

## Retinal Sensitivity and Fixation Stability Changes during Repeated Microperimetry

Zsuzsanna Szepessy<sup>1,2\*</sup>, Mirella T S Barboni<sup>1,3</sup>, Zoltán Zsolt Nagy<sup>1</sup> and János Németh<sup>1,2</sup>

<sup>1</sup>Department of Ophthalmology, Semmelweis University, Budapest, Hungary

<sup>2</sup>Bionics Innovation Center, Budapest, Hungary

<sup>3</sup>Department of Experimental Psychology, Institute of Psychology, University of Sao Paulo, Brazil

\*Corresponding author: Zsuzsanna Szepessy, Department of Ophthalmology, Semmelweis University, Budapest, Hungary, Tel: + 3620-8258540; Fax: +361-2100309; E-mail: szepzsu@yahoo.com

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### Abstract

**Purpose:** To determine and compare the intersession test-retest variability of different microperimetric parameters in healthy volunteers and age-related macular degeneration (AMD) patients by MAIA microperimetry.

**Methods:** Twenty-four eyes of 12 healthy volunteers and 22 eyes of 11 AMD patients were included in this study. Microperimetry examinations were performed three times on each eye of all participants by MAIA microperimetry (CenterVue, Padova, Italy). The second measurement was performed on the same day and the third measurement one week after the first test. Retinal light sensitivity, stability of fixation, and macular integrity were recorded. Statistical analysis was performed by Microsoft Excel software and StatSoft Statistica software.

**Results:** During the examinations, the average threshold had not changed significantly ( $p > 0.475$ ) in time in healthy and AMD patients. Fixation stability was relatively constant (nearly 100%) in healthy subjects as compared to the increase in the improving eye condition of AMD patients ( $p = 0.042$ ). Macular integrity was stable in both groups during the examinations.

**Conclusion:** A learning effect was found in fixation stability of AMD patients by MAIA microperimetry. The improvement in fixation stability might be considered, especially prior to biofeedback training protocols in AMD patients.

**Keywords:** Age-related macular degeneration; Fixation stability; Macular integrity; MAIA microperimetry; Reproducibility; Retinal sensitivity

### Introduction

Microperimetry is a noninvasive technique that combines functional and structural measures of the retina, allowing clinicians to correlate the retinal light sensitivity to the morphological changes in the evaluated area. Microperimetry assesses the sensitivity of different locations in the retina [1-3]. This technique is very similar to standard automated perimetry, with the advantage of allowing precise topographic correlations of macular/retinal anatomy and pathology. The other advantage of the new microperimetry instruments is the retinal landmark tracker (eye-tracking technology), which corrects eye movements during the examination; thus, microperimetric parameters are independent of the quality of fixation [3,4]. For long-term follow-up examinations, the previous examination data can be loaded; thus, the repeated stimulus presents in exactly the same retinal location with the same intensities used in the first examination, thereby allowing an accurate comparison of the functional assessments in the follow-up examinations.

Microperimetry provides information in the form of threshold sensitivity, fixation stability, and macular integrity [3,4]. Threshold sensitivity is based on subjective tests similar to standard automated

perimetry. Patients are expected to respond when stimuli of different intensities are projected at known locations within specified retinal areas. Fixation stability is an objective test performed by retinal landmark tracking. Macular integrity shows the functionality of the retina, namely the macular retinal sensitivity [3,4].

Other devices for visual field testing such as the Humphrey or Octopus perimeters were analyzed in detail for test-retest variability [5,6]. The purpose of this study was to determine and compare the intersession test-retest variability of different microperimetric parameters in young, healthy volunteers and in patients with age-related macular degeneration (AMD) by using Macular Integrity Assessment (MAIA) microperimetry. The other aim is to evaluate the possible learning effect on the mean sensitivity and fixation stability among the tests in these two groups of subjects.

### Methods

This prospective study was performed at the Bionics Innovation Center and in the Department of Ophthalmology of Semmelweis University (Budapest, Hungary) on 23 consecutive Caucasian patients, including 7 males and 16 females, who were divided into two groups.

Group 1: Twenty-four eyes of 12 healthy volunteers with age ranging from 21 to 27 years (mean age  $23.8 \pm 1.6$ ) were included in this study. Inclusion criteria were best-corrected visual acuity of 20/20, no history

of any current ocular or systemic disease, and a normal-appearing macula in non-contact lens biomicroscopy.

Group 2: Twenty-two eyes of 11 AMD patients, aged from 58 to 77 years (mean age: 68.5 ± 7.4), were included in this study. Inclusion criteria were non-exudative, age-related macular degeneration in both eyes. Patients with a history of any other macular disease (epiretinal fibrosis, diabetic maculopathy), exudative AMD, or intravitreal anti-VEGF treatment were excluded from the study.

All patients were treated in accordance with the tenets of the Declaration of Helsinki. Institutional Review Board approval was obtained for the study protocol (Semmelweis University Regional and Institutional Committee of Sciences and Research Ethics). Written informed consent was obtained from all participants in this study.

All patients underwent a comprehensive eye examination, including best-corrected visual acuity (BCVA) and complete slit-lamp examination. In group 2, optical coherence tomography was used to quantify retinal thickness and exclude exudative AMD cases.

Microperimetry examinations were performed on each eye (undilated) of all participants in the study by using the same microperimetry system, MAIA (CenterVue, Padova, Italy) by the same experienced examiner. The microperimetry examination was performed after explanation of the method to all participants and an adaptation time of 5 min to the darkened room. Pupillary dilation was not used.

Both eyes of all participants were tested monocularly three times with undilated pupil. The second measurement was performed on the same day, one hour after the first measurement and the third measurement one week after the first test. In group 1, the right eye was always examined first and then the left eye. In group 2, the better eye of each patient was first examined, followed by the worse eye.

Retinal light sensitivity, stability of fixation, and macular integrity were recorded.

### Macular integrity assessment system (MAIA)

The MAIA system provides real-time eye-tracking through the examination performed by scanning laser ophthalmoscopy. For a detailed description of the technique, see Rohrschneider et al. [3].

The expert protocol used in the present study consists of 37 macular points tested in three concentric circles of 1°, 3°, and 5° from the center point with 12 points in each concentric circle (plus the measurement of the central point). Stimuli were set using standard parameters: Goldman-based size III stimuli against a background of 1.27 cd/m<sup>2</sup> for the 4-2 threshold strategy. The duration of the stimulus presentation was 200 msec. Maximum stimulus luminance was 318 cd/m<sup>2</sup>, which permitted a stimulus presentation ranging from 0 to 36 decibel (dB). The observer's task was to press a button to indicate the presence of the light spot whenever it was detected. Visual field locations of reduced sensitivity required brighter stimuli to reach threshold and had lower dB sensitivity values. Similarly, higher dB values represented more sensitive retinal locations.

Statistical analysis was performed by Microsoft Excel and StatSoft Statistica software. Mean and standard deviations (SDs) of light threshold, fixation stability, and macular integrity, and the coefficient of variability (COV) of the average threshold and the fixation stability were calculated for each group separately. The average thresholds were compared among the three consecutive measurements by one-way ANOVA. SDs and COVs of the four parameters obtained were compared (two-tailed Student's t-test). Moreover, a correlation test was applied to compare the three measurements (Spearman's rank correlation coefficient). A p-value of less than 0.05 was considered as statistically significant.

	Group 1–Control						Group 2–AMD					
	1 <sup>st</sup> test		2 <sup>nd</sup> test		3 <sup>rd</sup> test		1 <sup>st</sup> test		2 <sup>nd</sup> test		3 <sup>rd</sup> test	
	OD	OS	OD	OS	OD	OS	BE	WE	BE	WE	BE	WE
AVE	30.9	31.2	31.4	31.5	31.3	31.2	24.8	18.6	25.0	17.1	24.3	17.9
SD	0.9	0.7	0.9	0.9	0.7	0.9	2.6	5.3	3.3	5.6	3.1	5.9

**Table 1A:** Average (AVE) and standard deviation (SD) of the average threshold (in dBs) for each examination in both groups (OD=Oculus Dextrum (right eye); OS=Oculus Sinistrum (left eye); BE=Better Eye; WE=Worse Eye).

	Group 1-Control						Group 2-AMD					
	1 <sup>st</sup> test		2 <sup>nd</sup> test		3 <sup>rd</sup> test		1 <sup>st</sup> test		2 <sup>nd</sup> test		3 <sup>rd</sup> test	
	OD	OS	OD	OS	OD	OS	BE	WE	BE	WE	BE	WE
AVE	3.2	2.4	3.2	2.5	2.7	2.1	84.1	92.7	80.3	84.4	86.4	93.6
SD	2.6	1.7	6.3	1.8	3.8	1.8	22.8	17.0	27.9	34.7	18.8	17.3

**Table 1B:** Average (AVE) and standard deviation (SD) of macular integrity (in a range scale from 0 to 100, where 0 is normal and 100 is abnormal) for each examination in both groups (OD=Oculus Dextrum (right eye); OS=Oculus Sinistrum (left eye); BE=Better Eye; WE=Worse Eye).

	Group 1						Group 2					
	1 <sup>st</sup> test		2 <sup>nd</sup> test		3 <sup>rd</sup> test		1 <sup>st</sup> test		2 <sup>nd</sup> test		3 <sup>rd</sup> test	
	OD	OS	OD	OS	OD	OS	BE	WE	BE	WE	BE	WE
Mean	97.8	97.9	98.7	98.8	99.1	99.6	78.3	80.0	89.5	80.2	95.9	82.7
SD	3.3	2.3	1.8	1.5	1.8	0.7	23.1	23.7	15.7	21.3	7.6	24.8

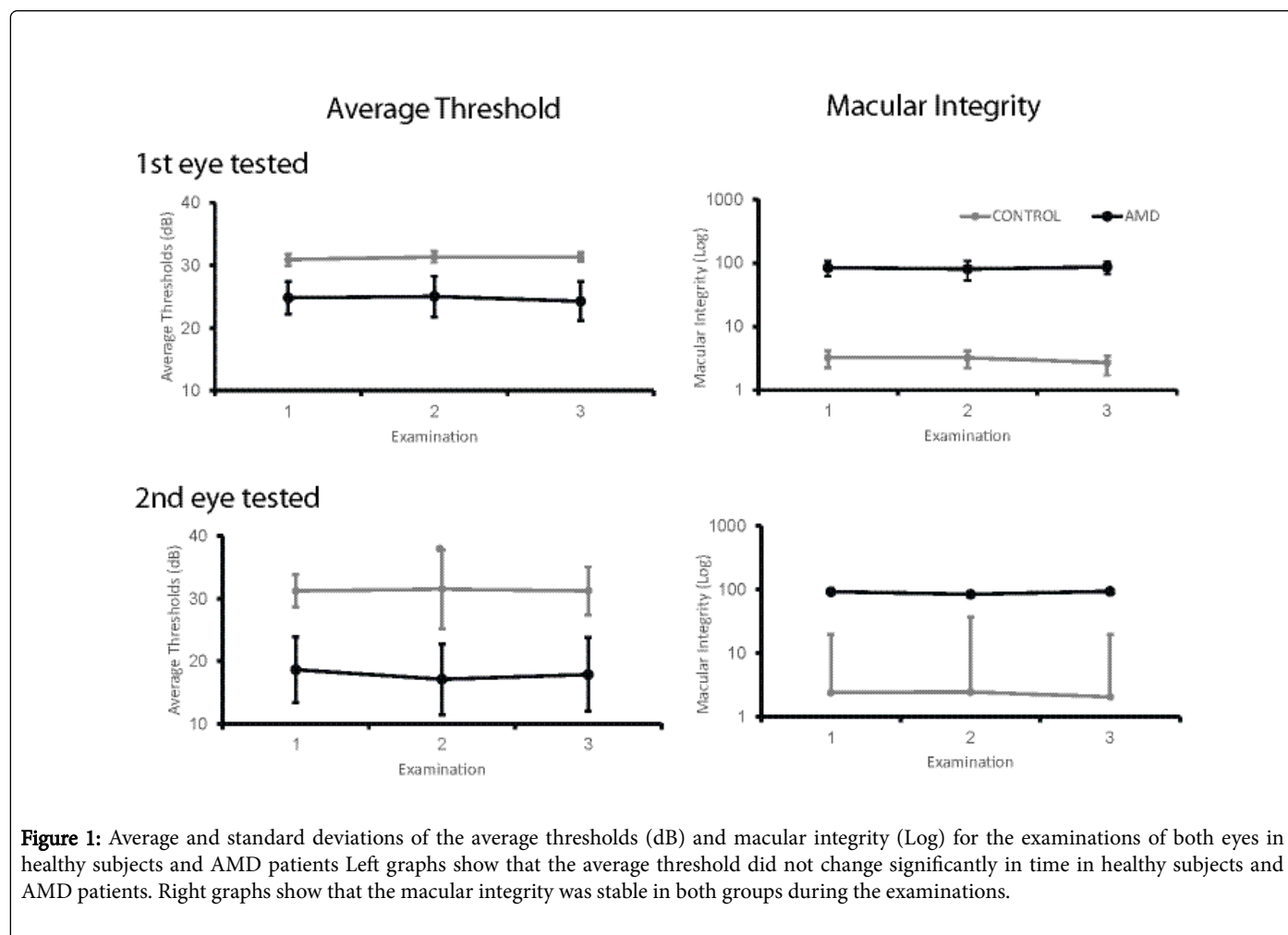
**Table 1C:** Fixation stability (%) of different groups (OD=Oculus Dextrum (right eye); OS=Oculus Sinistrum (left eye); BE=Better Eye; WE=Worse Eye).

## Results

The average threshold data are shown in Table 1A for each eye and for each group separately. During the three examinations, group 1 showed similar average sensitivity between the first (right) and the second (left) eye tested (first measurement:  $p=0.381$ ; second measurement:  $p=0.741$ ; and third measurement:  $p=0.816$ ). As expected, the average sensitivity was significantly different ( $p=0.024$ ) between the first (better) and second (worse) eye tested in group 2 (first measurement:  $p=0.010$ ; second measurement:  $p=0.001$ ; and third

measurement:  $p=0.006$ ). The average sensitivity was significantly lower in both eyes of AMD patients than in the healthy eyes ( $p<0.001$  in both eyes), as expected.

Figure 1 (left graphs) shows that the average threshold did not change significantly in time in group 1 (first eye tested  $p=0.252$  and second eye tested  $p=0.458$ ) and group 2 (first eye tested  $p=0.276$  and second eye tested  $p=0.718$ ). However, the variability of the average threshold was significantly higher in AMD patients than in the group of healthy volunteers ( $p=0.003$ ).



**Figure 1:** Average and standard deviations of the average thresholds (dB) and macular integrity (Log) for the examinations of both eyes in healthy subjects and AMD patients. Left graphs show that the average threshold did not change significantly in time in healthy subjects and AMD patients. Right graphs show that the macular integrity was stable in both groups during the examinations.

Table 1B shows the macular integrity results for both groups. Macular integrity was significantly worse for the AMD group ( $p<0.001$

in both eyes), as expected, but it was stable in both groups during the examinations (Figure 1, right graphs), group 1 (first eye tested  $p=0.989$

and second eye tested  $p=0.971$ ) and group 2 (first eye tested  $p=0.526$  and second eye tested  $p=0.647$ ).

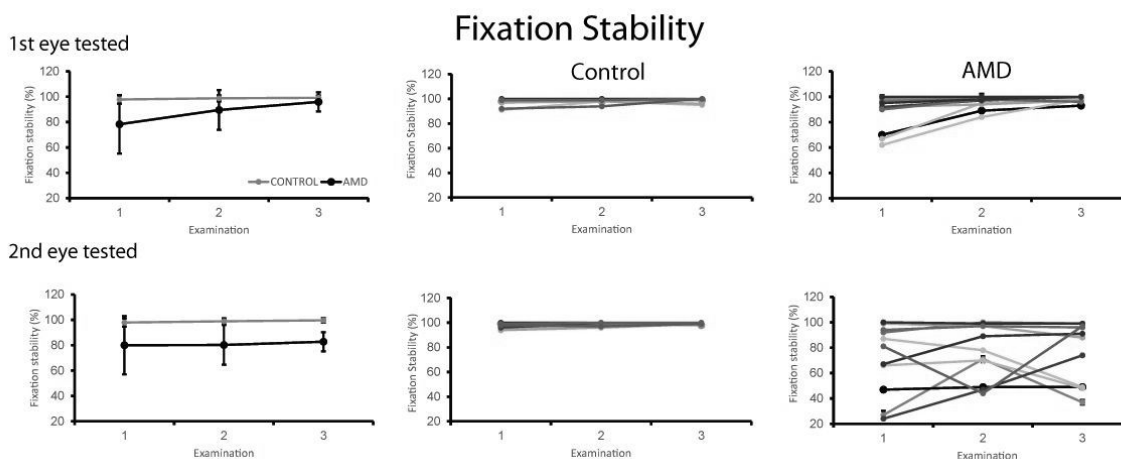
Fixation stability results (in %) are presented in Table 1C for each eye and for each group separately. Fixation stability was relatively constant (near 100%) in the healthy subjects as compared to an increase in AMD patients (Figure 2). The fixation stability of the better eye in AMD patients significantly improved during the examinations ( $p=0.042$ ), as shown in Figure 2, upper graphs (left and right), and reached a very high value, similar to those in the healthy volunteers. However, the worse eye of AMD patients did not show such tendency (Figure 2, lower graphs, left and right).

To further assess the agreement between both groups for the different examinations, the coefficient of variability (COV) of the average threshold and the fixation stability were calculated in both groups (Figure 3, upper graphs). Despite higher COV values for the

AMD group for fixation stability, the analysis of COV indicated a good agreement in both groups for the different examinations.

To quantify reproducibility, the mean differences of the standard deviation (SD) of the average threshold and fixation stability were calculated in both groups (Figure 3, lower graphs). The SD was higher for group 2 (AMD) than for group 1 (Control) for the average threshold ( $p=0.002$ ) and for fixation stability ( $p=0.001$ ). However, the standard deviation was relatively similar between group 1 and group 2 for the average threshold compared with that for the fixation stability.

Finally, we found a positive correlation between the measurements performed on the first day (average of two examinations) and the third measurement for the average threshold ( $R^2=0.8$ ,  $p=0.002$ ) and for macular integrity ( $R^2=0.7$ ,  $p=0.009$ ) in AMD patients that was not found in the healthy control group ( $R^2=0.2$ ,  $p=0.568$  and  $R^2=0.1$ ,  $p=0.835$ , respectively, Figure 4).



**Figure 2:** Fixation stability (%) for the examinations of both eyes in healthy subjects and AMD patients. The left graphs show the average values and standard deviations, while the middle and right graphs present the individual values. Fixation stability was relatively constant (nearly 100%) in the healthy subjects. The fixation stability of the better eye in AMD patients significantly improved during the examinations. The worse eye of AMD patients did not show such tendency.

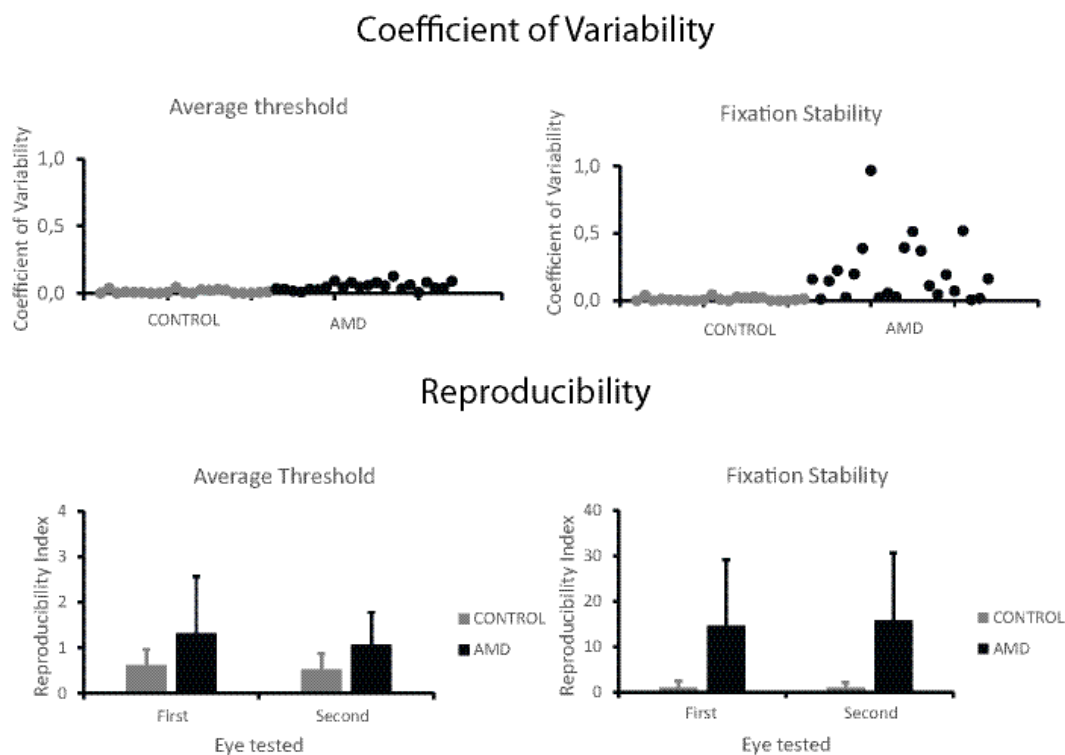
## Discussion

Our results suggest excellent reproducibility using MAIA microperimetry in healthy volunteers and AMD patients.

Any new diagnostic imaging device requires evaluation of reproducibility and variability because good reproducibility is a mandatory condition for reliable examination. Intersession test-retest variability of different microperimetric parameters with SLO perimetry and MP-1 Nidek microperimetry, such as average threshold, fixation stability, and macular integrity, within different populations has been reported recently [2,4,7-10].

As shown in earlier studies, automatic fundus perimetry and the first microperimetry that uses a true eye-tracking system (MP1) allow accurate, repeatable, and topographically specific examination of retinal sensitivity [4,7-12].

A number of studies have investigated test-retest variability of mean sensitivity with MP-1 microperimetry [4,7,8]. Weingessel et al. [4], for instance, showed good reliability for macular sensitivity and fixation stability in healthy subjects and AMD patients by using (MP-1) in patients with different macular diseases and showed that the test-retest variability is lowest for mean sensitivity and highest for point-wise sensitivity. Wong et al. [8] investigated the intersession test-retest variability of topography- and threshold-based parameters, and a statistically significant decline in mean sensitivity from the first to both second and third tests was detected. Nidek MP-1 microperimetry. Chen et al. [7] analyzed fixation stability recorded during microperimetry



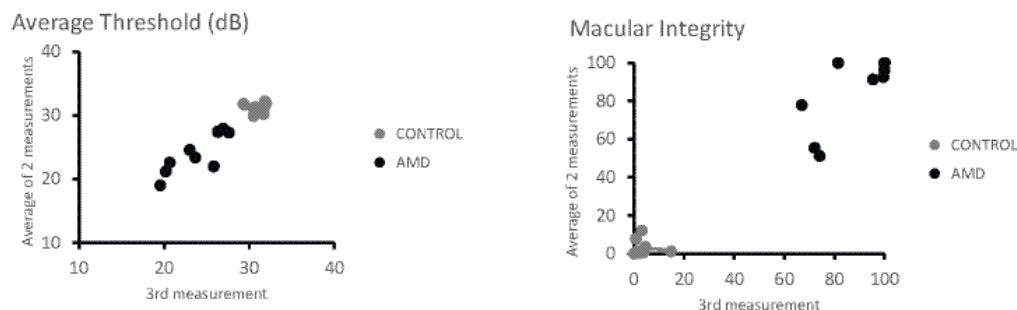
**Figure 3:** Coefficient of variability and reproducibility of average thresholds and fixation stability in healthy subjects and AMD patients. Upper graphs show the coefficient of variability (COV) of the average threshold and the fixation stability in both groups. Lower graphs show the mean differences of the standard deviation (SD) of the average threshold and fixation stability. The SD was higher for AMD group than for Control group for the average threshold and for fixation stability.

MAIA microperimetry was used only in children by Jones et al. [13]. Their results indicated that microperimetry is also feasible in children. Their data showed children's lower sensitivities, which were correlated with their poorer fixation stability. Molina-Martín et al. [14] found consistent measurements of retinal sensitivity in normal subjects by using the MAIA system. In 2017, Wong et al. [15] also used MAIA microperimetry to determine the test-retest variability in fixation-threatening glaucoma. Their data suggested that microperimetry reliability in glaucoma patients is worse than in healthy controls, and they demonstrated no learning effect in microperimetry over three testing sessions.

In our current study, we collected data from 3 repetitions of the microperimetry test in two groups (healthy adult volunteers and AMD patients) by using MAIA microperimetry. We studied non-exudative AMD patients to detect the potential difference in reproducibility between the healthy and AMD groups for retinal light thresholds, fixation stability, and macular integrity.

The learning effect is an important issue in many psychophysical tests. Several studies showed that the individual experience influences the results of standard automated perimetry [5,6,16-20]. In our study, all individuals had no previous experience with any type of microperimetry. In the analysis of the learning curve, we have considered that the second eye measurement is affected by the previous examination of the first eye.

During the three examinations, healthy subjects and AMD patients showed similar average sensitivity between the first and the second eye tested. Average thresholds have not changed significantly in time during the tests of healthy volunteers and AMD patients. Other parameters such as macular integrity also did not show significant differences across repeated tests. However, the AMD group shows inhomogeneity due to larger SDs of the mean light threshold and macular integrity and larger coefficients of variation.



**Figure 4:** Correlation between the measurements performed on the first day (average of two examinations) and the third measurement for the average threshold and for macular integrity in both groups.

There was no improvement in threshold sensitivity and macular integrity between the first and the second or third examination sessions. Average threshold and macular integrity do not seem to be affected by repeated measurements in normal and AMD eyes. These results strongly suggest that there is no learning effect of retinal average sensitivity and macular integrity by using MAIA microperimetry. In the literature, Wu et al. [11] showed a significant learning effect on mean sensitivity between the first and the second test sections in AMD patients with MPI microperimetry. In contrast, Wong et al. [15] demonstrated no learning effect on the mean sensitivity in glaucoma patients by using MAIA microperimetry.

The learning effect on the mean sensitivity by performing standard automated perimetry is well described in the literature in cases of normal and primary open-angle glaucoma [5,6,16-20]. In our study, there was no significant change in mean sensitivity during the three examinations. By standard automated perimetry, fixation/fixation stability in the patients could not be followed; there are no data for fixation in perimetry values. Possibly, the fixation of the patients with glaucoma might be improved by standard automated perimetry during repeated examinations. Thus, the learning effect on the mean sensitivity might be detected well by automated perimetry.

Fixation stability, the precision of eye fixation when one fixates intently on a stimulus for a certain period of time, is a fundamental component of visual performance.

Fixation stability seems constant in healthy subjects in contrast to the improvement found during the tests in AMD patients in the best eye alone. There was an increase in fixation stability between the first, second, and third examination sessions in the better eye of patients in the AMD group. A learning effect was seen in fixation stability in the better eye of AMD patients, but there was no learning effect in their worse eye or in healthy adult volunteers. In healthy subjects, the absence of improvement might be because their fixation stability was nearly 100% at the first examination and therefore could not be further improved. The lack of learning effect in the fixation stability of the worse eye of the AMD patients might be secondary to patient fatigue or the worse eye (with worse macular functions) should have more

tests to reach stable consistency and accuracy in fixation stability on the same fixation location of the retina.

It is important to note that the mean age of the healthy subjects was  $23.8 \pm 1.6$  years, while that of the AMD patients were  $68.5 \pm 7.4$  years. Rohrschneider et al. [3], Weingessel et al. [4], and Morales et al. [21,22] found a decrease in fixation stability with an increasing age in normal subjects, and older observers showed greater variability in their fixations. Age might be a significant factor for fixation loss, but microperimetry is a psychophysical test; thus, it might present a learning effect for fixation stability. In our study, there was an increase in fixation stability in the better eye of AMD patients between the first and second, and between the second and third examination sessions. This might be because the participants of our study did not forget the positive learning effect of the first and second examinations over a short period (one week). Intersession test-retest variability in the learning effect over longer test-retest intervals remains to be investigated. In contrast to our results, Weinglass et al. [4] stated that older participants forgot the positive learning effect of the previous examination over a short period (less than a month). These results could also be attributed to the correlation of the learning effect with factors other than age, as shown in several studies in the literature [16-19].

We suggest that repeated measurements are required prior to microperimetry biofeedback training protocols in AMD patients. With microperimetry biofeedback training, patients with macular diseases who have lost foveal fixation capabilities are trained to relocate their preferred retinal locus (PRL) into an area with better sensitivity. This training to relocate the PRL can improve the fixation behavior and, thereby, visual performance [21-23,24,25]. Several authors have demonstrated that this training is effective in patients with loss of central vision secondary to macular pathologies, particularly in cases with geographic atrophy secondary to AMD [21,23,24,26]; however, it has also been reported that patients with macular disease may use two or more PRLs for fixation [24,25,27]. In our study during three examinations, the fixation stability improved in the better eye of AMD patients, but the stable consistency and accuracy in fixation stability on the same fixation location (same retinal locus/correct choice of the

new fixation point [PRL] required more tests and biofeedback trainings.

Our study results suggest excellent reproducibility by using MAIA microperimetry in different groups of participants. Further, our study demonstrates good reliability of MAIA microperimetry. This technique can be used to measure and follow up on exact macular function in patients with macular diseases. Improvement in the fixation stability might be considered, especially prior to the biofeedback training in AMD patients. Based on the improvement found in fixation stability, we suggest planning biofeedback training on repeated examinations.

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