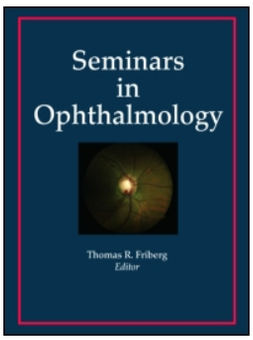

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ORIGINAL ARTICLE

Biofeedback Low Vision Rehabilitation with Retimax Vision Trainer in Patients with Advanced Age-related Macular Degeneration: A Pilot Study

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ABSTRACT

Purpose: To evaluate the effectiveness of Visual Evoked Potential (VEP) biofeedback rehabilitation in selected low vision patients with advanced age-related macular degeneration (AMD).

Design: Retrospective observational cohort study.

Methods: Patients affected by advanced AMD, central macular atrophy with unstable fixation and best corrected visual acuity (BCVA) between 20/100 and 20/320 were considered. Selected patients underwent fundus photography and microperimetry with fixation analysis for the selected eye (highest BCVA). Ten consecutive training sessions of 10 min each were performed twice a week in the selected eye with Retimax Vision Trainer (CSO, Florence). BCVA, reading acuity and reading speed, contrast sensitivity, fixation, retinal sensitivity and quality of life questionnaire (VFQ-25) were evaluated at baseline and 7 days following the final session.

Results: Significant improvements in terms of BCVA [p = .011], reading speed [p = .007], VFQ-25 score [p = .007], retinal sensitivity [p = .021] and fixation stability in the central 2° and 4° [p = .048; p = .037] post-treatment were observed for the 9 patients enrolled, with insignificant improvements observed in reading acuity and contrast sensitivity [p = .335; p = .291].

Conclusions: Preliminary results support VEP biofeedback rehabilitation improvements for visual function and quality of life in advanced AMD patients with low vision.

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KEYWORDS
Age-related macular degeneration (AMD); low vision; biofeedback rehabilitation; plasticity of fixation; microperimetry

INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of severe visual loss and legal blindness in the western population over the age of 65.[1] It is a chronic, degenerative and progressive disease, generally bilateral, which often leads to an irreversible deterioration of the central vision due to the development of geographic atrophy and fibrotic macular scars.[2,3]

Despite the improvements registered in recent years, mostly due to the introduction of new treatments for the neovascular form, the advanced stage of AMD is still a disabling disease resulting in low central vision and poor prognosis[4] and there are no effective therapies currently available. Patients with central vision loss try to fixate objects using a healthy eccentric area of the retina, known as Preferred Retinal Locus (PRL), that is generally located at the border of the atrophy.[5–8] These patients can benefit from rehabilitation programs with "biofeedback" mechanisms that instruct the patient to move fixation from the central degenerated macular area to the PRL.[9–15] This can be achieved through a biofeedback rehabilitation program obtained with the microperimetry or with visual evoked potentials (VEP) real-time analysis.

The Retimax (CSO, Firenze, Italy) is a medical device for the detection, amplification and visualization of ocular electrical conduction. It is a versatile tool that is mainly used for diagnostic purposes for ocular electrophysiological investigations; it can also be used for therapeutic purposes thanks to a configuration designed for visual rehabilitation programs ("Vision Trainer" module). It combines VEP measurement to an auditory biofeedback system useful in low-vision rehabilitation: the vision trainer integrates ocular electrophysiology and biofeedback techniques generating a return signal based on VEP. The VEP recorded at the level of the visual cortex is detected and analyzed real-time by the machine, then it is sent back to the patient as feedback in the form of an acoustic signal. The intensity of this acoustic signal is related to the amplitude and latency of the VEP which are an expression of the quality of vision. During the training the patient is guided in real-time to improve his visual performances: the more the patient maintains a stable fixation with the healthy paracentral PRL, the greater and more stable the intensity of the sound will be. During the different rehabilitative sessions, the patient learns to voluntarily control and coordinate the ocular movements,[16] to progressively increase visual performance by the stimulation of the visual pathway and the exploitation of the plasticity mechanism of the visual system.[17–19] The Vision Trainer program has been used for the visual rehabilitation of patients affected by amblyopia and acquired brain injury with excellent results in terms of improved visual function.[20,21] To our knowledge, there are no current studies available

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investigating the utility of VEP biofeedback rehabilitation for AMD patients.

The aim of this study is to assess the efficacy of VEP biofeedback rehabilitation with Retimax Vision Trainer in patients with low vision (best corrected visual acuity between 20/100 and 20/320 and unstable fixation) due to advanced stage AMD.

METHODS

Retrospective review of ophthalmological charts of the initial 9 consecutive patients treated with Retimax vision trainer rehabilitation at the Institute of Ophthalmology, University of Modena (Italy) was performed. Patient visits and rehabilitation were registered between May and November 2018. The study was approved by the local Ethical Committees (prot. NO. 3513/19) and adheres to the tenets of the Declaration of Helsinki with written informed consent obtained from each patient.

The inclusion criteria were advanced atrophic AMD with best corrected visual acuity (BCVA) between 20/100 (0.7 logMar) and 20/320 (1.3 logMar) in the better eye, unstable fixation, <90 years old, and good patient compliance. Exclusion criteria included active neovascular AMD, glaucoma, optic nerve disease/abnormalities, diabetic retinopathy, previous ocular surgery other than cataract intervention and patients unable to collaborate during the Retimax or the microperimetric evaluation.

All patients underwent a complete ophthalmic examination at baseline with the following examinations: BCVA, contrast sensitivity, reading abilities, vision-related quality of life test (VFQ-25), microperimetry with fixation analysis.

BCVA was evaluated with the Early Treatment Diabetic Retinopathy Study (ETDRS) charts (Lighhouse Int., New York, NY) at 4 meters and the assessment was in letters.

Contrast sensitivity was evaluated with Pelli-Robson charts at 2 meters and the assessment was in letters and converted to logMar.

Reading abilities were evaluated with MNRead charts (Precision Vision La Salle Illinois, Usa,) distributed in Italian version by Carl Zeiss Jena GmbH, Germania. The charts were used at 40 cm distance. For all patients with added a + 3.00 spheric lens. Maximum reading speed was measured in words per minute (wpm), reading acuity was assessed in logMAR units.

Microperimetry was performed using the spectral domain OCT (OCT-SLO, Optos, Scotland, UK) following pupil dilation with 0.5% tropicamide and 2.5% phenylephrine and a period of adaptation of 20 minutes to dim room illumination. A pattern with 28 locations in the macular area was used to assess sensitivity; "white" test lights (stimulus size Goldmann III, 200 ms in duration) were presented on a dim "white" background (1.27 cd/m2) using a 4–2 procedure. The patient was asked to maintain fixation on a 2° green point (fixation target) during the test and the non-tested eye was occluded. Retinal sensitivity was obtained and recorded with the average sum of all test locations obtained during the test. Retinal sensitivity was retested during the follow up at the same points using the "retest mode" in the machine which recalls the landmarks used in the previous exams allowing a perfect overlapping of the new exam image with the previous one.

To assess the impact of low vision on daily life, the patients were subjected to questionnaire National Eye Institute Visual Functioning Questionnaire-25 (VFQ-25) translated into Italian.[22] All these exams were prior to and following rehabilitation. Final assessment was performed 7 days after the final session in all cases.

Rehabilitation was performed on the eye with the highest BCVA. Each patient underwent 10 sessions of 10 min each of visual training with Retimax Vision Trainer (CSO, Firenze, Italy), two sessions per week.

Rehabilitative Procedure

The patient is placed in a seated position at about 60–80 cm from the pattern stimulator monitor. After carefully cleaning of the skin with "nuprep" skin gel, electrodes are applied using "Ten20" conductive paste configured as in the VEP test recording. The negative electrode (black) is applied according 10–20 system of electrodes placement on the FPz position, the positive electrode (red) on the Oz position and the Earth electrode (green) in the Cz position.

The patient is fitted with a corrective lens over the selected eye (highest BCVA) for rehabilitation. The session is performed under scotopic conditions keeping the other eye closed. Prior to initiating training, each subject is left to adapt to the ambient room light for 10 min, until a natural pupil diameter of approximately 5 millimeters is obtained.

During the examination a structured stimulus appears on the screen in the form of a alternating chess board at the reversal rate of 15 reversal per second with a fixation target (red point) in the center of the screen. In our study, we used the standard chessboard used in pattern 60' VEP at the reversal rate of 15 reversal per second.

Whilst the patient fixates the target stimulus from the optical pathways through to the cortical visual areas is created and read by surface electrodes, which then produce a bioelectric VEP. During the session, the patient is instructed to maintain the target using the retinal area that produces the real-time sound (highest amplitude VEP with lower latency; a continuous, uninterrupted sound) and therefore a better visual perception (Figure 1). The sound is more intense and continuous when the patient fixates with a healthy area of the retina and is intermittent when the fixation is interrupted. The aim of the training is to ensure that the patient uses a retinal area in which the biological activity is at its best.

During the session, the operators (SP, VR) monitored the progress of the fixation and the intensity of the sound, encouraging patients' consistent attention to the sound produced.

The study data were collected and divided into pre- and post-rehabilitation values for each patient and compared. For statistical analysis we used the software R (A language and environment for statistical computing, version 3.3.3, R Foundation for Statistical Computing, Vienna, Austria). Given the non-normal distribution verified with the Shapiro-Wilk test and the low sample, the pre and post rehabilitation values were compared with the one-sided Wilcoxon Signed Rank Test. Since the number of comparisons was small, the p-values have not been corrected by the number of comparisons made in the Wilcoxon test run. The significance is established for values of $p < .05$

Figure 1. A training session with the Retimax Vision Trainer.

RESULTS

Nine eyes with the highest BCVA of nine patients (7 males and 2 females, 7 right eyes and 2 left eyes) were included in the study. The average age was 79.3 years old (range 68–89). All demographic characteristics and results are shown in Table 1. Results refer to final follow-up 7 days following the 10th and final training session.

BCVA, reading speed, quality of life, macular sensitivity and 2° and 4° fixation improved significantly, whereas the improvements observed with contrast sensibility and reading acuity were not significant, see Figures 2 and 3 and Table 2.

DISCUSSION

VEP biofeedback rehabilitation is a relatively new training system that has proven to be useful for visual function improvement in different ophthalmological diseases.[20,21] The current study reports improved BCVA, reading speed, quality of life, macular sensitivity and 2° and 4° fixation, contrast sensibility and reading acuity in the eye with the highest baseline BCVA in a pilot study of 9 patients. To our knowledge, this is the first report of VEP biofeedback rehabilitation for patients with low vision for advanced AMD.

Biofeedback rehabilitation aims to induce learning for voluntary control over visual fixation and, unlike other instruments in which the biofeedback sound is generated by the proximity of patients' fixation to a healthy area of the retina established by the operator, a feedback based on the amplitude of a recorded VEP is established through electrodes placed on the patients' cortex. The process is therefore operator-independent. The feedback from the Vision Trainer guides the patient in an independent search for fixation on the retinal point that generates a wider VEP response by inducing a progressive voluntary control of eye movements, especially saccadics movements.[19] Fixation in the retinal area that generates the maximum VEP results in an improvement in overall visual performance. Moreover, the neuroplasticity mechanism of the nervous system allows the nerve stimulus to bypass any alterations present on the visual pathways, reaching the occipital cortex through a remodeling of the neural network with the creation of new synapses.[17] A limitation of this device is that it is not "fundus-controlled", thus it is not possible to train the retinal area with best functional characteristic but the training is performed on the patient's spontaneous PRL.

VEP biofeedback rehabilitation has been reported for the rehabilitation of patients affected by amblyopia[20] and acquired cerebral damage[21]; both studies documented significant improvements in visual acuity of post-rehabilitation patients without any substantial significant changes pre-/post-VEP electrofunctional values. Veneruso et al.[20] also reported an improvement of the fixation in the central 2 and 4 degrees.

Table 1. Demographic data and results; Pre, baseline values; Post, values at 7 days following the final training session; BCVA expressed in ETDRS chart letters seen at 4 meters.

				Visual Acuity (ETDRS letters)		Contrast sensibility (logSC)		Reading speed (W/m)		Reading Acuity (logMar)		Macular sensitivity (dB)		Fixation within 2° (%)	
Patient	Age	Sex	Eye	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	75	F	R	30	34	1.25	1.4	38.5	57.5	0.1	0.1	10.3	10.8	71	83
2	72	M	R	8	10	1.4	1.4	16.9	18	0.5	0.4	1.2	3.9	64	97
3	68	M	R	20	22	0.95	1.4	38.6	54	0.3	0.2	2.4	2.9	47	80
4	87	M	L	8	23	1.4	1.4	51.4	77.1	0.1	0.1	3.4	4.4	32	55
5	89	F	L	15	23	0.8	0.95	21.9	21.6	0.2	0.4	1.6	1.9	70	62
6	84	M	R	5	9	1.25	1.4	12.3	14.6	0.4	0.3	4.2	4.8	53	71
7	85	M	R	4	24	0.8	1.25	15.9	32.7	0.5	0.4	0.2	2.2	66	74
8	80	M	R	35	38	1.25	0.95	26.1	31.8	0.2	0.2	8.4	9.9	74	68
9	74	M	R	32	38	1.4	1.4	31.8	41.5	0.3	0.3	10.3	13.2	43	65

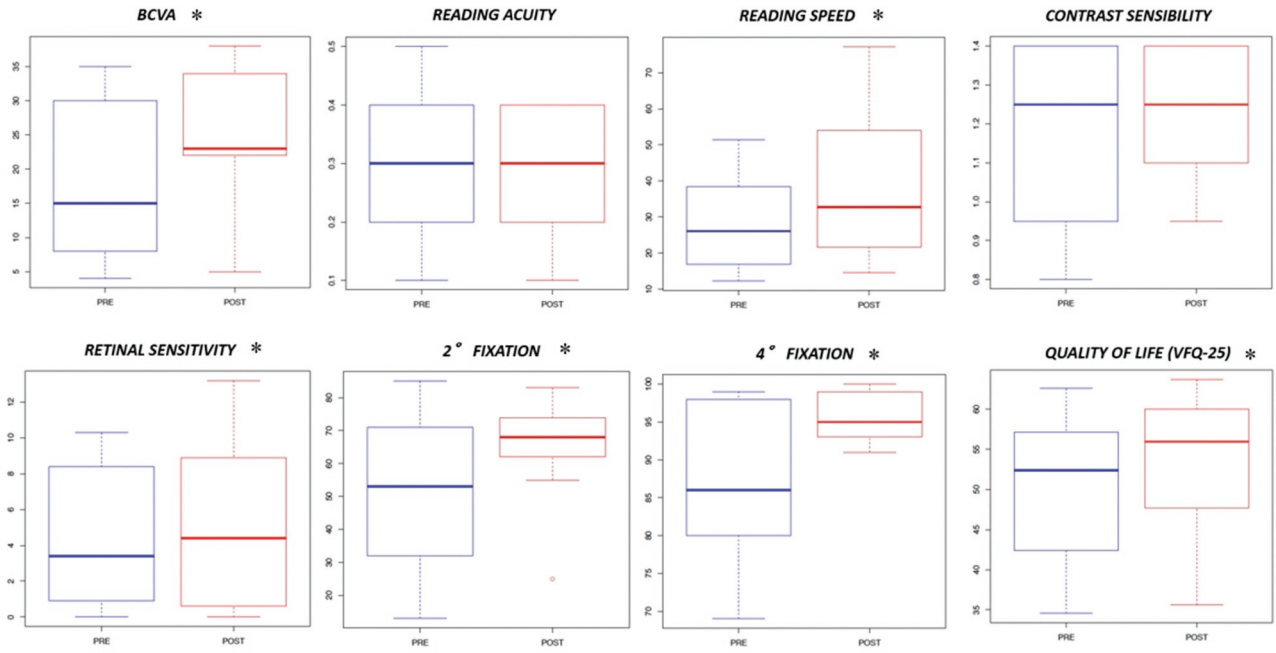

Figure 2. Box plot with whiskers indicating 95% confidence intervals for baseline and post-rehabilitation vision function assessments. *Assessments statistically significant ($p < .05$).

Table 2. Summary of the pre-post results with mean improvement (expressed in %) and *p*-value (significance $p < .05$).

	Pre	Post	Mean improvement (%)	P-Value
BCVA (*ETDRS letters*)	17.67	24.11	+36.5%	p = .011
Contrast Sensibility (*logSC*)	1.17	1.22	+4.3%	p = .335
Reading acuity *(logMAR)*	0.29	0.27	+7.4%	p = .291
Reading Speed *(WpM)*	28.09	38.76	+38%	p = .007
Quality of life *(VFQ-25)*	49.59	53.87	+8.6%	p = .007
Macular Sensitivity *(dB)*	4.34	5.21	+20%	p = .021
Fixation 2° *(%)*	52.22	64.67	+23.8%	p = .048
Fixation 4° *(%)*	87.33	95.78	+9.7%	p = .037

AMD has previously been treated with microperimeter biofeedback rehabilitation systems and a meta-analysis for AMD patients, published in 2016[23] including 9 studies (885 eyes), evaluated reading speed (n = 5) and mood and patients' depression scores (n = 3). A significant improvement in reading speed (regardless of rehabilitation type) was reported, whilst mood and depression scores remained unchanged.

Two recent articles[24,25] compared the effectiveness of low vision rehabilitation in patients affected by AMD with the Nidek MP-1 microperimeter using two different technique: one method used the standard sound biofeedback and the other used a biofeedback associated with a projection of a visual luminous pattern in place of the fixation target. Vingolo et al.[24] showed that the luminous flickering biofeedback stimulus presented a statistically significant improvement in training the patients to modify their PRL in comparison to standard acoustic biofeedback. The Amore et al. study,[25] noted improved parameters for all visual function assessments performed, with the exception of contrast sensitivity, with more benefits obtained with the flickering pattern biofeedback training.

Another recent study[14] also confirmed the utility of the MAIA microperimeter biofeedback rehabilitation to train

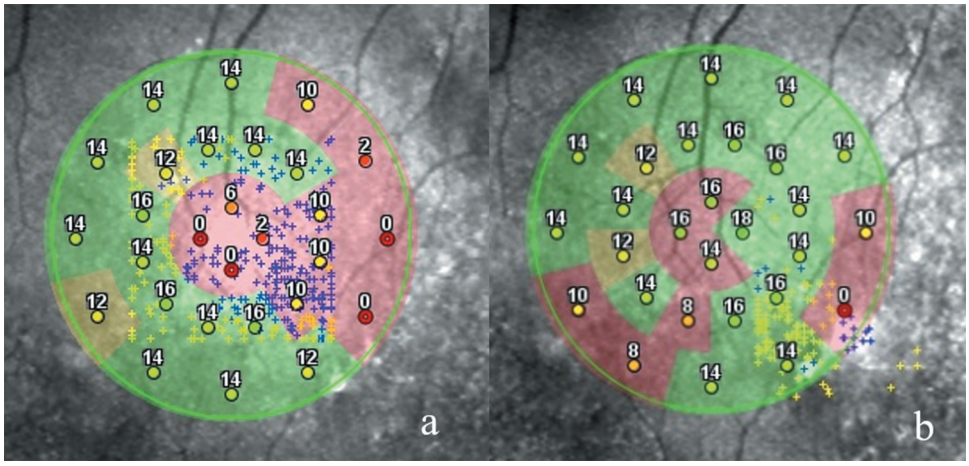

Figure 3. Microperimetry images with fixation points at baseline (a) and after the training sessions (b) in patients n. 3.

a healthy retinal area in seventy-seven consecutive AMD patients with bilateral central vision loss. Daibert Nido et al.[15] in a retrospective review of 30 cases, also confirmed the utility of the same tool in AMD patients, reporting improvements for visual acuity but a negative trend for fixation stability.

The results obtained in the current study are in line with existing literature dedicated to AMD rehabilitation showing an improved visual function in the trained eye and improved quality of life. However, differently to the microperimetric PRL rehabilitation which is based on the training of a PRL established by the physician, Retimax visual rehabilitation presents the advantage to train the patient's spontaneous PRL thus being operator-indipendent. By listening to the effective visual performances registered real-time at the level of the occipital cortex, the patient can learn to use the portion of the retina that generates the maximum VEP response inducing a progressive voluntary control over eye movements and increasing visual performances through the stimulation of the visual pathway.

Interestingly, the majority of patients assigned a subjective improvement in everyday skills following training and requested the continuation of rehabilitative sessions at our center.

This study is not without some limitations. Firstly, the retrospective nature of the data collection, the small sample size and the lack of a control group of untreated patients limit the reliability of the results obtained. Secondary, since the main outcome measure of this study was taken one week after the last rehabilitative session, we could not state how long the benefit related to the treatment may be maintained overtime. However, this pilot study, along with patient request for continued training, deserves further prospective series with longer follow up to confirm these preliminary results. Further, technical data obtained with the microperimeter (retinal sensitivity and fixation) could have been slightly inaccurate due to the unstable fixation of patients that could have affected the projection of retinal stimuli despite the eye-tracking system present in the machine.

In conclusion, the current pilot study suggests that the non-invasive VEP biofeedback rehabilitation can be successfully used to improve visual function and quality of life in AMD patients. Further investigations are needed to confirm these preliminary results.

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Declaration of Interest

None of the authors have conflict of interest with the submission.

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