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## Research Article

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# Preferred Retinal Locus Location, Fixation Stability and Visual Function in Stargardt Disease and Age-Related Macular Degeneration

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## Abstract

### Purpose

To compare preferred retinal locus (PRL) location and fixation characteristics between Stargardt disease and age-related macular degeneration (AMD), and to examine their associations with visual and functional outcomes.

### Methods

This prospective, observational, comparative cross-sectional study included 43 participants: 14 with genetically confirmed Stargardt disease and 29 with AMD. Eighty-five eyes were evaluable: 28 with Stargardt disease, 18 with neovascular AMD, and 39 with non-neovascular AMD. Fixation was assessed using MAIA microperimetry. PRL location and eccentricity, P1, P2, BCEA63, and BCEA95 were recorded, together with high- and low-contrast visual acuity, binocular reading speed, and DADV score. Eye-level analyses used generalized estimating equations to account for inter-eye correlation.

### Results

Eccentric fixation was observed in 78.6% of Stargardt eyes and 38.6% of AMD eyes. Stargardt disease was associated with higher odds of eccentric fixation than AMD considered as a single group (OR = 5.91; 95% CI, 1.62–21.62;  $p = 0.007$ ). Median PRL eccentricity was 7.20° (IQR 4.19–10.32) in Stargardt disease, 2.64° (IQR 0.63–6.02) in neovascular AMD, and 3.35° (IQR 2.03–5.12) in non-neovascular AMD. PRL eccentricity showed a non-normal distribution and is therefore described using the median and interquartile range. Greater PRL eccentricity was associated with poorer high- and low-contrast visual acuity, lower P1 and P2 values, larger BCEA measures, slower reading, and lower DADV scores.

### Conclusion

Stargardt disease and AMD showed distinct PRL patterns. Greater PRL eccentricity was associated with poorer visual acuity, reduced fixation stability, and worse functional performance.

**Keywords:** preferred retinal locus; Stargardt disease; age-related macular degeneration; microperimetry; fixation stability; visual function

## Key Points

### What is already known

Preferred retinal loci develop frequently after central macular damage, but their location, eccentricity and stability vary substantially between patients and diseases.

### What this study adds

Eccentric fixation was more frequent in Stargardt disease than in age-related macular degeneration, and PRL eccentricity was associated with visual acuity, fixation stability, reading speed and vision-related functional dependence.

### Clinical relevance

PRL location, eccentricity and stability should be evaluated together when characterising fixation behaviour and planning visual rehabilitation in macular disease.

## Abbreviations

| Abbreviation | Definition                                 |
|--------------|--------------------------------------------|
| AMD          | Age-related macular degeneration           |
| BCEA         | Bivariate contour ellipse area             |
| CI           | Confidence interval                        |
| DADV         | Daily Activities Dependence on Vision      |
| ETDRS        | Early Treatment Diabetic Retinopathy Study |
| FDR          | False discovery rate                       |
| GEE          | Generalized estimating equations           |
| IQR          | Interquartile range                        |
| MAIA         | Macular Integrity Assessment               |
| OR           | Odds ratio                                 |
| PRL          | Preferred retinal locus                    |
| VA           | Visual acuity                              |

## Introduction

Central vision loss caused by macular disease disrupts foveal fixation and compromises visually demanding activities, particularly reading, face recognition, and visual search. When the fovea can no longer provide a reliable reference for fixation, many patients adopt an eccentric retinal area that assumes part of the functional role previously served by the damaged central retina. This area, commonly referred to as the preferred retinal locus (PRL), becomes a new reference point for fixation and visual exploration [1-4].

Although the PRL is widely regarded as an adaptive response to central retinal damage, its development is not uniform, and its location, eccentricity, and stability vary widely across patients and macular disorders.

The formation of a PRL has been reported in a high proportion of eyes with central scotoma, especially in advanced age-related macular degeneration (AMD) [1]. However, the selected retinal locus does not necessarily correspond to the area with the highest residual sensitivity, the best structural preservation, or the greatest visual acuity [4, 5]. Some patients establish a relatively stable eccentric locus, whereas others continue to fixate near the former fovea or within an area of reduced retinal function. Recent studies have also shown that a subgroup of eyes with macular disease does not develop a clearly identifiable natural PRL [6]. This heterogeneity suggests that eccentric fixation should not be regarded as an inevitable or homogeneous response to central vision loss.

PRL topography may also have functional consequences. In advanced AMD, superior and nasal locations have been reported frequently, although considerable interindividual variation remains [1, 7]. The distance between the PRL and the former fovea has been associated with fixation stability and visual acuity [1, 6], while unstable fixation has been linked to reduced reading performance [1, 7, 8]. Nevertheless, the optimal PRL location is still debated. A locus closer to the former fovea may preserve higher spatial resolution, but proximity alone does not guarantee adequate sensitivity or stable fixation. Conversely, a more eccentric locus may lie in healthier retina but impose a greater limitation on visual resolution. These competing factors make it unlikely that PRL location alone can fully explain functional performance.

The temporal characteristics of macular damage may contribute to the variability in fixation behaviour. Stargardt disease commonly begins in childhood, adolescence, or early adulthood, whereas AMD is generally diagnosed later in life. The two conditions also differ in etiology, progression, lesion morphology, symmetry, and duration of visual loss. These differences may influence how fixation strategies are acquired and consolidated over time. Longitudinal observations in patients with newly developed macular disease have shown that the retinal locus of fixation may change during the first months after central visual loss before becoming more stable [9]. Experimental models of progressive scotoma have similarly suggested that the rate and pattern of central field loss may affect the location and stability of fixation [10]. In juvenile Stargardt disease, longer disease duration and earlier onset have also been associated with more extensive functional impairment and changes in fixation behaviour [11].

Despite these observations, direct comparisons between Stargardt disease and AMD remain limited. Separate studies have described a predominance of superior PRL locations in Stargardt disease, whereas a more heterogeneous topographic distribution has been reported in AMD [12, 13]. However, most studies have focused on a single diagnosis, small heterogeneous samples, or the effect of fixation training rather than on the spontaneous fixation pattern itself. In addition, PRL location, eccentricity, and stability are often examined separately, even though they are likely to represent related but distinct components of fixation behaviour. A direct comparison between an inherited macular dystrophy of typically earlier onset and a degenerative macular disease of later onset may therefore provide clinically relevant information, although any observed

differences must be interpreted in the context of disease-specific morphology and duration rather than age at onset alone.

The functional assessment of patients with macular disease should also extend beyond conventional high-contrast visual acuity. High-contrast acuity provides an important measure of spatial resolution but may underestimate difficulties experienced under reduced contrast or during sustained visual tasks. In bilateral neovascular AMD, contrast sensitivity and binocular reading speed have shown closer relationships with vision-related quality of life than high-contrast acuity alone [14]. Contrast sensitivity has also been associated with structural macular involvement, while low-contrast or low-luminance tests can reveal functional deficits not fully captured by standard visual acuity [14-17]. Combining microperimetric measures with high- and low-contrast acuity, reading performance, and patient-reported visual function may therefore provide a more complete characterisation of the clinical relevance of PRL behaviour.

The purpose of this study was to compare PRL location and fixation characteristics between Stargardt disease and AMD and to determine how PRL eccentricity relates to visual acuity, fixation stability, reading performance and vision-related functional dependence. We hypothesised that the distribution of central and eccentric fixation would differ between Stargardt disease and AMD and that greater PRL eccentricity would be associated with poorer visual and functional performance. These analyses were intended to clarify whether PRL location, eccentricity and stability provide complementary information when characterising fixation behaviour in central macular disease.

## **Methods**

### **Study design and participants**

This prospective, observational, comparative, cross-sectional study was conducted within the routine clinical activity of a low-vision and visual rehabilitation clinic. Participants were referred by the patient organisations Asociación Mácula Retina and Fundación Retina España or were recruited from patients already scheduled for assessment at the clinic. All participants had a previous ophthalmological diagnosis of Stargardt disease or age-related macular degeneration (AMD). In participants with Stargardt disease, the diagnosis had also been genetically confirmed.

A total of 43 participants were included: 14 with Stargardt disease and 29 with AMD. Both eyes were assessed whenever visual acuity and fixation measurements could be obtained reliably. Of the 86 potentially eligible eyes, 85 were included in the eye-level analyses: 28 eyes with Stargardt disease, 18 with neovascular AMD, and 39 with non-neovascular AMD. One eye was excluded because it had no measurable vision and fixation and visual function could therefore not be assessed. Participant inclusion and the distribution of eyes across diagnostic groups are summarised in Online Resource 2

All clinical and functional assessments were performed by three trained examiners (Juan E. Cedrún-Sánchez, Ainhoa M. Armas-González, and Amina Bensserghine-Karmossi) following the same assessment procedures.

Eligible participants had bilateral or asymmetric macular disease that was clinically stable at the time of assessment and were able to complete the visual acuity and microperimetry

procedures. Eyes with clinically significant media opacities that could interfere with visual acuity or fundus tracking, including cataract, were excluded. None of the participants had previously undergone eccentric viewing training, microperimetric biofeedback, or another structured fixation rehabilitation programme.

### **Visual acuity assessment**

Monocular visual acuity was assessed with the fellow eye occluded and with the refractive correction used for distance vision. High-contrast and low-contrast visual acuity were measured using Early Treatment Diabetic Retinopathy Study charts at 100% and 10% contrast, respectively.

Testing was initially performed at 4 m. When participants were unable to identify any optotypes at that distance, the testing distance was reduced until a measurable response was obtained. Visual acuity results were expressed in logarithm of the minimum angle of resolution units, taking the testing distance into account. Near visual acuity was assessed binocularly at a working distance of 25 cm using a standardised near addition of +4.00 D.

The difference between low- and high-contrast visual acuity was calculated for each eye as:

$$\text{Low-contrast deficit} = 10\% \text{ contrast visual acuity} - 100\% \text{ contrast visual acuity}$$

Higher positive values therefore indicated a greater deterioration in visual performance under reduced-contrast conditions.

### **Microperimetry and fixation assessment**

Fixation behaviour and macular sensitivity were assessed monocularly using the MAIA microperimeter (Macular Integrity Assessment; CenterVue, Padova, Italy). No cycloplegic or mydriatic agents were used during the visual and microperimetric assessments. Before testing, participants underwent a 5-minute period of dark adaptation. During this period, clinical history was reviewed, with particular attention to the onset of visual symptoms, and the DADV (Daily Activities Dependence on Vision) questionnaire was administered.

Participants first completed a Fast examination using a seen/not-seen response strategy to confirm their understanding of the procedure and familiarise them with the task. This preliminary examination was not included in the analysis. The subsequent New Expert Exam was performed using the standard 4–2 threshold strategy and was retained for analysis. The standard macular grid comprised 37 test points covering a 10°-diameter central macular field. Goldmann III stimuli were presented for 200 ms against a mesopic background luminance of 1.27 cd/m<sup>2</sup>. The device provided a dynamic range of 36 dB.

A red circular fixation target with a diameter of 1° was used whenever visible. When the target could not be perceived because of the central scotoma, a larger red circular target with a diameter of 15° was used. Participants were instructed to maintain fixation on the target throughout the examination.

The device incorporates fundus tracking and permits simultaneous characterisation of fixation location and stability. The following fixation parameters were recorded for each evaluable eye:

- P1;
- P2;
- bivariate contour ellipse area encompassing 63% of fixation points;
- bivariate contour ellipse area encompassing 95% of fixation points.

P1 and P2 represent the percentage of fixation points located within the central 2° and 4° areas reported by the device, respectively. Higher P1 and P2 values indicate a greater concentration of fixation points around the fixation centroid.

Fixation stability was also described using the classification proposed by Fujii et al. Fixation was considered stable when P1 was greater than 75%, relatively unstable when P1 was 75% or less but P2 was greater than 75%, and unstable when both P1 and P2 were 75% or less.

The bivariate contour ellipse area represents the retinal area containing a specified proportion of fixation points. BCEA63 and BCEA95 were expressed in square degrees. Smaller BCEA values indicate a more spatially concentrated and therefore more stable fixation pattern.

### **Preferred retinal locus location**

The preferred retinal locus was identified from the distribution of fixation points obtained during microperimetry. Its location was classified as central, superior, inferior, nasal, or temporal with respect to the former foveal location.

Central or eccentric PRL location was based on the original clinical classification recorded during the microperimetric assessment. PRLs classified as eccentric were further according to their predominant anatomical direction from the former fovea as superior, inferior, nasal, or temporal. Cartesian coordinates and calculated PRL eccentricity were analysed as continuous measures and were not used retrospectively to reclassify borderline cases.

When the anatomical foveal location could not be identified directly, it was estimated according to the anatomical criterion described by Tarita-Nistor et al., with the former fovea assumed to lie approximately 15.5° temporal and 1.3° inferior to the centre of the optic disc. An example of PRL identification and eccentricity measurement is shown in Online Resource 1.

Horizontal and vertical PRL coordinates were recorded in degrees. PRL eccentricity, defined as the distance between the estimated former fovea and the active PRL, was calculated as:

$$dPRL = \sqrt{x^2 + y^2}$$

where  $x$  and  $y$  represent the horizontal and vertical displacement of the PRL, respectively. Greater dPRL values indicate a more eccentric fixation location.

### **Exploratory central-fixation phenotype**

An exploratory phenotype was defined to identify eyes that continued to fixate close to the former foveal location despite reduced high-contrast visual acuity. Eyes were classified as presenting this pattern when the PRL remained within the central 4° area and high-contrast visual acuity was worse than 0.4 logMAR. Central fixation was defined according to the original clinical classification recorded during microperimetry [3, 13]. The visual acuity threshold was used as an operational study criterion. This phenotype was treated as a descriptive clinical classification and not as a direct measure of neuronal plasticity, cortical reorganisation, or failure of neuroadaptation.

### **Reading performance**

Reading performance was assessed binocularly at a working distance of 25 cm using the validated Spanish Radner-Vissum reading test and a standardised near addition of +4.00 D. Reading speed was recorded in words per minute and analysed as a participant-level variable.

### **Vision-related functional dependence**

Vision-related functional limitations were assessed using the validated Daily Activities Dependence on Vision questionnaire [18]. The instrument contains nine items evaluating difficulty in performing visually demanding daily activities. Each item was scored from 0 to 2, and the overall score was transformed to a 0–100 scale as follows:

$$\text{DADV score} = \frac{\text{sum of item scores}}{\text{number of items answered}} \times 50$$

Higher scores indicate less difficulty in performing vision-dependent daily activities and better perceived visual function. The DADV score was analysed at participant level.

### **Outcome measures**

The primary outcome was the difference in the distribution of central versus eccentric PRL between Stargardt disease and AMD. The primary analysis compared Stargardt disease with AMD considered as a single diagnostic group. A secondary analysis examined Stargardt disease, neovascular AMD, and non-neovascular AMD separately.

Secondary eye-level outcomes included:

- PRL eccentricity;
- directional PRL location;
- P1 and P2;
- BCEA63 and BCEA95;
- high-contrast visual acuity;
- low-contrast visual acuity;

- low-contrast deficit.

Secondary participant-level outcomes included reading speed and DADV score.

### **Statistical analysis**

Participant-level and eye-level variables were analysed separately. Continuous variables were summarised as mean  $\pm$  standard deviation or median and interquartile range, as appropriate, and categorical variables as frequencies and percentages. Participant-level comparisons between Stargardt disease and AMD were performed using Student's t test or the Mann–Whitney U test, depending on the distribution of continuous variables. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate.

Because both eyes from the same participant could be included, eye-level outcomes were analysed using generalized estimating equations (GEE), with participant as the clustering variable and an exchangeable working correlation structure. Continuous outcomes were modelled using a Gaussian distribution and identity link, whereas central versus eccentric PRL location was analysed using a binomial distribution and logit link. For the primary analysis, AMD subtypes were combined. A secondary model included Stargardt disease, neovascular AMD, and non-neovascular AMD as separate diagnostic groups. BCEA63 and BCEA95 were log-transformed before inferential analysis because of their right-skewed distributions.

The association between high- and low-contrast visual acuity and the relationships between PRL eccentricity and eye-level visual or fixation outcomes were also examined using GEE. Participant-level associations of mean PRL eccentricity with reading speed and DADV score were examined using linear regression models adjusted for diagnostic group and heteroscedasticity-robust standard errors. Mean PRL eccentricity was calculated from both evaluable eyes; when only one eye was evaluable, the value from that eye was used. Directional PRL categories were summarised descriptively because of the small number of observations in several categories. Only measurements obtained from the New Expert Exam were included in the analyses; the preliminary Fast examination was used exclusively for.

Missing data were not imputed. Associations between PRL eccentricity and the visual and functional outcomes reported in Table 4 were adjusted for multiple testing using the Benjamini–Hochberg false discovery rate procedure. All tests were two-sided, statistical significance was set at  $p < 0.05$ , and effect estimates were reported with 95% confidence intervals.

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 32.0 (IBM Corp., Armonk, NY, USA).

### **Ethical considerations**

The study protocol complied with the principles of the Declaration of Helsinki and was approved by the Clinical Research Ethics Committee of Hospital Clínico San Carlos, Madrid, Spain, on 14 February 2025 (Protocol No. 25/698-IC\_P\_CE). Before any study-

specific assessment, all participants received information about the nature and procedures of the study and provided written informed consent.

## Results

### Participant characteristics

A total of 43 participants were included: 14 with Stargardt disease and 29 with age-related macular degeneration (AMD). The overall mean age was  $63.37 \pm 18.63$  years. Participants with Stargardt disease were significantly younger than those with AMD ( $41.43 \pm 14.72$  vs  $74.00 \pm 7.94$  years, respectively;  $p < 0.0001$ ). The mean age at diagnosis was  $23.3 \pm 10.4$  years in the Stargardt group and  $66.9 \pm 9.3$  years in the AMD group.

Women accounted for 57.1% of participants with Stargardt disease and 44.8% of those with AMD, with no significant difference in sex distribution between groups ( $p = 0.449$ ). Of the 86 potentially eligible eyes, 85 were included in the eye-level analyses: 28 eyes with Stargardt disease, 18 with neovascular AMD, and 39 with non-neovascular AMD. One eye was excluded because it had no measurable vision and fixation and visual function could therefore not be assessed.

### Visual function at participant level

Near visual acuity was poorer in participants with Stargardt disease than in those with AMD ( $1.01 \pm 0.49$  vs  $0.63 \pm 0.37$  logMAR, respectively;  $p = 0.0081$ ). Reading speed was lower in the Stargardt group than in the AMD group, with median values of 33.5 words/min (IQR, 21.5–56.8) and 56.0 words/min (IQR, 40.0–83.0), respectively ( $p = 0.046$ ). Similarly, the mean DADV score was lower in participants with Stargardt disease ( $51.98 \pm 28.55$ ) than in those with AMD ( $60.54 \pm 19.61$ ), without a significant between-group difference ( $p = 0.2562$ ).

### Eye-level visual and fixation characteristics

High- and low-contrast visual acuity differed significantly across the three diagnostic groups, with the highest mean logMAR values observed in Stargardt disease. PRL eccentricity also differed significantly between groups and was greatest in Stargardt disease. No significant differences were found in low-contrast deficit or in the fixation stability measures P1, P2, BCEA63, and BCEA95. Eye-level visual and fixation characteristics are summarised in Table 1.

**Table 1** Eye-level visual and fixation characteristics according to diagnostic group

| Variable                       | Stargardt disease<br>(n = 28 eyes) | Neovascular AMD (n = 18 eyes) | Non-neovascular AMD<br>(n = 39 eyes) | Overall<br>p value |
|--------------------------------|------------------------------------|-------------------------------|--------------------------------------|--------------------|
| High-contrast VA,<br>logMAR    | $0.85 \pm 0.35$                    | $0.53 \pm 0.57$               | $0.59 \pm 0.42$                      | <b>0.026</b>       |
| 10% low-contrast<br>VA, logMAR | $1.14 \pm 0.32$                    | $0.86 \pm 0.63^a$             | $0.87 \pm 0.41$                      | <b>0.021</b>       |

| Variable                        | Stargardt disease<br>(n = 28 eyes) | Neovascular AMD (n = 18 eyes) | Non-neovascular AMD<br>(n = 39 eyes) | Overall<br>p value |
|---------------------------------|------------------------------------|-------------------------------|--------------------------------------|--------------------|
| Low-contrast deficit,<br>logMAR | 0.28 ± 0.21                        | 0.35 ± 0.23 <sup>a</sup>      | 0.28 ± 0.20                          | 0.534              |
| P1, %                           | 41.39 ± 33.13                      | 50.11 ± 31.73                 | 40.72 ± 25.75                        | 0.579              |
| P2, %                           | 69.57 ± 26.07                      | 75.33 ± 24.52                 | 72.77 ± 24.57                        | 0.788              |
| BCEA63, deg <sup>2</sup>        | 12.42 ± 11.93                      | 10.63 ± 12.72                 | 12.08 ± 13.98                        | 0.721              |
| BCEA95, deg <sup>2</sup>        | 37.23 ± 35.75                      | 31.79 ± 38.11                 | 36.16 ± 41.87                        | 0.723              |
| PRL eccentricity,<br>deg        | 7.20 (4.19–10.32)                  | 2.64 (0.63–6.02)              | 3.35 (2.03–5.12)                     | <b>0.035</b>       |

*Continuous variables are presented as mean ± standard deviation or median (IQR), as appropriate. PRL eccentricity is presented as median (IQR) because of its non-normal distribution. Overall comparisons were performed using generalized estimating equations with an exchangeable working correlation structure to account for the inclusion of both eyes from the same participant. BCEA63 and BCEA95 were log-transformed for inferential analyses because of their right-skewed distributions. Overall p values are unadjusted and should be interpreted as secondary analyses. No multiplicity-adjusted pairwise comparisons are presented. AMD, age-related macular degeneration; VA, visual acuity; PRL, preferred retinal locus; BCEA, bivariate contour ellipse area.*

<sup>a</sup>Low-contrast visual acuity and low-contrast deficit were available for 16 of the 18 eyes with neovascular AMD.

### Relationship between high- and low-contrast visual acuity

High- and low-contrast visual acuity were strongly associated across all diagnostic groups, and this relationship remained significant after accounting for the inclusion of both eyes from the same participant ( $p < 0.001$ ). Mean low-contrast visual acuity was poorer than high-contrast visual acuity in all three diagnostic groups, with a mean deficit exceeding two ETDRS lines. The relationship between both measures is shown in Figure 1.

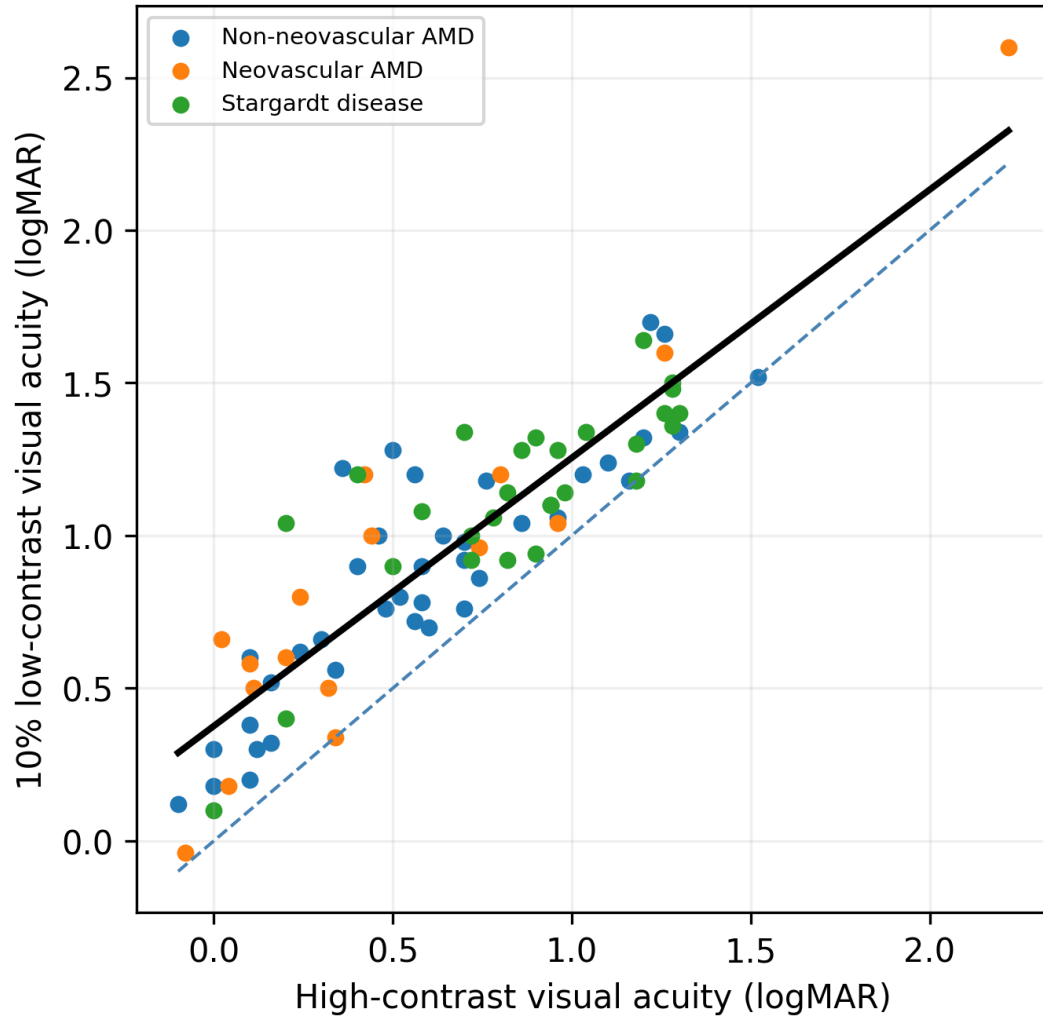


**Fig. 1** Relationship between high- and low-contrast visual acuity according to diagnostic group. Points are colour-coded by diagnosis. The solid line represents the overall regression, and the dashed line indicates equality between high- and low-contrast visual acuity measurements.

### Preferred retinal locus location

Eccentric fixation was observed in 22 of 28 eyes with Stargardt disease (78.6%) and in 22 of 57 eyes with AMD (38.6%). In the primary GEE analysis, eyes with Stargardt disease had higher odds of presenting an eccentric PRL than eyes with AMD considered as a single diagnostic group (OR = 5.91; 95% CI, 1.62–21.62;  $p = 0.007$ ).

In the secondary analysis separating AMD subtypes, eccentric fixation was observed in 7 of 18 eyes with neovascular AMD (38.9%) and in 15 of 39 eyes with non-neovascular AMD (38.5%). The overall distribution of central and eccentric PRL differed significantly across the three diagnostic groups ( $p = 0.027$ ).

Among eyes with Stargardt disease, the most frequent eccentric PRL location was superior, followed by inferior and nasal locations. In neovascular AMD, eccentric PRLs were predominantly located superiorly, whereas non-neovascular AMD showed a more heterogeneous distribution, including superior, nasal, and temporal locations. The complete distribution is shown in Table 2.

**Table 2** Distribution of preferred retinal locus location by diagnostic group and AMD subtype

| PRL location                           | Stargardt disease<br>(n = 28 eyes) | Neovascular AMD (n = 18 eyes) | Non-neovascular AMD<br>(n = 39 eyes) | Overall <i>p</i><br>value |
|----------------------------------------|------------------------------------|-------------------------------|--------------------------------------|---------------------------|
| Central                                | 6 (21.4%)                          | 11 (61.1%)                    | 24 (61.5%)                           |                           |
| Superior                               | 9 (32.1%)                          | 6 (33.3%)                     | 4 (10.3%)                            |                           |
| Inferior                               | 6 (21.4%)                          | 1 (5.6%)                      | 0 (0.0%)                             |                           |
| Nasal                                  | 5 (17.9%)                          | 0 (0.0%)                      | 6 (15.4%)                            |                           |
| Temporal                               | 2 (7.1%)                           | 0 (0.0%)                      | 5 (12.8%)                            |                           |
| <b>Eccentric PRL,<br/>any location</b> | <b>22 (78.6%)</b>                  | <b>7 (38.9%)</b>              | <b>15 (38.5%)</b>                    | <b>0.027</b>              |

*Data are presented as number of eyes and percentage within each diagnostic group. The overall comparison of central versus eccentric fixation was performed using generalized estimating equations with a binomial distribution and exchangeable working correlation structure to account for the inclusion of both eyes from the same participant. Directional PRL categories are presented descriptively because of the small number of observations in several categories. AMD, age-related macular degeneration; PRL, preferred retinal locus.*

### Central fixation despite reduced visual acuity

Among the 41 eyes classified as having a central PRL, 12 had high-contrast visual acuity worse than 0.4 logMAR. This pattern was observed in 3 of 28 Stargardt eyes (10.7%), 1 of 18 neovascular AMD eyes (5.6%), and 8 of 39 non-neovascular AMD eyes (20.5%). Overall, it was present in 12 of the 85 evaluable eyes (14.1%).

When the analysis was restricted to eyes with central fixation, reduced high-contrast visual acuity was present in 3 of 6 Stargardt eyes (50.0%), 1 of 11 neovascular AMD eyes (9.1%), and 8 of 24 non-neovascular AMD eyes (33.3%). These findings identify a subgroup of eyes in which fixation remained close to the former foveal location despite impaired spatial resolution. The distribution of this exploratory phenotype is summarised in Table 3.

**Table 3** Central preferred retinal locus according to high-contrast visual acuity

| Central PRL phenotype                         | Stargardt disease (n = 28 eyes) | Neovascular AMD (n = 18 eyes) | Non-neovascular AMD (n = 39 eyes) | Total (n = 85 eyes) |
|-----------------------------------------------|---------------------------------|-------------------------------|-----------------------------------|---------------------|
| Central PRL, all eyes                         | 6 (21.4%)                       | 11 (61.1%)                    | 24 (61.5%)                        | 41 (48.2%)          |
| Central PRL with VA $\leq 0.4$ logMAR         | 3 (10.7%)                       | 10 (55.6%)                    | 16 (41.0%)                        | 29 (34.1%)          |
| Central PRL with VA $> 0.4$ logMAR            | 3 (10.7%)                       | 1 (5.6%)                      | 8 (20.5%)                         | 12 (14.1%)          |
| VA $> 0.4$ logMAR among eyes with central PRL | 3/6 (50.0%)                     | 1/11 (9.1%)                   | 8/24 (33.3%)                      | 12/41 (29.3%)       |

*Data are presented as number of eyes and percentage of all eyes within each diagnostic group, except for the final row, in which percentages were calculated using only eyes with a central PRL as the denominator. Central fixation was defined as a PRL located within the central 4° area. The combination of central fixation and high-contrast visual acuity worse than 0.4 logMAR was considered an exploratory operational phenotype and not a direct measure of neuronal plasticity or neuroadaptation. AMD, age-related macular degeneration; PRL, preferred retinal locus; VA, visual acuity.*

### Topographic distribution of the preferred retinal locus

The spatial distribution of the PRL relative to the former foveal location is shown separately for right and left eyes in Figure 2. In both right- and left-eye plots, Stargardt disease showed a broader and more eccentric PRL distribution, with a predominance of superior locations and additional inferior and nasal PRLs. In contrast, PRLs in both AMD subgroups were more frequently concentrated within or close to the central 4° area. In neovascular AMD, eccentric PRLs were predominantly located superiorly, whereas non-neovascular AMD showed a more heterogeneous distribution, including nasal and temporal locations. The greater spatial displacement observed in Stargardt disease was consistent with the higher mean PRL eccentricity reported in Table 1.

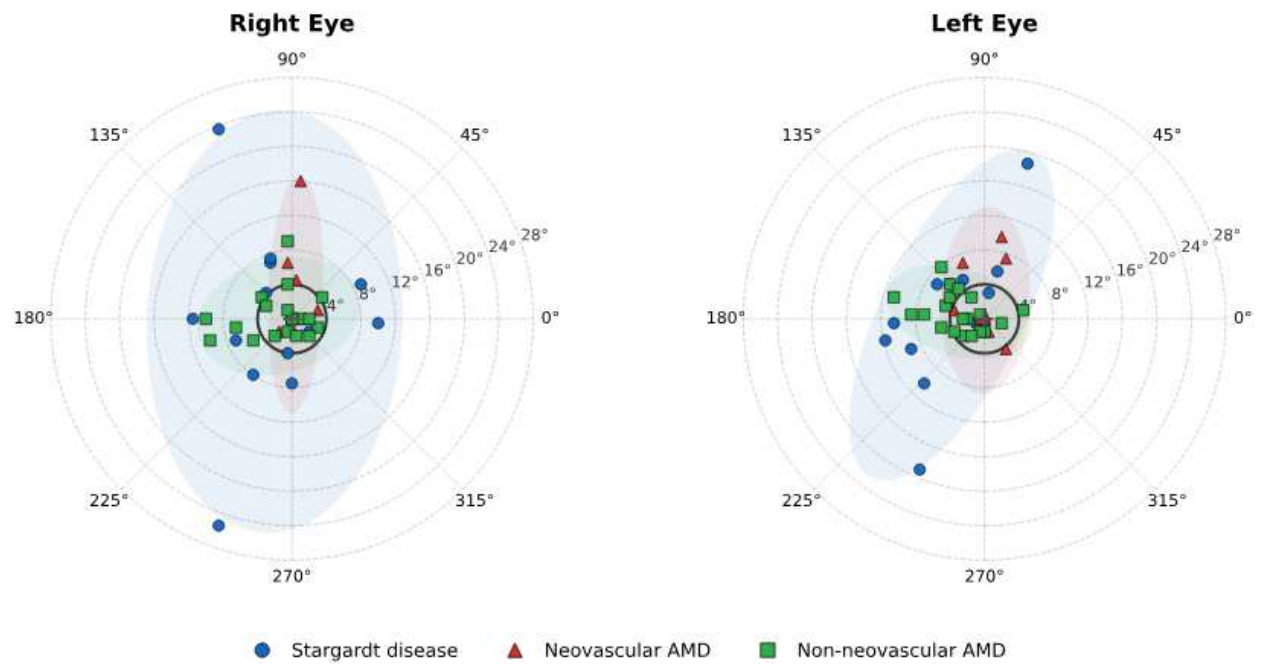


**Fig. 2** Topographic distribution of the preferred retinal locus (PRL) in right and left eyes according to diagnostic group. Each marker represents one eye, and the origin indicates the estimated former foveal location. The solid black circle indicates the 4° eccentricity boundary, and dashed concentric circles indicate 4° intervals up to 28°. Shaded areas represent descriptive 95% covariance ellipses calculated separately for each diagnostic group and eye.

### Relationship between PRL eccentricity and visual and fixation outcomes

Greater PRL eccentricity was associated with poorer visual acuity and reduced fixation stability. After adjustment for diagnostic group, each 1° increase in dPRL was associated with an increase of 0.047 logMAR in high-contrast visual acuity and 0.036 logMAR in 10% low-contrast visual acuity. Greater eccentricity was also associated with lower P1 and P2 values and with larger BCEA63 and BCEA95 values, indicating a less concentrated fixation pattern.

At participant level, greater mean PRL eccentricity was associated with lower reading speed and lower DADV scores. These associations remained statistically significant after adjustment for diagnosis and after false discovery rate correction. The complete results are presented in Table 4.

**Table 4** Associations between preferred retinal locus eccentricity and visual and functional outcomes

| Outcome                     | Analysis level | n  | $\beta$ per-1° increase in dPRL | 95% CI         | p value | FDR-adjusted p value |
|-----------------------------|----------------|----|---------------------------------|----------------|---------|----------------------|
| High-contrast VA, logMAR    | Eye            | 85 | 0.047                           | 0.030 to 0.064 | <0.001  | <0.001               |
| 10% low-contrast VA, logMAR | Eye            | 83 | 0.036                           | 0.016 to 0.056 | <0.001  | 0.001                |

| Outcome                  | Analysis level | n  | $\beta$ per-1° increase in dPRL | 95% CI         | p value | FDR-adjusted p value |
|--------------------------|----------------|----|---------------------------------|----------------|---------|----------------------|
| P1, %                    | Eye            | 85 | -2.54                           | -3.80 to -1.28 | <0.001  | <0.001               |
| P2, %                    | Eye            | 85 | -1.69                           | -2.50 to -0.89 | <0.001  | <0.001               |
| Log-transformed BCEA63   | Eye            | 85 | 0.079                           | 0.027 to 0.130 | 0.003   | 0.003                |
| Log-transformed BCEA95   | Eye            | 85 | 0.078                           | 0.027 to 0.129 | 0.003   | 0.003                |
| Reading speed, words/min | Participant    | 43 | -3.70                           | -6.10 to -1.31 | 0.002   | 0.003                |
| DADV score               | Participant    | 43 | -2.09                           | -3.69 to -0.49 | 0.010   | 0.010                |

**Table note.** Eye-level associations were analysed using GEE adjusted for diagnostic group and clustered by participant. Participant-level associations were analysed using linear regression adjusted for diagnostic group with robust standard errors. BCEA63 and BCEA95 were log-transformed.  $\beta$  represents the expected change per 1° increase in PRL eccentricity. P values were adjusted using the Benjamini–Hochberg false discovery rate procedure.

AMD, age-related macular degeneration; BCEA, bivariate contour ellipse area; DADV, Daily Activities Dependence on Vision; PRL, preferred retinal locus; VA, visual acuity.

### Diagnosis-specific relationship between PRL eccentricity and high-contrast visual acuity

The relationship between PRL eccentricity and high-contrast visual acuity is shown in Figure 3. Greater PRL eccentricity was associated with poorer high-contrast visual acuity in the GEE model adjusted for diagnostic group, as reported in Table 4. Descriptive within-group correlations were strongest in Stargardt disease ( $r = 0.717$ ,  $p < 0.001$ ), followed by neovascular AMD ( $r = 0.582$ ,  $p = 0.011$ ). In non-neovascular AMD, the association was weaker and did not reach statistical significance ( $r = 0.296$ ,  $p = 0.067$ ). These within-group correlations were descriptive and did not account for inter-eye correlation.

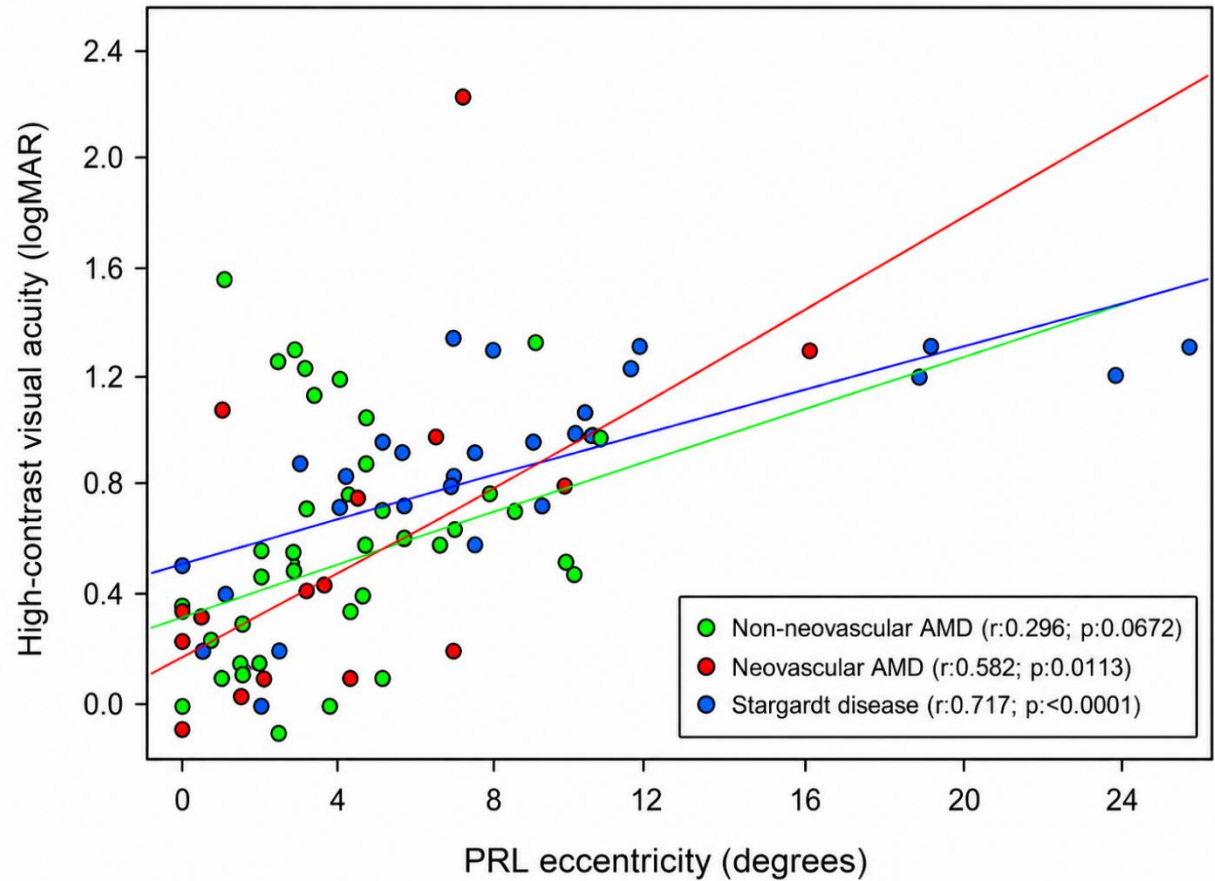


**Fig. 3** Relationship between preferred retinal locus eccentricity and high-contrast visual acuity according to diagnostic group. Lines represent diagnosis-specific linear fits.

## Discussion

The main finding of this study was that the distribution of central and eccentric PRL locations differed substantially between Stargardt disease and AMD. Eyes with Stargardt disease were more likely to present an eccentric PRL and showed greater PRL eccentricity, whereas central fixation was more frequent in both AMD subgroups. Despite these topographic differences, conventional fixation stability measures did not differ significantly between diagnostic groups.

Greater PRL eccentricity was nevertheless associated with poorer high- and low-contrast visual acuity, lower P1 and P2 values, larger BCEA measures, slower reading, and greater vision-related functional dependence. These findings suggest that PRL location, eccentricity, and stability provide complementary rather than interchangeable information about fixation behaviour. The absence of between-group differences in conventional fixation stability measures, despite marked differences in PRL location and eccentricity, indicates that these variables describe distinct dimensions of fixation behaviour.

The higher frequency of eccentric fixation in Stargardt disease is consistent with previous reports describing predominantly superior or extrafoveal fixation in this condition [12]. In contrast, PRL location in AMD has been reported to be more variable, with frequent superior and nasal locations but considerable interindividual heterogeneity [1, 13]. Earlier work involving large low-vision populations also showed that PRL location varies according to the position and extent of the macular scotoma [19]. The present comparison extends these observations by showing that the difference was not limited to directional distribution: eyes with Stargardt disease had almost six-fold higher odds of eccentric fixation than eyes with AMD when both AMD subtypes were considered together. However, this finding should not be interpreted as direct evidence that younger age at disease onset produces greater neural plasticity. Stargardt disease and AMD also differ in lesion morphology, progression, symmetry, disease duration, and residual foveal function, all of which may influence the retinal location adopted for fixation.

The PRL should be interpreted as a task-dependent and dynamic retinal locus. The retinal area identified during steady monocular fixation may not coincide with that used during reading, pointing, visual search, or natural viewing [20, 21], and longitudinal observations have shown that fixation location may evolve during the months following central visual loss [9]. Its development may be influenced by lesion progression, residual foveal function, retinal sensitivity, and previous oculomotor experience. The natural PRL may therefore represent a functional compromise rather than the selection of an anatomically optimal retinal location [3, 6].

Greater PRL eccentricity was associated with poorer visual performance even after adjustment for diagnostic group. Each additional degree of eccentricity was accompanied by poorer high- and low-contrast visual acuity, reduced concentration of fixation points within the central 2° and 4° areas, and larger BCEA values. This relationship is physiologically plausible because spatial resolution decreases with retinal eccentricity. Nevertheless, PRL selection is unlikely to be determined solely by the retinal location providing the best acuity. Bernard and Chung found that visual acuity at the spontaneously adopted PRL was not necessarily superior to that measured at other retinal locations surrounding the scotoma [22]. Structural preservation, retinal sensitivity, lesion borders, oculomotor history, and task requirements may therefore contribute jointly to PRL selection.

The associations with reading speed and DADV score broaden the clinical relevance of PRL eccentricity. Greater mean dPRL was associated with slower reading and greater dependence in visually demanding daily activities, even after adjustment for diagnosis. Fixation stability has previously been associated with reading performance in patients with recently developed macular disease and in advanced AMD [1, 7, 8]. PRL direction may also influence reading characteristics, although the magnitude of this effect varies across studies and languages [23]. The present findings indicate that the distance between the PRL and the former fovea may contribute to functional performance in addition to fixation stability.

These participant-level associations should nevertheless be interpreted cautiously. Reading and DADV were assessed binocularly, whereas PRL measurements were obtained monocularly and summarised across eyes. Binocular function in macular disease

depends on interocular asymmetry, binocular summation or inhibition, ocular dominance, and the correspondence between the retinal loci used by the two eyes. A recent review emphasized that monocular fixation measurements cannot fully represent binocular oculomotor control or functional vision [24]. This distinction may partly explain why patients with similar monocular PRL characteristics can show different levels of reading performance or daily visual dependence.

A clinically relevant subgroup retained fixation within the central 4° area despite high-contrast visual acuity worse than 0.4 logMAR. This exploratory pattern was present in 14.1% of all evaluable eyes and in 29.3% of eyes with a central PRL. Previous studies have shown that some eyes with macular disease continue to use the former foveal region, use multiple loci, or fail to develop a clearly identifiable natural PRL [6, 19]. The present operational phenotype may therefore help identify eyes in which central fixation persists despite limited spatial resolution. However, it should not be interpreted as proof of absent neuronal adaptation or cortical reorganisation. Structural imaging and pointwise retinal sensitivity would be required to determine whether fixation occurred within functioning residual retina, at the lesion border, or within an absolute scotoma.

Low-contrast visual acuity was poorer than high-contrast visual acuity in all diagnostic groups, with a mean loss exceeding two ETDRS lines. Although the magnitude of the low-contrast deficit did not differ significantly between groups, its presence across Stargardt disease and both AMD subtypes indicates that conventional high-contrast acuity does not fully capture functional impairment. Contrast-related measures have shown clinically relevant associations with macular morphology and vision-related functional dependence in AMD [14, 15]. Low-contrast and low-luminance tests may also identify deficits that are less evident under conventional high-contrast conditions [16, 17]. The strong correlation between both acuity measures does not make low-contrast assessment redundant; rather, it quantifies the additional visual loss experienced under less favourable conditions.

The findings may have implications for visual rehabilitation. Microperimetric biofeedback aims to improve fixation stability or train a selected retinal locus with favourable sensitivity and anatomical characteristics. Early studies in AMD reported improvements in fixation behaviour and visual performance after microperimetric training [25]. Subsequent studies in central scotoma populations also described improvements in fixation stability, visual acuity, retinal sensitivity, and reading performance [26, 27]. More recent interventions using MP-3 microperimetry have reported gains in visual acuity, reading speed, fixation stability, and quality of life [28]. A systematic review concluded that biofeedback is promising but emphasized considerable heterogeneity in patient selection, training duration, outcome measures, and methodological quality [29]. Consequently, the current cross-sectional findings cannot establish that patients with a central or highly eccentric PRL would necessarily benefit from relocation training.

Prism-induced image relocation may represent an additional rehabilitation strategy. Although prisms can produce a measurable displacement of the PRL in some patients with central vision loss, evidence of sustained improvement in reading or everyday visual function remains limited [30]. Prism prescription should therefore be individualised and

integrated into a broader low-vision rehabilitation programme rather than based solely on PRL topography.

Several limitations should be acknowledged. First, the sample was relatively small, particularly after separating neovascular and non-neovascular AMD, limiting detailed modelling of directional PRL categories. Second, the marked age difference between Stargardt disease and AMD is intrinsic to the diseases but prevents age from being separated cleanly from diagnosis, disease duration, progression, and lesion morphology. Third, the cross-sectional design does not establish when the PRL developed or whether its location remained stable over time. Although participants completed a preliminary Fast examination before the full threshold test, previous evidence indicates that a brief examination may not completely eliminate the microperimetric learning effect [31]. Fourth, structural lesion characteristics and pointwise retinal sensitivity were not incorporated into the analyses, preventing assessment of whether the PRL occupied the best preserved retinal area. Fifth, reading and DADV were binocular participant-level outcomes, whereas fixation variables were obtained monocularly and averaged across eyes. Finally, although GEE accounted for the inclusion of both eyes, the modest number of participants warrants caution when interpreting secondary and exploratory associations.

## Conclusions

Stargardt disease and age-related macular degeneration showed distinct patterns of preferred retinal locus location. Eccentric fixation was substantially more frequent and more distant from the former fovea in Stargardt disease, whereas central fixation predominated in both AMD subtypes. Greater PRL eccentricity was associated with poorer high- and low-contrast visual acuity, reduced fixation stability, slower reading, and greater vision-related functional limitation. These findings support a multidimensional assessment of fixation that considers PRL location, eccentricity, stability, and functional performance. Longitudinal studies integrating microperimetry, retinal imaging, and binocular functional measures are needed to determine the clinical significance of these fixation patterns and their potential relevance for targeted visual rehabilitatio

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### **Competing interests**

The authors declare no competing interests.

### **Author contributions**

Conceptualization: Juan E. Cedrún-Sánchez and F. Javier Povedano-Montero; Methodology: Juan E. Cedrún-Sánchez, Ricardo Bernárdez-Vilaboa and F. Javier Povedano-Montero; Investigation: Juan E. Cedrún-Sánchez, Carla Otero-Currás, Ainhoa M. Armas-González and Amina Benserghine-Karmossi; Data curation: Juan E. Cedrún-Sánchez, Carla Otero-Currás and F. Javier Povedano-Montero; Formal analysis: F. Javier Povedano-Montero; Visualization: Juan E. Cedrún-Sánchez and F. Javier Povedano-Montero; Writing—original draft preparation: Juan E. Cedrún-Sánchez and F. Javier Povedano-Montero; Writing—review and editing: Carla Otero-Currás, Ainhoa M. Armas-González, Amina Benserghine-Karmossi, Ricardo Bernárdez-Vilaboa and F. Javier Povedano-Montero; Supervision: Ricardo Bernárdez-Vilaboa and F. Javier Povedano-Montero; Project administration: F. Javier Povedano-Montero. All authors read and approved the final manuscript.

### **Ethics approval**

The study was approved by the Clinical Research Ethics Committee of Hospital Clínico San Carlos on 8 October 2025 (Protocol No. 25/698-IC\_P\_CE).

### **Consent to participate**

Written informed consent was obtained from all participants.

**Data availability**

The data supporting the findings of this study are available from the corresponding author upon reasonable request, subject to ethical and data-protection restrictions.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

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