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MP-1 Biofeedback: Luminous Pattern Stimulus Versus Acoustic Biofeedback in Age Related Macular Degeneration (AMD)

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Abstract In this study we evaluated the efficacy of visual rehabilitation by means of two different types of biofeedback techniques in patients with age related macular degeneration (AMD). Thirty patients, bilaterally affected by AMD, were randomly divided in two groups: one group was treated with an acoustic biofeedback (AB group), the other was treated with luminous biofeedback of a black and white checkerboard flickering during the examination (LB group). All patients underwent a complete ophthalmological examination. Rehabilitation consisted of 12 training sessions of 10 min for each eye performed once a week for both groups. Both groups showed better visual performance after rehabilitation and luminous flickering biofeedback stimulus showed a statistically significant improvement in training the patients to modify their preferred retinal locus in comparison to acoustic biofeedback. This suggests that it might be possible in the damaged retina to override dead photoreceptor and outer retinal layers and involve residual surviving cells, as well as amplify and integrate retinal and brain cortex plasticity by using other spared channels towards associative pathways.

Keywords Age related macular degeneration (AMD) · Visual rehabilitation · MP-1 microperimetry · Retina · Biofeedback · Pattern stimulus

Introduction

Age related macular degeneration (AMD) is a major public health issue as the leading cause of severe visual impairment in the elderly in the Western world (Eye Disease Prevalence Group 2004a, b). Typically, AMD is classified into early and late forms. Early AMD is characterized by the presence of soft drusen and pigmentary changes in the macular area. Late AMD is further divided into a "dry" form, geographic atrophy (GA), and a "wet" form, choroidal neovascularization. The overall prevalence of early and late AMD among Americans >40 years of age is estimated to be 7.3 and 1.8 million respectively. The prevalence of late AMD is estimated to increase to 3.0 million in 2020 (Eye Diseases Prevalence Research Group 2004a, b). Its increase is related to the increase of the mean age of the population (Bird et al. 2005), and to the increase of certain risk factors, such as smoking (Christen et al. 1996; Khan et al. 2006; Seddon et al. 1996), animal fatty acids and a diet rich in protein (Cho et al. 2001; Mares-Perlman et al. 1995).

Until a few years ago, the final result of AMD was legal blindness. In 2000 the introduction of new therapies for the treatment of active choroidal neovascularization (CNV), such as verteporfin with photodynamic therapy and intravitreal anti-VEGF drugs (pegaptanib, bevacizumab, ranibizumab and others), has radically changed the visual outcome of these patients (Shak et al. 2009).

Registration on clinicaltrial.gov: NCT01243645.

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As a result patients that 10 years ago were severely visually impaired (often blind), now have highly variable severities of low-vision, depending on the morphological characteristics of the residual scar.

AMD is accompanied by considerable consequences regarding the psychosocial quality of life. A substantial body of research literature now indicates an increased rate of depression and substantial loss of everyday capabilities in AMD patients; however, individual differences are large and part of the explanation lies in differences in the ability of the patient to cope with every day problems. The need for psychosocial support for sufferers of AMD is barely met at present (Wahl et al. 2008). Relinquishing valued activities in older patients with vision loss caused by AMD is also associated with an increased risk of cognitive decline. These data suggest the importance of promoting optimal cognitive and physical health in patients with AMD (Rovneret et al. 2009). With rehabilitation, many patients with impaired vision can attain independence, retain their jobs, and lessen their reliance on social services and institutions (Carter 1994).

As explained in previous studies, our approach to rehabilitation is based on biofeedback techniques to increase visual function in patients with different macular diseases (Vingolo et al. 2007, 2009a). The biofeedback technique using the MP-1 Microperimeter (NIDEK Technologies, Padua, Italy) has been designed both to stabilize fixation behavior and to improve retinal sensitivity. Our previous studies with acoustic biofeedback techniques demonstrated the possibility to improve visual performance, such as distant and near visual acuity, reading speed, reading comprehension, etc., by stabilizing and/or relocating the preferential retinal location (PRL) in a much more useful area of the retina thus increasing fixation stability, probably using the residual cerebral plasticity in the adult visual cortex (Vingolo et al. 2007, 2009a). Recent studies have demonstrated that a flickering visual stimulus is useful in the rehabilitation of patients with homonymous visual fields defects and hereditary tapetoretinal degeneration (Henriksson et al. 2007; Raninen et al. 2007; Vingolo et al. 2009b). Therefore we decided to evaluate whether luminous flickering stimulus biofeedback rehabilitation on the MP-1 Microperimeter could be effective in the rehabilitation of low-vision patients at the end stage of AMD and compare it to acoustic biofeedback training.

Methods

We enrolled 30 patients (18 women and 12 men), ranging in age from 61 to 88 with a mean of 76.13 ± 6.16, bilaterally affected by neovascular AMD from the Medical Retina Unit of the Department of Ophthalmology, University La Sapienza of Rome, Polo Pontino, A. Fiorini Hospital from August 2009 to July 2010.

The diagnosis of neovascular AMD was based on a complete ophthalmological examination including anterior and posterior segment biomicroscopy, Fluorescein Angiography (Heidelberg HRA2 FA module Heidelberg, Germany), spectral domain OCT (Heidelberg HRA-2 OCT module Heidelberg, Germany), and microperimetry with MP-1 (NIDEK Technologies Padua, Italy).

Patients with other eye diseases (i.e., glaucoma, myopia, retinal detachment, etc.), who were uncooperative, or had media opacities were excluded.

All enrolled patients had undergone their last anti-VEGF injection at least 6 months before the enrollment, showed an absolute central scotoma at least 2° in diameter, and were visual and clinically stable.

Informed consent to participate in the study was obtained from all patients. The ethics committee of our institution approved the study protocol. All the procedures adhered to the tenets of the Declaration of Helsinki.

Patients were randomly divided in two groups: rehabilitation using acoustic biofeedback (AB) or employing luminous pattern biofeedback (LB).

All the patients underwent the same rehabilitation protocol, which consisted of the below:

- assessment of best corrected visual acuity (BCVA) with an Early Treatment Diabetic Retinopathy Study (ETDRS) chart (Metrovision, Clermond Ferrand, France); BCVA was expressed in logMAR values obtained at a distance of 4 m with the best refractive correction;
- assessment of near visual acuity, determined at 30 cm with near correction adjusted for the age of patients;
- reading speed, determined for each eye using standard black on white text of high frequency non-technical words randomly originated by Virtual-IPO software (Eye.com s.r.l. Palermo, Italy) on a computer screen, adapted to the best performing size for patients conditions. Words were presented in sentences and punctuation characters were not used. The length and the size of the passage to be read was adapted to the patient's visual acuity. For patients with the worst visual acuity a text of at least 30 words was presented. The patient was instructed to read the screen for 60 s, and the ophthalmologist recorded the number of correctly read words. The same text was used at each visit, but sentences were randomly generated. Particular attention was paid to create sentences of comparable difficulty. The unit used for character size was the electronic point, which corresponds to 1/72 (0.0138) inches or 0.35277 mm.
- Microperimetry: microperimetry analysis was performed using the automated Humphrey 10–2 threshold

test program with 4–2 strategy. 1° or 2° single cross were chosen as the fixation target. Stimulus size was Goldmann III with intensity ranging from 0 to 20 dB. Examination started after a 2-min demonstration pre-test to avoid a learning effect. Examinations requiring longer than 10 min were excluded from the trial. Background luminance was 1.27 cd/mq. An auto-tracking system calculates the horizontal and vertical shifts relative to the reference during the examination recording the area of fixation;

- After selection of the better PRL both groups underwent low vision rehabilitation in 12 training sessions of 10 min once a week with the MP-1 Microperimeter.

Patients in the AB condition were treated as described in our previous studies with acoustic MP-1 biofeedback (Vingolo et al. 2007, 2009a). Patients were asked to move their eyes according to an audio feedback, which advised them when they were getting closer to the target PRL; patients in the LB condition were treated with a black and white checkerboard pattern superimposed on the fixation target (a red cross or a red circle). Pattern dimension was related to the patient's residual visual function. Patients were asked to look at a fixation target and the stimulus flickered when they were fixating with the desired PRL. The pattern superimposed onto the fixation point constituted of a black and white reversal checkerboard of different dimension (15′–30′–60′ projected on the retina), flickering at 4 Hz. It was developed by the Nidek Technologies Company Engineering team as an implementation of the biofeedback examination of MP-1 Microperimeter.

All of the procedures were followed on a monitor and results were stored on hard disk. The PRL to be trained with the biofeedback examination in group AB and in group LB was a 1° diameter circle, if possible over the scotoma, (i.e., on the superior retinal field) with an appropriate retinal sensitivity to ensure the reinforcement of fixation behavior and fluent reading. It has been demonstrated that reading speed improves if a newly trained retinal locus (TRL) is established in an area that is more favorable for reading (Nilsson et al. 2003). The new PRL was chosen by the ophthalmologist, who paid particular attention to the width of the retinal area (for fluent reading patients must be able to read at least four letters) and to its sensitivity (Nilsson et al. 2003). If the PRL was already positioned in the area that would have been chosen by the ophthalmologist, it was decided to reinforce the fixation behavior and not to change the PRL location. All investigations were performed on the better eye only, as fixation behavior under binocular conditions is thought to be determined by the better eye rather than the patient's dominant or preferred eye (Crossland et al. 2004; Kanabarou et al. 2003). The fellow eye was occluded using a simple eye-patch. Subjects were not prescribed low vision aids before training began.

All measurements (i.e., BCVA distant and near, microperimetry, fixation test, and biofeedback) were performed with the patient's best correctable prescription employed.

The assessment of distant and near visual acuity, reading speed test, microperimetry, fluorescein angiography, and spectral domain optical coherence tomography (OCT) were repeated at the end of low-vision rehabilitation (i.e., after 3 months).

All data were collected by an optometrist, independent from the authors, who was "blind" with respect to patient treatment assignment.

Statistical Analysis

We used the Statistical Package for the Social Sciences (SPSS) for Windows, version 19.0 for all analyses. Analyzed parameters were tested in a 2 × 2 repeated-measures analysis of variance (ANOVA) with factors "group" (AB vs. LB) and "session" (before versus after rehabilitation). Bonferroni tests were used for posthoc analyses. Statistical differences at baseline between the two groups were evaluated with a series of independent t tests. p values less than 0.05 were considered to indicate statistical significance.

Results

Clinical Outcome

At the end of the study none of the patients demonstrated morphological changes. There was no recurrence or reactivation of the CNV during the follow up period (i.e., after 3 months). Four patients (4 eyes, 2 from group AB and 2 from group LB) showed a moderate increase of dye leakage at FA and a mild increase in retinal thickness in OCT scans, indicating a worsening of their pathology and an incomplete terminal stage of neovascular AMD. These patients were not included in the statistical analysis.

Subjective Changes

All patients in both groups reported being satisfied after the training, and noted subjective improvements in their visual function, being able to read faster and smaller character sizes and reporting to move better even in their familiar environment. After the training they were asked "did the training help you in your daily life activities?", "are you satisfied with what you have achieved after the training?" The reply to these questions were "yes or no" and they all replied "yes".

Visual Acuity and Mean Retinal Sensitivity

ANOVA of BCVA and mean retinal sensitivity disclosed a main effect for the sessions factor and for the interaction of session by group, but not an effect for group. Posthoc analysis showed BCVA significantly increased after treatment in the LB group, but there was no change in the AB group, while post hoc analysis showed significantly increased mean retinal sensitivity in the AB group, but no change in the LB group.

Mean data and relative statistical parameters are shown in Table 1. Figure 1 shows an example of retinal sensitivity improvement in one patient assigned to the LB group.

Reading Speed

ANOVA of reading speed revealed a main effect for session and the interaction of session by group (but no main effect for,group). Posthoc analysis showed reading speed significantly increased after treatment in the LB group, but there was no significant change in the AB group (see Table 1).

Fixation Behavior

The fixation data are presented in 2 ways. The ANOVA analysis of fixation behavior revealed a main effect for session and the interaction of session by group (but no main effect for group alone). Posthoc analysis showed fixation behavior increased significantly in response to LB (but not for AB) (see Table 1).

In a second analysis, the fixation points recorded were classified into three groups. Fixation was regarded as "stable" if more than 75 % of the fixation points were inside the 2° diameter circle (about 700 microns), as "relatively unstable" if less than 75 % were inside the 2° diameter circle but more than 75 % were inside the 4° diameter circle, and as "unstable" if less than 75 % of the fixation points were inside the 4° diameter circle (Fujii et al. 2002). The number of eyes falling into each category are presented in Table 2.

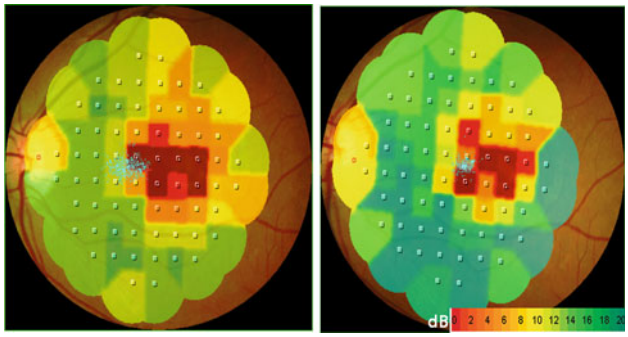

Fig. 1 The retinography with the overimposed sensitivity map of the left eye of one patient from the LB group, who demonstrated an average response to the treatment. On the *left*: sensitivity map before the training; on the *right*: sensitivity map after the training. It can be observed an improvement of retinal sensitivity (retinal sensitivity range 0–20 dB at the *left* of the figure) as well as fixation behavior after the visual rehabilitation

Discussion

In this study we demonstrated that acoustic and visual biofeedback are both useful in the treatment of late stage of AMD and that a luminous flickering stimulus could perfom better than acoustic biofeedback in certain situations. Our results show a rather unexpected amelioration in retinal sensitivity, fixation behavior, and all of the functional tests performed.

Table 1 Mean ± 1 SD of LogMAR visual acuity, retinal sensitivity, fixation behavior, reading speed observed in the AB and LB groups before and after rehabilitation

	AB Group		LB Group		Group	Session (pre-post)	Session × Group	*p* value
	Pre	Post	Pre	Post				
Visual acuity (logMAR)	0.94 ± 0.16	0.90 ± 0.16	0.92 ± 0.14	0.85 ± 0.16	F = 0.831, $p = 0.370$	F = 8.845, $p = 0.006$	F = 1.900, $p = 0.179$	0.02
Retinal sensitivity (dB)	8.40 ± 2.29	10.13 ± 2.20	8.53 ± 2.07	9.33 ± 2.47	F = 0.19, $p = 668$	F = 17.43, $p < 0.001$	F = 2.37, $p = 0.135$	0.002
Fixation behavior (%)	40.87 ± 11.36	43.33 ± 11.54	39.33 ± 12.83	45.33 ± 14.65	F = 0.00, $p = 0.959$	F = 26.99, $p < 0.001$	F = 4.70, $p = 0.039$	0.000095
Reading speed (w/m)	44.60 ± 9.38	47.40 ± 8.55	46.33 ± 6.67	54.33 ± 7.53	F = 2.62, $p = 0.117$	F = 18.61, $p < 0.001$	F = 4.31, $p = 0.047$	0.0006

Pre before treatment; *PosT* after rehabilitation; *dB* decibels; % % of fixations points within the 2° diameter circle (see text); *w/m* words read per minute

Table 2 Number of eyes revealing each level of fixation as a function of treatment and time

	AB Group Pre	AB Group Post	LB Group Pre	LB Group Post
Level of fixation				
Stable	0	3	0	4
Relatively unstable	10	10	9	11
Unstable	5	2	6	0

A luminous flickering stimulus has already been used in ophthalmology. A training technique for the treatment of homonymous visual field defects, known as visual restoration therapy (VRT), similar to the pattern stimulus biofeedback described above, was proposed by Kasten and Sabel (1995) in Germany. They developed the VRT strategy theorizing that neurons, subserving so-called transition zones areas between the intact visual field and the absolute field defect, continue to function albeit at a sub-threshold capacity, at least one year after an acute event, in patients with optic nerve damage. VRT provides stimulation to increase the frequency of utilization of these neurons with the goal of increasing their gain, thereby resulting in the restoration of at least a portion of the visual field defect (Kasten and Sabel 1995; Kasten et al. 1998; Poggel et al. 2004; Sabel and Kasten 2000; Sabel et al. 2004). Support for this therapy is offered by data utilizing Tuebingen automated perimetry (TAP), high resolution perimetry (HRP), and scanning laser ophthalmoscope (SLO) indicating significant border shifts, improved reaction time, and fewer missed stimuli following VRT (Horton 2005).

The usefulness of a flickering visual stimulus was evaluated in our previous study on retinitis pigmentosa patients performed with Visual Pathfinder (LACE inc) where we demonstrated an increase in visual acuity and transient visual evoked potential (VEP) P100 wave amplitude after a training with high contrast stimulus (Vingolo et al. 2009b). In that study, however, there was a bias due to the incomplete awareness of the patients of his/her fixation during the training. Furthermore at that time we could not test retinal sensitivity progression. Despite these limitations the results were subjectively very impressive to the patients and statistically significant.

In this study we could observe fixation behavior and demonstrated that pattern stimulation can help the brain to exercise and stabilize a new PRL by increasing attention modulation and providing patients with macular diseases and central scotoma a more efficient PRL for visual tasks.

Various hypotheses regarding the mechanisms of visual function improvement after visual training techniques can be put forth. There could be improvement in ocular motor control and in 'searching capacity', and discriminating capacities both of the retina and the visual cortex and associated areas (Kasten et al. 1998, Vingolo et al. 2009b). Animal model experiments have demonstrated the existence of flexibility of the adult visual system after retinal lesions as a result of modifications of the neuronal receptor fields not only in the visual cortex, but also in downstream structures such as the superior colliculli and lateral geniculate body (Maffei and Fiorentini 1976).

The possibility of a cortical reorganization secondary to local retinal dysfunction has been recently suggested (Parisi et al. 2010). Furthemore it was suggested that the improvement of visual field after intensive training with a flicker stimulation can induce cortical reorganization in adult patients (Hericksson et al. 2007; Raninen et al. 2007). Subjective variables such as learning effect, motivation, level of attention, psychophysical capacities and influence of the examiner may play a role in the determination of the results.

Complex pattern stimulations have significant recognition shapes that could increase inner retinal integrative processes and optimize stimulus lock-in, processing and recognition and facilitate brain transmission.

Our results, as demonstrated by other authors (Baker et al. 2005),s uggest that it might be possible in the damaged retina to override dead photoreceptor and outer retinal layers and involve residual surviving cells, as well as amplify and integrate retinal and brain cortex plasticity by using other spared channels towards associative pathways mediated, for example, via horizontal or amacrine cells.

In the present world any therapy offering a rehabilitative effect for chronically disabled patients should be widely welcomed by patients and care providers, especially for diseases such as terminal stage AMD where rehabilitation is the only choice for patients. Moreover regardless of the cause, visual damage has been associated with significant impact in daily function, including decreased enjoyment reading and watching television, moderate restriction to daily activities, and an increased risk of falling that reduce patient's visual quality of life. Rehabilitation techniques should be welcomed for the treatment of visually impaired people.

Conflict of interest There is no conflict of interest, and the paper has never been presented in a meeting.

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