Use of MAIA Microperimetry in Routine Tertiary Retinal Practice

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ABSTRACT

Background: Microperimetry is well established as a psychophysical outcome measure in clinical trials and is increasingly used in routine retinal practice for patients with visual symptoms. However, there is sparse evidence indicating the value of microperimetry in the clinical setting as distinct from the research setting. The aim of this study was to describe the usefulness of the MAIA microperimeter in tertiary retinal practice.

Method: A total of 80 eyes of 48 patients presenting to a private tertiary medical and surgical retina practice were retrospectively reviewed. Sixty-two eyes had retinal or macular pathology and nine had no retinal or macular pathology clinically present. Diagnosis classification information was missing for nine eyes. Visual acuity, clinical examination, optical coherence tomography (OCT) and Macular Integrity Assessment (MAIA) microperimetry were performed, and presenting symptoms recorded. Primary outcome measures were best corrected visual acuity (BCVA; LogMAR letters), macular integrity index (MII), average threshold sensitivity (ATS; dB) and test duration (minutes). Secondary outcome measures were pattern of visual field loss and fixation stability.

Results: MII was strongly related to BCVA and ATS (Spearman's rho = -0.305, $p = 0.006$; $r = -0.767$, $p < 0.0001$ respectively). Four groups were identified, including three abnormal groups and one normal group: i) focal scotoma (21 eyes); ii) reduced average threshold with poor fixation (31 eyes); iii) reduced average threshold with normal fixation (20 eyes); and iv) normal (8 eyes). MII ($p < 0.0001$) and ATS ($p < 0.0001$) were significantly different between abnormal and normal eyes. Overlap was present in results of abnormal and normal eyes, and no sole microperimetry outcome measure was unequivocally able to distinguish between the three abnormal groups, or between normal and abnormal eyes.

Conclusions: MAIA MII is strongly related to ATS and BCVA. Different patterns of visual field loss are described, but no single microperimetry parameter distinguished normal from abnormal patients. It is crucial to interpret microperimetry results appropriately in the clinical context.

Keywords: Microperimetry, fundus perimetry, macular integrity analysis, scotoma, retinal sensitivity

INTRODUCTION

Microperimetry (fundus perimetry) is a psychophysical diagnostic technique correlating sensitivity threshold of individual points on the retina with ophthalmoscopic retinal appearance in real time. Location of fixation sites at the fovea and macula enable accurate follow-up examination (test-retest) as stimuli are projected directly onto the retina and the same retinal point is monitored via eye-tracking.[1,2]

The earliest microperimetry measurements were made manually by projecting visual stimuli onto the retina through a direct ophthalmoscope.[3] The first commercially available device projected a stimulus under Scanning Laser Ophthalmoscope (SLO) observation (Rodenstock Instruments, Munich, Germany), however full automation and follow-up comparison was not possible.[4] In 2002, the first fully-automated microperimeter (MP-1) was introduced.[5] The MP-1 microperimeter (Nidek Technology, Gamagori, Japan) enabled automatic real-time alignment of fixation and a larger fundus field of view compared with the SLO (MP-1 = 44° × 36°; SLO = 33° × 2°). Normative age-related threshold data and test-retest accuracy have been published for the MP-1 microperimeter.[6,7] Recent advances have combined the investigation of structural changes in the retina using optical coherence tomography (OCT) with microperimetry: Optos OCT/

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SLO microperimeter (Optos, Dunfermline, Scotland)[8] and OPKO/OTI microperimeter (OPKO Instrumentation, Florida, USA).[9] Normative age-related threshold data and test-retest accuracy are currently under investigation.[9,10]

The Macular Integrity Analysis microperimeter (MAIA, CenterVue, Padova, Italy)[11] further advanced SLO technology by enhancing imaging and offering a wider sensitivity range (0-36 dB) and software improvements. Whilst the MAIA cannot overlap OCT images with microperimetry results, it does have several useful features in that it captures real-time black and white fundus images continuously throughout an examination and quantifies the stability of a patient's fixation or retinal locus. Results are known to correlate with inner plexiform layer thickness measured on Cirrus OCT scanning.[12] However, to date, limited normative age-related[13] and intra-session test-retest data have been reported.[14]

The MAIA microperimeter projects stimuli directly onto the retina in random order using either a supra-threshold or a 4-2 staircase strategy to accurately measure macular threshold sensitivity at 37 or 61 pre-determined retinal locations over the central 10° of the retina.[15] Whilst these pre-set examination patterns are most commonly used, custom configuration of different patterns is also possible and may be useful in both the clinical and research settings. Perimetric stimuli are equivalent to a Goldmann size III target and the maximum stimulus intensity is 1,000 apostilbs (asb). MAIA microperimetric outputs include average threshold sensitivity (ATS), fixation stability, and macular integrity index (MII). Average threshold represents the arithmetic mean of all threshold sensitivity responses, recorded in decibels (dB). Fixation location is automatically evaluated by the microperimeter. Throughout testing, an automated eye-tracking system registers eye movements 25 times per second and plots the distribution over the SLO fundus image, adjusting stimulus projection location according to deviations in eye position. Fixation stability is classified as 'stable', 'relatively unstable', or 'unstable' depending on the percentage of fixation points made within two circles of 1 and 2 degree radius, respectively from the geometrical centre of all fixation points. A unique

Table 1. Examples of the use of microperimetry in describing ocular conditions and their response to treatment

Subspecialty	Diagnosis	Sub-classification
Retina	Retinal dystrophies	Retinitis pigmentosa[17] Vitelliform macular dystrophy[18] Stargardt fundus flavimaculatus[19] Goldmann-Favre syndrome[20] Gyrate atrophy[21] X-linked retinoschisis[22] Occult macular dystrophy[23]
	Age-related macular degeneration	Atrophic[24-27] Neovascular[28]
	Retinal vein occlusion	Cystoid macular oedema in branch retinal vein occlusion[29-31] Cystoid macular oedema in central retinal vein occlusion[32]
	Diabetic eye disease	Diabetic macular oedema[33]
	Inflammatory retinal conditions	Acute zonal occult outer retinopathy[34] Unilateral acute idiopathic maculopathy[35] Cystoid macular oedema in uveitis[36]
	Other retinal conditions	Macular telangiectasia type I and II[37,38] Hydroxychloroquine retinal toxicity[39] Central serous chorioretinopathy[40,41] Myopic choroidal neovascularisation[42] Photic maculopathy[43]
	Vitreo-retinal surgery	Retinal detachment[44] Macular hole[45] Epiretinal membrane peel[46]
Glaucoma		Open-angle glaucoma[47,48] Angle-closure glaucoma[47] Advanced glaucoma[48,49]
Neuro-ophthalmology[50]		Multiple sclerosis[51] Optic disc oedema Optic atrophy Optic neuropathy Leber's hereditary optic neuropathy Thyroid-associated orbitopathy

output of the MAIA microperimeter is the MII, a proprietary statistical parameter that is calculated by incorporating the patient's age, ATS and fixation stability index.[2] It is derived by comparison with the manufacturer's normative data and describes the likelihood of threshold values differing significantly from normal values. The basis of MII calculation is not published. Macular integrity is reported as 'normal' (loss no greater than 40%), 'suspect' (loss between 40 and 60%), or 'abnormal' (loss greater than 60%).[11]

Recognised problems using MAIA microperimetry are similar to standard automated perimetry and are inherent in psychophysical testing. These include familiarity with testing procedures, patient compliance and understanding, sensitivity to patient movement, the need for undilated pupils during the test, in addition to standardised background lighting, and problems with mesopic background.

Microperimetry has been extensively used as a research tool[1] in phenotyping and monitoring treatments for diverse retinal conditions, and to a lesser extent glaucoma and neuro-ophthalmology (Table 1). In addition, microperimetry is commonly used in teaching low vision patients to improve visual function.[16] However, microperimetry use differs in clinical practice where patients present with symptoms, the diagnosis may not be immediately apparent and there is no opportunity for test-retest to validate results. Therefore, the aim of this study is to describe the usefulness of MAIA microperimetry in patients with visual symptoms in tertiary retinal practice.

METHOD

Design

This study was designed as a retrospective, non-randomised observational case series. Consecutive patients presenting to a retinal clinic who were tested with MAIA microperimetry as part of routine care were identified from records between December 2012 and October 2013 at a private tertiary ophthalmic practice. Included were cases of all age groups and all visual acuity levels, with the presence and type of retinal disease not specified as a criterion. No patient had previous experience in using the MAIA microperimeter, however some patients had prior experience in other types of visual field testing such as the Humphrey Visual Field Analyser. All procedures and protocols conformed to the provisions of the Declaration of Helsinki 1995, as revised in Edinburgh 2000, and patients provided informed consent for all testing procedures used.

Procedure

The chief complaint or presenting symptom of each participant was recorded. All participants underwent routine clinical examination. Best corrected visual acuity (BCVA) measurements were performed with either back-illuminated Snellen or Early Treatment of Diabetic Retinopathy Study (ETDRS) charts, placed at 6 and 4 m, respectively. Snellen fractions were converted to their equivalent score in logarithm of minimum angle of resolution (LogMAR) letters. Spectral-domain OCT macular scans were acquired using the Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, CA) or Spectralis HRA + OCT (Heidelberg Engineering, Heidelberg, Germany). Dilated fundus examination was conducted by one of two retinal ophthalmologists (HM or WH) and the diagnosis, if any, was recorded.

All participants underwent microperimetric examination using the MAIA microperimeter by one of four trained examiners. Indication for testing was to assist in understanding presenting symptoms and disease. Testing was performed undilated. When pupils were dilated prior to requesting microperimetry, patients attended for microperimetry testing at a subsequent appointment. When both eyes were assessed, microperimetry was performed in the two eyes on the same day. The right eye was always tested first by convention and several minutes rest allowed between testing. Microperimetry was conducted in a darkened room as recommended by the manufacturer and participants were dark adapted for between 5 and 10 minutes. This dark adaptation time reflects the use of the MAIA in clinical practice and time allowance between patients and tests. Refractive correction was not worn as the refractive status of all participants was within the range accounted for by the automatic focus of the SLO (-15 to +10 dioptres).

Standard factory-set parameters were used with respect to the fixation target, stimuli and background luminance. A red circular fixation target measuring 1° in diameter was used. White Goldmann size III stimuli were presented for 200 milliseconds against a white background of 1.27 cd/m^2, using an expert 4-2 staircase strategy. A radial stimulus array was used with fixed distance between stimuli in the array. The maximum stimulus luminance was 318.47 cd/m^2 and stimulus attenuation ranged from 0 to 36 dB. The examiner remained present in the room at all times during testing.

Outcome measures

Primary outcome measures were BCVA (LogMAR letters), macular integrity index (MII), average threshold sensitivity (ATS; dB) and test duration (minutes). Secondary outcome measures were fixation stability and pattern of visual field loss. The pattern of visual field loss was categorised (by HM or WH) as 'full', 'generalised depression', 'focal scotoma' or 'ring scotoma'. Classification by MAIA algorithms of MII and ATS into 'normal', 'suspect' and 'abnormal' was not recorded. Demographic information pertaining to patient age and gender was also collected.

Table 2. Summary data for patients undertaking MAIA microperimetry

Clinical group	**Group 1** **Focal scotoma**	**Group 2** **Reduced average threshold & poor fixation**	**Group 3** **Reduced average threshold & normal fixation**	**Group 4** **Normal threshold & fixation**	**Comparison of abnormal group & normal group**	**Comparison between abnormal groups**
	ABNORMAL			**NORMAL**	**p-value**	**p-value**
Number of eyes	21	31	20	8		
	72			8		
Age mean (years) (Range, SD)	63 (26 - 90, ±19.45)	79 (38 - 92,±10.40)	80 (69 - 91, ± 6.40)			**p=0.001**
	75 (26 - 92, ±14.80)			63 (38 - 74, ±11.82)	**p=0.006**	
BCVA mean (# letters read correctly) (Range, SD)	76 (28 - 95, ±15.86)	63 (26 - 88, ±19.46)	68 (49 - 85, ±68.25)			**p=0.018**
	68 (26 - 95, ±17.24)			82 (69 - 90, ±8.21)	**p=0.0017**	
Macular integrity index median (Interquartile range) Range	100 (99.5 - 100) 49.9 - 100	100 (97.3 - 100) 1.3 - 100	99.95 (99.1 - 100) 72.7 - 100			p=0.80
	52 (16.2 - 65.8) 1.3 - 100			52 (16.2 - 65.8) 10 - 93.1	**p=0.000**	
Average threshold median (dB) (Interquartile range) Range	22.3 (16.9 - 24.6) 7.8 - 26.6	16.1 (3.4 - 23.7) 0 - 26.9	20.85 (14.8 - 22.3) 0 - 25.9			p=0.12
	20.85 (11.95 - 23.75) 0 - 26.9			27.9 (26.8 - 28.5) 24.6 - 29.5	**p=0.000**	
Test duration mean (minutes)	OU 6.12 OD 6.09 OS 6.15	OU 7.27 OD 8.54 OS 6.46	OU 5.93 OD 5.81 OS 6.07			**p=0.004**
	OU 6.56 OD 6.89 OS 6.28			OU 5.71 OD 5.97 OS 5.26	**p=0.036 (OU)**	

Following observation of the raw data, eyes were divided into 'normal' or 'abnormal' groups by either of the trained vitreoretinal ophthalmologists (HM or WH). Normal eyes comprised eyes thought by the examiners to be normal and symptoms not related to macular pathology, or unaffected second eyes. Normal eyes fulfilled each of the following four criteria: i) no retinal or macular pathology clinically present; ii) normal ATS; iii) full field; and iv) stable fixation. Abnormal eyes included those eyes that fulfilled two or more of the following criteria: i) presence of retinal or macular pathology; ii) reduced ATS; iii) either focal or diffuse field loss; or iv) fixation either unstable, relatively unstable or stable. The abnormal group was further sub-divided into three groups dependent on pattern of visual field loss and stability of fixation (Figure 1, Table 2).

Data analyses

All patient data was de-identified prior to statistical analysis. None of the data was normally distributed, therefore non-parametric statistical tests were used for analysis.

Receiver operating characteristic (ROC) curves were constructed to investigate the ability of ATS and MII to predict normal versus abnormal status.

Predictors of BCVA were analysed with linear regression. Categorical values of age, gender, MII, ATS, test duration and fixation status were considered for inclusion in the model. Predictors of normal versus abnormal status were analysed with logistic regression. Two separate models were developed, one for the entire sample and one for those with normal ATS values. Categorical values of age, gender, MII and test duration were considered for inclusion in the model for the entire sample. ATS was added as a continuous variable in the model for those with normal ATS values.

A forward stepwise selection process (with a p-value of 0.05 to enter) along with the Karlson, Holm and Breen (KHB) method of examining confounders (using a 20% coefficient confounding percentage cut-off) was used to select covariates for inclusion in each of the models. All analyses were performed using either SPSS v21 or Stata v12.

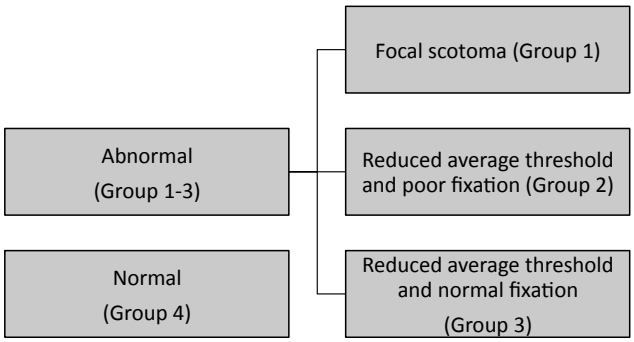

Figure 1. Division of eyes into normal or abnormal (with sub-groups) based on pattern of field loss.

Table 3. Diagnoses of patients undertaking MAIA microperimetry

Diagnosis	Frequency (N)	Percentage
Normal	9	11.3
Plaquenil maculopathy	4	5.0
Atrophic AMD	24	30.0
Neovascular AMD	12	15.0
Epiretinal membrane peel	4	5.0
Macular telangiectasia	2	2.5
Macular hole	3	3.8
Central serous retinopathy	4	5.0
Proliferative diabetic retinopathy	2	2.5
Cystoid macular oedema	1	1.3
Acute zonal occult outer retinopathy	2	2.5
Macular drusenosis	3	3.8
Legionnaire retinopathy	1	1.3
Total	**71**	**88.8**
Missing	9	

RESULTS

Eighty eyes (38 right, 42 left; 56 female, 24 male) of 48 patients presenting to a retinal clinic within a private tertiary ophthalmic practice were retrospectively reviewed (Table 2). Participants were aged 26 to 92 years (mean 73.31 ±15.55).

Of the 80 eyes, 62 had a diagnosis of retinal or macular pathology (Table 3). Nine eyes had no retinal or macular pathology clinically present. Diagnosis classifications were missing for nine eyes. Thirteen diagnoses were identified (Table 3), the most common being age-related macular degeneration (atrophic 30%, neovascular 15%). The most common presenting symptoms were difficulty reading (36.3%), scotoma (15.0%), reduced vision (11.3%) and distortion (10.0%) (Table 4).

Based on the definitions of normal and abnormal outlined previously, eight eyes were identified as fulfilling all of the criteria for 'normal' and as such, were classified into the 'normal' group. The remaining 72 eyes fulfilled two or more of the criteria for 'abnormal' and therefore were classified into the 'abnormal' group. Eyes in the abnormal group were further divided into three sub-groups based on pattern of visual field loss and fixation stability. Table 2 shows the frequency of eyes in these three sub-groups.

The mean age of the normal group was significantly younger (63 ±11.82 years) compared with the abnormal group (75 ±14.80 years) (Mann Whitney: U = -2.76, p = 0.006). Within the abnormal group, Group 1 was significantly younger (63 ±19.45 years) compared with Groups 2 or 3 (79 ±10.40 years and 80 ±6.40 years, respectively) (Kruskal-Wallis: H(3) = 13.9, p = 0.001).

BCVA ranged from 26 to 95 letters (mean 69 ±17.03 letters). On average, the normal group correctly read 14 letters more than the abnormal group and this was statistically significant (Mann Whitney: U = -1.87, p = 0.017). When comparing the abnormal groups, Groups 1 and 3 had better BCVA than Group 2 (Kruskal-Wallis: H(3) = 8.07, p = 0.018).

The distribution of ATS across the four groups is shown in Figure 2 and Table 2. The distribution of values for ATS differed between normal and abnormal eyes (Mann Whitney: U = -4.51, p = 0.000). Group 2 patients (by definition of clinical category) demonstrated lowest reduced average threshold (16.1 dB) and broadest result spread (0 – 26.9 dB) by comparison with other patients, but the three abnormal groups did not differ significantly (Kruskal-Wallis: H(3) = 4.33, p = 0.12).

The distribution of scores for MII was spread across most of the possible values for the normal and abnormal groups

Table 4. Presenting symptoms of patients undertaking MAIA microperimetry

Presenting symptom	Frequency (N)	Percentage
Difficulty reading	29	36.3
Distortion	8	10.0
Asymptomatic	7	8.8
Film over vision	2	2.5
Reduced vision	9	11.3
Deteriorating vision	3	3.8
Monocular diplopia	4	5.0
Scotoma	12	15.0
Glare sensitivity	1	1.3
Floaters	2	2.5
Total	**77**	96
Missing	3	

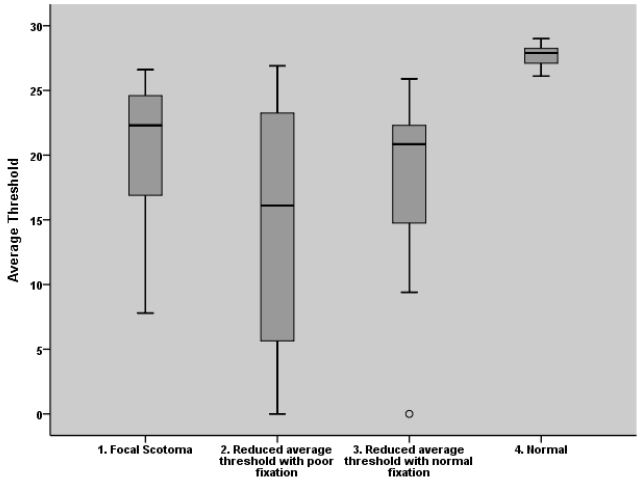

Figure 2. Average threshold sensitivity (ATS) for clinical sub-groups.

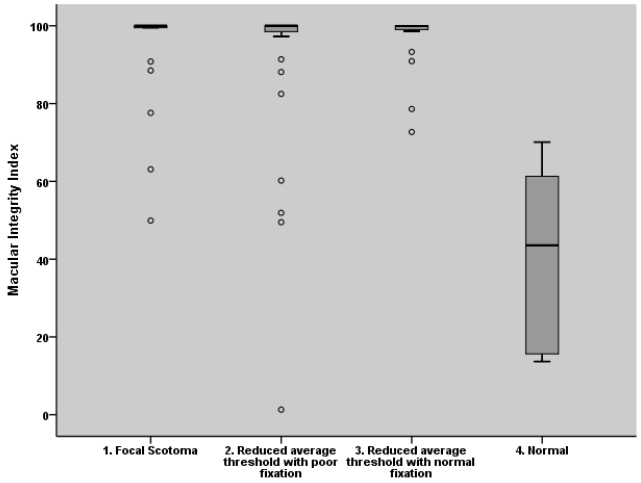

Figure 3. Macular integrity index (MII) for clinical sub-groups.

(Figure 3, Table 2). The distribution of values for MII differed significantly between abnormal and normal eyes (Mann Whitney: U = -4.69, p = 0.000), but MII did not differ significantly within the three abnormal groups (Kruskal-Wallis: H(3) = 0.46, p = 0.80).

Figure 4 shows the relationship between MII and BCVA letters. A statistically significant, albeit weak, relationship was found (Spearman's rank correlation; rho = -0.305, p = 0.006).

The relationship between MII and ATS was examined. Whilst these indices are both calculated from the same sensitivity data, this was done because the algorithm for calculating MII has not been published and so, it was performed as a validation of the algorithm. If no relationship was found, this would cast doubt on the usefulness of the MII. A statistically significant relationship was found between MII and ATS (Spearman's rank correlation; rho = -0.767, p = 0.000) when all groups were combined (Figure 5).

Review of Table 2 shows a useful ATS discriminatory value that has the potential to differentiate normal from abnormal eyes. A discriminatory ('cut-off') value for average threshold of approximately 25 dB (falling somewhere between the range of 24.6 and 26.9 dB) was identified as having the potential to distinguish normal from abnormal status. This cut-off value and/or range might help to delineate normal from abnormal. Upon closer investigation of ATS between the abnormal eyes, it was not possible to discriminate between the three different abnormal groups.

A ROC curve was constructed to further investigate the ability of ATS to predict normal status [Area under the ROC curve (AUROC) = 0.988 (95% CI, 0.967, 1.00), Figure 6a]. Based on this, ATS is a useful predictor in discriminating

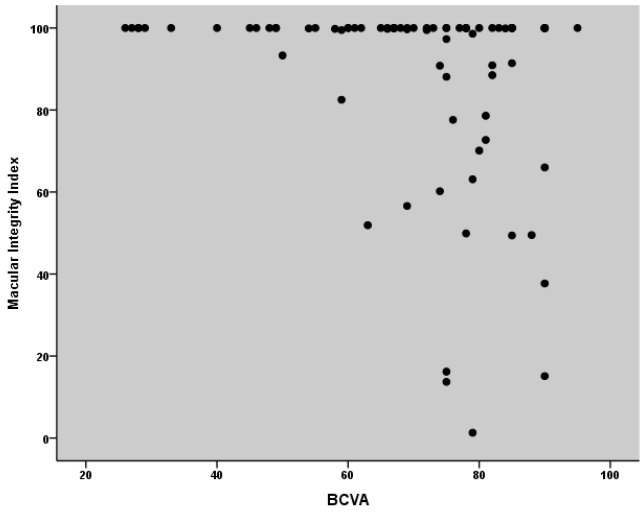

Figure 4. Relationship between macular integrity index (MII) and BCVA letters.

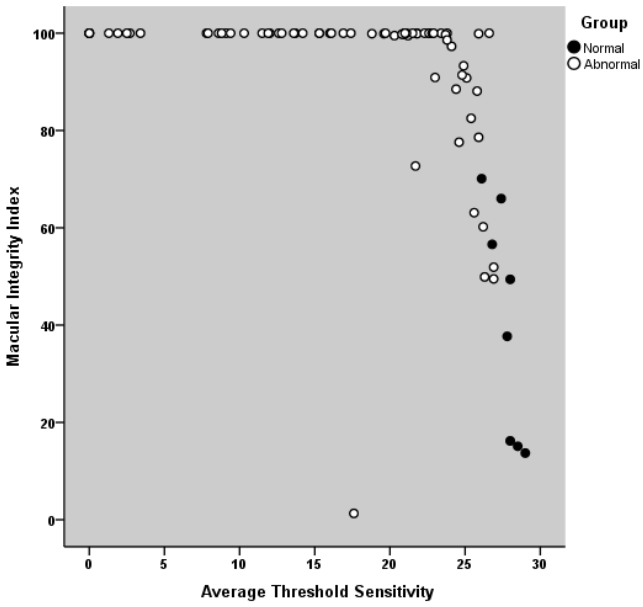

Figure 5. Relationship between macular integrity index (MII) and average threshold sensitivity (ATS), normal versus abnormal group.

normal from abnormal. A ROC curve confirmed that this is also the case for MII [AUROC = 0.964 (95% CI 0.923, 0.100), Figure 6b].

Average test duration for patients, irrespective of eye being tested, was 5.71 minutes (range: 5.08 – 8.53) for those in the normal group and 6.56 minutes (range: 2.44 – 16.39) for those in the abnormal group (Table 2). The average test duration for the normal group was significantly faster than the abnormal group (Mann Whitney: U = -2.09, p = 0.036). Figure 7 shows test duration by eye and by group; the right eye was always tested first. The group with reduced average threshold and poor fixation had larger variation in testing

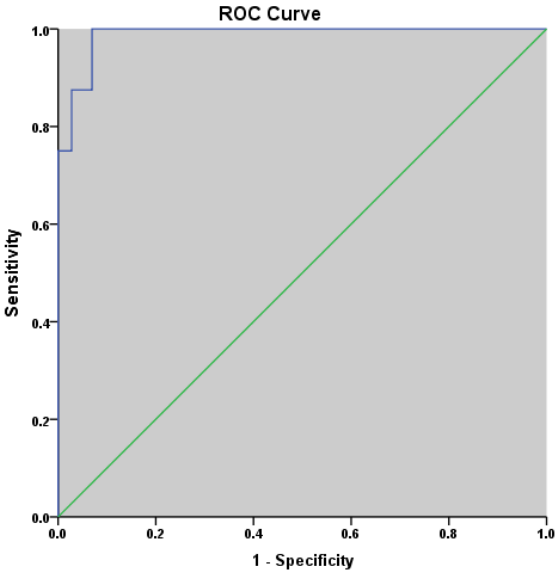

Figure 6a. ROC curve of ability of average threshold sensitivity (ATS) to discriminate normal from abnormal.

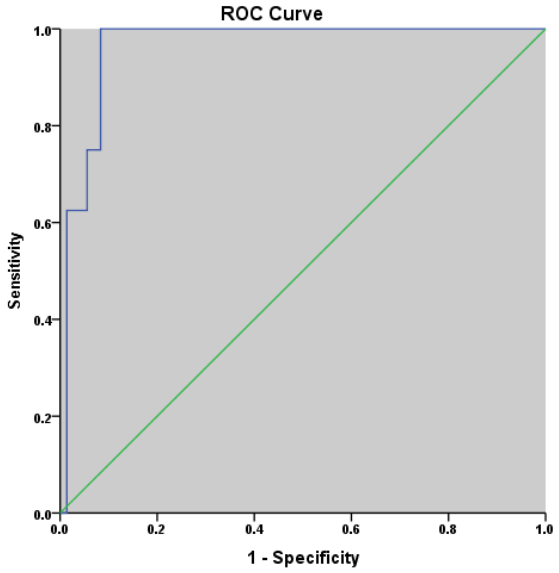

Figure 6b. ROC curve of ability of macular integrity index (MII) to discriminate normal from abnormal.

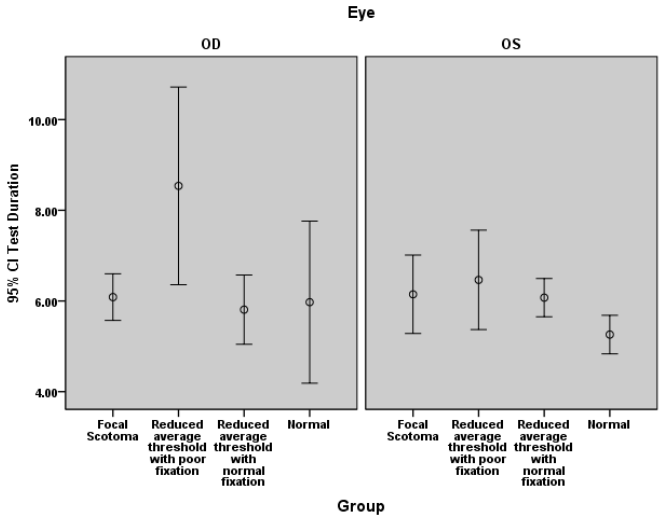

Figure 7. Test duration (minutes), by group and eye.

time compared with the other groups (Kruskal-Wallis: H(3) = 13.32, p = 0.004) and whilst there was an improvement in test duration for the left eye (6.46 minutes) compared with the right (8.54 minutes) suggesting a learning effect, this did not reach statistical significance (Mann Whitney: U = -1.81, p = 0.07). There were no significant differences in average test duration when comparing right and left eyes for the normal group (Mann Whitney: U = -0.75, p = 0.56), abnormal group (Z = -1.11, p = 0.27), or when the abnormal group was divided further (Group 1: Z = -5.28, p = 0.61; Group 2: Z = -1.81, p = 0.07, Group 3: Z = -0.46, p = 0.66).

A forward stepwise linear regression was undertaken to determine which variables might be predictive of BCVA. Any variable with a coefficient significant at the 25% level in univariate analysis was considered for inclusion in the stepwise selection process. The variables of age, gender, MII, ATS and fixation status met this criterion. Test duration did not and was therefore excluded. Each variable was individually added to age, which had the largest effect size. Only fixation status was found to be significant at 5%. Table 5 shows the results of the simple model. The remaining variables were individually added to age and fixation status. None were significant at 5%. The confounding effects of gender, MII, ATS and test duration on the model with age and fixation status were examined. ATS and test duration were found to confound effect sizes by more than 20% and added to the model. Table 6 shows the results of the final (confounding) model. The final model included age, fixation status, ATS and test duration.

The confounding model (Table 6) has an *r2* value of 0.3431 indicating that it explains 34% of the variation seen in BCVA. It has an Akaike information criterion (AIC) of 666 which indicates that the fit of the model after taking into consideration the number of variables is not quite as good as the simple model (Table 5) which excludes the confounders and had an AIC of 664. However, this difference was very

Table 5. Results from multivariate linear regression of BCVA with clustered sandwich estimator of variance (simple model – no confounders)

	Coefficient	95% CI		p-value
Age (reference: 26 – 65)				
67 – 75 yrs	-2.54	-12.35	7.27	0.607
76 – 83 yrs	-5.62	-15.33	4.08	0.252
84 – 92 yrs	-17.85	-27.83	-7.87	**0.001**
Fixation status (reference: Stable)				
Unstable	-8.83	-15.88	-1.78	**0.015**
Intercept	80.44	73.48	87.39	**<0.001**

Table 6. Results from multivariate linear regression of BCVA with clustered sandwich estimator of variance (confounding model)

	Coefficient	95% CI		p-value
Age (reference: 26 – 65)				
67 – 75 yrs	-4.16	-15.83	7.51	0.477
76 – 83 yrs	-5.75	-16.57	5.07	0.290
84 – 92 yrs	-16.97	-30.68	-3.25	**0.016**
Fixation status (reference: Stable)				
Unstable	-7.36	-15.64	0.92	0.080
ATS (reference: Normal)				
Suspect	-1.81	-17.87	14.26	0.822
Abnormal	-9.96	-20.42	0.49	0.061
Duration (reference: <5'38")				
5'38" to <6'09"	-9.96	-9.96	-9.96	-9.96
6'09" to <7'05"	-9.96	-9.96	-9.96	-9.96
≥7'05"	-9.96	-9.96	-9.96	-9.96
Intercept	82.64	76.10	89.18	**<0.001**

small. The simple model has an *r2* of 0.2627. The likelihood ratio test cannot be conducted on models with robust variance estimators, however an exploratory analysis showed no significant difference in the fit of the two models following removal of the clustering.

Logistic regression was used to analyse predictors of normal versus abnormal status. Two models were developed. The first model analyses the results of all eyes and does not include ATS (*Full sample* model). The second model includes ATS as a variable with a piecewise relationship with normal/abnormal status. That is, for all eyes with ATS lower than 25dB, the odds of having an abnormal status is 100%. As ATS increases from 25dB, the odds of having an abnormal status decrease in a linear fashion. Because the odds ratio (OR) cannot be calculated for ATS values less than 25dB, the model automatically excludes eyes in that range. Therefore the second model includes only eyes with normal ATS (*Normal ATS* model: ATS > 25 dB, *n=19*). All of the eyes with unstable fixation were classified as being abnormal and therefore no OR can be calculated for fixation status.

Any variable with any coefficient significant at the 25% level in univariate analysis was considered for inclusion in the stepwise selection process. As seen in Table 7, age, MII and test duration met this criterion for the *Full sample* model and age, MII, and ATS met this criterion for the *Normal ATS* model (Table 8). The forward stepwise process was carried out using the same method as that described for the BCVA linear regression model.

Because the only variable to be included in the final *Full sample* model was MII, the results of the final model are as seen in Table 7. Compared to those with a normal MII, the odds of having an abnormal status are 136 times higher for those with an abnormal MII (OR 136, 95%CI 15 1250, $p < 0.001$. For suspect MII: OR 8.02, 95%CI 0.44 82.43, $p = 0.180$).

Because the only variable to be included in the final *Normal ATS* model was ATS itself, the results of the regression are as seen in Table 8. For each increase in 1 dB from 25 dB, the odds of having an abnormal status decrease by 94% (OR 0.06, 95%CI 0.01 0.38, $p = 0.003$).

Table 7. Results from univariate logistic regression of MAIA status with clustered sandwich estimator of variance (full sample model)

	OR	95% CI		p-value
Age (reference: <65 years)				
≥65 years	8.33	1.20	58.03	**0.032**
Gender (reference: Male)				
Female	1.46	0.22	9.58	0.695
MII (reference: Normal)				
Suspect	6.00	0.44	82.43	0.180
Abnormal	136.00	14.80	1249.62	**<0.001**
Duration (reference: <6 mins)				
≥6 mins	1.46	1.46	1.46	1.46

Table 8. Results from univariate logistic regression of MAIA status with clustered sandwich estimator of variance (normal ATS model)

	OR	95% CI		p-value
Age (reference: <65 years)				
≥65 years	4.44	0.46	42.62	0.196
Gender (reference: Male)				
Female	1.60	0.16	15.81	0.688
MII (reference: Normal/supect)				
Abnormal	8.00	1.67	38.37	**0.009**
Duration (reference: <5m36s)				
<5m36s	1.20	0.15	9.33	0.862
ATS (continuous variable)				
Per dB	0.06	0.01	0.39	**0.003**

DISCUSSION

In this retrospective review of 48 patients (80 eyes) presenting to a private tertiary ophthalmic practice, eyes were divided into normal and abnormal clinical groups. The abnormal group was further sub-divided into three categories based on pattern of visual field loss and fixation stability. The four resulting groups differed in age, with normal patients and patients with focal scotomata being significantly younger. The groups also differed significantly with respect to BCVA, with the normal group reading on average more letters than the abnormal group. Within the abnormal groups, Groups 1 and 3 also read on average more letters than Group 2 and this was statistically significant. As expected, test times were significantly shorter in the normal group.

In using microperimetry clinically, it is important to be able to distinguish normal from abnormal results. Outcome measures were numerical ATS and MII, and did not include manufacturer's classification into 'normal', 'suspect' or 'abnormal' due to limited published normative data. The distribution of ATS scores differed significantly between normal and abnormal eyes, but did not differ significantly between the three abnormal groups. ATS was found to be potentially useful in discriminating between normal and abnormal groups. A discriminatory value for average threshold of approximately 25 dB (falling between the range of 24.6 and 26.9 dB) was identified as having the potential to differentiate normal from abnormal eyes. A ROC curve confirmed that ATS was highly reliable in differentiating normal from abnormal eyes, with the AUROC curve almost equal to one (0.988). Whilst an approximate discriminatory value for average threshold was detected, a more precise cut-off score could not be identified and no single parameter was unequivocally able to differentiate between normal and abnormal status, or between the three sub-classifications of abnormal.

Overlap was present between the results of normal and abnormal clinical groups, with the distribution of MII scores in both groups being spread across most of the possible values. Whilst MII was not found to differ significantly between the three abnormal groups, it did differ significantly between normal and abnormal eyes. A ROC curve also found MII to be highly predictive of normal versus abnormal status.

The repeatability of patient responses is an important consideration when interpreting the results of psychophysical testing. A recent study of patients with AMD tested using the MAIA microperimeter found a significant improvement in mean threshold sensitivity between the first and second microperimetry examinations, but not for subsequent examinations conducted within the same session, suggesting a learning effect.[14] Our study did not demonstrate a learning effect within a single test session, with no significant difference in test duration between first and second eyes tested, similar to results of previous research in patients with macular pathology assessed using the Nidek MP-1 microperimeter.[7]

Given the lack of a single variable capable of distinguishing between normal and abnormal macular function, the three patterns of abnormal results are potentially useful in understanding the basis of symptoms and signs. Generalised depression is probably the most difficult to interpret following a single test session, without identified focal macular pathology clinically, due to learning effect reported by others.[14]

Although the algorithm used for calculation of MII has not been published, using reverse calculations from raw data to MII, we found, as expected, a statistically significant relationship between MII and ATS when all clinical groups were combined. Forward stepwise linear regression found age, fixation status, ATS and test duration to be significant predictors of BCVA.

This study is limited by retrospective design, lack of test-retest data, lack of normative data to interpret threshold data, and lack of knowledge of the algorithms used to calculate the MII. Only a small number of eyes were included in the normal group and these controls were not age-matched. The large age range of participants (26 – 92 years) is a limitation of this study with respect to the discriminatory value for ATS. The authors acknowledge that absolute values do not account for age-related changes in threshold, and therefore a discriminatory 'range' would be more appropriate. Two different visual acuity charts were used. Whilst test standardisation would have been ideal, this was not achievable owing to retrospective design.

Microperimetry is gaining increasing interest as a clinical tool for the evaluation of visual function in retinal diseases and other ocular pathologies. It is being used as an adjunct to visual acuity testing, conventional perimetry and electrophysiology in the functional assessment of real-life patients. In the clinical setting, the main indication for microperimetry testing is in instances where dissociation exists between objective BCVA and symptoms reported by the patient, particularly with respect to difficulty reading. This type of dissociation is often apparent in patients with early or intermediate dry AMD whereby the patient has intact foveal vision but an annular area of geographic atrophy surrounding the spared fovea (ring scotoma). The advantage of microperimetry testing is the ability to document poor fixation and parafoveal microscotomata that severely reduce the usefulness of what might appear 'normal' vision, that is BVCA in the order of 20/20 (85 letters) to 20/30 (75 letters). Parafoveal loss can severely reduce reading efficiency when all other parameters are normal. This is because the perifoveal annulus assists the fovea to track letters or words on a single line. Aside from microperimetry testing, there are few ways to quantify this particular function.

Thus, the clinical usefulness of the MAIA microperimeter lies in its ability to assess parafoveal macular function where central foveal function is normal or near-normal. BCVA represents the gold standard in terms of assessing central foveal function. However, there is limited reliable testing available to assess parafoveal macular function. Whilst the Amsler grid is ideal for detecting the presence/absence of distortion, it is a subjective test and does not allow for measuring and quantifying areas of low threshold sensitivity. Other types of automated perimetry testing, such as the Humphrey Visual Field Analyser, are well placed to assess peripheral vision but not necessarily parafoveal macular function as they are not discriminatory in this small zone.

CONCLUSION

In principal, MAIA microperimetry allows for the detection of areas of paracentral dysfunction. The threshold sensitivity level (dB) is then of some second order use to detect progression over time. Fixation stability measured by the MAIA microperimeter also provides an indication of how difficult it is for the patient to achieve peak visual function. It can give an indication as to whether the patient employs a visual scanning technique to search for letters on the visual acuity chart versus being able to instantly detect the optotype or test stimulus. Thus, MAIA microperimetry is useful in the clinical setting to identify and monitor those with parafoveal macular dysfunction not identified by BCVA or conventional perimetry testing. However, it is important to recognise that the results of MAIA microperimetry need to be interpreted with some caution until more normative data is published and the methods for calculating MII are openly defined. The potential clinical use for microperimeters is likely to increase as the use of overlay SLO and OCT functionality becomes more widespread.

ACKNOWLEDGEMENTS

The authors would like to gratefully acknowledge Myra McGuinness and Sophie Rogers for providing statistical advice.

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