Article

Effect of Background Brightness on Preferred Retinal Loci in Patients With Macular Disease

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Purpose: To evaluate the effect of background brightness on the preferred retinal locus (PRL) in patients with macular disease.

Methods: The study included 27 eyes (27 patients) with macular disease. Microperimetry (MP) was performed to evaluate the PRL and retinal sensitivity (RS) at 10 cd/m^2. A prototypical device was used to evaluate the PRL at 650 cd/m^2. Patients were divided into two groups: central fixation (CF) and eccentric fixation (EF).

Results: The PRLs under different brightness levels differed significantly ($P < 0.001$) in 15 of 27 eyes (two of 13 eyes in the CF group and 13 of 14 eyes in the EF group). The best-corrected visual acuities (BCVAs) in eyes with different PRLs were significantly worse ($P = 0.019$) than in eyes with one PRL, although the foveal RS did not differ significantly. In patients with BCVAs over 0.1, the PRLs differed in four of 13 eyes in the CF group and in three of four eyes in the EF group ($P > 0.05$); in patients with BCVAs of 0.1 or lower, the PRLs differed in one of four eyes and 10 of 10 eyes, respectively ($P = 0.011$).

Conclusions: In patients with macular disease, PRLs can change depending on the surrounding brightness. It may be beneficial to evaluate PRLs under brighter background conditions (e.g., in ambient light) when performing visual rehabilitation for these patients.

Translational Relevance: This study provides important information for visual rehabilitation of patients with macular disease.

Introduction

Central vision loss (CVL) develops in patients with a macular disease such as age-related macular degeneration (AMD). CVL affects many aspects of daily life, including reading,[1] face recognition,[2] driving,[3] and watching television and movies.[4] Patients with CVL tend to use eccentric fixation (EF), and a new retinal area, the so-called preferred retinal locus (PRL),[5] develops to view a target as a result of loss of foveal function and central fixation (CF). Because training to use the PRL is conducted during visual rehabilitation of patients with CVL, evaluation of the PRL is important.

Microperimetry (MP) is a technique that has been used to assess retinal sensitivity (RS) while directly observing the fundus under real-time conditions.[6–9] Using recently developed, commercially available instruments, such as the NIDEK MP-3 (NIDEK, Gamagori, Japan) and MAIA (CenterVue, Padova, Italy), eye-tracking systems can facilitate precise examinations at the correct location even under unstable fixation. The usefulness of MP for detecting functional retinal changes, for longitudinal assessments, and for evaluating the effectiveness of treatments of macular diseases has been reported.[10–15] Moreover, MP is one of the most commonly utilized approaches for evaluating the PRL. Previous studies have reported on PRL assessment using MP for EF training to stabilize the fixation,[16,17] although earlier studies have also reported that patients with CVL have multiple PRLs depending on various conditions.[4,18–21] In fact, one study reported that the location of the PRL during a daily task such as watching videos can differ from that found during a fixation task when

using MP.[4] Therefore, assessing the PRL using conventional MP might be limited by several conditions, one of which is background brightness. The background brightness of conventional MP is set to 10 cd/m^2 or 1.27 cd/m^2 to detect fine disturbances in retinal function. Compared with the general environment, the background brightness levels for MP examinations are dark. Differences in PRLs based on the stimulus illuminance have been reported,[22] but differences in the background brightness have not been reported.

The aim of the current study was to evaluate the effect of background brightness on PRLs in patients with AMD. We discuss the importance of the conditions for PRL evaluation when performing visual rehabilitation for patients with AMD.

Methods

Patients were recruited to visit the low-vision clinic at Asahikawa Medical University Hospital from September to November 2016. All participants provided written informed consent. The procedures used in this study adhered to the tenets of the Declaration of Helsinki. The Ethics Committee of Asahikawa Medical University approved the study protocol.

Twenty-seven eyes of 27 patients (20 males and 7 females; mean age $\pm$ SD, 71.2 $\pm$ 7.7 years) were recruited who had a retinal disorder that affected their macula such as a best-corrected visual acuity (BCVA) $\leq$ 0.3 in the poorer eye. Patients underwent a standard ophthalmic examination including visual acuity (VA) assessment; slit-lamp biomicroscopy; fundus examination; color fundus photography using the TRC-50 DX (Topcon, Tokyo, Japan); cross-sectional optical coherence tomography (OCT) by spectral-domain OCT (RTVue-XR Avanti; Optovue Inc., Fremont, CA) or swept-source OCT (DRI-OCT Triton; Topcon); fluorescein angiography; indocyanine green angiography using the Heidelberg Retina Angiograph 2 (HRA2; Heidelberg Engineering, Heidelberg, Germany) for the diagnosis of macular disease; and PRL evaluation using standard MP (NIDEK MP-3) and a prototypical scanning laser ophthalmoscope (SLO) device (Tomey Corporation, Aichi, Japan). In the current study, we wanted to clarify PRL behavior in patients whose PRLs have not been established and who need future PRL training. The patients with binocular macular disease would already have an established PRL in the better eye; therefore, we selected the eye with the poorer BCVA. Patients were excluded if they currently had any other ocular disease or a history of any other ocular disease except for a macular disease, a history of PRL
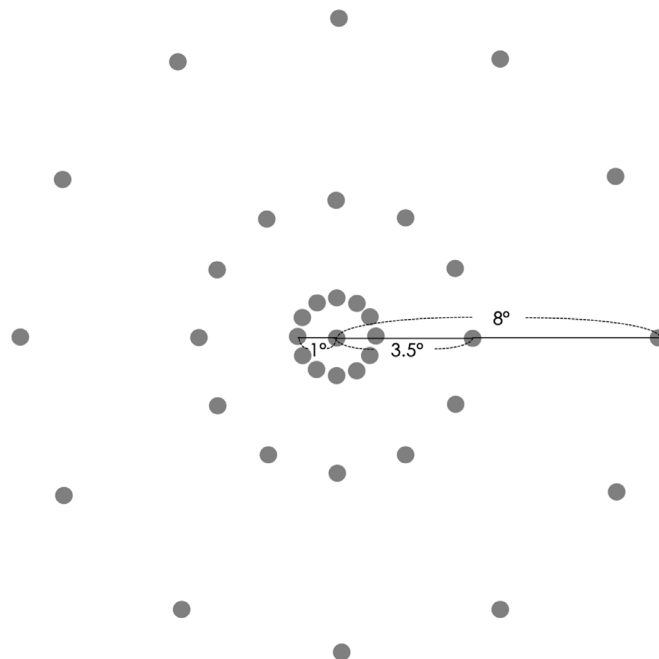
Figure 1. The RS was measured at 37 points; each dot represents an RS test point on the fundus (i.e., at the center and 1°, 3.5°, and 8° from the center). The foveal area RS values are defined as the average of the center and 12 points within each degree.

training, or rapidly progressive macular disease within 6 months.

Evaluation of RS and PRLs

Retinal sensitivity was evaluated using standard MP. We used four paracentral fixation targets (crosses) oriented in four directions. The patients were asked to fixate at the assumed central position from the four fixation targets in order to not move their eyes during the RS examination. The standard RS evaluation pattern of MP for macular disease in our hospital was used, which includes 37 test points in the central 16 degrees (Fig. 1A). The size of the stimuli was standard Goldmann III (108 μm on the retina), and the background brightness was 10 cd/m^2.

Two PRLs were evaluated under different background brightness levels. We wanted to compare the PRLs under different conditions of background brightness using two devices; therefore, all other conditions, including cross size, that might affect the PRLs were identical. We provided an explanation to the patients before the examination. The PRL was first evaluated by MP under 10 cd/m^2, which is the standard background brightness used in visual field examinations such as Humphrey perimetry and Goldmann perimetry, as well as MP. A cross consisting of the same size horizontal and vertical lines

(width $\times$ length, 0.3 $\times$ 3° of the visual axis) was used as the fixation target. Patients were instructed to fixate on the target at their most preferred position for at least 20 seconds. After the examination, the program automatically displayed the PRL on the fundus image, and the image location was calculated based on the distribution of the fixation points from the center of the fixation target.

The PRL under a higher background brightness was then evaluated using a prototypical SLO device. The background brightness used in our prototype device was 650 cd/m^2, which corresponds to daytime illumination for precise visual work performed inside a house, for example, to evaluate the PRL in the daily life of a patient. A light-emitting diode of 150 lumens was used with wavelengths of 617, 520, and 459 nm. The contrast was 1000:1. The image projection method was digital light processing, which projected at a 48° angle. Real-time retinal images were acquired at a 45° angle using an 850-nm laser diode and a 30-Hz line scan. On the display, we observed any fixation target that overlapped the retinal images in real time and, therefore, were able to evaluate the fixation area to see the target on the patient's retina. A cross that was the same size as that used for standard MP served as the target. We instructed patients to fixate on the target at their most preferred position. When the fixation stabilized, we captured the fundus image of the target.

Data Analysis

To compare the PRL locations under different background brightness levels, using the retinal vasculature as a guide, images of the PRLs obtained using standard MP and the prototypical SLO device were superimposed manually. This process was performed using Photoshop CS4 (Adobe, San Jose, CA). If the distance between the centers of the crosses exceeded 4° of the visual axis, we considered the two to be in different positions (Fig. 2). Based on the PRL location determined by standard MP, patients were divided into two groups: the CF group, in which the PRLs were at the fovea or parafovea (within a 4° circular area from the foveal area), and the EF group. To obtain the foveal RS, we calculated the average of the retinal sensitivities at the center and 12 points within 1° of 37 examined points.

The categorical values were compared using the Mann–Whitney *U*-test and Fisher's exact test. Statistical analyses were performed using EZR[23] (Jichi Medical University Saitama Medical Center, Amanumacho, Japan), a graphical user interface for R 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria), and a modified version of R Commander
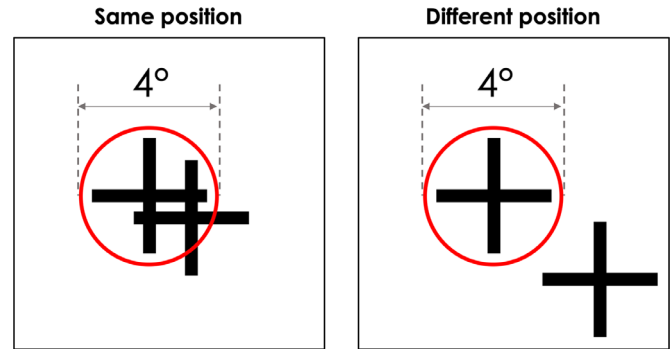
Figure 2. Definition of same or different PRLs under different background brightness levels. When images of the PRLs obtained using the standard MP and prototypical SLO device were superimposed, "same" position was defined as the distance between the center of the crosses being less than 4° of the visual axis, and "different" position was defined as a distance over 4° of the visual axis.

(Rcmdr 2.5.3). All measurements are expressed as the mean $\pm$ SE. All *P* values were based on two-sided tests; $P < 0.05$ was considered statistically significant.

Results

Seventeen patients had a diagnosis of wet AMD; three, chorioretinal atrophy; three, myopic choroidal neovascularization; two, dry AMD; one, chronic central serous central serous chorioretinopathy; and one, multifocal posterior pigment epitheliopathy (Table 1).

The PRLs under different brightness levels differed in 15 of 27 eyes (56%). The PRLs differed in two of 13 eyes (15%) in the CF group and in 13 of 14 eyes (93%) in the EF group, a difference that reached significance ($P < 0.001$). PRLs toward the fovea, peripherally, and superonasally or superiorly were seen in nine (60%), one (7%), and five (33%) eyes, respectively. The BCVAs in eyes with different PRLs were significantly worse than in those with the same PRLs ($P = 0.019$). The foveal RS values in eyes with different PRLs tended to be lower than in those with the same PRLs, but the difference did not reach significance (Table 2). Figure 3 shows typical examples of PRLs in the same and different locations in the CF and EF groups.

In patients with BCVAs over 0.1, the PRLs under different brightness levels differed in four of 13 eyes (31%) in total: one of nine eyes (11%) in the CF group and three of four eyes (75%) in the EF group, but the difference was not significant ($P = 0.0517$) (Fig. 4). In patients with BCVAs of 0.1 or lower, the PRLs differed in 11 of 14 eyes (79%) in total, which was significantly higher than in the patients with BCVAs over 0.1 ($P = 0.021$) (Table 2). In addition, one of four eyes

Table 1. Patient Characteristics

Patient	Age (y)	Eye	Sex	Diagnosis	BCVA	Foveal RS (Mean ± SD)	Fixation Group	PRL Location
1	68	OS	M	CRA	0.1	1.3	EF	Different
2	63	OD	M	Wet AMD	0.2	15.5	EF	Different
3	70	OS	M	Wet AMD	0.08	1.7	EF	Different
4	77	OD	M	Wet AMD	0.04	0.2	EF	Different
5	77	OS	M	Wet AMD	0.07	0.0	EF	Different
6	79	OD	M	Wet AMD	0.1	0.2	EF	Different
7	72	OD	M	Wet AMD	0.06	0.0	EF	Different
8	78	OD	M	Dry AMD	0.3	0.0	EF	Same
9	61	OD	M	mCNV	0.2	9.7	EF	Different
10	78	OD	M	Wet AMD	0.2	1.2	CF	Same
11	79	OS	M	Wet AMD	0.2	3.2	CF	Same
12	67	OD	F	Wet AMD	0.1	5.2	CF	Different
13	76	OD	F	mCNV	0.03	1.2	CF	Same
14	79	OD	M	Wet AMD	0.3	0.0	CF	Same
15	66	OS	F	Wet AMD	0.2	7.5	CF	Same
16	79	OS	M	Wet AMD	0.05	17.3	CF	Same
17	68	OS	M	Wet AMD	0.1	20.7	CF	Same
18	66	OS	M	Wet AMD	0.2	23.0	CF	Different
19	68	OD	M	Dry AMD	0.2	18.8	CF	Same
20	80	OD	M	Wet AMD	0.3	16.7	CF	Same
21	70	OS	M	Wet AMD	0.3	21.2	CF	Same
22	48	OS	M	Chronic CSC	0.2	0.0	EF	Different
23	73	OD	F	CRA	0.09	0.0	EF	Different
24	68	OS	M	MPPE	0.09	0.0	EF	Different
25	83	OS	F	Wet AMD	0.3	13.3	CF	Same
26	64	OS	F	mCNV	0.09	2.3	EF	Different
27	66	OS	F	CRA	0.09	1.0	EF	Different

OS, left eye; OD, right eye; CRA, chorioretinal atrophy; mCNV, myopic choroidal neovascularization; CSC, central serous chorioretinopathy; MPPE, multifocal posterior pigment epitheliopathy.

(25%) in the CF group and 10 of 10 eyes (100%) in the EF group had different PRLs, a difference that reached significance ($P = 0.011$) (Fig. 4). Three eyes had PRLs with the bright background located within the deep scotomatous areas evaluated by standard MP (Fig. 5).

Discussion

The current study showed that the PRLs differed under different brightness levels in more than half of the patients with macular diseases. Fine changes in retinal functioning can be estimated more easily under lower background illumination.[24] Consequently, a deep scotomatous area detectable under lower background brightness might be undetectable under a bright background. Thus, the conventional condi-

tion of background brightness for standard MP (1.27 cd/m^2 or 10 cd/m^2) would be useful for evaluating the fine changes in retinal diseases.[25,26] In contrast, we should consider the possibility that standard MP may be unsuitable for evaluating the PRLs for visual rehabilitation in patients whose PRLs differ under different brightness levels. Because VA and reading performance have improved when using over 2000 lux in patients with a macular disease,[27,28] we used a background brightness corresponding to 2000 lux. We speculated that examinations conducted under such a background may be useful for evaluating the fixation areas and for visual rehabilitation in low-vision clinics based on daily activities. We will need to study whether there is a direct link to PRLs in brighter illumination and vision rehabilitation.
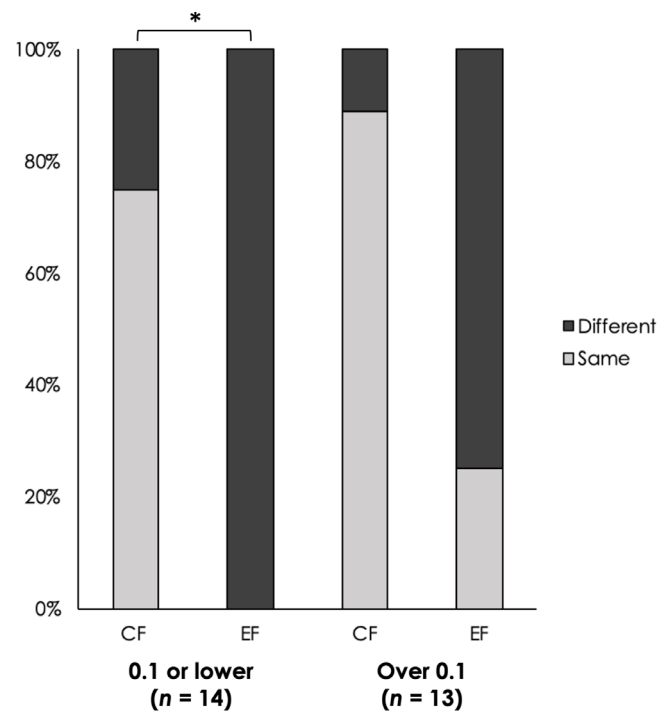
Table 2. Locations of PRLs Based on Various Parameters

| | PRL Location | | |
Parameter	Same ($n = 12$)	Different ($n = 15$)	P
BCVA (logMAR), median (95% CI)	0.70 (0.52–0.77)	1.04 (0.85–1.07)	0.019[a]
Foveal RS (dB), median (95% CI)	10.4 (1.2–17.7)	1.0 (0–3.8)	0.072[a]
MP-3 PRL location, *n*			<0.001[b]
CF group	11	2	
EF group	1	13	
BCVA, *n*			0.021[b]
Over 0.1	9	4	
0.1 or lower	3	11	

[a]Mann–Whitney *U*-test.
[b]Fisher's exact test.
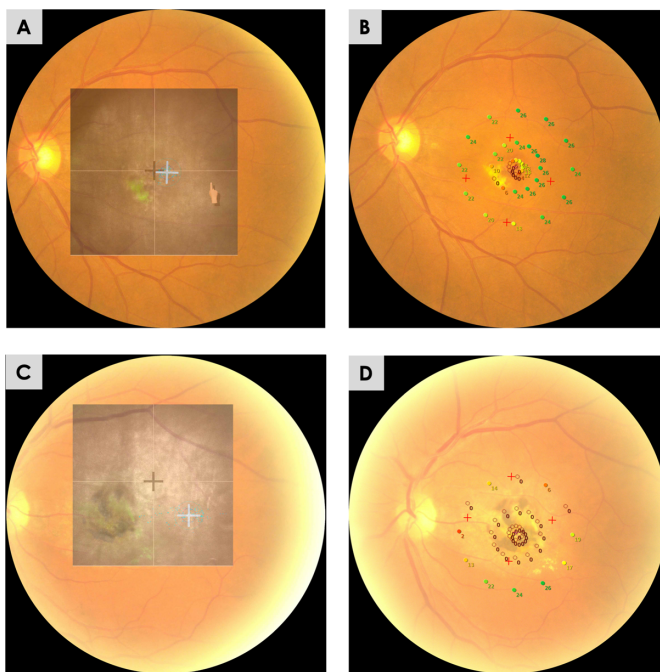
Figure 3. Typical examples of same and different PRLs. (**A**, **B**) A 66-year-old woman with wet AMD; the result shows same PRLs and those areas belonging to the CF group. (**C**, **D**) A 77-year-old man with wet AMD; the result shows different PRLs and those areas belonging to the EF group. In (**A**) and (**C**), the image from the prototypical SLO device is superimposed on the image from the MP-3. The crosses indicate locations of the PRLs evaluated by standard MP (*white crosses*) and by the prototypical SLO device (*black crosses*). (**B**) and (**D**) show imaging of RS using the MP-3.

Figure 4. The PRL group and the match rate of the two PRLs when subdivided based on a BCVA of 0.1 or lower and a BCVA of over 0.1. With the former, the rate of different PRLs is significantly higher in the EF group (*$P < 0.05$ by Fisher's exact test).

BCVA was significantly lower in eyes with different PRLs than in eyes with the same PRLs, but the foveal RS did not differ significantly in either group. In addition, the shift of the PRLs under different brightness levels occurred in many eyes with a BCVA of 0.1 or lower and with EF evaluated by standard MP under conventional background brightness levels. With regard to the eyes of patients with EF, they cannot use the central retinal area, and the BCVA would not be assessable in the central area. Therefore, the PRL changes would tend to occur when the central visual function is impaired. In our study, the PRLs evaluated by standard MP were not in the foveal area in the EF group. Thus, the foveal RS may be unrelated to shifting of the PRL. A previous study reported that the results of standard MP indicated that patients with EF resulting from loss of the central visual field used
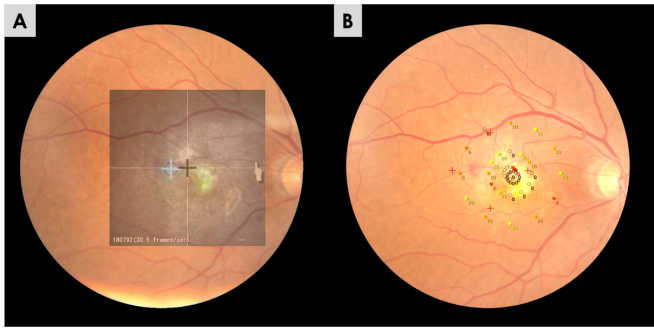
Figure 5. A typical case of eyes with PRLs under bright background levels that were located within the deep scotomatous area evaluated by standard MP in a 79-year-old man with wet AMD. The crosses indicate the locations of the PRLs evaluated by standard MP (*white crosses*) and by the prototypical SLO device (*black crosses*). (**A**) The image from the prototypical SLO device is superimposed on an image obtained using standard MP and shows different PRLs. (**B**) The *black cross* is within the 0-decibel-deep scotomatous area.

multiple PRLs depending on the visual task.[19] Further, different PRLs can develop depending on the brightness of the objects used in the visual tasks.[22] Therefore, the current results suggest that shifting of the PRL may occur easily in eyes with EF as a result of central visual impairment, and PRLs in the periphery tend to be affected easily by the background brightness. When patients with macular degeneration enter a dark room from a brighter place, their vision sometimes requires time to adjust, likely because of impaired dark adaptation[29,30] or because of PRL changes that change the central position in their visual field. We should be aware that small changes in brightness that individuals with normal vision would not notice can affect visual performance, such as reading, in patients with AMD due to changes in the PRL, especially in eyes with lower VA and EF. In contrast, we found that eyes with CF could use the central area in low background brightness and the CF was also retained in a bright background.

When we used a bright background with standard MP, some patients had PRLs in the deep scotomatous area. We speculated that not only does the extent of the visual field change but also the distribution of the RS, depending on the background brightness, may affect the PRL. Some reports have indicated that PRL training using standard MP was effective in patients with a macular disease,[31,32] but another study reported that reading speed did not improve significantly.[33] In previous reports, the location of the trained retinal loci (TRL) for PRL training is selected in valuable retinal locations—that is, the area closest to the initial PRL[34] or the superior hemiretinal field[31]—by using MP. These studies reported improved reading ability; however, these are the results of training performed under the dark background used in MP. Based on the

current study, it might be possible to select an effective TRL location based on the brightness used during daily life tasks by evaluating the patient using a brighter background, an observation that requires further investigation.

The current study had several limitations. We performed the study using two different systems, because the background brightness of the commercially available MP offered brightness levels of only 10 cd/m^2 or 1.27 cd/m^2, and our prototype device had a brightness level of only 650 cd/m^2. Therefore, we could not perform the measurements under different conditions with the same system, although we could compare the results evaluated by the commercially available MP. We could not quantitatively evaluate the fixation pattern using our prototypical SLO device or compare the pattern with that in standard MP, because our device did not have a fixation analysis algorithm. We did not to assess the reproducibility of the PRLs locations, as we examined them only once. It is unclear whether these multiple PRL locations are truly separate or whether they are unrepeatable local increases in frequency caused by the stochastic nature of short measurement periods. We only used a cross as a target in the current study, but it has been reported that patients use various retinal areas based on the task.[19,35] Further studies are required to investigate the relationship between background brightness and visual tasks.

In conclusion, PRLs may change depending on the surrounding brightness in patients with a macular disease. Because conventional MP can only evaluate PRLs in a background darker than that of daily life, the PRLs may differ when evaluated in the environment used for visual rehabilitation. Therefore, it would be beneficial to evaluate PRLs under brighter background conditions, such as the ambient light used in this study, when performing visual rehabilitation for these patients. To determine if evaluating PRLs under a brighter background condition is useful for visual rehabilitation in patients with macular disease, further investigation is necessary; however, we believe that this study provides important information regarding visual rehabilitation in patients with macular disease.

Acknowledgments

Disclosure: **T. Ro-Mase**, None; **S. Ishiko**, None; **A. Yoshida**, None

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