with one-way repeated-measures analyses of variance. For the BE, the test of within-subjects effect failed to reach significance, $F(2, 28) = 3.1$, $P = 0.058$, but the test of within-subjects contrasts was significant $F(1, 14) = 5.2$, $P = 0.04$, partial $\eta^2 = 0.67$. This indicates that the PRL distance from the former fovea increased linearly with the passage of time, from $4.0 \pm 2.9^\circ$ in visit 1, to $4.4 \pm 3.3^\circ$ in visit 2, to $5.0 \pm 3.9^\circ$ in visit 3. For the WE, no significant difference in the three visits was found: the mean distance was $5.1 \pm 3.9^\circ$ in visit 1, $4.1 \pm 2.9^\circ$ in visit 2, and $5.2 \pm 4.1^\circ$ in visit 3.

Changes in the Polar Angle

Separate paired-samples t -tests showed that the polar angle did not differ significantly between the two visits, both for BE and WE. The descriptive statistics of this measure for both visits and eyes are shown in the Table. Changes in polar angle (Δ PRL polar angle) did not correlate with time between the visits for both eyes. The Δ PRL polar angle data were highly variable, as shown in Figure 3. The absolute values of the Δ PRL polar angle were $37 \pm 60^\circ$ for the BE and $50 \pm 76^\circ$ for the WE, but these values did not differ significantly between the two eyes.

Because the polar angle represents the counter-clockwise angle centered at the fovea from the horizontal axis to the PRL, inflated Δ PRL polar angle values may occur when the PRL location changes from

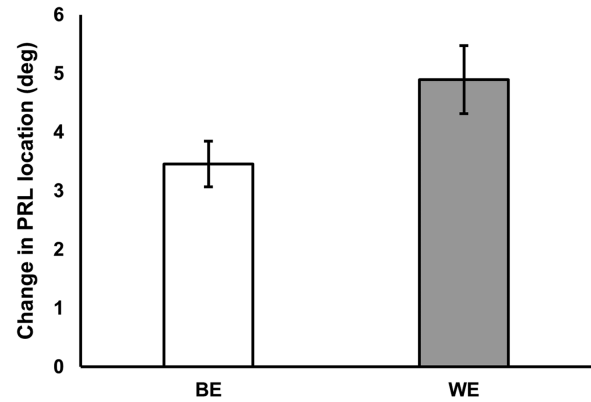


Figure 4. Differential map analysis values for the BE and WE. The error bars represent ± 1 standard error.

the first or second quadrant (i.e., 0° to 90° or 90° to 180°) to the fourth quadrant (i.e., 270° to 360°) or vice versa. We found two such cases for the BE and three cases for the WE. When we adjusted these values with the smaller angle difference (i.e., 270° was replaced by 90° twice for the BE, and 230° , 350° , and 275° were replaced with 130° , 10° , and 95° , respectively, for the WE), the absolute values of the Δ PRL polar angle became $30 \pm 39^\circ$ for the BE and $37 \pm 48^\circ$ for the WE, and the statistical results were consistent with those reported on original data.

For the subgroup with data from three visits, no significant differences in polar angle were found. The mean polar angle was constant in the three visits for the BE: $182 \pm 84^\circ$ in visit 1, $190 \pm 75^\circ$ in visit 2, and $186 \pm 86^\circ$ in visit 3. For the WE, the mean polar angle changed from $147 \pm 70^\circ$ in visit 1, to $153 \pm 79^\circ$ in visit 2, and to $177 \pm 88^\circ$ in visit 3, but, owing to high variability in the data, the differences among these values were not significant.

Differential Map Analysis

Although the PRL distance from the former fovea and the polar angle measure the PRL location with respect to the former fovea, the differential map analysis measures the distance between the clusters of fixation from visit 1 to visit 2. Differential map analysis showed that the mean change in the PRL location was $3.5 \pm 2.8^\circ$ for the BE and $4.9 \pm 4.1^\circ$ for the WE. A paired-sample t -test showed that there was a significant difference in differential map analysis values between the two eyes, $t(50) = 2.7$, $P = 0.01$. The results are shown in Figure 4. That is, there was a larger change in PRL location in the WE than in the BE between the two visits. Differential map analysis values did not correlate with the time between the two visits for the BE or for the WE.

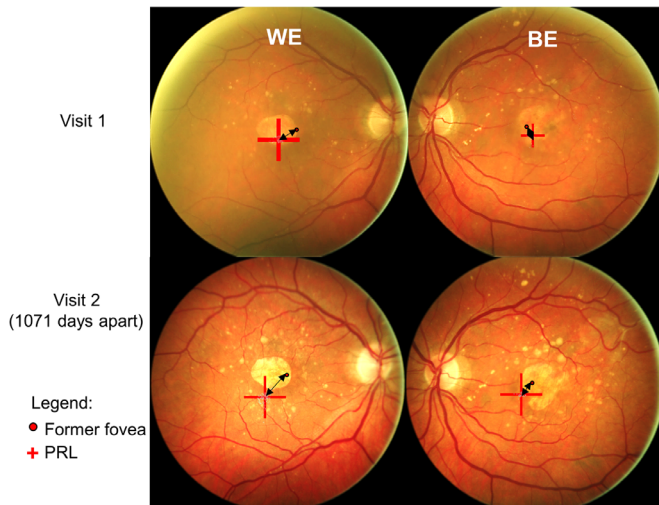


Figure 5. Example showing how central scotomas can progress asymmetrically from the fovea. The PRL may not be in the proximity of the former fovea, particularly for the WE, as shown in the left panel from this example. Rather, this PRL developed to be in a corresponding retinal location to than from the BE.

Scotoma Size

Scotoma size was estimated as the average of the maximum horizontal and vertical dimensions of the central lesions measured on the fundus photograph. For both eyes, scotoma size increased significantly from $11.5 \pm 6.8^\circ$ to $12.7 \pm 6.9^\circ$, $t(50) = 7.6$, $P < 0.001$ for the BE, and from $13.9 \pm 5.6^\circ$ to $15.2 \pm 5.9^\circ$, $t(50) = 6.1$, $P < 0.001$ for the WE, as shown in the Table. Changes in scotoma size (Δ scotoma size) did not correlate with time between the visits for both eyes.

Central scotomas can develop asymmetrically and the PRLs are not always in the proximity of the former fovea, particularly for the WE, as exemplified in Figure 5. In addition, for 33% of cases the center of the fixation target fell on the scotoma in the WE, as shown in Figure 2, suggesting that no functional PRL was actually present in this eye.

For the subgroup with data from three visits, one-way repeated measures analyses of variance showed that the scotoma size increased significantly in the BE, $F(2, 28) = 11.2$, $P < 0.001$, partial $\eta^2 = 0.45$, and in the WE, $F(2, 28) = 28.1$, $P < 0.001$, partial $\eta^2 = 0.65$. For the BE, scotoma size increased from $10.8 \pm 6.8^\circ$ in visit 1, to $11.8 \pm 6.7^\circ$ in visit 2, to $12.7 \pm 6.7^\circ$ in visit 3. For the WE, scotoma size increased from $12.0 \pm 5.1^\circ$ in visit 1, to $13.5 \pm 5.1^\circ$ in visit 2, and to $14.7 \pm 4.5^\circ$ in visit 3. All pairwise comparisons were significant for both analyses, largest $P = 0.026$.

Predictors of the Change in PRL Location

For each eye, a multiple regression analysis was conducted to determine what measurements predicted the change in PRL location from visit 1 to visit 2. Specifically, the outcome variable was the differential map analysis and the independent variables (i.e., the predictors) were (1) PRL distance from the former fovea in both visits, (2) PRL polar angle in both visits, and (3) scotoma size in both visits.

Initially, all the variables were introduced into the model simultaneously. For the BE, the regression model was significant, $R^2 = 0.27$, $F(6, 44) = 2.6$, $P = 0.03$, with an intercept of 2.1. However, the standardized regression coefficients were significant only for PRL distance in visit 1, $\beta_1 = -0.69$, $P = 0.007$, and for PRL distance in visit 2, $\beta_2 = 0.84$, $P = 0.001$. That is, the scotoma size and PRL polar angle did not explain a significant amount of variance in differential map analysis values. Subsequently, we performed another multiple regression analysis in which only the two significant predictors were maintained. With only the PRL distance in visit 1 and visit 2 in the analysis, the model changed very little from the previous analysis: $R^2 = 0.22$, $F(2, 48) = 6.9$, $P = 0.002$, with an intercept of 2.8, and significant standardized regression coefficients of $\beta_1 = -0.65$, $P = 0.005$ for PRL distance in visit 1, and $\beta_2 = 0.82$, $P = 0.001$ for PRL distance in visit 2. Therefore, only the second regression model was retained, producing the following regression equation for the BE:

$$\text{Differential map analysis}_{\text{BE}} = 2.8 - 0.65 \\ \times \text{PRL distance}_{\text{visit 1}} + 0.82 \text{PRL distance}_{\text{visit 2}}$$

A similar regression analysis was performed for the WE, but the model was not significant ($P = 0.1$) and none of the predictors were significant with P values for the regression coefficients ranging from 0.08 to 0.64. We further investigated whether changes in PRL location in the BE would explain the variance in the differential map analysis of the WE. That is, we performed a regression analysis using the differential map analysis for the BE as the predictor and that for the WE as the outcome variable. The regression model was significant, $R^2 = 0.20$, $F(1, 49) = 12.1$, $P = 0.001$, with an intercept of 2.6, and a significant standardized regression coefficient $\beta_{\text{BE}} = 0.45$, $P = 0.001$. Figure 6 shows the relationship between the two variables. The regression equation is:

$$\text{Differential map analysis}_{\text{WE}} = 2.6 + 0.45 \\ \times \text{Differential map analysis}_{\text{BE}}$$

Although the regression models were highly significant for both the BE and the WE, the amount of

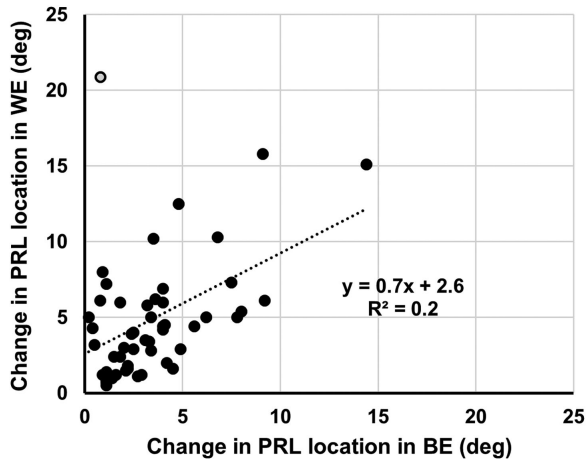


Figure 6. Relationship between the change in PRL location in the WE and in the BE. The measurements represent the differential map analysis values showing the change in the PRL location from visit 1 to visit 2. The data point filled with gray (0.8°; 20.9°) is an outlier, but there was no reason to eliminate it.

variance explained by the models was modest (i.e., only about one fifth). For the WE, the dataset contains an outlier shown in Figure 6 as a grey-filled point with (0.8°; 21.9°) coordinates. Removing this outlier from the dataset results in doubling the amount of variance explained by the model to $R^2 = 0.42$. However, upon detailed examination of this case, we found no reason to eliminate it from the analysis.

Discussion

In this study we examined changes in PRL location with the passage of time in the BE and WE of patients with central vision loss primarily owing to AMD. The main findings are that (1) for the BE, the PRL distance from the former fovea increases with disease progression while maintaining a relatively constant polar angle, and (2) for the WE, changes in the PRL location depend on changes in the PRL of the BE rather than on its own measures. Although the study used monocular measures, the results suggest a recalibration of the oculomotor system that is referencing at the PRL of the BE, which—as it has been previously shown^{7–10}—drives fixational control during binocular viewing.

In the BE, PRL distance from the former fovea increased slightly but significantly from one visit to the next, while maintaining a relatively constant polar angle. For the WE, the PRL distance from the former fovea did not change on average, but for 39% of cases it actually decreased with time. Figure 2 shows

an example of a patient whose PRL moved farther into eccentric retina in the BE and closer toward the center in the WE to come into corresponding position with that from BE. The PRL in the WE fell on the scotoma, but the 20° fixation cross whose arms landed on functional retina facilitated the eye position recording. This clearly indicates that no functional PRL was evident in the WE during visit 2, but the referencing of gaze position occurred at a location corresponding to the PRL from the BE, rather than at the fovea. The large cross could have facilitated centering its middle on the former fovea while the peripheral endings of the cross could have still landed on functional retina, but this was not what we observed.

The location of a functional PRL (i.e., landing on functional retina) is typically at the edge of the scotoma, but not always at the shortest distance from the former fovea and this finding is consistent with past research.² Figure 5 shows an example where the retina seems to be functional in the proximity of the former fovea in the WE, and yet the PRL develops at a greater distance, but in a corresponding retinal location with that from BE, and maintains its location 3 years later. It is surprising that this happens in the WE during monocular viewing when binocular vision's requirements of retinal correspondence are not applicable. This finding suggests a recalibration of the visual system set for binocular viewing—the natural viewing condition—which is maintained during monocular viewing with the WE. What drives this recalibration? In situations such as these, where the monocular PRLs are in corresponding locations and fall on functional retina, we suspect that the recalibration is driven by a visual system that is striving to maintain or improve binocular visual functions, including the need for a single unified percept (i.e., cyclopean percept) and the preservation of residual stereopsis. However, for cases with large interocular damage and monocular PRLs in noncorresponding locations, the recalibration may be determined by the eye that drives binocular control, which typically is the BE.^{9,10} It has been suggested that the BE is also the dominant eye for fixation. Although this recalibration is driven by the stronger eye, it may result in the fixation target to disappear into the scotoma in the WE during binocular viewing,⁷ and this may compromise aspects of binocular function, for example, binocular summation.

Furthermore, the multiple regression results showed that the change in PRL location in the BE is determined by the distance from the former fovea in visit 1 and visit 2, and not by the polar angle or scotoma size. The finding that the scotoma size did not explain any significant amount of variance in the change in PRL location

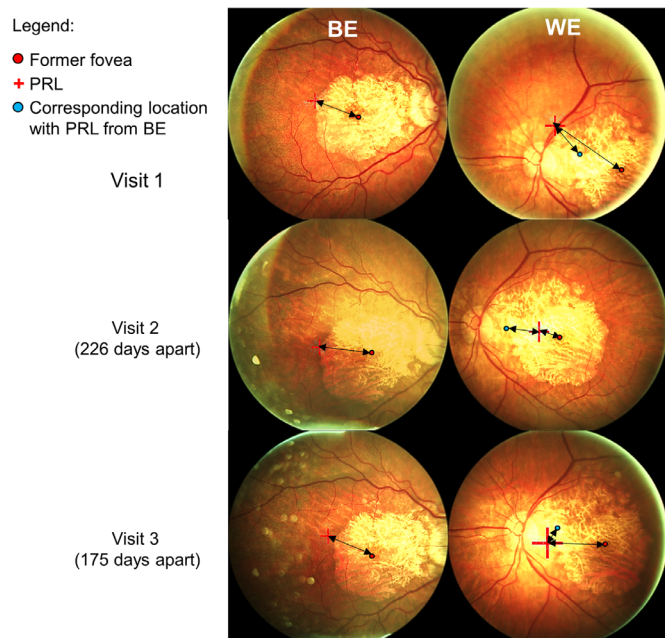


Figure 7. Example of change in PRL location in the BE and in the WE over a 401-day interval (226 + 175 days) and recorded in three visits. The PRL fell on the functional retina in the BE and its location was stable. The variability in the location of the PRL in the WE decreases considerably if it is examined relative to a location in retinal correspondence with the BE's PRL (represented by the *blue circle* on the fundus photographs of the WE).

reflects the fact that the scotoma does not develop symmetrically around the fovea; rather, it has a wide variety of shapes and its development is not uniform in all directions. (This suggests a serious shortcoming of studies using gaze-contingent simulated scotomas that use symmetrical scotomas centered at the fovea.) For the WE, a change in the PRL location was tied to changes in the PRL location of the BE, rather than its own measures, further suggesting the referencing of the oculomotor system to the PRL in the BE. However, it is important to note that, for both the BE and the WE, the amount of variance explained by the predictors used in the regression models was modest.

Figure 7 exemplifies how the variability of the PRL location in the WE decreases if it is considered relative to the presumably new reference point of the oculomotor system, a location corresponding with the PRL in the BE. As can be seen in this figure, the PRL location in the BE is stable over multiple visits both in terms of distance from the former fovea and polar angle, but the location of the PRL in the WE varies remarkably when considered relative to the former fovea. If there were a recalibration of the oculomotor system with the reference to the PRL of the BE, then—because the WE is yoked to the BE—the reference location in the WE should be at the corresponding retinal location

of the PRL in the BE, as illustrated as the blue circle in the right panel of the Figure 7. The variability in its location decreases considerably if it is examined relative to this reference location (i.e., new referencing of the oculomotor system) rather than to the former fovea. We found that 31% of cases ($n = 16$) from our sample showed a similar pattern to the case exemplified in Figure 7, whereas 45% of cases ($n = 23$) had the monocular PRLs in corresponding retinal locations and/or in proximity to the former fovea in both eyes. Moreover, 16% of cases ($n = 8$) did not show any pattern (i.e., noncorresponding PRLs, no evidence of re-referencing), and for 8% of cases ($n = 4$) the results were inconclusive.

These findings highlight the importance of distinguishing between the BE and the WE when examining the PRL in patients with central vision loss.^{20,21} This distinction is particularly important in the context of devising rehabilitation techniques that focus on PRL relocation.²² Our study reveals a complex story that points to a possible role of binocular vision in determining the change in monocular PRL location in the WE with disease progression. Further investigations should be conducted to confirm these findings.

A limitation of this study is that scotoma size was not precisely calculated as the area of the lesion^{1,23}; rather, it was estimated based on the maximum horizontal and vertical dimensions of the central damage measured on the fundus photographs. This or similar methods have been used before.^{1,24,25} The area of the scotoma can be estimated with a built-in software after microperimetry examination with the MP-1, but the accuracy of this measurement is not known, and the manufacturer's manual suggests caution when using the tool. Nevertheless, we do not have this information for the patients included in this study, and future research should address this issue using better software and image processing technology. Also, it would have been interesting to examine the relationship between the change in PRL location and change in visual acuity with disease progression. This analysis was not performed because we did not have the complete visual acuity dataset for all patients (i.e., visual acuity of the BE and WE, for visit 1 and visit 2; that is, four data points per patient). Nevertheless, analyses of the decline in visual acuity with AMD progression have been previously reported.²⁶ In addition, the BE was identified as the eye with the smallest scotoma and best fixation stability, but no functional measures (i.e., visual acuity, contrast sensitivity) were used to define it. However, most of the cases in our research database had clear interocular differences in central retinal damage and it was not difficult to identify the BE based on our criteria.

Finally, the location of the PRL was estimated as the centroid of fixation cluster, which is also the centroid of the bivariate contour ellipse area; this location could have been affected in a small degree by the non-normality of the horizontal and vertical eye position distributions recorded during fixation which has been shown to exist.^{18,19}

In conclusion, this research showed that, for the BE, the PRL distance from the former fovea increases with disease progression while maintaining a relatively stable polar angle from the former fovea. The change in PRL location with disease progression in the WE depends modestly on the status of the BE, rather than on changes in the WE's own measures. These results reflect the need for retinal correspondence of the PRLs in asymmetrically damaged eyes and suggest a recalibration of the oculomotor system with its reference location at the PRL from the BE.

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