Research Article

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2024.57.008955

Using the Microperimeter to Guide Searching Eye Movements in the Presence of a Central Scotoma

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ARTICLE INFO

Received: June 16, 2024

Published: June 24, 2024

Citation: Villani Gianfrancesco M, Nalini Yuri, Morales Marco U and Küster Stephan. Using the Microperimeter to Guide Searching Eye Movements in the Presence of a Central Scotoma. Biomed J Sci & Tech Res 57(1)-2024. BJSTR. MS.ID.008955.

ABSTRACT

Purpose: to investigate whether the microperimeter can provide a useful setting to train searching eye movements in the presence of a central scotoma.

Methods: baseline retinal sensitivity and fixation evaluations were performed with the MAIA microperimeter on five eyes/subjects with eye disease and five normally seeing eyes/subjects. Subsequently, the participants with scotoma were guided to perform searching eye movements by an operator who had simultaneous direct view of the participant's live fundus image and of the MAIA Multi-fixation target set. Outcome measures were the percentage of targets seen by the participant and the rate of target detection through different phases of the training.

Results: all the participants with scotoma were able to detect the MAIA Multi-fixation targets albeit at a lower number and rate compared to the control subjects. The percentage of targets found by the participants with scotoma increased significantly with searching eye movements guided by an operator who used the superimposed target set image on the fundus as a reference for directions ($\chi 2$ (2) = 7.684, P= .021).

Conclusions: the MAIA Multi-fixation can be used for a visual search task besides its standard purpose to provide a fixation target during microperimetry. However, such use of the microperimeter still requires manual intervention. Future studies are needed to determine if the visual search improvements achieved with this kind of training will transfer to real life.

Keywords: Microperimeter; Central Scotoma; Eye Movements

Abbreviations: CDVA: Corrected Distance Visual Acuity; MAIA: Macular Integrity Assessment; SLO: Scanning Laser Ophthalmoscope

Introduction

Microperimetry is the gold standard to evaluate topographic retinal sensitivity and fixation location and stability [1-6]. It is a greatly valued tool in the assessment of low vision due to diseases of the retina and the optic pathways. In terms of training, microperimeters can offer the possibility to perform biofeedback in order to increase fixation stability [7-12]. In this type of setting, the operator can rely on the results of microperimetry to choose the optimal area of the patient's fundus that will be the target of the biofeedback training. The microperimeter's embedded eye tracking system keeps the biofeedback stimulus on the precise chosen retinal location. After a sequence of biofeedback sessions, the outcome is evaluated by fixation analysis performed by microperimetry with the purpose to achieve a higher stability of the retinal fixation location. Outside of the microperimeter's environment, many different training strategies have been suggested to enhance the residual visual capabilities of the low vision person and to compensate for vision loss [13-17]. For example, studies have investigated the training of visual perception, of eye movements, or both, using outcome measures such as near visual acuity, reading speed, and performance of activities of daily living in people with central vision loss [18-20].

Eye movements training has been shown to improve reading speed in patients with macular degeneration even with little direct practice in reading sentences but instead concentrating on having subjects practice control of eye positions and eye movements [15]. In their study, Seiple, et al. [15] created a customized lab setting in which the experimenter could view the patient's fundus image and a (letter) target overlaid on the fundus at the retinal location of the stimulation. This is similar to what we are suggesting in the present study but with the use of a microperimeter and its embedded set of targets. In a condition of extensive visual field loss such as it happens with homonymous visual fields defects, which can variably encroach on the central visual field, compensatory training consisting of large explorative saccades has proven to be effective in selectively reducing saccadic reaction times to the stimuli on the scotoma side so that patients showed improvements in a natural search task (table test) and in natural scene exploration [21], although no benefit was achieved on a central visual function such as reading performance.

In the case of central visual field loss, compensatory training should aim at making smaller and accurate eye movements tuned to compensate for the direction and distance of the scotoma border from the fixation location [22]. In this framework, the simultaneous view of the live fundus image and of the superimposed target can be very valuable for the trainer not only to verify the extent and accuracy of the eye movements but also to provide guidance to the patient for such explorative task. The MAIA Multi-fixation embedded in the MAIA microperimeter (Centervue SpA, Padova, Italy) provides a set of targets that are seen by the operator as superimposed on the patient's live fundus image. Single or multiple targets of the MAIA Multi-fixation can be lit on (or switched off) so that the patient also can see them into the microperimeter, although this system has to be operated manually outside of the automated microperimetry procedure.

Our goal was to evaluate the hypothesis that small and accurate eye movements can be trained within the microperimeter in order to compensate for a central scotoma, while imaging the fundus and simultaneously viewing the superimposed fixational landmarks. This approach requires prior knowledge of the central scotoma plot achieved by microperimetry, a live fundus image provided by a fundus camera, simultaneous viewing of the fundus and the stimuli during the training as provided by the MAIA Multi-fixation, and the possibility to provide feedback to the patient to guide the explorative eye movements.

Materials and Methods

Five adult participants were selected from a low vision clinic in Verona, Italy, on the basis of the presence of a central dense scotoma in both eyes either at the fovea or within 2 degrees from it, as plotted by MAIA microperimetry. The disease causing the scotoma condition could vary among participants. Since microperimetry only works monocularly, their better seeing eye was chosen for the training with the microperimeter. Corrected distance visual acuity (CDVA) for all subjects was measured with ETDRS charts at 4m. The control group consisted of five right eyes of five normally seeing adult subjects without eye disease. The study complied with the tenets of the Declaration of Helsinki and was approved by the institutional review board at the Centro Riabilitazione Ipovedenti e Microperimetria (CRIM) of Verona, Italy. All participants gave their informed consent prior to entering the study. The study is registered in the German Clinical Trials Register (DRKS-ID: DRKS00021645).

Baseline microperimetry was performed in all subjects with the standard examination settings of the MAIA, which consists of a 10° testing area, Goldmann III size white LED stimuli, 0.8° diameter red circle as the central fixation target, and an SLO-fundus image controlled by a 25 Hz retinal eye-tracker. Projection strategy was the "4-levels-fixed", meaning that 4 different stimuli intensities were used: 25 dB, 15 dB, 5 dB, and 0 dB. This strategy provides an assessment of "good", "medium", "bad" or "scotomatous" retinal sensitivity. It is a supra-threshold strategy designed to have a fast assessment of retinal sensitivity on patients with known pathologies [23]. A dense scotoma was defined as an area of complete loss of retinal sensitivity in the tested area resulting from missing responses when a stimulus of maximum luminance (1000 asb) was projected on a specific retinal area.

During the training, real-time imaging of the fundus was supplied by the MAIA SLO fundus camera. The fixation targets were provided by the MAIA Multi-fixation system, which is an array of 20 cross-shaped LEDs, originally designed to furnish an alternative fixation target for microperimetry to the standard round target of 0.8°. To that purpose, the examiner can select one of the cross-shaped LEDs as a fixational landmark for microperimetry. These cross-shaped targets have each a diameter size of 1.2° and are distributed on an evenly spaced 5 by 5 elements grid with a total width of the grid of 10.8°, centered on the MAIA standard round central fixation target [24]. Before starting the microperimetry automated protocol, the MAIA shows to the examiner all the multiple fixational targets of the Multi-fixation onto the patient's live fundus image and allows to switch on and off one (or more) target by touch-screen so that the selected target(s) becomes visible also to the patient, until the examiner finalizes the choice of a single target for the subsequent microperimetry.

By exploiting such manual target selection mode of the MAIA Multi-fixation as explained above, we developed a novel custom eye-movements training strategy using the Multi-fixation LED array projected on the real-time SLO retinal image of the participant. The operator had a continuous view of all the targets superimposed on the retinal image and could switch on and off specific targets manually via touch-screen, either one-by-one or more than one simultaneously, in order to make them visible to the participant. The training was divided into three phases and completed in one session not longer than 45 minutes, including a few minutes of rest in between

the phases. In phase 1, the participant was asked to keep his/her fixation on the central fixation target as steady as possible. The operator randomly switched on and off the eccentric cross-shaped targets one by one. The participant was instructed to keep fixation on the central round target at the best of his/her capabilities, to alert the operator whenever the central round target disappeared from view, and to say if any eccentric target became visible. Before proceeding to the next phase, questions were asked to the participant about the location of the perceived targets with reference to the central round target in order to stimulate scotoma awareness, such as if the round central fixation landmark was disappearing at any moment, and on which side of the round landmark could most of the cross-shaped targets be seen.

In phase 2, the participants were allowed to perform searching eye movements, which means that they were asked to fixate directly on the appearing targets wherever they were projected. The MAIA standard central round target was kept always "on" both to the operator and to the participant as a reference landmark for directions. The operator could provide verbal directional cues when the subject did not detect the target. Such cues were based on the observation of the live fundus image and the knowledge of the overlaid scotoma plot, fixation and target location. When moving the eye, the participant was asked to look for the cross-shaped target by rotating the eye in the direction of the scotoma covering the distance to the target until it could be entirely seen (Figure 1). Additional individual instructions consisted of reminding to the participant to "look again at the central round target" or to "search for the cross more toward…" a specific direction relative to the scotoma location as referred to the central round target. In the final phase 3, the central round target was turned off, the participants were free to move their eyes to look for the targets as needed, and guidance from the operator was limited to encouragements such as to keep searching if any target was not seen, but without providing any directional cues.

Figure 1: Figures 1A &1B. Overlay of the MAIA Multi-fixation Target Set on the retina of a participant with central scotoma caused by geographic atrophy at the *macula. A*. The MAIA Multi-fixation Target Set is superimposed on the live fundus image. The red arrow points at the geographic atrophy at the macula. The thin red line marks the border of the area of geographic atrophy corresponding to the central scotoma as determined by baseline microperimetry. Targets in blue color are visible only to the operator. Targets in red color are displayed on both sides, i.e., to the operator and to the participant. The preferred retinal locus is eccentric and temporal to the fovea, and it is aligned with the small round target in red color at the center of the Multi-fixation grid. White arrowhead points at a cross-shaped target that falls within the scotoma, and therefore it is not seen by the participant. In the dialog at the bottom of the image, white words in the first line belong to the operator, while yellow words in the second line are spoken by the participant. B. Following an appropriate eye movement toward the direction of the scotoma, the position of the scotomatous area has shifted laterally relative to the target that was previously not seen. Therefore, the cross-shaped target in red color (white arrowhead) now lies on healthy retina just beyond the border of the central scotoma (thin red line) and can be seen by the participant in its entirety.

Control subjects completed microperimetry and task phases 1 and 2. Since they had no scotoma, it was deemed unnecessary to run phase 3 for them. The percentage of targets found (targets found/projected) was the primary outcome measure for all task phases. Additionally, target detection rate was measured as the number of targets detected per task duration. The testing sessions were video-recorded from the MAIA embedded-display and later analyzed for the purposes of this study. Time measurements were drawn from the video-recordings. For the statistical analyses, the Shapiro-Wilk test was used to gauge for relatively normal distributions of data, even though the sample sizes were small in this pilot study [25]. Data were presented descriptively in terms of average, median, and standard deviation (STD) when the distribution was normal, or by average, median and interquartile ranges between 25% and 75% (IQR 25%-quartile to

75%-quartile) when the distribution departed from normality. Comparisons between groups (study vs control group) were analyzed with the Student's t-test for independent samples when values were normally distributed or with the Mann-Whitney U test when values departed from normality.

Intra-group comparisons for three or more repeated measures were performed with the Friedman test for repeated-measures when dealing with values that were not normally distributed. In the case of a positive Friedman test, a post-hoc pairwise Wilcoxon signed-rank test was performed to detect which pairs in particular differed from each other. If the Friedman test result was not statistically significant, then post-hoc tests were not performed. Intra-group comparisons for two repeated measures were performed using the t-test for two dependent means when values were normally distributed. Significance level (α) was set at 0.05 for all statistical tests. The data analysis software used was SPSS (SPSS Inc, Chicago, IL, USA).

Results

Study group mean age was 34.8 years-old (median 40; STD= 9.4), ETDRS CDVA was 0.62 logMAR (median 0.7; STD= 0.37 logMAR). Bivariate contour ellipse area @95% analysis showed an average area value of 22.14°^{2} (median 12.10°^{2}; STD= 23.68°^{2}). Tables 1 & 2 show the relevant clinical information to describe each of the participants in the scotoma group, including their age, ocular diagnosis, CDVA, location of their fixation relative to their scotoma, fixation stability according to previously published definitions [26], and an analysis of fixation based on 95% bivariate contour ellipse area [27]. The vision loss was long-standing in all cases. The control group mean age was 41.2 years-old (median 40; STD= 9.4), which was not statistically significantly different from the age of the study group (t (5) = -0.72, P =.493). All control subjects had a CDVA of 0.0 logMAR, which was better than the visual acuity in the scotoma group (t (5) = 3.58, P = .007) (Z = 1.98, P = 0.048). Fixation was central and stable in all control subjects. Bivariate contour ellipse area @95% analysis showed an average area value of 0.84°^{2} (median 0.5°^{2}; STD= 0.79°^{2}), which did not appear to be statistically different between the scotoma and control groups (t (5) = 2.01, P = .079).

Table 1: Scotoma Group Baseline Characteristics.

Participant	Age (years)	Eye	Pathology	CDVA (LogMAR)	Fixation Location	Scotoma-side to fixation
1	62	OD	Dry AMD†	0.7	E	Right
2	21	OD	R-HH‡	0	C	Right
3	23	OD	JMD §	0.9	E	Below
4	25	OS	JMD §	0.9	E	Below
5	43	OS	RP ¶	0.5	C	Ring
AVE	34.8			0.62		
MED	25			0.7		
STD	17.6			0.37		

Note:

Footnotes & abbreviations:

Pathology column: † dry age-related macular degeneration (DRY AMD); ‡ right-homonymous hemianopia (R-HH); § juvenile macular degeneration (JMD); ¶ retinitis pigmentosa (RP).

Visual acuity column: corrected distance visual acuity (CDVA).

Fixation location column: central (C) or foveal; eccentric (E) or extra-foveal

Scotoma-side to fixation column: position of the scotoma border on the microperimetry plot relative to the retinal fixational location

Results rows: average (AVE); median (MED); standard deviation (STD)

Table 2: Sizes and Shapes of Central Scotomas.

Participant	Eye	Size X*	Size Y*	Shape	Distance*	Fixation Stability	95% Bcea Area
1	OD	11°	15°	disciform	3.5°	unstable	50.6°²
2	OD	>10°	>10°	hemifield	1°	stable	1.2°²
3	OD	3°	5°	semicircular	7°	rel unstable	12.1°²
4	OS	2°	2°	circular	8°	unstable	44.5°²
5	OS	>10°	>10°	ring	2°	stable	2.3°²
AVE							22.14°²
MED							12.10°²
STD							23.68°²

Note: Footnotes & abbreviations:

Size X column: horizontal scotoma diameter

Size Y column: vertical scotoma diameter

Scotoma-side to fixation column: position of the scotoma border relative to the retinal fixational locus

Distance column: distance (°) of the fixational locus (fovea or PRL) from the nearest scotoma border

Fixation stability column: stable, relatively unstable or unstable, as graded by Fuji et al. [26]

95% BCEA area (°²) column: area of 95% bivariate contour ellipse area (BCEA)

Results rows: average (AVE); median (MED); standard deviation (STD)

*Measures were drawn from the measurement grid superimposed on the microperimetry as provided by the MAIA.

In phase 1, the mean percentage of cross-shaped targets found by the scotoma participants was 57.8% (median 69.2%; interquartile range 64.3-70.6%). Indeed, only the targets projected outside of the scotomatous areas were detected in this phase, supporting the observation that the participants were quite capable to hold their fixation on the reference landmark. The lowest proportion of eccentric targets was seen by the participant with the ring scotoma (7.1%), while the highest one was seen by the participant with age related macular degeneration (77.8%). On the contrary, all control subjects could locate every eccentric target (100%) easily even in this phase because they had an intact central visual field, in contrast with the study group (Mann–Whitney U = 0; critical value of U at P < .05 is 2; Z = -2.502; P = .012) (Figure 2).

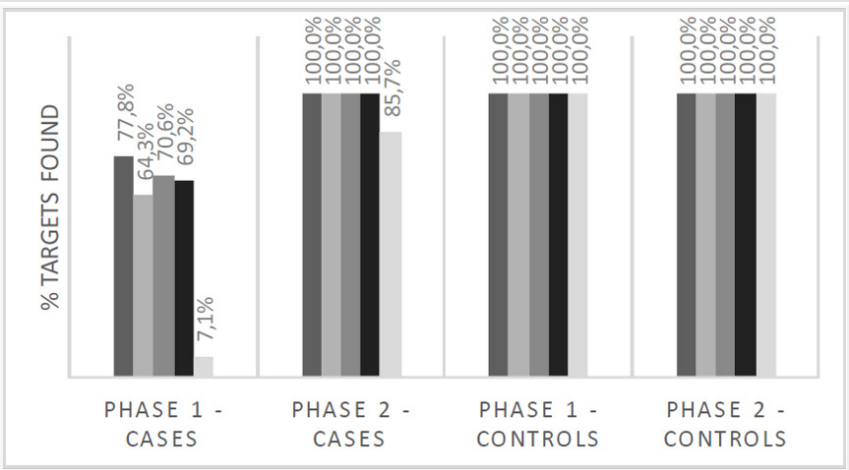

Figure 2: Percentage of cross-shaped targets found by the scotoma and the control group in task phase 1 (fixation on the central round landmark, no eye movements allowed) and in task phase 2 (guided searching eye movements). The participants with scotoma increased the percentage of targets found with the help of eye movements training in phase 2. Control subjects kept the 100% level of success as in task phase 1.

Target detection rate in phase 1 in the scotoma group was on average 6.5 targets/minute (median 7.8; interquartile range 6.8-8.4) while in the control group it was on average 22.3 targets/minute (median 21.4; STD= 1.4), significantly better than for scotoma patients (Mann–Whitney U = 0; critical value of U at P < .05 is 2; Z = -2.502; P = .012) (Figure 3). In phase 2, the percentage of targets detected by the scotoma group increased to an average of 97.1% (median 100%; interquartile range 100-100%), which was significantly higher than that one in phase 1 (post-hoc Wilcoxon signed-rank test, Z = -1.7, P = .007). In fact, almost all scotoma patients were able to detect all the targets (100%) when searching with guided eye movements. The participant with the ring scotoma was the only one to score less than 100%, although her performance improved from 7.1% to 85.7% when compared to phase 1. As expected, controls showed no increase in the percentage of targets found compared to phase 1 because of an obvious ceiling effect.

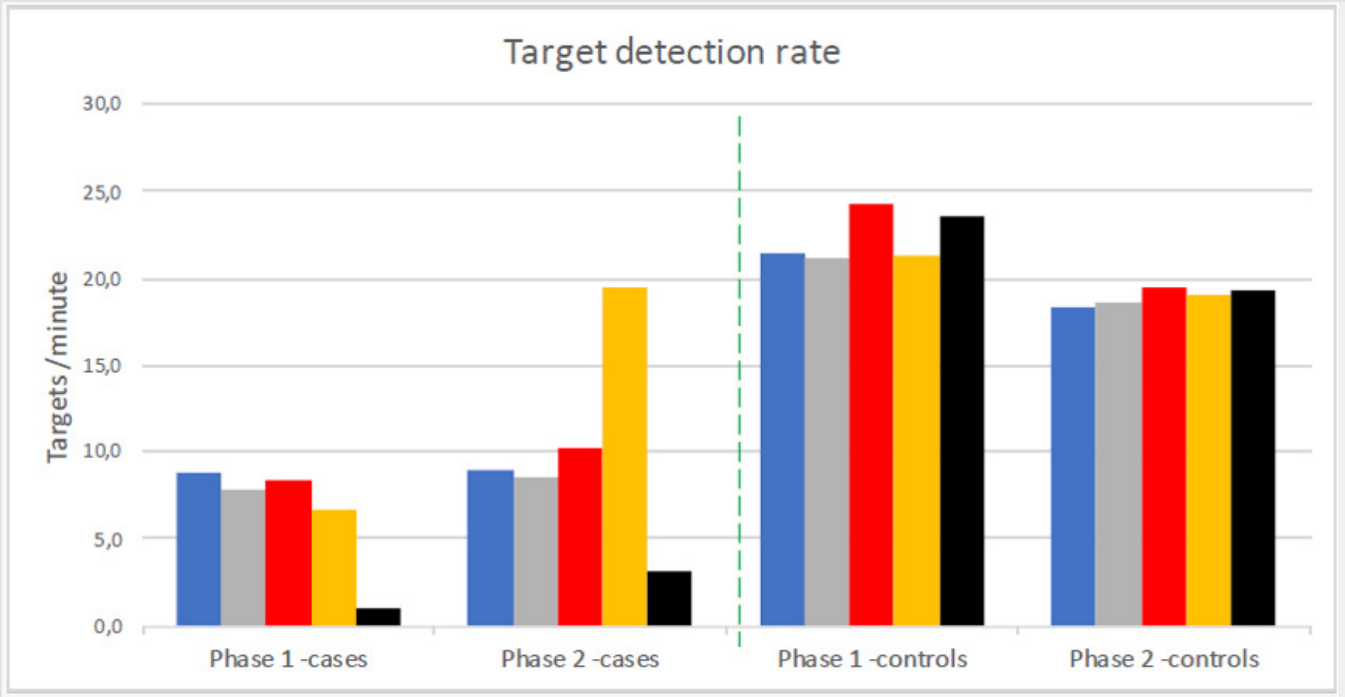

Figure 3: Target detection rate. Bar graph of the target detection rate (number of targets detected per minute) in task phases 1 and 2 for each of the five participants in the scotoma (cases) and control (controls) groups.

Target detection rate in phase 2 was 10.1 targets/minute on average (median 8.9; STD= 5.9) in the scotoma group, and 18.9 targets/minute on average (median 19.0; STD= 0.5) in the control group. The performance of the control group was significantly better than the scotoma group (t (5) = -3.341, P = .010). Interestingly, target detection rate in the control group was slightly but significantly lower in phase 2 than in phase 1 (paired t (5)= -7.041; P = .002).Finally, in phase 3, during free search with no central fixation landmark and no voice operator aids, scotoma subjects were able to find an average of 75.0% of targets (median 90%; STD= 28.7%), with a mean target detection rate of 11.28 targets/minute (median 10.2; STD= 5.36). Overall, there was a statistically significant difference in the percentage of targets found by the scotoma participants in the three task phases (Friedman Test for Repeated-Measures, $\chi 2$ (2) = 7.684, P = .021).

Post-hoc analysis with the Wilcoxon signed-rank test found a statistically significant difference between phase 1 and phase 2 only (Z = -1.7, P = .007; see above), suggesting that the overall increase in the percentage of targets found was related to guided eye movements (phase 2) rather than to free search (phase 3). On the other hand, the scotoma group's target detection rate was not statistically significant different across the three task phases (Friedman Test for Repeated-Measures, $\chi 2$ (2) = 5.158, P = .076). However, it should be noted that the greatest improvement in rate from phase 1 to phase 2 belonged to a young participant with a small central scotoma and a large distance between the scotoma border and the eccentric fixation location.

Discussion

This pilot study shows the feasibility to accurately monitor and guide (small) explorative eye movements in the presence of a central scotoma with a commercially available microperimeter, the MAIA, which can be operated as a possible environment for visual search

training. This study demonstrates that live fundus imaging and the knowledge of macular perimetry can support guided eye movements training to detect targets in the central visual field and to improve visual search efficiency in the presence of a central scotoma. The benefits of such setting are valuable in particular when searching saccades need to be accurate and fine-tuned on small targets. In our small sample there was considerable heterogeneity of diagnoses and baseline characteristics among the participants. They all had in common the presence of a dense scotoma variably invading the central visual field, a condition which is known to be a relevant cause of visual impairment [28,29]. However, the quality of their fixation ranged from stable, to relatively unstable, to unstable (Table 2). Previous observations in the literature support the possibility that patients with substantial visual impairment, dense central scotoma (typically, but not exclusively, a ring scotoma), and variably reduced visual acuity, can retain their central fixation and good fixation stability [30,31].

We studied a patient with right homonymous hemianopia and another one with a large ring scotoma who both suffered profound visual fields disruption, even if of a different extent and origin, and yet retained a stable fixation. The training was divided into three consecutive phases, from forcing fixation onto the standard MAIA central round target in phase 1, to guided explorative eye movements in phase 2, and finally to free search in phase 3, not only to study the possible contribution of each component to a hypothesized, subsequent increase in visual search efficiency, but also because each phase should prepare for the next one. An alternate approach could have been to allow free search eye movements from the beginning and to check a posteriori if the search performance data would fit with the scotoma condition and location. However, this was not what we did because, as also shown in the literature [32-34], the use of a marker for fixation increases fixation stability (whether fixation is foveal or extra-foveal), saccades accuracy and scotoma awareness. So, our approach was deliberately chosen to include a stepwise training procedure beginning with using a marker for fixation in phase 1, instead of just free search repetitions.

Keeping fixation as steady as possible as in phase 1 led to the lowest percentage of targets found by our scotoma participants. If the training had stopped there, all the missing visual information due to the presence of the scotoma would have remained unseen. Therefore, one might say that the steadier the fixation, the lower the visual search efficiency in the presence of a scotoma. Instead, in terms of steps of training, using a marker for fixation to increase fixation stability would impart some level of control on fixation that can prepare for more accurate searching eye movements when they are allowed, such as in phase 2. In phase 2, verbal directional cues and the presence of an orientation landmark drove the eye of the participants to new gaze positions calibrated on the positive visual feedback provided by the detection of a cross-shaped target. In phase 3, free search alone did not seem to be as effective. These findings may support the suggestion that teaching patients with central scotoma to look in the direction of the scotoma can help them to acquire missing visual information while increasing their scotoma awareness [33].

It is also encouraging to note that scotoma patients were all able to follow this training protocol and most of them increased their target detection ability even up to 100%. However, due to the small sample sizes of this pilot study, it would be important to conduct larger investigations to determine if these preliminary findings are replicable in other study populations. In the literature, it has been shown that a search test can be a useful tool for the assessment of impaired vision and that the outcomes of a search-and-identify task are related to functional measures, such as MN-read reading speed in low vision patients [35]. In our study, it is suggested that the time needed to detect the presence of a target in the central visual field is more influenced by the presence of a dense central scotoma than by fixation stability.

Target detection rate did not increase significantly from phase 1 to phase 2 in the scotoma group, and even decreased significantly in the control group. This could potentially be due to some inaccuracy in recording the measurements since all the procedures were manual, but an alternative explanation might be that eye movements are time consuming, both for scotoma and control participants. Control subjects had an intact central visual field and could immediately see the targets as they were presented even with a steady eye. Asking them to move their gaze toward the target before signaling the target as asked in phase 2 could impose a delay in the responses, which finally proved to be statistically significant in our study, although small in magnitude. Such a delay was not present in the scotoma participants. A possible interpretation is that when a target is immediately seen because it falls on an area of intact visual field, eye movements are not necessary and even time consuming. On the contrary, when a target is not seen initially, moving the eyes in the correct direction is crucial in order to collect the missing visual information.

A selective and accurate eye movement toward the direction of the scotoma, even if time consuming, is well rewarded with finding the target. Therefore, selective eye movements in the presence of a dense scotoma, rather than random eye movements, should be the goal of explorative eye movements training [21,33,35]. A limitation of this study design is that in phase 2, it is not possible to determine whether the verbal directional cues from the operator or the ability to freely use eye movements were more responsible for the improved performance in the scotoma group compared to their results in phase 1 without either of those aspects. Individual instructions such as repeated encouragements to search for a target in a specific direction could account for additional delays because they require some time to be heard and processed by the participant. Also, it is not possible to determine if the difference between phases 2 and 3 was related to the absence of the round central fixation target or the lack of verbal directional cues from the operator in phase 3. Finally, the ideal goal would be that the scotoma awareness and the searching proficiency gained during guided explorative eye movements would transfer into

a higher visual search efficiency in real life. This is still far from being demonstrated by this study and will require additional research. Also, future studies will need to elucidate the duration of the training that would be required to reach the maximum level of performance in order to transfer to real life.

Conclusion

This pilot study supports the feasibility of accurate eye movements training with the MAIA Multi-fixation target set in the presence of a dense central scotoma of various origin. In this environment, it appears possible to compensate for missing visual information when stimuli fall on central scotomatous areas by using eye movements that are fine-tuned on the visual feedback of the target upon receiving verbal cues from the operator who is able to see the participant's live fundus image and the superimposed MAIA Multi-fixation targets set. This feasibility study involved a small sample that was not powered to detect significant differences between groups, yet there were some observed important trends for improved performance in the scotoma group when guided explorative eye movements were allowed (phase 2) versus keeping the eye as steady as possible (phase 1). The described training procedure needs to be refined, automated, and standardized. Automation of the procedure would allow for easier operation of the device and more accurate quantitative measures. A general limitation of the current microperimeter's based technology is that it works only monocularly. Eventually, future studies supported by these recommended technology upgrades will need to determine if this type of training can translate to situations outside of the microperimeter, such as improved performance on activities of daily living that are relevant to low vision persons.

Acknowledgements

The authors would like to thank their academic mentors and all the low vision rehabilitation team.

Conflict of Interest

The authors declare that there are no economic interests, nor any conflict of interest related to this work. One of the authors (M.U. Morales) was a consultant for Centervue in the past, but this condition has long ceased, and no conflict of interest related to this study exist.

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ISSN: 2574-1241

DOI: 10.26717/BJSTR.2024.57.008955

Gianfrancesco M Villani. Biomed J Sci & Tech Res