



Fixation Stability and Preferred Retinal Locus in Advanced Age-Related Macular Degeneration

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Abstract

Objectives: To evaluate fixation stability and characteristics of the preferred retinal locus (PRL) in patients with advanced age-related macular degeneration (AMD).

Materials and Methods: Sixty-three eyes of 63 patients with AMD who presented to the low vision unit were included in this prospective study. Sociodemographic characteristics, eye examination findings, and reading performance results with the Minnesota Low Vision Reading test were evaluated. Microperimetry was used to evaluate fixation stability and PRL characteristics.

Results: There was unstable fixation in 68% of the eyes, relative stable fixation in 27%, and stable fixation in 5%. The mean PRL-foveal distance was $5.15^\circ \pm 3.31^\circ$ (range 0.75° - 14.2°). PRL-foveal distance was greater in cases with unstable fixation than cases with stable fixation ($p=0.023$). Distance of the PRL from the lesion margin was not associated with absolute scotoma size or fixation stability ($p=0.315$, $p=0.095$, respectively). PRLs were most frequently located in the nasal quadrant (31%), followed by the superior quadrant (26%) of the retina. There was no significant relationship between PRL location and fixation stability ($p=0.088$). Fixation stability was significantly associated with reading speed ($p=0.003$).

Conclusion: In advanced AMD, PRL-foveal distance is an important factor in fixation stability. Knowing the factors that affect fixation stability may be important in determining low vision rehabilitation strategies for these patients because of the strong association between fixation stability and reading speed.

Keywords: Low vision rehabilitation, fixation stability, microperimetry, preferred retinal locus, age-related macular degeneration

Introduction

In age-related macular degeneration (AMD), loss of retinal sensitivity at the macula causes central scotoma, thereby reducing visual acuity and fixation stability and leading to loss of central fixation. This causes difficulty in the performance of daily activities such as reading.^{1,2} Oculomotor adaptation results in the formation of well-defined “preferred retinal loci” (PRLs) in the healthier regions of the retina that focus on visual targets.^{3,4}

Microperimetry devices are currently used to evaluate the properties and stability of PRLs.⁵ According to the literature, 77% to 100% of patients with central scotoma develop a PRL,^{1,6,7,8} which is most commonly located in the nasal and superior retinal quadrants in AMD,^{7,9} and fixation stability was shown to be associated with PRL to fovea and lesion margin distances, lesion size, and distance visual acuity.^{1,6,9,10} Studies have also demonstrated a strong correlation between fixation stability and reading speed.^{11,12,13,14,15,16,17}

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As reading speed is highly affected by fixation stability, interventions that increase fixation stability are prioritized in modern low vision rehabilitation. Microperimetric PRL training with acoustic and visual stimuli (trained retinal locus; TRL) can increase fixation stability and improve reading speed.^{18,19,20} Sahli et al.¹⁹ reported an increase in reading speed and quality of life with TRL training performed with microperimetric biofeedback signals in patients with central scotoma, most of whom had AMD. Therefore, evaluating fixation stability and PRL characteristics is essential in central scotoma.

This study aimed to identify factors associated with fixation stability in advanced AMD and enable our results to be applied in visual rehabilitation to increase reading speed and quality of life. There are few studies in the literature that have analyzed PRL characteristics microperimetrically in such detail, including fixation stability and reading speed, and these studies must also be conducted in languages with different reading directions. Knowing the factors affecting PRL characteristics and stability to increase fixation stability during PRL training with microperimetric acoustic and visual biofeedback signals will guide treatment planning, implementation, and follow-up.

Materials and Methods

This prospective, cross-sectional study was approved by the local clinical research ethics committee (decision no: 26.03.2018/06-363-18). All study procedures were carried out in accordance with the Declaration of Helsinki and informed consent forms were obtained from all participants.

The 63 better-seeing eyes of 63 consecutive AMD patients presenting to the vision research and low vision rehabilitation unit between August 2018 and September 2019 were included in the study. Patients who met the following criteria were included in the study: had best corrected visual acuity (BCVA) of 0.5-1.3 logMAR (Snellen 20/400-20/60) in the better-seeing eye, had atrophic AMD or stable exudative AMD not treated with intravitreal injection in the last 6 months, were over 55 years of age, were a native speaker of Turkish, and for the reading performance test, had completed at least primary school education, had the mental capacity to understand the MNREAD test rules, perform the test, and had no neurological or mental illness that would interfere with reading. Patients who declined to participate, were illiterate, had previously received low vision rehabilitation or TRL training, or were using low vision aids were excluded from the study. Patients with vision-impairing ocular pathologies other than AMD, such as diabetic retinopathy, glaucoma, optic atrophy, and hereditary retinal diseases, and those with systemic diseases that may affect vision, such as diabetes mellitus, were also excluded.

After completing the patients' sociodemographic forms, all patients underwent a detailed eye examination including BCVA assessment, anterior and posterior segment examination, low vision evaluation, MNREAD test, and contrast sensitivity (CS) test. Macular lesion size and vision-related quality of life scores were determined. The patients were asked how long they had

not been able to read because of their eye problem and this time was recorded as the "reading interruption" in the data form. This information was obtained from patients and their relatives. The patients' BCVA was assessed using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart as logMAR, and reading acuity was tested with MNREAD-TR and recorded in M units. CSV-1000 was used for the CS test. The classical CSV-1000 test is performed at varying spatial frequencies (3, 6, 12, and 18 cycles per degree [cpd]) at a distance of 2.5 meters.²¹ However, since our study group was low vision, they had difficulty at the standard test distance and the test distance and cpd values were reduced by half. The size of the macular lesion was calculated by the fundus autofluorescence Image Finder program and recorded as mm². Visual quality of life was assessed using the NEI-VFQ-25-TR, which was validated in Turkish by Toprak et al.²² The questionnaire was administered by the same technician (B.S.) and scores were calculated by the same ophthalmologist (D.A.).

Reading performance was assessed using MNREAD-TR charts, which were validated in Turkish by Idil et al.²³ The charts test near visual acuity as logMAR and M (1M=0.4 logMAR) and include 19 sentences, of which the largest is 8M (1.3 logMAR) and the smallest is 0.12 M (-0.5 logMAR). Four parameters are evaluated: reading acuity (RA), critical print size (CPS), maximum reading speed (MRS), and the reading accessibility index (ACC). RA is the smallest print size that the person can read without significant error, MRS is the fastest reading speed when not limited by print size, and CPS is the smallest print size that can be read at this speed. Assuming the normal MRS is 200, the average reading speed for the top 10 sentences of the MNREAD chart (the print sizes most commonly encountered in daily life) is divided by 200 to obtain ACC (normal=1.0).²⁴

MAIA microperimetry (Centervue, Padova, Italy) was used to evaluate fixation stability and PRL characteristics. Fixation stability was determined according to Fuji's clinical classification.²⁵ This classification is based on the percentage of fixation points within a 1° (P1) and 2° (P2) radius of the foveal center. The presence of 75% of fixation points within the 1-degree area (P1>75%) is regarded as stable fixation. If more than 75% of fixation points do not fall within this 1-degree area but are within the 2-degree area (P1<75% and P2>75%), it is called relatively stable fixation. Fixation is considered unstable when both P1 and P2 are below 75%. Bivariate contour ellipse area is the size (in mm²) of the elliptical area encompassing 63% (BCEA63) and 95% (BCEA95) of fixational eye movements. Retinal sensitivity is between 0 and 36 decibels. Macular integrity index (MII) is evaluates an individual's responses according to the age-matched mean value for the population. An MII value lower than 40% is considered normal, 40-60% is suspicious, and higher than 60% is regarded as abnormal. P1, P2, BCEA63, BCEA95, and retinal sensitivity are parameters that can be obtained directly from the microperimeter (Figure 1).

Information derived from the microperimetry test results was also used to investigate fixation characteristics. The grid-shaped screen image obtained from microperimetry was printed on A4 paper and the PRL location, PRL distance from the fovea,

PRL distance from the lesion edge, and absolute scotoma size were calculated. A ruler was used for measurements and values calculated in mm were converted to degrees and recorded (1 square in the grid of the microperimeter screen corresponds to 1 degree). If the location of the fovea could not be determined because of advanced AMD, an estimated location of the fovea was marked at 15.5° temporal and 1.3° inferior to the optic disc center.²⁶ To describe PRL location, the retina was divided into 4 equal quadrants centered on the fovea and PRL location was classified as superior, inferior, temporal, nasal, or central (within 4° of the foveal center) (Figure 2).⁹ All measurements were performed by a single ophthalmologist (D.A.) to avoid interobserver variability.

Statistic Analysis

The IBM SPSS Statistics version 20.0 package (IBM Corp, Armonk, NY) was used for statistical analyses. For numerical measurements, the assumption of normal distribution was tested using the Shapiro-Wilk test and comparisons of means between two groups were performed using t-test or Mann-Whitney U test as necessary. Comparisons between multiple groups were performed using one-way analysis of variance or the Kruskal-Wallis test. Bonferroni, Scheffé, and Tamhane tests were used as appropriate for pairwise comparisons between groups. In all tests, p<0.05 was accepted as significant.

Results

The study included 41 men and 22 women with a mean age of 77.49±8.56 (58-93) years. The left eyes of 36 patients (57%) and the right eyes of 27 patients (43%) were included. The mean symptom duration was 4.73±4.09 years, daily reading habit was 2.1±2.23 hours, reading interruption was 2.58±3.08 years, vision-related quality of life score was 47.5±11.4, and the near activities subscale score was 29.0±12.4.

The patients' mean distance and near visual acuities were 0.66±0.2 logMAR and 2.63±2.46 M, respectively. AMD was atrophic in 48% of the patients and exudative in 52%; lesion size ranged from 1.110 to 24.568 mm² (mean 7.162±4.671 mm²). CS test results were 10.62±9.49 dB and 4.46±3.93 dB for 1.5 cpd and 3 cpd (low spatial frequencies) and 12.3±11.2 dB and 21.0±15.1 dB for 6 cpd and 9 cpd (medium spatial frequencies), respectively. According to the MNREAD chart, mean RA was 0.86±0.34 logMAR (range, 0.12-1.80 logMAR), CPS was 1±0.35 logMAR (range, 0.32-1.90 logMAR), MRS was 70.2±37.23 words/min (wpm) (range, 19-160 wpm), and ACC was 0.27±0.21 (range, 0-0.69).

Retinal sensitivity, P1, P2, BCEA63, and BCEA95 values were obtained directly from microperimetry. Fixation stability was unstable in 43 eyes (68%), relatively stable in 17 eyes (27%), and stable in 3 eyes (5%) (Table 1). Retinal location of the PRL was nasal in 31%, superior in 19%, inferior in 16%, central in 16%, and temporal in 11% of eyes. In left eyes, the most common location was the nasal quadrant (36%), while in right eyes, the most common location was the superior quadrant (31%). The mean PRL-fovea distance was 5.15°±3.31° (range,

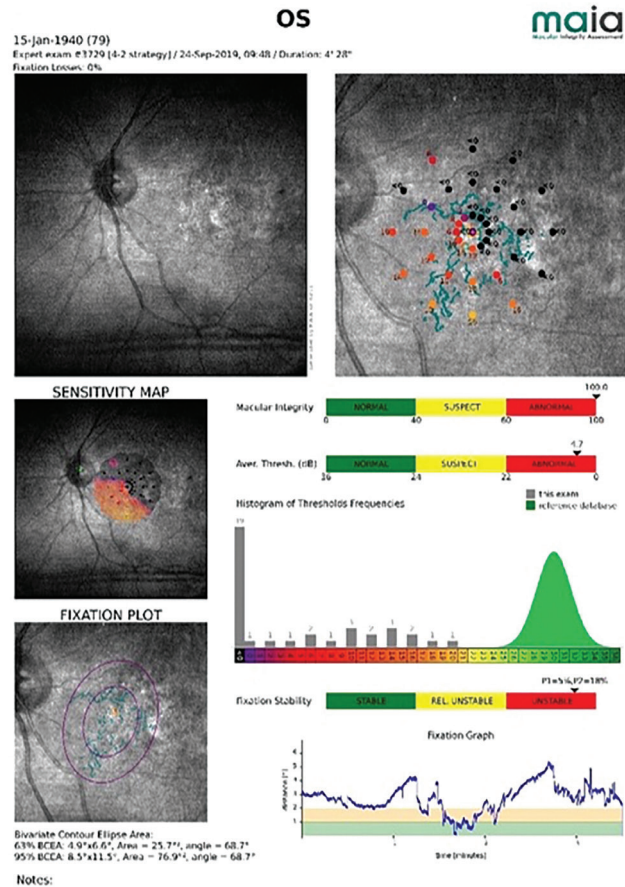


Figure 1. Example of microperimetry output for an eye with AMD
AMD: Age-related macular degeneration

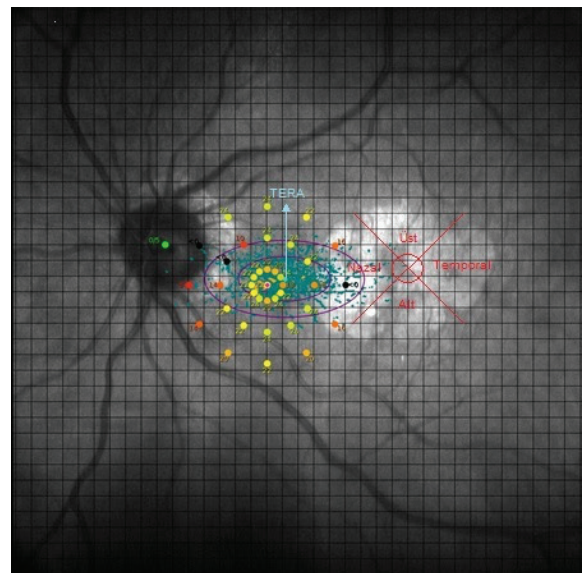


Figure 2. Division of the retina into quadrants centered on the fovea

0.75°-14.2°). The PRL was to the left of the absolute scotoma in 29% of eyes and to the right in 22% of eyes. The mean absolute scotoma size was 16°±15° (range, 0°-62°). Forty-two eyes (67%) had absolute scotoma at the fovea. The results obtained from microperimetry indirectly using special measurements are shown in Table 2.

There was no statistically significant relationship between fixation stability and distance or near visual acuity (p=0.072 and p=0.312, respectively). When the stable and relatively stable fixation groups were combined, distance visual acuity was significantly lower in eyes with unstable fixation compared to those with stable or relatively stable fixation (p=0.041). Reading

speed was 148.7±12.7 wpm in the stable fixation group, 80.9±41.1 wpm in the relatively stable group, and 60.5±28.5 wpm in the unstable fixation group. There was a statistically significant relationship between reading speed and fixation stability (p=0.003). In the unstable fixation group, CS values at low (3 cpd) and medium (6 cpd and 9 cpd) spatial frequencies were lower compared to the relatively stable fixation group (p=0.019, p=0.038, and p=0.011, respectively).

There was no significant relationship between fixation stability and the retinal location of the PRL and whether this location was in the right or left eye (p=0.088 and p=0.199, respectively). Fixation stability also showed no statistical association with absolute scotoma size (p=0.095), PRL location relative to the absolute scotoma (p=0.05), or distance of the PRL to the lesion margin (p=0.315). However, distance of the PRL to the fovea was significantly associated with fixation stability (p=0.023) (Table 3).

The PRL was significantly farther from the fovea in eyes with unstable fixation than in eyes with stable fixation (p=0.023). The relationship between PRL-fovea distance and fixation stability is shown in Figure 3.

Discussion

PRLs that develop through adaptive mechanisms for fixation in advanced AMD are generally extrafoveal and unstable, which are critical factors in reducing reading ability. It has been reported that fixation stability is strongly associated with reading speed,¹¹⁻¹⁷ and is affected by distance visual acuity, lesion size, and PRL distance to the fovea and lesion margin.^{1,6,9,10} In our study, we observed that PRLs were extrafoveal in 85% and unstable in 68% of eyes with advanced AMD, fixation stability was affected by PRL-fovea distance, and there was a strong association between fixation stability and reading speed.

Studies have shown that the PRL, which replaces the nonfunctioning fovea in eyes with central scotoma, is less stable as its distance from the fovea increases.^{6,9,10,27} The mean PRL-fovea distance in AMD was reported to be 6.69°±7.4° by Erbezci and Oztürk⁹ and 6.25°±2.38° by Sahli et al.,¹⁹ while Fujita et al.²⁸ reported distances between 5° and 11°. In our study, the mean PRL-fovea distance was 5.15°±3.31° (range, 0.75°-14.2°). This value was determined to be 5.64°±3.41° in the unstable fixation group and 2.04°±0.56° in the stable fixation group, showing that the PRL-fovea distance was greater in eyes with unstable fixation compared to those with stable fixation. We attribute the effect of PRL-fovea distance on fixation stability to the fact that retinal resolution and sensitivity are highest at the fovea. Chung et al.²⁹ reported that retinal resolution decreased further from the fovea.

Various studies have demonstrated that reading speed decreases with poorer fixation stability.¹¹⁻¹⁷ In our study, reading speed was 148.7±12.7 wpm in the stable fixation group, 80.9±41.1 wpm in the relatively stable group, and 60.5±28.5 wpm in the unstable group. There was a strong statistical association between reading speed and fixation stability

		Mean ± SD
MII		99.8±1.6
Mean retinal sensitivity (dB)		10.8±6.5
P1		25.5±20.4
P2		56.2±23.4
BCEA 63		17.3±10.8
BCEA 95		51.6±32.4
		n (%)
Fixation stability	Stable	3 (5)
	Relatively stable	17 (27)
	Unstable	43 (68)

MII: Macular Integrity Index, P1: Percentage of fixation points in a 1° radius circle, P2: Percentage of fixation points in a 2° radius circle, BCEA: Bivariate contour ellipse area, SD: Standard deviation

		Mean ± SD
PRL-fovea distance (°)		5.15±3.31
PRL-lesion margin distance (°)		1.84±2.66
Absolute scotoma size (°)		16.0±15.0
		n (%)
PRL location	Nasal quadrant	19 (31)
	Superior quadrant	16 (26)
	Inferior quadrant	10 (16)
	Central	10 (16)
	Temporal quadrant	7 (11)
PRL location relative to absolute scotoma	Left of the scotoma	18 (29)
	In the scotoma	14 (22)
	No absolute scotoma	11 (17)
	Below the scotoma	9 (14)
	Right of the scotoma	7 (11)
	Above the scotoma	4 (6)
Foveal absolute scotoma	Yes	42 (67)
	No	21 (33)

PRL: Preferred retinal locus, SD: Standard deviation

Table 3. Relationship between ocular parameters and fixation stability				
Characteristic	Fixation Stability			p
	Stable	Relatively stable	Unstable	
	Mean ± SD	Mean ± SD	Mean ± SD	
Distance visual acuity (logMAR)	0.50±0.0	0.62±0.23	0.68±0.20	0.072
Near visual acuity (M)	1.2±0.35	3.04±2.98	2.57±2.3	0.312
Lesion size (mm ²)	4963.0±6268.9	6764.9±6518.4	7472.4±3694.4	0.131
Maximum reading speed (wpm)	148.7±12.7	80.9±41.1	60.5±28.5	0.003
Low-frequency CS (1.5 cpd) (dB)	10.0±5.0	15.35±13.73	11.26±10.26	0.264
Low-frequency CS (3 cpd) (dB)	10.67±4.62	30.47±19.7	17.91±11.57	0.019
Mid-frequency CS (6 cpd) (dB)	5.33±2.31	16.71±13.34	8.58±6.6	0.038
Mid-frequency CS (9 cpd) (dB)	3.33±3.18	7.06±5.8	3.51±2.39	0.011
Absolute scotoma size (°)	6.33±10.97	11.35±11.45	18.53±15.89	0.095
PRL-lesion margin distance (°)	0±0	1.52±1.24	2.08±3.03	0.315
PRL-fovea distance (°)	2.04±0.56	4.49±3.00	5.64±3.41	0.023
	n (%)	n (%)	n (%)	
Retinal location of PRL				
Inferior quadrant	1 (33)	2 (12)	7 (17)	0.088
Nasal quadrant	0 (0)	6 (35)	13 (31)	
Central	2 (67)	3 (18)	5 (12)	
Superior quadrant	0 (0)	2 (12)	14 (33)	
Temporal quadrant	0 (0)	4 (24)	3 (7)	
PRL location relative to absolute scotoma				
Right	0 (0)	3 (18)	4 (9)	0.050
Left	0 (0)	7 (41)	11 (26)	
Inside	0 (0)	0 (0)	14 (33)	
Below	1 (33)	1 (6)	7 (16)	
Above	0 (0)	2 (12)	2 (5)	
No absolute scotoma	2 (67)	4 (24)	5 (12)	

PRL: Preferred retinal locus, wpm: words per minute, CS: Contrast sensitivity, cpd: cycles per degree, dB: decibels, SD: Standard deviation

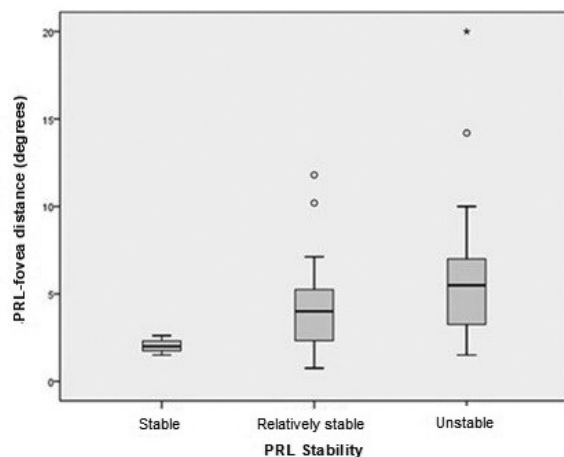


Figure 3. Relationship between fixation stability and PRL-fovea distance (°outlier, *extreme outlier)

PRL: Preferred retinal loci

($p=0.003$). Reading function requires good detail detection, which itself requires foveal and stable fixation. Giacomelli et al.¹⁷ stated that improved fixation translated to improved visual capacity. We believe that the decrease in reading speed associated with poorer fixation stability is related to this.

In the literature, single/multiple PRL development in AMD has been reported at different rates (77%-100%),^{1,6,7,8} and most are located extrafoveally. Greenstein et al.⁶ reported that all patients in their study developed a PRL, of which 73.3% were extrafoveal and 26.6% were foveal in location. In our study, we observed that 98.4% of patients developed a single PRL that was extrafoveal in 84% and foveal in 16% of the eyes. Fixation was unstable in 68%, relatively stable in 27%, and stable in 5% of the cases. We attribute the low fixation stability in our study to the patients having low vision, advanced AMD, symptom duration longer than 6 months, and mostly extrafoveal PRLs. Karaçorlu et al.³⁰ also observed no stable and central fixation in patients with symptom duration longer than 6 months.

Retinal localization of PRLs is still not fully understood, and in 25% of cases the PRL is not in a favorable location.³¹ While there are some studies suggesting that location may be relevant in terms of reading,^{7,32} others showed no relationship between PRL location and reading speed.^{2,33,34} Evidence indicates that PRLs are usually located to the left of the scotoma.^{1,2,7,9,35} However, PRLs can develop in any retinal quadrant.^{9,34,35} In AMD, the most common PRL location is the nasal quadrant, followed by the superior quadrant.^{7,9,19} Similarly, in our study, we determined that the PRL was located in the nasal retinal quadrant in 31%, superior quadrant in 26%, inferior quadrant in 16%, and temporal quadrant in 11% of eyes, while 16% of PRLs were located centrally. We detected no statistically significant relationship between PRL location and fixation stability. Similarly, Farzaneh et al.²⁷ found no significant relationship between PRL location on the retina and fixation stability in native Persian-speaking AMD patients.

Erbezci and Oztürk⁹ reported that fixation stability was associated with distance BCVA and that fixation in the affected eye became unstable with greater PRL-fovea distance, PRL to lesion margin distance, and lesion size. When we grouped the eyes in our study as stable, relatively stable, and unstable, distance BCVA was not associated with fixation stability. However, when we combined the stable and relatively stable group, a statistically significant relationship emerged. The absence of a statistical relationship initially is likely due to the small number of eyes in the stable fixation group. Similarly, in our study there was no statistically significant relationship between fixation stability and scotoma size or PRL-lesion margin distance, but we observed that scotomas were larger and PRLs further from the lesion margin in eyes with unstable fixation.

Spatial and temporal CS tests in patients with maculopathy have demonstrated moderate to strong correlation between reading speed and CS.³⁶ In our study, eyes with unstable fixation showed lower CS at low and medium spatial frequencies compared to eyes with relatively stable fixation. This may be related to the higher PRL-fovea distance in this group and the lower retinal sensitivity and resolution in this area of the retina.

Study Limitations

CS tests modified for people with low vision could not be used for our patients because they were not available in our clinic. In addition, as all participants were Turkish-speakers, studies with broader participation in different languages are needed to investigate the effect of PRL location on the retina on fixation stability.

Conclusion

In this study, we observed that fixation stability was affected by PRL distance from the fovea and was strongly associated with reading speed. Given the close relationship between fixation stability and reading speed, awareness of the factors affecting fixation stability in advanced AMD is crucial to restore reading ability in low vision rehabilitation. The results of this study may be both strategically and prognostically useful in the planning

and implementation of microperimetric treatment (TRL) to improve fixation stability in low vision rehabilitation centers.

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Ethics

Ethics Committee Approval: This prospective, cross-sectional study was approved by the local clinical research ethics committee (decision no: 26.03.2018/06-363-18).

Informed Consent: Obtained.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: D.A., S.A.İ., Concept: D.A., S.A.İ., Design: D.A., S.A.İ., Data Collection or Processing: D.A., Analysis or Interpretation: D.A., S.A.İ., Literature Search: D.A., Writing: D.A.

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