Binocularity Principles of PRL Development in Patients With Macular Disease

Luminita Tarita-Nistor[1] and Mark S. Mandelcorn[2,3]

[1]Krembil Research Institute, Donald K Johnson Eye Institute, University Health Network, Toronto, Canada
[2]Department of Ophthalmology and Vision Sciences, University of Toronto, Toronto, Canada
[3]Department of Ophthalmology, Toronto Western Hospital, University Health Network, Toronto, Canada

Correspondence: Luminita Tarita-Nistor, Donald K. Johnson Eye Institute, Krembil Research Institute, Toronto Western Hospital, 399 Bathurst St, FP 6-212, Toronto, Ontario, M5T 2S8, Canada; lumi.tarita-nistor@rogers.com.

Received: April 20, 2022
Accepted: July 29, 2022
Published: August 17, 2022

Citation: Tarita-Nistor L, Mandelcorn MS. Binocularity principles of PRL development in patients with macular disease. *Invest Ophthalmol Vis Sci.* 2022;63(9):19. https://doi.org/10.1167/iovs.63.9.19

Purpose. We tested the hypothesis that binocularity requirements for correspondence play a role in establishing the preferred retinal locus (PRL) in macular degeneration.

Methods. Monocular PRL locations in 202 eyes of 101 patients with macular degeneration (79 ± 10 years) were recorded with the MP1 microperimeter. Corresponding PRLs were those with similar polar angle and distance from former fovea in the better eye (BE) and the worse eye (WE).

Results. On average, the PRL in the BE was in the foveal proximity at 1.1 ± 0.99 degrees for 55 patients (foveal-driven PRL) and eccentrically at 6.9 ± 3.4 degrees for 46 patients with central lesions involving the fovea (peripheral-driven PRL). For the foveal-driven PRL group, the PRL in the BE was not affected by the status of the WE. In 100% of cases, the monocular PRL in the WE was in a corresponding location either on functioning retina or onto the lesion, or would fall onto the lesion during binocular viewing. For the peripheral-driven PRL group, the PRL location depended on the lesion size in both eyes to maximize correspondence and/or the function of peripheral vision during binocular viewing. In this group, PRL correspondence status was different for those with equal, unequal, or extensive lesions in both eyes.

Conclusions. Binocularity requirements for correspondence play an important role in determining the PRL location. We formulated two principles based on whether the BE has foveal sparing (foveal-driven PRL) or central lesions affecting the fovea (peripheral-driven PRL). The PRL should be evaluated in the framework of binocular viewing.

Keywords: age-related macular degeneration, preferred retinal locus (PRL), binocular vision, oculomotor mechanics

The human visual system is exquisitely designed to facilitate depth perception and to provide a singular, stable, and clear image by combining the visual inputs from the 2 eyes that are spatially separated by about 6 cm in the frontal plane of the head. To achieve this performance, the oculomotor system coordinates the movements of the two eyes using the fovea — the point on the retina that provides the sharpest vision — as the reference position. Because the natural viewing is binocular, the visual system has developed to be the most proficient in this naturalistic condition.[1] An overwhelmingly larger part of the primary visual cortex processes visual information coming from the foveae of both eyes compared to that receiving visual information from a peripheral retinal location.[2,3]

Macular degeneration destroys central vision and damages the reference point of the oculomotor system,[4–8] with severe consequences for visual performance.[9–13] Understanding the oculomotor control during binocular viewing of patients with central vision loss has been enormously challenging for several reasons. First, patients adapt to the loss of central vision by developing a preferred retinal locus (PRL)[14] but, currently, the PRL location on the retina can be identified only with monocular instruments such as microperimeters; we can infer the PRL locations during binocular viewing only indirectly using research laboratory-based methods that are difficult to access and/or use.[6] Second, the PRL is used to perform visual tasks and redirect the eye movements consistently to this reference point; in other words, the PRL serves as the pseudo-fovea.[5] However, this role may be assumed only by the PRL in the better eye (BE) and not necessarily by that in the worse eye (WE). Macular degeneration is typically asymmetric,[15] affecting one eye more than the other, and it has been shown that the characteristics of the PRL in the BE are different from those in the WE.[16] For example, the monocular PRL in the WE may fall onto the central scotoma (lesion) and/or on the noncorresponding retinal location relative to the PRL in the BE. Finally, the monocular PRLs in the noncorresponding retinal locations may not reflect their actual location during binocular viewing.[17] It is unlikely that the oculomotor system utilizes noncorresponding PRLs during binocular viewing because this would lead to alignment problems and might result in double vision, unless the visual input from the WE is suppressed during binocular viewing. Indeed, evidence from eye-tracking recordings suggests that the PRL in the WE shifts location when viewing conditions change from monocular to binocular so that

the WE's fixation can be in the corresponding position with that of the BE, even at the expense of this PRL landing onto the area of the central lesion.[6] This kind of shift is rarely observed for the PRL in the BE.[18,19] These findings suggest that patients have relatively good eye alignment; the BE has the ability to bring the WE into alignment during binocular viewing regardless of the extent of retinal damage in the weaker eye.[20]

Although it is possible to identify the monocular PRL with imaging instruments, we do not have a clear understanding of what determines its location on the retina. A few hypotheses have been proposed: (1) the function-driven PRL hypothesis proposes that the PRL location is dictated by the need to perform certain visual tasks, such as reading; (2) the performance-driven PRL hypothesis suggests that the part of the retina that provides the best vision determines the PRL location; and (3) the retinotopy-driven PRL hypothesis predicts that the PRL location is at the border of the scotoma.[21] Each of these hypotheses has merits, but none is fully satisfactory: for example, it has been shown that the monocular PRLs can be found in locations unsuitable for reading,[22–24] not always at a place that would provide the best visual performance,[25] and at times not quite at the border of the scotoma, particularly for the WE.[8,16,26]

Herein, we propose a new hypothesis for the PRL location that is dictated by the binocularity requirements for correspondence. Given the evidence from eye-tracking studies that the PRL in the BE drives binocular control in most cases,[6,18] we considered this monocular PRL as the stable reference point and examined the requirements for correspondence for that in the WE. In addition, in view of the large cortical representation of the foveal input[2,3] and the fact that the PRL in people with normal vision is fixed at the fovea,[27] we considered whether the BE had (i) any foveal sparing or (ii) a central lesion that engulfed the fovea. The following two principles are proposed:

Principle I: Foveal-Driven PRL

If there is a functioning retina within the foveal proximity in the BE, then the PRL in this eye is at the fovea or, if this is not available, at the shortest distance from it. During binocular viewing, the PRL in the WE will always be located in the corresponding location with the PRL in the BE regardless of the extent of retinal damage in the WE. The monocular PRL in the WE will have three possible locations: (1) in the corresponding location and on the functioning retina if it is available; (2) in the noncorresponding location but on the functioning retina at the edge of the central lesion, although this PRL will move in a corresponding location during binocular viewing; and (3) in the corresponding location, within the central lesion.

Principle II: Peripheral-Driven PRL

If a functioning retina is not available within the foveal proximity in the BE, the PRL in this eye is on the peripheral functioning retina, but its location depends on the status of the WE. The following three situations are possible. (1) Equal-sized central lesions: the monocular PRL in the BE is at a location that allows for a PRL on the retinal correspondence and on a functioning retina in the WE, rather than being at a shortest distance from the former fovea. (2) Unequal-sized central lesions: the monocular PRL in the BE is found at the shortest distance from the former fovea, whereas that in the WE is closer to a location that corresponds to the PRL location in the BE rather than to the former fovea. (3) Extensive central lesions (>20 degrees): the PRL in the BE can change location to optimize residual vision depending on the task, whereas the PRL in both eyes may have limited functionality.

To test these hypotheses, we reviewed the PRLs in both eyes of patients with macular degeneration, recorded in the same visit. Unless otherwise specified, when we refer to the PRL, we mean the PRL recorded during monocular viewing with microperimeters.

Methods

Participants

In this retrospective study, data from patients with macular degeneration who had fixation stability examination performed in both eyes, in the same session, with the MP1 microperimeter (Nidek Technologies Srl, Padova, Italy) were retrieved from our 16-year research database. In total, fixation stability examinations from 202 eyes of 101 patients (mean age 79 $\pm$ 10 years old) were included. All participants were part of various research studies for which informed consent was obtained and which adhered to the tenets of the Declaration of Helsinki. Patients were included only if they had no other serious ocular eye diseases and no neurological or cognitive impairments. Those with mild cataract were also included. Patients were recruited from the Eye Clinic at the Toronto Western Hospital and the tests were performed on the same day as their regular visit to the ophthalmologist. For each patient, the BE was typically identified as the eye with a PRL on a functioning retina, with better fixation stability and a smaller central lesion. This was a straightforward process in most cases because typically the disease is not symmetric and affects one eye more than the other. In 10 cases, the BE was the eye with better fixation stability but with a larger lesion measurement; in these cases, the BE had either a ring scotoma or a patchy scotoma with an overall size that was larger than that in the WE. In one case, the BE was identified as the eye with poorer fixation stability, but with a PRL on a functioning retina, located at 2 degrees from the former fovea; in this case, the other eye had a dense lesion and the PRL landed right onto it. This patient maintained a stable fixation in the WE with the help of an enlarged fixation cross that had its endings landing outside the visible lesion. This patient's visual acuity was available, and this information confirmed that the BE was correctly identified. Laboratory-based measures of visual acuity were available for 136 eyes from 68 patients. These measurements were obtained with the Early Treatment Diabetic Retinopathy Study visual acuity test using a letter-by-letter scoring system and reported in logMAR units. Among these patients, six (9%) had equal visual acuities in both eyes, whereas for all the others (91%) visual acuity in the BE was superior to that in the WE. For those with equal visual acuity in the two eyes, the BE had a smaller visible lesion and/or better fixation. In two cases with equal damage and PRLs located on functioning retina in the two eyes, but with no available visual acuity data, the BE was identified as the eye with better fixation stability. In three cases with approximately equal and extensive lesions in the two eyes, the BE had the PRL on a functioning retina in far periphery, but with poorer fixation stability than that in the WE. In these cases, the PRLs in the WEs were always located onto the large lesion and fixation stability was recorded using an enlarged fixation cross.

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Apparatus

Data were recorded with the MP-1 microperimeter using the stand-alone fixation module (i.e. not recorded during microperimetry examination) for short durations of 15 to 30 seconds. This instrument allows only monocular examinations and is capable of recording the horizontal and vertical fixational eye position at a sampling rate of 25 Hz in real time. These fixational data points can be later registered on the color fundus photographs offline. The center of the fixational cluster is considered the PRL location and the dispersion of the fixational points represent fixation stability. The MP1 has a built-in polar grid that can be used to measure the PRL location relative to a landmark (i.e. former fovea) and the size of the central lesion. In addition, the fixation stability test result is quantified with the bivariate contour ellipse area (BCEA) and presented in the test's output.

Procedure

The testing was performed in a dark room without the use of mydriatic drops. Participants were seated with their head on the headrest of the MP1 and the short fixation examination was performed for each eye while the other eye was covered with an eyepatch. The fixation stimulus was a red cross with a typical size of 3 degrees projected on the graphics screen of the instrument, but in cases of poor vision, its size was increased for better visibility. Patients were asked to keep their gaze stable on the red cross and to blink as they needed. Then, the stand-alone fixation examination test was started and data were acquired for 15 to 30 seconds. At the end of the fixation examination, a color fundus photograph was taken. The fixation data points were registered with the fundus photograph offline.

The absolute location of the PRL was determined using two measures: (1) PRL distance from the former fovea, and (2) the polar angle. These measures were obtained with the MP1's built-in polar grid, placed with its center at the former fovea. The former fovea was estimated as the point with coordinates of (15.5 degrees, −1.3 degrees) relative to the middle of the optic disc, based on the average fovea location of people with a healthy retina.[24,28] Once placed, the radial distance from the grid's center to the middle of the fixation points cluster determined the PRL distance from the former fovea whereas the counter-clockwise angle from the horizontal axis to the PRL determined the polar angle. Corresponding monocular PRLs were considered those with similar distance from the former fovea and polar angle in the BE and the WE, with a greater tolerance for differences in polar angle for the PRLs situated in foveal proximity in the two eyes. The visible central lesion on the color fundus photograph was deemed as the scotoma. The polar grid was also used to measure the horizontal and vertical dimensions of the visible lesion, and the average of these two measurements was considered as the lesion size, measured in degrees.[8] Fixation stability was quantified with the 68% bivariate contour ellipse area (68% BCEA) value that was taken directly from the output of the fixation test generated by the MP1.

Data Analysis

The PRL location in the BE was used as the criterion to split the sample into two groups to test: (1) the foveal-driven PRL hypothesis if the PRL in the BE was in the foveal proximity, and (2) the peripheral-driven PRL hypothesis if the PRL in the BE was in eccentric retina. The correspondence of the monocular PRLs in the two eyes was analyzed for each group. In addition, the outcome measures such as PRL distance from former fovea, polar angle, lesion size, and fixation stability were quantified for the BE and WE in each group. Because the polar angle data are circular, they were analyzed with the Watson's U^2 nonparametric test to compare the distributions of two samples, and with the Watson-Williams F test for multiple comparisons of mean direction. The watson.two.test and the watson.williams.test functions from the Circular package 0.4–95 in R version 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria) were used to perform the circular data analysis. For the Watson's U^2 test, the BE's and the WE's polar angle data were assumed to be independent samples. For the other outcome measures, data were analyzed with parametric tests, such as paired-samples *t*-tests and mixed-factorial analyses of variance (ANOVAs), as well as with nonparametric tests, such as Wilcoxon signed-ranks test, using IBM SPSS Statistics for Windows version 28.01.1 (IBM Corp., Armonk, NY, USA). A logarithmic transformation was applied to the BCEA values in order to produce a normal distribution. The effects of the eye (BE and WE) and subgroup on the outcome measures (excluding the polar angle) were tested separately for the foveal- and peripheral-driven PRL groups with 2 × 3 mixed-factorial ANOVAs, using a univariate criterion with a Greenhouse-Geisser correction. The familywise error rate across the pairwise comparisons was controlled with a Bonferroni approach. Alpha level was set at 0.05 for all tests.

Results

Foveal-Driven PRL

The PRL in the BE was in the foveal proximity for 55 patients (mean age 79 ± 8 years), with an average distance from the former fovea of 1.1 ± 0.99 degrees (range = 0–3 degrees, 95% confidence interval [CI] = 1.1 ± 0.26 degrees). The location of these PRLs may have been foveal in the majority of patients; the reported offset and variability could represent individual differences in the fovea location relative to the middle of the optic disc. In people with healthy vision, the variability in the fovea location from the middle of the optic disc is between 0.86 and 1.1 degrees in the horizontal direction and between 0.71 and 0.9 degrees in the vertical direction.[24]

In the WE, the PRL was at a significantly larger distance from the former fovea (Wilcoxon signed-ranks test $z = 4.8$, $P < 0.001$), fixation stability was poorer ($t(54) = 5.78$, $P < 0.001$), and the central lesion size was bigger ($t(54) = 4.76$, $P < 0.001$) than in the BE. Moreover, the distribution (around a circle) of the polar angle for the PRLs in the WE was significantly different from that for the PRLs in the BE, Watson's $U^2 = 0.29$, $P < 0.05$. Visual acuity was available for 41 patients (75%) in this group. In this group, visual acuity of the BE (mean visual acuity, 0.35 ± 0.20 logMAR) was significantly better than that of the WE (mean visual acuity, 1.08 ± 0.73 logMAR, $t(40) = 6.57$, $P < 0.001$).

We further explored the correspondence of the monocular PRL in the WE with that in the BE. The PRL in the WE had three possible positions relative to the PRL in the BE: subgroup A on functioning, corresponding retinal location ($N = 13$); subgroup B on functioning, noncorresponding retinal location ($N = 16$); and subgroup C on corresponding,

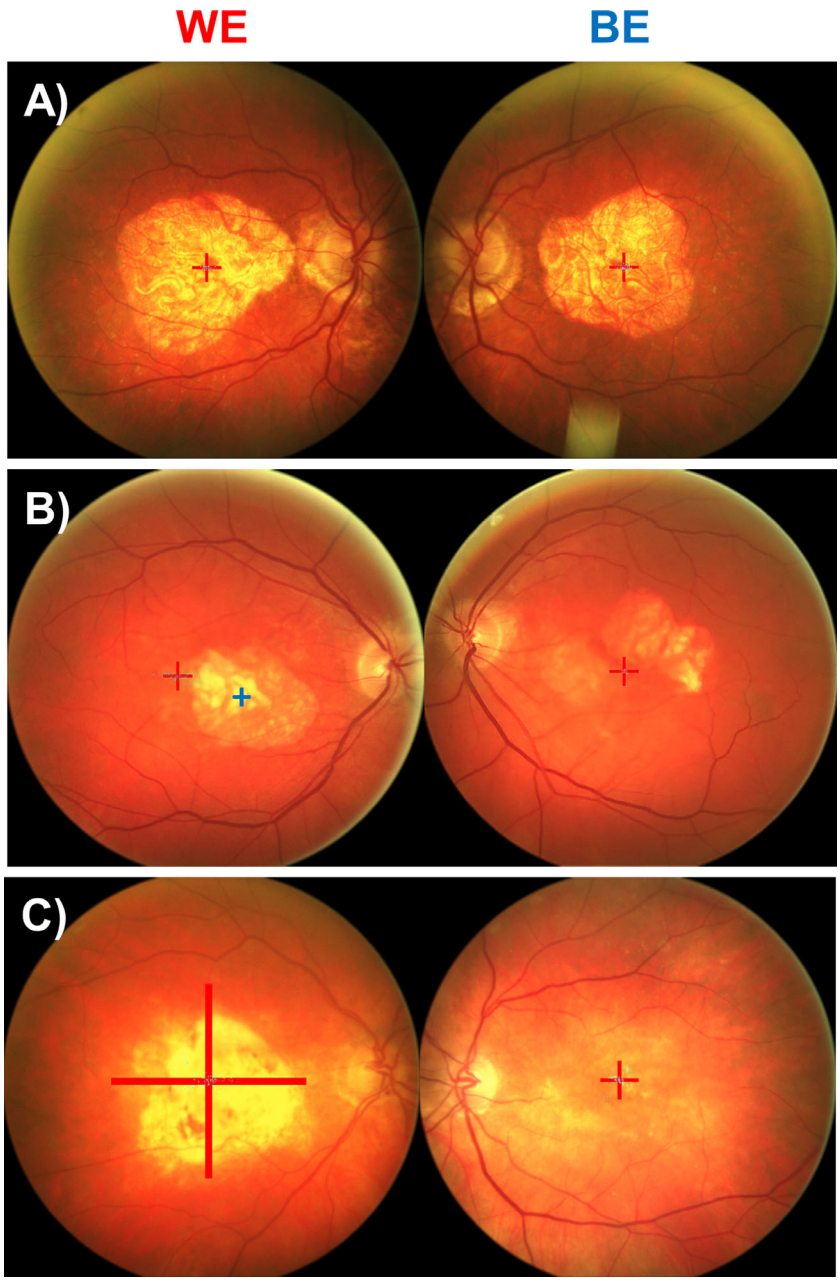

Figure 1. Foveal-driven PRL. For patients with the monocular PRL in the BE in foveal proximity, the monocular PRL in the WE had three possible locations. Panel (**A**) shows a patient with large central lesions and with foveal sparing in both eyes, with the PRLs in the two eyes in corresponding, functioning retinal locations. Panel (**B**) shows a case of a patient with the PRL in the WE on functioning, but not in corresponding retinal location with that in the BE; the corresponding PRL would fall onto the central lesion, as illustrated by the blue cross. Panel (**C**) shows a patient with a PRL in the WE that is not on functioning retina (it falls onto the central lesion), but it is in corresponding location.

nonfunctioning retinal location ($N = 26$). These 3 situations covered 100% of the cases; no PRL was located further away in eccentricity in the BE to allow for a PRL on functioning and corresponding retinal location in the WE. Examples from each subgroup are shown in the panel from Figure 1.

We further examined whether there were any differences in the outcome measures for the three subgroups. For this, we first used separate 2 (eye: BE and WE) × 3 (subgroups: A, B, and C) mixed-factorial ANOVAs for the linear data; that is, 3 separate analyses for PRL distance from the former fovea, fixation stability, and lesion size. For the PRL distance from the former fovea, the main effect of eye ($F(1,52) = 62.1$, $P < 0.001$, partial $\eta^2 = 0.54$), the subgroup effect ($F(2,52) = 10.2$, $P < 0.001$, partial $\eta^2 = 0.28$), and the eye × subgroup interaction effect ($F(2,52) = 29.2$, $P < 0.001$, partial $\eta^2 = 0.53$) were all significant. Pairwise comparisons after the significant interaction revealed that in subgroup B, the PRL distance from the former fovea was greater for the WE than for the BE ($P < 0.001$). In addition, the PRL distance from the former fovea in the WE was significantly greater in subgroup B than in subgroups A and C ($P < 0.001$). For the logBCEA, the main effect of eye ($F(1,52) = 27.3$, $P < 0.001$, partial

Table 1. Mean (±SD) of the Four Outcome Measures of the BE and the WE for the Three Subgroups in the Sample of Patients With the PRL in the BE in Foveal Proximity

	Subgroup A	Subgroup B	Subgroup C
PRL distance (degrees)			
BE	0.9 ± 0.9	1.1 ± 1.1	1.2 ± 1.0
WE	1.0 ± 1.1	4.7 ± 2.5	1.9 ± 1.3
68% logBCEA (degrees^2)			
BE	−0.53 ± 0.27	−0.31 ± 0.45	−0.28 ± 0.56
WE	−0.23 ± 0.45	0.09 ± 0.45	0.19 ± 0.53
Lesion size (degrees)			
BE	10.2 ± 5.2	7.6 ± 5.5	7.0 ± 5.8
WE	12.0 ± 3.4	11.9 ± 4.2	11.8 ± 4.5
PRL polar angle (degrees)*			
BE	96 ± 115	88 ± 106	129 ± 117
WE	111 ± 131	183 ± 85	133 ± 102
Abs (BE-WE)†	28.4	85.3	41.9

* The polar angle data are circular, but the means (±SD) are also reported as linear data as well, for ease of comparison with other reports.

† The mean direction of circular data.

$\eta^2 = 0.34$) was significant, but there was no interaction effect and the subgroup effect also failed to reach significance ($P = 0.055$). Overall, fixation stability was better for the BE than for the WE. For the lesion size, the main effect of eye was significant, $F(1,52) = 17.7$, $P < 0.001$, partial $\eta^2 = 0.25$, but there was no significant interaction or subgroup effect. Overall, the lesion size in the BE was smaller than that in the WE. For the polar angle, we first reduced the analysis to a simple comparison for three groups by computing the absolute difference between the BE and WE values (i.e. abs [polar angle BE- polar angle WE]) and then analyzed the data with the Watson-William F test for circular data. The analysis was not significant, $F(2,52) = 0.82$, $P = 0.45$. The means (±SD) of the outcome measures are shown in Table 1 along with the circular means of the absolute difference between the polar angles of the 2 eyes, for the 3 subgroups.

The median absolute difference in the PRL distance from the former fovea between the 2 eyes was 0 degrees (range = 0–1.5 degrees) for subgroup A, 3.75 degrees (range = 0–7 degrees) for subgroup B, and 0.5 degrees (range = 0–3 degrees) for subgroup C. In subgroup B, the only case with equal PRL distance from the former fovea in both eyes (i.e. difference of 0 degrees in this measure) had the PRLs at eccentricity of 2 degrees, but at much different polar angles and were not in corresponding retinal locations. Likewise, the median absolute difference in the lesion size between the 2 eyes was 0.5 degrees (range = 0–9.5 degrees) for subgroup A, 2.75 degrees (range = 0.5–19 degrees) for subgroup B, and 4.75 degrees (range = 0.5–19 degrees) for subgroup C.

Peripheral-Driven PRL

The PRL in the BE was located in the functioning peripheral retina for 46 patients (mean age = 78 ± 12 years), at an average distance from the former fovea of 6.9 ± 3.4 degrees (range = 3–19 degrees; 95% CI = 6.9 ± 0.97 degrees). In the WE, the PRL was at a significantly larger distance from the former fovea (Wilcoxon signed-ranks test $z = 2.99$, $P = 0.003$), fixation stability was poorer ($t(45) = 4.58$, $P < 0.001$), and the central lesion size was bigger ($t(45) = 5.5$, $P < 0.001$) than in the BE. The distribution (around a circle) of the polar angle for the PRLs in the WE was not significantly different from that of the PRLs in the BE, Watson's $U^2 =$ 0.04 < critical value of 0.18 for alpha level of 0.05. In this group, visual acuity was available for 27 patients (59%). For them, visual acuity of the BE (mean visual acuity = 0.66 ± 0.25 logMAR) was significantly better than that of the WE (mean ± SD = 0.98 ± 0.42 logMAR, $t(26) = 3.8$, $P = 0.008$).

As with the previous analysis, we explored the correspondence of the monocular PRL in the WE with that in the BE. The monocular PRL in the WE had three possible positions relative to the PRL in the BE, depending on the lesion size in both eyes: subgroup D on functioning, corresponding retinal location observed in patients with similar central lesions in the two eyes ($N = 15$), subgroup E on noncorresponding retinal location generally closer to a point corresponding to the PRL in the BE rather than to its former fovea, observed in patients with unequal lesions in the two eyes ($N = 19$), and subgroup F at extreme eccentricity or not developed, observed in patients with extensive damage (lesion size >20 degrees) in the two eyes ($N = 12$). Examples from each subgroup are shown in the panels in Figure 2.

For this analysis too, we examined whether there were any differences in the outcome measures for the 3 subgroups, using separate 2 (eye: BE and WE) × 3 (subgroups: D, E, and F) mixed factorial ANOVAs for the PRL distance from the former fovea, fixation stability, and lesion size. For the PRL distance from the former fovea, the main effect of eye ($F(1,43) = 4.7$, $P = 0.036$, partial $\eta^2 = 0.10$), the subgroup effect ($F(2,43) = 10.3$, $P < 0.001$, partial $\eta^2 = 0.32$), and the eye × subgroup interaction effect ($F(2,43) = 3.7$, $P = 0.033$, partial $\eta^2 = 0.15$) were all significant. Pairwise comparisons after the significant interaction revealed that in subgroup E, the PRL distance from the former fovea was significantly larger in the WE than in the BE ($P < 0.001$). In addition, for the BE, the PRL distance from the former fovea was significantly larger in subgroup F than in subgroups D and E ($P < 0.001$), whereas for the WE, it was only significantly larger in subgroup F than in subgroup D ($P = 0.009$). For the logBCEA, the eye ($F(1,43) = 19.2$, $P < 0.001$, partial $\eta^2 = 0.31$), subgroup ($F(2,43) = 4.1$, $P = 0.02$, partial $\eta^2 = 0.16$), and eye × subgroup ($F(2,43) = 3.9$, $P = 0.03$, partial $\eta^2 = 0.15$) interaction effects were all significant. Pairwise comparisons after the significant interaction showed that in subgroup E, fixation stability was significantly poorer in the WE than in the BE ($P < 0.001$). In addition, for the BE, fixation stability was poorer in subgroup F than in subgroup

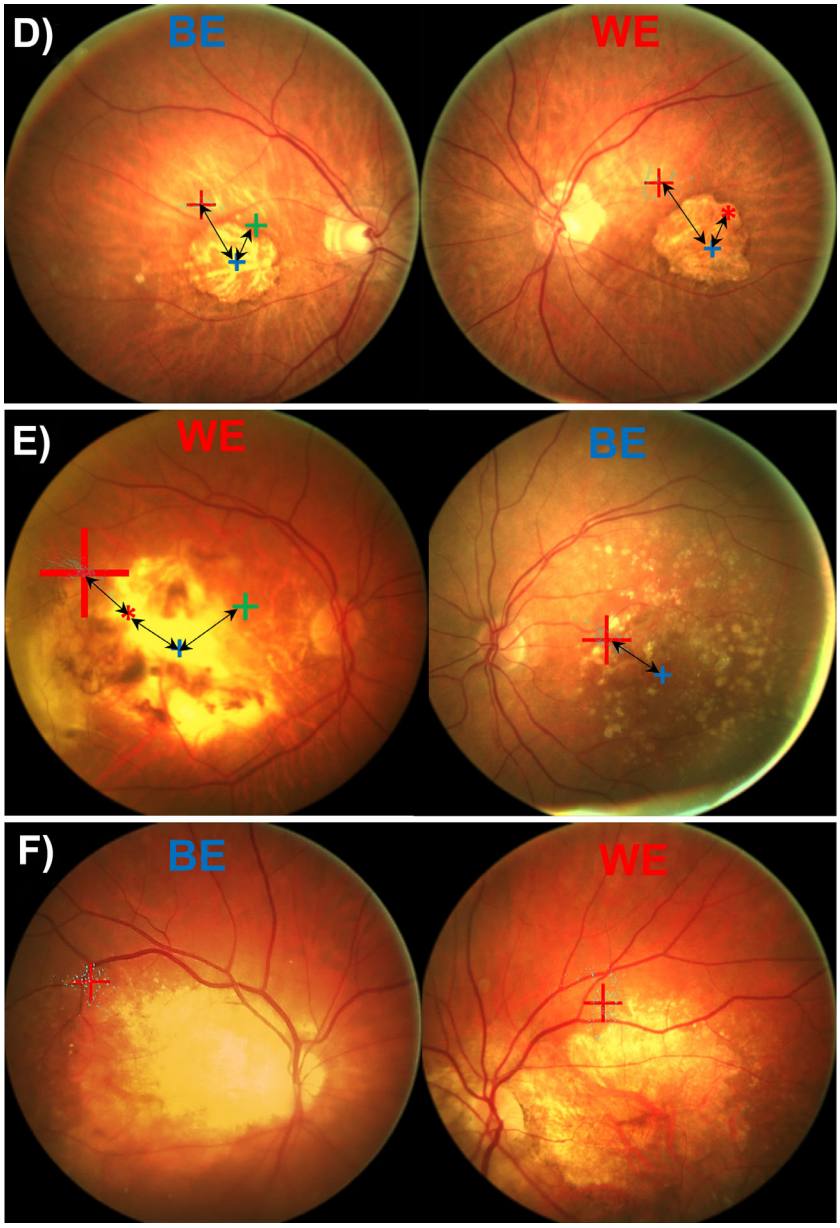

Figure 2. Peripheral-driven PRL. For patients with monocular PRL in the BE in eccentric retina, the PRL locations depends on the nature of the central lesions in both eyes. Panel (**D**) shows a patient with equal damage to the two eyes; the PRL in the BE is at a distance that allows retinal correspondence in the WE and not at the closest distance from the former fovea (symbolized by the green cross). Panel (**E**) shows a case of a patient with unequal lesions to the two eyes; the PRL in the WE is at a closer distance from a location corresponding to the PRL in the BE (*red star*) rather than from the former fovea (*blue cross*), even when functioning retina at smaller eccentricity is available (*green cross*). Panel (**F**) shows a patient with extensive central retinal damage in both eyes; the PRLs develop in far eccentricity.

E ($P = 0.04$) but the comparison between subgroup F and subgroup D failed to reach significance ($P = 0.06$). Moreover, for the WE, fixation stability was better in subgroup D than in subgroup F ($P = 0.04$), but the comparison between subgroup D and subgroup E failed to reach significance ($P = 0.06$). Likewise, for the lesion size, the eye ($F(1,43) = 47.5$, $P < 0.001$, partial $\eta^2 = 0.53$), subgroup ($F(2,43) = 51.7$, $P < 0.001$, partial $\eta^2 = 0.71$), and eye × subgroup interaction effects ($F(2,43) = 29.6$, $P < 0.001$, partial $\eta^2 = 0.58$) were all significant. Pairwise comparisons after the significant interaction showed that in subgroup E the lesion size was significantly smaller in the WE than in the BE ($P < 0.001$). In addition, for the BE, the lesion size was significantly larger in subgroup F than in subgroups D and E ($P < 0.001$), whereas for the WE, it differed significantly for all subgroups ($P < 0.001$). For the polar angle, we first reduced the analysis to a simple comparison for 3 groups by computing the absolute difference between the BE and WE values; the Watson-William F test was not significant, $F(2,43) = 0.45$, $P = 0.64$. The means (±SD) of the outcome measures are shown in Table 2. For ease of comparison with other reports, we also included the values of the polar angle as linear, along with the mean direction of the computed circular variable for the three subgroups.

The median absolute difference in the PRL distance from the former fovea between the 2 eyes was 0 degrees

Table 2. Mean (±SD) of the Four Outcome Measures of the BE and the WE, for the Three Subgroups in the Sample of Patients With the PRL in the BE in Retinal Eccentricity

	Subgroup D	Subgroup E	Subgroup F
PRL distance (degrees)			
BE	5.5 ± 1.4	5.5 ± 2.1	10.8 ± 3.7
WE	5.8 ± 1.9	7.9 ± 3.4	10.8 ± 6.5
68% logBCEA (degrees^2)			
BE	0.20 ± 0.43	0.19 ± 0.40	0.59 ± 0.41
WE	0.34 ± 0.53	0.73 ± 0.51	0.80 ± 0.31
Lesion size (degrees)			
BE	11.8 ± 3.4	12.9 ± 4.2	25.7 ± 4.0
WE	12.6 ± 3.0	20.1 ± 3.9	26.3 ± 4.3
PRL polar angle (degrees)*			
BE	138 ± 62	158 ± 64	118 ± 60
WE	137 ± 67	138 ± 79	115 ± 98
Abs (BE-WE)†	25.4	40.7	26.3

* The polar angle data are circular, but the means (±SD) are also reported as linear data, for ease of comparison with other reports.
† The mean direction of circular data.

(range = 0–2 degrees) for subgroup D, 2 degrees (range = 0–8 degrees) for subgroup E, and 0 degrees (range = 0–8 degrees) for subgroup F. Likewise, the median absolute difference in the lesion size between the 2 eyes was 0.5 degrees (range = 0–3 degrees) for subgroup D, 7 degrees (range = 2–16 degrees) for subgroup E, and 0 degrees (range = 0–3.5 degrees) for subgroup F. In subgroup E (i.e. unequal lesions), 2 patients had a difference in lesion size of only 2 degrees, produced by a large but relatively functional lesion in the BE (i.e. 17 degrees and 18 degrees, respectively). For them, the PRL in the BE was located at an eccentricity of 4 degrees and 5 degrees, respectively.

Visual acuity for the BE and for the WE are presented for all subgroups (i.e. subgroups A to F) in Table 3, based on the available data. Visual acuity results for subgroup F should be interpreted with caution because it includes data from only three patients.

Discussion

The knowledge about what determines the location of the PRL is important not only from a basic science perspective to understand the oculomotor adaptation when its reference position is altered, but also from a clinical perspective because this information is crucial for deciding the course of treatment, intervention, and rehabilitation in patients with macular degeneration. The existing theories cannot fully explain the PRL location.[21] In this study, we proposed a new hypothesis for the PRL location based on binocularity requirements for correspondence, and we tested it on a large number of patients. Our hypothesis considers (1) the fact that macular degeneration is often asymmetric affecting one eye more than the other, (2) the natural viewing condition is binocular whereas the PRL location is recorded during monocular viewing, (3) monocular PRL in the BE usually drives binocular control, and (4) there is a need for PRL correspondence during binocular viewing (unless the WE is suppressed). The results presented in this study strongly support our hypothesis. The foveal-driven PRL and peripheral-driven PRL principles are discussed separately below.

Foveal-Driven PRL

We hypothesized that the PRL is in the foveal proximity in the BE if functioning central retina exists in this eye. This monocular PRL also drives binocular control regardless of the status of the WE and is never found at a larger eccentricity to facilitate retinal correspondence with the PRL in the WE. In other words, this PRL location in the BE will be fixed for monocular and binocular viewing. This is because during foveal viewing there is a strong neural activation involving the large foveal retinotopic cortex, which is unlikely to be silenced in favor of a weaker peripheral stimulation.[29] The human visual system has developed in such a way as to use the fovea as the reference point for the oculomotor system – an evolutionistic mechanism that may be difficult to suppress.[30] Therefore, in these patients with the monocular PRL in the BE in the foveal proximity, the monocular PRL in the WE may have three possible locations, as follows. First, if a functioning retina exists in the foveal proximity in the WE as well, the PRL is found on a corresponding central location (see Fig. 1A). These patients are likely to have good visual acuity and residual stereopsis but may have deficiencies in reading abilities. Second, in some patients with absolute central lesions in the WE, the monocular PRL in this eye is on eccentric functioning retina, but on a noncorresponding location (see Fig. 1B). For these patients, this PRL in the WE should move its location during binocular viewing to be in a corresponding position with that of the BE but this location will fall onto the central lesion (see blue cross in Fig. 1B). Third, other patients with absolute central scotoma in the WE have the PRL in a corresponding location with that from the BE, even though it falls onto the central lesion (see Fig. 1C). Regardless of whether the monocular PRL in the WE in patients with central damage in this eye is on functioning retina or not (i.e. Figs. 1B, C), the binocular need for correspondence will lead to the same result, namely this PRL will fall onto the central lesion during binocular viewing. Consequently, these patients may be more prone to binocular inhibition of visual functions.[12,17,31] Interestingly, these 3 situations explain 100% of cases of patients with a PRL in the BE in the foveal proximity, providing strong support for the foveal-driven PRL principle particularly for the simple task of fixation. Evidence from binocular recordings during a fixation task also indicates that indeed the monocular PRL in the

Table 3. Mean (±SD) Visual Acuity for the BE and the WE for all Subgroups, Based on the Available Data

	Foveal-Driven PRL (logMAR)Subgroup			Peripheral-Driven PRL (logMAR)Subgroup		
	A (10/13)	B (13/16)	C (18/26)	D (13/15)	E (11/19)	F (3/12)*
BE	0.32 ± 0.2	0.36 ± 0.2	0.37 ± 0.2	0.61 ± 0.2	0.63 ± 0.2	1 ± 0.27
WE	0.66 ± 0.4	0.94 ± 0.4	1.38 ± 0.9	0.79 ± 0.2	1.24 ± 0.5	1 ± 0.12

The number of patients for whom the visual acuity data were available is shown in brackets along with the total number of patients included in each subgroup.
* Interpret with caution; visual acuity data were available from only 3 patients in subgroup F.

BE also drives binocular control,[6,18,19,32] but more research involving other tasks is needed to strengthen this conclusion. These patients are not likely to respond well to rehabilitation techniques involving PRL relocation, although this needs to be confirmed in future studies.

Peripheral-Driven PRL

We also hypothesized that when the central lesion involves the foveal region in the BE, the monocular PRL is on functioning peripheral retina at the border of the visible lesion at a location that increases the chance for visual input from both eyes. In other words, the monocular PRL location depends on the status of the other eye to maximize correspondence and the function of peripheral vision during binocular viewing. Depending on the size of the central lesion, three situations can be encountered, as follows. First, for patients with approximately equal damage in both eyes, the PRL in the BE is found in the peripheral retina at a location that allows for correspondence on the functioning retina for the PRL in the WE. This means that the PRL is not necessarily at the shortest distance from the former fovea, but rather in a location to maximize the peripheral input from both eyes. The example shown in Figure 2D shows that the functioning retina was available at a shorter distance from the former fovea (green cross in Fig. 2D) than the recorded PRL in the BE; however, if that location is selected instead, the corresponding PRL in the WE would have fallen onto the lesion (red star in Fig. 2D). The actual PRL in the BE at a larger distance from the former fovea allows for the occurrence of a corresponding PRL in the WE on the functioning retina. We found that 100% of patients with approximately equal central lesions involving the fovea have monocular PRLs on a functioning retina in both eyes and in corresponding locations. The neural activation of the visual cortex is smaller in area for peripheral compared to foveal input and the strength of this activation depends mostly on the eccentricity per se rather than the angular location at a given eccentricity.[33] Therefore, it is reasonable to assume that methods of rehabilitation involving PRL retraining to a location more favorable for reading would be beneficial for these patients given that the trained PRL changes only the polar angle but retains the same eccentricity and the trained PRLs fall onto functioning corresponding locations in both eyes.

Second, for patients with unequal damage to the two eyes, the monocular PRL in the BE is at the border of the central lesion, at the shortest distance from the former fovea and it is most likely the new reference point for the oculomotor system. We found that for these patients, a corresponding PRL in the WE would fall onto the lesion in 100% of cases. The PRL in the WE is not always functional (i.e. falling onto the central lesion in 47% of cases), in a noncorresponding retinal location with that in the BE, but generally closer to a location corresponding to the PRL in the BE than to its former fovea (i.e. in 68% of cases). Figure 2E shows an example of a patient with the PRL in the BE at a closest available functioning retina from the former fovea. The PRL in the WE is at a location that is closer to the corresponding PRL in the BE (red star in Fig. 2E) rather than the former fovea, even when a functioning retina is available at a smaller eccentricity (green cross in Fig. 2E). This suggests that the monocular PRL in the BE also drives binocular control, bringing the WE into alignment during binocular viewing. Rehabilitation efforts for improving fixation stability and PRL relocation to a more suitable location for reading when healthy retina exists at the same eccentricity should focus only on the BE.

Third, for patients with extensive damage (lesion size >20 degrees) in the two eyes, the PRL in the BE is at extreme eccentricity (see Fig. 2F). In our previous research, we found that in these cases the PRL in the BE is likely to shift position from monocular to binocular viewing[6] suggesting that the location of this PRL is plastic and likely used sporadically for the short task at hand, such as spot reading or fixation for a brief period. Its eccentricity may be too strenuous for sustained function, and it may have limited functional usability. For these people, the monocular PRL in the WE is either found in far periphery beyond 12 degrees eccentricity (50% of cases) or not developed (50% of cases). A corresponding location with the PRL in the BE would fall onto the central lesion in the WE in 83% of cases. Given the mobility of the location of the PRL in the BE in patients with extensive central lesions demonstrated in our previous work, we refrain from proposing that this PRL drives binocular control, although we recommend that methods of PRL rehabilitation should be used for both eyes for these patients to optimize their residual vision. Alas, the improvement of visual function is expected to be marginal.

Outcome Measures

An extensive and detailed analysis has been performed for the outcome measures of the 202 eyes (101 BE and 101 WE) with macular degeneration included in this study: PRL distance from the former fovea, polar angle, fixation stability, and lesion size. For both those included in the foveal-driven PRL group and in the peripheral-driven PRL group, one clear conclusion emerges: overall, the monocular characteristics of the PRL in the BE are different from those of the PRL in the WE. Therefore, it is paramount that a distinction between the BE and the WE is made when evaluating the PRL and its relationship with visual functions. This is an important conclusion that we previously emphasized because typically the monocular PRL in the BE also drives binocular control whereas the WE's need for binocular correspondence and oculomotor coordination often would result in dramatic changes in the PRL characteristics in this eye when the viewing condition changes from monocular to binocular viewing.[6,18,19,32] Moreover, this study shows that the monocular PRL in the WE might fall onto the central lesion and, therefore, any relationships between PRL characteristics and visual functions are irrelevant, unless they are evaluated in the framework of binocular function. It has been shown that patients with monocular PRLs in noncorresponding locations are more likely to show binocular inhibition of visual functions.[12,17]

Two notable exceptions regarding the need to distinguish between the BE and the WE are in patients with foveal sparing in both eyes (i.e. foveal-driven PRL, subgroup A) and in those who have the sizes of the central damage approximately equal in the two eyes (i.e. peripheral-driven PRL, subgroup D). In each of these two subgroups, the outcome measures of the BE and the WE are relatively equivalent, resulting in the monocular PRLs being in corresponding retinal locations and on a functioning retina in both eyes. For these patients, the monocular and binocular characteristics of the PRLs are expected not to change from monocular to binocular viewing. These patients are most likely to preserve some binocular visual functions, such as residual stereopsis and binocular summation.

Caveats

The data presented in this paper were recorded during a fixation task, but the question of whether the same PRL is used for other tasks remains to be elucidated. In our opinion, the foveal-driven PRL is not likely to change location significantly with the task because the oculomotor system is designed to use the fovea as the reference position; the eye movements used to perform more naturalistic tasks, such as reading, cooking, or watching television, are made using this reference point. However, a peripheral-driven PRL could change its location with the task more easily, as evidenced by the successful training of a new PRL for reading.[34] In addition, Crossland and colleagues[35] examined the PRL in the BE for fixation on a point and for reading single words. Visual inspection of the PRLs for the two tasks indicated that, generally, eye position data overlap, but they seem to do so more for the patients with a PRL closer to the fovea (i.e. foveal-driven PRL) than for those with a PRL in the eccentric retina (i.e. peripheral-driven PRL), as shown in their figure 1. In addition, for the specific task of fixation, it appears that the PRL in the BE of patients with long-lasting macular disease maintains its overall location over time, suggesting that the oculomotor system recalibrates its reference point to this location with the passage of time.[8] If this recalibration occurs, it is likely that the PRL would serve the role of a pseudo-fovea and eye movements used in more naturalistic tasks are made using this reference point. However, more research is needed to confirm these suppositions.

Although we did not specifically report multiple PRLs for any of the eyes, the principles we propose imply that some eyes would use two PRLs whereas others only one for the simple task of fixation, when the viewing condition changes from monocular to binocular viewing. Specifically, we assumed that the monocular PRL in the BE also drives binocular control and — if the monocular PRL in the WE is not in a corresponding location with that from the BE — the WE would have to use a different PRL for binocular viewing that is aligned with the PRL in the BE (unless the WE is suppressed). In addition, for patients with extensive damage to the two eyes who have monocular PRLs in extreme eccentricity, we were reluctant to assume that there is one PRL that drives binocular control. We have shown that for these patients the PRLs in both eyes can move with the viewing condition.[6] Therefore, the principles we propose allow for the existence of multiple PRLs, particularly for the WE with a noncorresponding monocular PRL, or when both eyes have extensive damage, but less so in those with the PRL in the BE near the fovea. The issue of multiple PRLs used for the same task under different viewing conditions is important, but their incidence reported in the literature appears to be low for the BE. In their seminal paper, Lei and Schuchard[36] reported that the PRL changed location with the illuminance level but only in 9.7% of their sample (31 eyes from 28 out of 288 patients). Among these, only 3 patients shifted the PRL in both eyes; in 25 patients, the PRL shifted in only one eye. They also reported that this happened only for patients with relative scotomas, but not all patients with a relative scotoma had a PRL shift. A much higher incidence of PRL shift (15 out of 27 eyes) was detected with change in brightness level, but this was reported only for the monocular PRLs in the WE, particularly for those situated in the eccentric retina (13 out of 15 eyes).[37] Moreover, in their excellent paper, Reinhard and colleagues[38] found 2 PRLs in the same eye in only 3 instances out of 60 eyes with Stargardt's disease. Using the kernel density estimator, Crossland and colleagues[39] found multiple PRLs in patients with newly developed macular disease, but this suggests that the PRL takes time to establish. Indeed, they later reported that the number of patients using only one PRL increased substantially in a span of 1 year from disease onset.[40]

Conclusion

In this study, we tested the hypothesis that binocularity requirements for correspondence play an important role in determining the PRL location in patients with macular degeneration. We formulated two principles based on whether the BE has foveal sparing (foveal-driven PRL) or central lesions affecting the fovea (peripheral-driven PRL). Accordingly, the monocular PRL in the WE has different conditions, but should be evaluated in the context of binocular vision, because there are situations in which the characteristics of the monocular PRL in this eye become meaningless in the more naturalistic binocular viewing. From the data analyzed in this study, it appears that the visual system in macular degeneration is driven by principles that tend toward optimizing the function of the whole visual system and not just components of the system. Based on the information presented here, a classification system of the PRL location emerges that enhances our understanding of how the visual system works in macular disease and how this information can be used in visual rehabilitation and amelioration in these patients.

Acknowledgments

Disclosure: **L. Tarita-Nistor**, None; **M.S. Mandelcorn**, None

References

1. Howard IP. *Seeing in depth: Basic mechanisms. Volume 1.* Oxford, England, UK: Oxford University Press; 2012:4–8 and 317–356.
2. Horton JC, Hoyt WF. The representation of the visual field in human striate cortex. A revision of the classic Holmes map. *Arch Ophthalmol.* 1991;109(6):816–824.
3. Dougherty RF, Koch VM, Brewer AA, Fischer B, Modersitzki J, Wandell BA. Visual field representations and locations of visual areas V1/2/3 in human visual cortex. *J Vis.* 2003;3(10):586–598.
4. Van der Stigchel S, Bethlehem RA, Klein BP, Berendschot TT, Nijboer TC, Dumoulin SO. Macular degeneration affects eye movement behavior during visual search. *Front Psychol.* 2013;4:579.
5. White JM, Bedell HE. The oculomotor reference in humans with bilateral macular disease. *Invest Ophthalmol Vis Sci.* 1990;31(6):1149–1161.
6. Tarita-Nistor L, Eizenman M, Landon-Brace N, Markowitz SN, Steinbach MJ, González EG. Identifying absolute preferred retinal locations during binocular viewing. *Optom Vis Sci.* 2015;92(8):863–872.
7. González EG, Mandelcorn MS, Mandelcorn ED, Tarita-Nistor L. Effect of visual feedback on the eye position stability of patients with AMD. *Vision (Basel).* 2019;3(4):59.
8. Tarita-Nistor L, Mandelcorn MS, Mandelcorn ED, Markowitz SN. Effect of disease progression on the PRL location in patients with bilateral central vision loss. *Transl Vis Sci Technol.* 2020;9(8):47.
9. Monés J, Rubin GS. Contrast sensitivity as an outcome measure in patients with subfoveal choroidal neovasculari-

sation due to age-related macular degeneration. *Eye (Lond).* 2005;19(11):1142–1150.
10. Lovie-Kitchin J, Feigl B. Assessment of age-related maculopathy using subjective vision tests. *Clin Exp Optom.* 2005;88(5):292–303.
11. Ergun E, Maár N, Radner W, Barbazetto I, Schmidt-Erfurth U, Stur M. Scotoma size and reading speed in patients with subfoveal occult choroidal neovascularization in age-related macular degeneration. *Ophthalmology.* 2003;110(1):65–69.
12. Silvestri V, Sasso P, Piscopo P, Amore F, Rizzo S, Devenyi RG, Tarita-Nistor L. Reading with central vision loss: binocular summation and inhibition. *Ophthalmic Physiol Opt.* 2020;40(6):778–789.
13. Tarita-Nistor L, González EG, Markowitz SN, Steinbach MJ. Binocular interactions in patients with age-related macular degeneration: acuity summation and rivalry. *Vision Res.* 2006;46(16):2487–2498.
14. Crossland MD, Engel SA, Legge GE. The preferred retinal locus in macular disease: toward a consensus definition. *Retina.* 2011;31(10):2109–2114.
15. Schuchard RA, Naseer S, de Castro K. Characteristics of AMD patients with low vision receiving visual rehabilitation. *J Rehabil Res Dev.* 1999;36(4):294–302.
16. Kisilevsky E, Tarita-Nistor L, González EG, Mandelcorn MS, Brent MH, Markowitz SN, et al. Characteristics of the preferred retinal loci of better and worse seeing eyes of patients with a central scotoma. *Can J Ophthalmol.* 2016;51(5):362–367.
17. Sverdlichenko I, Mandelcorn MS, Issashar Leibovitzh G, Mandelcorn ED, Markowitz SN, Tarita-Nistor L. Binocular visual function and fixational control in patients with macular disease: A review. *Ophthalmic Physiol Opt.* 2022;42(2):258–271.
18. Tarita-Nistor L, Brent MH, Steinbach MJ, González EG. Fixation stability during binocular viewing in patients with age-related macular degeneration. *Invest Ophthalmol Vis Sci.* 2011;52(3):1887–1893.
19. Kabanarou SA, Crossland MD, Bellmann C, Rees A, Culham LE, Rubin GS. Gaze changes with binocular versus monocular viewing in age-related macular degeneration. *Ophthalmology.* 2006;113:2251–2258.
20. Verghese P, Tyson TL, Ghahghaei S, Fletcher DC. Depth perception and grasp in central field loss. *Invest Ophthalmol Vis Sci.* 2016;57(3):1476–1487.
21. Cheung SH, Legge GE. Functional and cortical adaptations to central vision loss. *Vis Neurosci.* 2005;22(2):187–201.
22. Guez JE, Le Gargasson JF, Rigaudiere F, O'Regan JK. Is there a systematic location for the pseudo-fovea in patients with central scotoma? *Vision Res.* 1993;33(9):1271–1279.
23. Sunness JS, Applegate CA, Haselwood D, Rubin GS. Fixation patterns and reading rates in eyes with central scotomas from advanced atrophic age-related macular degeneration and Stargardt disease. *Ophthalmology.* 1996;103(9):1458–1466.
24. Tarita-Nistor L, González EG, Markowitz SN, Steinbach MJ. Fixation characteristics of patients with macular degeneration recorded with the mp-1 microperimeter. *Retina.* 2008;28:125–133.
25. Bernard JB, Chung STL. Visual acuity is not the best at the preferred retinal locus in people with Macular Disease. *Optom Vis Sci.* 2018;95(9):829–836.
26. Denniss J, Baggaley HC, Brown GM, Rubin GS, Astle AT. Properties of visual field defects around the monocular preferred retinal locus in age-related macular degeneration. *Invest Ophthalmol Vis Sci.* 2017;58(5):2652–2658.
27. Kilpeläinen M, Putnam NM, Ratnam K, Roorda A. The retinal and perceived locus of fixation in the human visual system. *J Vis.* 2021;21(11):9.
28. Timberlake GT, Sharma MK, Grose SA, Gobert DV, Gauch JM, Maino JH. Retinal location of the preferred retinal locus relative to the fovea in scanning laser ophthalmoscope images. *Optom Vis Sci.* 2005;82:177–185.
29. Dilks DD, Julian JB, Peli E, Kanwisher N. Reorganization of visual processing in age-related macular degeneration depends on foveal loss. *Optom Vis Sci.* 2014;91(8):e199–e206.
30. Land M. Eye movements in man and other animals. *Vision Res.* 2019;162:1–7.
31. Tarita-Nistor L, Brent MH, Markowitz SN, Steinbach MJ, González EG. Maximum reading speed and binocular summation in patients with central vision loss. *Can J Ophthalmol.* 2013;48(5):443–449.
32. Tarita-Nistor L, Brent MH, Steinbach MJ, González EG. Fixation patterns in maculopathy: from binocular to monocular viewing. *Optom Vis Sci.* 2012;89(3):277–287.
33. Dilks DD, Baker CI, Peli E, Kanwisher N. Reorganization of visual processing in macular degeneration is not specific to the "preferred retinal locus". *J Neurosci.* 2009;29(9):2768–2773.
34. Tarita-Nistor L, González EG, Markowitz SN, Steinbach MJ. Plasticity of fixation in patients with central vision loss. *Vis Neurosci.* 2009;26(5-6):487–494.
35. Crossland MD, Crabb DP, Rubin GS. Task-specific fixation behavior in macular disease. *Invest Ophthalmol Vis Sci.* 2011;52:411–416.
36. Lei H, Schuchard RA. Using two preferred retinal loci for different lighting conditions in patients with central scotomas. *Invest Ophthalmol Vis Sci.* 1997;38(9):1812–1818.
37. Ro-Mase T, Ishiko S, Yoshida A. Effect of background brightness on preferred retinal loci in patients with macular disease. *Transl Vis Sci Technol.* 2020;9(11):32
38. Reinhard J, Messias A, Dietz K, et al. Quantifying fixation in patients with Stargardt disease. *Vision Res.* 2007;47(15):2076–2085.
39. Crossland MD, Sims M, Galbraith RF, Rubin GS. Evaluation of a new quantitative technique to assess the number and extent of preferred retinal loci in macular disease. *Vision Res.* 2004;44(13):1537–1546.
40. Crossland MD, Culham LE, Kabanarou SA, Rubin GS. Preferred retinal locus development in patients with macular disease. *Ophthalmology.* 2005;112(9):1579–1585.

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