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Project period: 2020.12.01 – 2023.11.30

Project closing report

Oculomotor modulation and visual performance in adult ophthalmic patients
Okulomotoros moduláció és látási teljesítmény felnőtt szembetegekben

Summary of results in Hungarian

A gyengénlátó betegeket segítő okulomotoros moduláción alapuló szemészeti rehabilitációt egyelőre kevés helyen alkalmazzák. A biofeedback fixáció tréning (BFT) körülbelül 15 évvel ezelőtt került be a klinikai alkalmazásokba mint ígéretes technika a fixáló szemmozgások, a vizuális teljesítmény és a látás minőségének javítására. Nem minden esetben figyelhető meg azonban mérhető klinikai javulás, még akkor sem, ha a BFT-t azonos diagnózisú betegeknél alkalmazzák. A BFT klinikai előrejelzőinek és a vizuális funkciókra gyakorolt lehetséges pozitív hatásainak meghatározása optimalizálhatja alkalmazásának költség-hasznosulását. A betegséggel nem összefüggő tényezők, mint például a páciens motivációja és a kezelő tapasztalata, szerepet játszhatnak a BFT hatékonyságában. A kutatásban felvetett hipotézis szerint az egyéni jellemzők befolyásolják a terápiás hatékonyságot. Egy másik vizsgált tudományos felvetés a BFT utáni okulomotoros modulációra vonatkozott, amely elterjedt, de nem feltétlenül ad jobb vizuális teljesítményt. Az elmúlt három évben a Semmelweis Egyetem Szemészeti Klinikáján, felnőtt betegek vizsgálata során elért eredmények alapján meghatározhatók a BFT sikerét befolyásoló klinikai tényezők. A klinikusok figyelembe vehetik az alapvizsgálatok során felmért egyéni szemészeti paramétereket, melyek alapján eldönthetik a BFT szükségességét “low vision” betegeknél.

Summary of results in English

Ophthalmic rehabilitation based on oculomotor modulation to aid patients with low vision are scarce. The biofeedback fixation training (BFT) moved into clinical applications about 15 years ago as a promising technique to enhance fixational eye movements, ameliorate visual performance and improve quality of vision. Unfortunately, measurable clinical improvements are not always observed even though BFT is applied identically to patients with equal diagnosis. To determine possible clinical predictors and potential positive effects of BFT on visual functions could optimize the cost benefit of its application. Disease non-related factors, such as patient’s motivation and trainer’s experience, might be involved in BFT efficacy. However, the hypothesis raised in this study was that individual characteristics may place a weight on therapeutic efficacy. Another issue investigated here concerned oculomotor modulation after BFT which is highly prevalent, but do not necessarily translate into improved visual performance. The results obtained during the past three years of investigation in the Department of Ophthalmology (Semmelweis University) examining and training ophthalmic adult patients shed a spark of light on the definition of clinical factors driving BFT success. Individual ophthalmic conditions assessed during the baseline examinations might be considered by the clinicians when deciding whether to prescribe BFT to low vision patients.

Background, goals of the project and applicability of the results

The stability of **fixational eye movements** (Figure 1) depends on voluntary and involuntary **oculomotor control** largely provided by **visual-guided inputs**. Deviations in sensorial inputs responsible for **high spatial resolution** and **color vision** in the central area of the retina called **macula**, may dramatically **impact the stability of the ocular fixation**. For instance, **macular scotoma**, as observed in patients with **age-related macular degeneration** (AMD; Figure 1), as well as unstable and **eccentric fixation**, as observed in patients with amblyopia (Figure 1), are associated with **disturbed fixation control** which may significantly **affect the quality of vision**. It has been demonstrated that **unstable ocular fixation** can be partially **compensated** with oculomotor **manipulation** even in late **adulthood**. It has been shown by several clinical research groups around the world that the **biofeedback fixation training** (BFT) can be **highly beneficial** for **enhancing the quality of vision** in patients with central (high-acuity) **vision loss**. However, the **clinical requirements** for fixational and visual gain after BFT **were completely unknown**. A **literature review** carried out during the preparation of this scientific report captured 16 studies reporting the **applicability and outcomes of BFT** using the equipment and protocol applied here in a **large spectrum of ophthalmic diseases** affecting fixation stability (Table 1 shows the single-condition investigation). However, information regarding **clinical predictors or critical baseline requirements** for the success of BFT was still **lacking**.

The present study sought to explore the **heterogeneity of BFT efficacy** and possible **clinical characteristics required to achieve full BFT success**. To accomplish the goals, different **visual functions** were measured: visual acuity (near and distance), contrast sensitivity, color vision, macular thresholds and stereovision. In addition, **standardized and alternative fixation stability parameters** were exported and calculated, respectively. The examinations were performed in a relatively large cohort of ophthalmic adult patients, including trained (N = 26) and non-trained (N = 14) patients who agreed to participate in the study providing a **documented consent**.

Baseline examinations provided unpublished information regarding the **extra-foveal color vision** and the associations between **fixation stability and contrast sensitivity**, as described below in the baseline section. The results were presented in the Annual Meeting of the Association for Research in vision and Ophthalmology (**ARVO**) in 2022 and 2023, respectively. The **follow-up results** showed that amblyopic patients with **relatively unstable fixation were more likely to benefit from the training** than amblyopic patients with stable or completely unstable (eccentric) fixation. Moreover, the **distance between the preferred fixation locus** (PRL) and the **anatomical fovea** strongly impacted the **efficacy of BFT** in patients with age-related macular degeneration (AMD). Regarding **visual gain after BFT** (with or without fixation improvements), it **remains partially obscure** why a more stable fixation after BFT will not necessarily result in visual improvements. It might be speculated that **factors not investigated by the present study**, such as cognitive functions, **may influence the clinical outcome**. The information obtained in the present study may contribute to **better understand the roles oculomotor control play on** monocular and binocular **vision** and to stablish **clinical requirements necessary for the therapeutic efficacy of BFT** in patients with central vision loss.

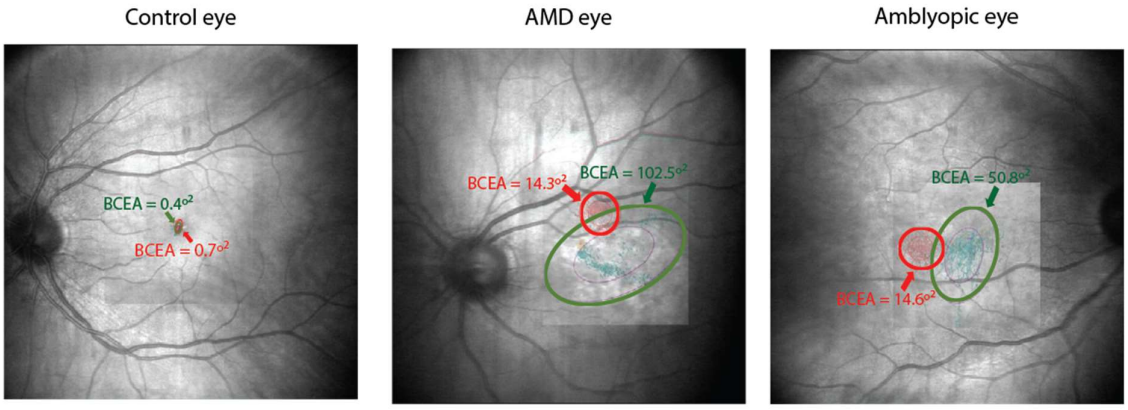


Figure 1. Fundus image and fixation stability of control, AMD and amblyopic eye. Stable fixation is associated with low BCEA (bivariate contour ellipses area) values in the control eye (left). AMD eye (middle) displays a large fixation area due to central (macular scotoma) while amblyopic eye (right) may show larger BCEA due to eccentric fixation. Baseline = green ellipses and values; follow-up = red ellipses and values.

Table 1. Most recent original articles reporting applicability and outcomes of BFT.

Reference	Ophthalmic condition	BFT	Main outcome
Caputo et al. 2021	Infantile nystagmus syndrome	12	BCEA improved, BCVA not
Daibert-Nido et al. 2021	Infantile nystagmus syndrome	10	Visual functions improved
Maneschg et al. 2021	Strabismus	4	BCEA improved
Misawa et al. 2023a	Hemianopsia	12	Quality of vision improved
Misawa et al. 2023b	Epiretinal membrane	1	Total improvement of symptoms
Sborgia et al. 2023	Macular hole	12	Fixation and sensitivity improved

BCEA=bivariate contour ellipses area; BCVA=best-corrected visual acuity

Project implementation and pilot investigations

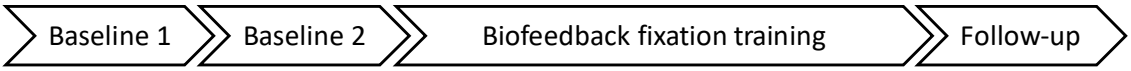
The first periods of the project were partially dedicated to **the preparation of manuscripts** and the **publication of previously initiated investigations** related to the topic of the project (Bankó et al. 2022; Barboni et al. 2020; Maneschg et al. 2021). The pilot studies provided relevant information regarding the protocol specifications for the measurement of **monocular and binocular visual functions**, the **selection of parameters** for applying the **biofeedback fixation training** (BFT) and the **development of Excel macros and MatLab routines** for the processing of fixation datasets using **alternative parameters** that were later **implemented to the raw data of the training files**. Contrast sensitivity and color vision **staircases** were calculated using **alternative methods** developed by Dr. Balázs Vince Nagy from the Budapest University of Technology and Economics (BME).

Normative data and calculated indexes of monocular and dichoptic **contrast sensitivity** were established in central and extra-foveal fixators, and in control eyes (Barboni et al. 2020). Moreover, the data analysis of a **previous study** applying stereoscopic **augmented reality based training in amblyopic patients**, revealed that proper **fixation stability is required for stereovision improvement following binocular therapy** (Bankó et al. 2022).

Pipelines and software development

These pilot investigations provided **major preliminary information** that were later used to define the **clinical protocols**. More importantly, the preliminary results allowed us to **define the pipelines** of the project, as shown below. Therefore, **setting the ground for the study**.

Data collection



Data processing and analysis

Baseline and follow-up examinations included a **complete ophthalmological examinations** provided by Dr. Ottó Maneschg (ophthalmologist specialist in amblyopia) and Dr. Mónika Ecsedy (ophthalmologist specialist in retina diseases). The examination included refraction, biomicroscopy to verify anterior segment integrity, fundus examinations and OCT to check retinal integrity in case of amblyopic patients and to classify the type of AMD in patients with macular degeneration. The **functional measurements** included best-corrected visual acuity (counting letters), contrast sensitivity, color vision, stereoacuity and the application of microperimetric examinations. The functional examinations as well as the **biofeedback fixation training** were performed by Dr. Mirella Barboni, the project coordinator, with the assistance of a 5th year medical student from the Semmelweis University.

The MatLab routines for **data processing and analysis** was developed in collaboration with Dr. Éva Bankó from the Brain Imaging Centre, Research Centre for Natural Sciences in Hungary.

Main findings

Baseline examinations were performed in 40 patients (18 amblyopic and 22 AMD) according to group-specific inclusion criteria. The **main findings** of the baseline examinations were:

1. The more the unstable fixation stability the lower the **visual acuity**, as it was already known.

2. Monocular **color vision** thresholds were within the normal limits in amblyopic patients with central fixation and severely affected in extra-foveal fixators both amblyopic and AMD patients. In addition, unbalanced binocular interactions interocular interactions affected color vision tresholds revealed by the dichoptic stimulation (Figure 2). Results presented at ARVO 2022 Annual Meeting:
https://iovs.arvojournals.org/article.aspx?articleid=2779416&resultClick=1
Manuscript under the final phase of preparation to be submitted to IOVS.

3. The absence of finely tuned fixational eye movements prevented high spatial resolution to take place. The data emphasized the importance of stable fixation in acuity and contrast tasks (Figure 3). Results presented at ARVO 2023 Annual Meeting:
https://iovs.arvojournals.org/article.aspx?articleid=2785856&resultClick=1

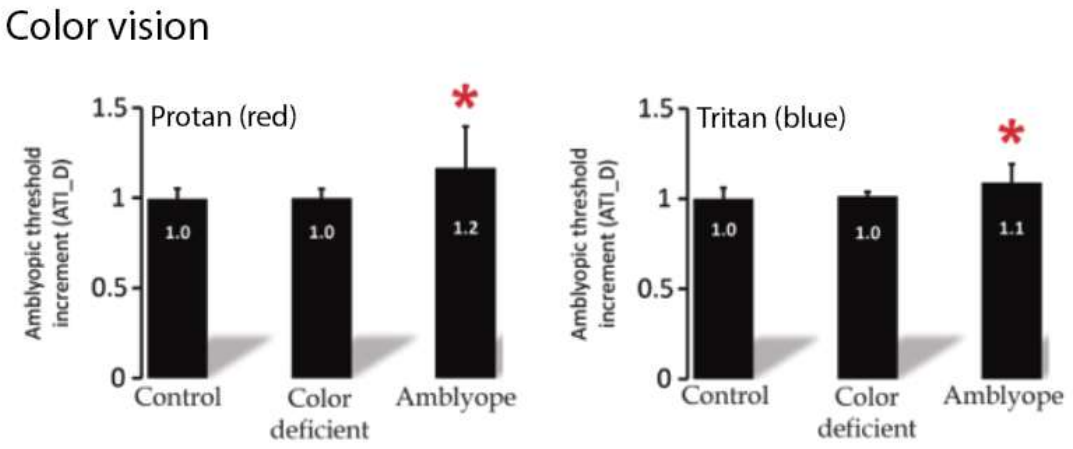


Figure 2. Baseline color vision. Comparison of dichoptic thresholds between controls, color deficient subjects and amblyopic patients. Protan and tritan interocular thresholds were significantly elevated in amblyopic subjects under dichoptic condition compared to both color normal and color deficient subjects (main effect of group: $F_{(2,34)}$=7.70, p=0.0017, group*vector $F_{(2,34)}$=0.40, p=0.67). Interestingly monocular interocular thresholds were comparable. The elevated interocular dichoptic thresholds in amblyopic patients were the result of unbalanced binocular interactions preventing the background noise presented to the amblyopic eye to influence color perception of the dominant eye.

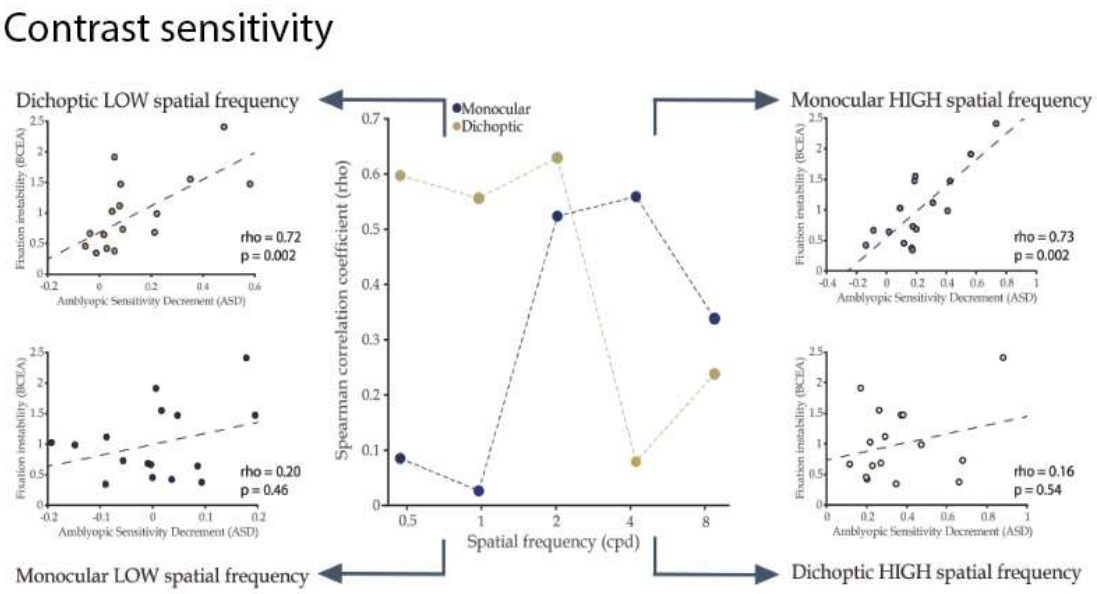


Figure 3. Baseline contrast sensitivity x fixation stability correlations. There was a significant correlation between fixations stability and contrast sensitivity at high spatial frequencies (SF) under monocular condition while the opposite pattern was found under dichoptic condition: significant correlation at low SFs showing that fixation stability differentially affects monocular and dichoptic contrast sensitivity.

The results of the **follow-up examinations** reveled **positive effects of BFT** on **fixation stability** as well as in **visual functions**. For instance, a more **stable ocular fixation** may be achieved with BFT in both AMD and amblyopic patients (Figure 4). However, if the **preferred retinal locus** (PRL) is located **near to the fovea** and **fixation is relatively unstable**, not completely unstable, **improvements in visual performance may be also achieved** in adult ophthalmic patients. In conclusion, **specific parameters might be observed by the clinicians** prior to prescribing BFT. **Future investigations** may consider to include **larger groups of ophthalmic patients** to provide reliable **correlations** between **ocular fixation improvements and positive changes from baseline** in visual performance.

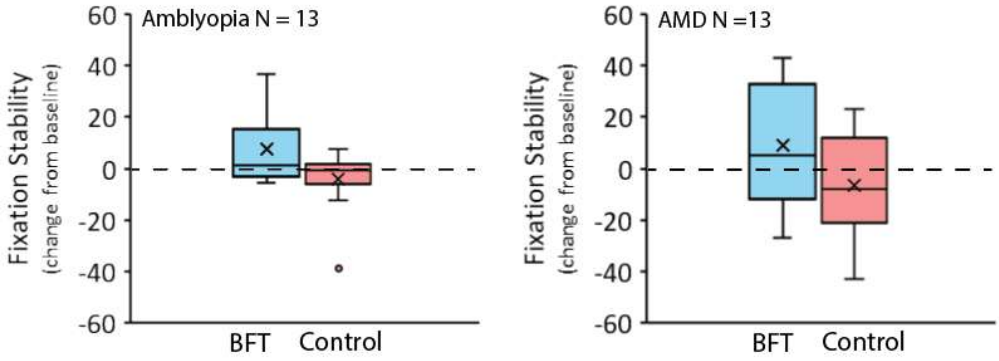


Figure 4. Fixation stability improvements after BFT. Mean/median (box = interquartile range [IQR]; whisker = minimum and maximum values). The change from baseline (CFB) was calculated for P0.5 and P1 for amblyopic and AMD patients, respectively. These fixation stability parameters are the percentage of fixation points within a certain area (0.5 or 1 degree) considering the center of the fixation cloud. BFT in blue are the results of the trained eyes (N = 13 for each group) and control in red represents the results of non-trained (control) eyes. Observe that in both groups CFB was in average positive while average control was close to zero (dashed lines = no changes from baseline). The complete results of the changes from baseline in fixation stability as well as in visual performance (visual acuity and contrast sensitivity) and quality of vision will be submitted for publication.

Involvement in Hungarian projects and international collaborations

During the period of the project, there was the involvement in Hungarian projects at the host institution in collaboration with Dr. Viktoria Szabo and Dr. Ditta Zobor from the ophthalmic-genetic group applying gene therapy in patients with retinal dystrophies and with the group of Dr. Daniel Hillier from the Institute of Cognitive Neuroscience and Psychology, Research Centre for Natural Sciences, which brought the opportunity to join an international consortium to investigate brain mechanisms in amblyopia.
https://www.neuron-eranet.eu/wp-content/uploads/Lay_UnscrAMBLY.pdf
International collaborations included the preparation of an invited review manuscript (Barboni et al. 2023) in collaboration with research groups from Germany (Prof. Jan Kremers), France (Dr. Cyrille Vaillend) and Brazil (Prof. Dora Ventura).
https://www.sciencedirect.com/science/article/pii/S1350946222000970?via%3Dihub

Research / budget plan and the application of the grant

The project was carried out following the original research and budget plan. However, because of COVID pandemic, in 2021 the scientific conferences were attended virtually. The grant budget was applied to personnel costs (full-time principal investigator's salary during the entire period of the project) and travel expenses to attend the scientific conferences in the second (2022) and third (2023) period of the project.

Future perspectives

In addition to results already presented / published, two original manuscripts are currently under the final stage of the preparation. A manuscript showing changes from baseline in fixation stability (Figure 4) and spatial vision (visual acuity and contrast sensitivity) as well as predictive factors, such as initial fixation stability, influencing biofeedback fixation training efficacy. A manuscript dedicated to "Foveal and extra-foveal color vision" is already prepared and it is going to be submitted to "Investigative Ophthalmology and Visual Science" (IOVS).

The implementation of the project three years ago in the framework of NKFI-OTKA brought the opportunity to be integrated into the scientific team of the Department of Ophthalmology at the Semmelweis University. Before the project ended, an associate scientist position was opened in the Department. The new contract was recently signed by Prof. Zoltán Zsolt Nagy. Therefore, the topic developed in the present project thanks to NKFI-OTKA grant will be a new research area in the Department. We are deeply grateful for the opportunity!

Publications

Original articles

Bankó ÉM, Barboni MTS, Markó K., Körtvélyes J., Németh J., Nagy ZZs, Vidnyánszky Z. 2022. "Fixation Instability, Astigmatism, and Lack of Stereopsis as Factors Impeding Recovery of Binocular Balance in Amblyopia Following Binocular Therapy." *Scientific Reports* 12(1):10311. doi: 10.1038/s41598-022-13947-y.

Barboni MTS, Joachimsthaler A, Roux MJ, Nagy ZZs, Ventura DF, Rendon A, Kremers J, Vaillend C. 2023. "Retinal Dystrophins and the Retinopathy of Duchenne Muscular Dystrophy." *Progress in Retinal and Eye Research* 95:101137. doi: 10.1016/j.preteyeres.2022.101137.

Barboni MTS, Maneschg OA, Németh J, Nagy ZZs, Vidnyánszky Z, Bankó EM. 2020. "Dichoptic Spatial Contrast Sensitivity Reflects Binocular Balance in Normal and Stereoanomalous Subjects." *Investigative Ophthalmology & Visual Science* 61(11):23. doi: 10.1167/iovs.61.11.23.

Maneschg OA, Barboni MTS, Nagy ZZs, Németh J. 2021. "Fixation Stability after Surgical Treatment of Strabismus and Biofeedback Fixation Training in Amblyopic Eyes." *BMC Ophthalmology* 21(1):264. doi: 10.1186/s12886-021-02020-3.

Conference abstracts

Barboni MTS, Maneschg OA, Nagy ZZs, Németh J. 2021. Biofeedback fixation training in amblyopia. *Investigative Ophthalmology & Visual Science*, 62, 619.

Barboni MTS, Urbin A, Edelmeyer M, Maneschg OA, Killik P, Németh J, Nagy ZZs, Banko EM, Nagy BV. 2022. Unbalanced binocular interactions in amblyopic color vision revealed by dichoptic color test. *Investigative Ophthalmology & Visual Science*, 63, 769.

Barboni MTS, Maneschg OA, Nagy ZZs, Németh J, Banko EM. 2023. Amblyopic fixation stability differentially affects monocular and dichoptic contrast sensitivity. *Investigative Ophthalmology & Visual Science*, 64, 36.

Barboni MTS, Joachimsthaler A, Roux MJ, Nagy ZZs, Ventura DF, Rendon A, Kremers J, Vaillend C. 2023. Retinal Dystrophins and the Retinopathy of Duchenne Muscular Dystrophy. ISCEV Symposium, Kyoto, Japan.

Maneschg OA, Barboni MTS, Killik P, Banko EM, Németh J, Nagy ZZs. 2023. Biofeedback fixation training as an important tool to supplement strabismic amblyopia treatment in adults – preliminary results.