Title: Biofeedback training to improve fixation stability, visual function outcomes, and quality of life in hemianopia cases

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PROTOCOL

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Background

Patients with brain injury secondary to stroke, surgery, or trauma frequently suffer from homonymous hemianopia, defined as vision loss in one hemifield secondary to retro-chiasmal lesion. About 45% of stroke survivors have homonymous hemianopia. A deficit in vision and spatial perception can cause slowdown of the rehabilitation progress in physiotherapy.

According to Kerkhoff [1] patients face three main visual behavioral problems: (1) impaired eye movements (including saccades) leading to defective visual and spatial exploration, (2) hemianopic reading deficit (hemianopic alexia) because of the parafoveal field loss and (3) deviated subjective midline. Hemianopic dyslexia is not simply the product of the visual field defect but is caused by a disorder of control of visual information processing and eye movements in reading.

Most importantly, the capability to read is fundamental for daily living and an essential prerequisite for education and success in our modern society, so this disorder can have a profound effect on patients' lives. Patients with visual field loss usually fail to adapt to their reading impairment (80% of cases). In these cases, word identification and the abilities to plan and guide reading eye movements are disturbed.

In spite of these facts, visual rehabilitation program on a larger scale is still missing in most rehabilitation centers and clinics. This is decurrent to the generalized belief that lesions of the lateral geniculate nucleus and striate cortex lead to a permanent loss of vision. According to scientific findings, this does not always have to be true.

Optical solutions have shown to be effective in helping visual impairments in hemianopia cases. Relatively small prismatic amounts may be tested and prescribed to this group, as the function of yoked prisms in these cases is to reduce the mismatch between their veridical objective and anomalous subjective sense of straight ahead to a perceptually acceptable level. Yoked prisms have been used by neuro-rehabilitative optometrists for decades, as well as others in the field such as occupational therapists, to improve ambulation and gait in hemianopia and/or hemiplegia. Approximately two-thirds of the patients may respond favourably to the yoked prisms. Statements such as 'the visual

space seems expanded', and observations such as having improved mobility, ambulation and eye–hand co-ordination, are positive prognostic indicators when prescribing yoked prisms in this diagnostic group.[2] Likewise, Padula[3] demonstrated that application of yoked prisms improved balance and posture. 'Improved posture, and the sense of feeling more stable while walking through the environment', as well as marked, absence of 'feeling of nausea and dizziness while walking' or 'objects to appear to move when walking'.

Bitemporal hemianopic visual field impairment frequently leads to binocular vision difficulties. Patients with bitemporal hemianopia with pre-existing exophoria complain of horizontal diplopia, sometimes combined with vertical deviation (with pre-existing hyperphoria). The symptoms are a result of the phoria decompensating into a tropia (hemi-slide) due to the lack of retinal correspondence between the remaining nasal fields of both eyes. Aligning the eyes with prisms can prevent diplopia if the bitemporal hemianopia is incomplete.[4]

Classic and effective saccadic compensatory training therapies are current.[5] They aim to reorganize the control of visual information processing and eye movements or, in other words, to induce or improve oculomotor adaptation to visual field loss. Such therapies involve the systematic and repetitive practice of specific eye movements for reading or for visual exploration. Patients learn to intentionally shift their eyes and, thus, their visual field border, into the area corresponding to their blind visual field. This shift brings the visual information from the blind hemifield into the seeing hemifield for further processing. Patients learn, therefore, to efficiently use their eyes "to keep the 'blind side' in sight". The training-induced, efficient oculomotor adaptation to visual field loss becomes manifest as a change of reading (or visual exploration) eye-movement patterns and indicates the functional reorganization of the control of visual information processing and eye movements.[6]

Biofeedback training for active eye movement control was never used in hemianopia cases before. Biofeedback training (BT) is the latest and newest technique for oculomotor control training in cases with low vision when using available modules in the new microperimetry instruments.[7–9] Studies in the literature highlighted positive benefits from using BT in a variety of central vision loss, nystagmus cases, and others.[10–18] The purpose of this study is to assess systematically the impact of BT in a series of cases with hemianopia and formulate guidelines for further use of this intervention in vision rehabilitation of hemianopia cases in general.

Rationale for the study

The deviation of the subjective midline in hemianopia cases brings visual perception from a line of objects in the surrounds to be at a much higher-level of perception/cognition, thus disturbing reading, gait and balance. Besides that, impaired saccades also cause wrong exploration patterns and deteriorated visual search. It results in the prolonged exploration time of a scene and can lead to significant problems in daily life such as inability to navigate around various obstacles (cars, people and other objects). It also causes a

cognitive deficit while extracting information from a visual scene. [1] A combination of factors such as reduced contrast sensitivity, impaired visual search and inaccurate fixation contributes to the matter.

Visual information extraction from the parafoveal visual field provides the basis for planning and guiding of reading eye movements. Therefore, patients with hemianopia have difficulties in shifting their gaze systematically from left to right (in right-sided field loss) or finding the beginning of a new line (in left sided field loss). Such eye movements are optimized by visual feedback. BT promotes luminous and auditory biofeedback, which potentializes its efficacy in vision rehabilitation.

BT in the microperimeter module provides the accurate and efficient oculomotor training necessary to relocate the subjective midline to the seeing field in 1-2^0 or even more, as needed. BT also improves dramatically fixation stability and saccades. The advantage of this training method over classic training is potentially great. Firstly, the highest retinal sensitivity convenient point can be identified considering the whole visual field. The microperimeter provides real time scrutiny of ocular movements on a screen, and the therapist is able to select precisely the trained retinal locus (FFT) to be used by the patient on top of the microperimeter visual field. Finally, according to the patients' response the FFT can be readjusted. Eight cases trained with BT for hemianopia in our low vision rehabilitation (LVR) service had marked improvements in fixation stability, and microperimeter fields.

Expansion of visual space in the direction of the blind field and compression of visual space in the direction of the seeing field may be a contributory factor to the altered perception of their egocentric directional sense and overall more veridical mapping of their visual space, as well as the resultant shift in their positional centre of gravity. We hypothesize that BT promotes this field relocation.

Conventional visual exploration training studies have confirmed that 10 to 25 training sessions in a 6-week period can be effective for hemianopia patients to adopt these strategies. BT is able to achieve significant results in 5 weekly sessions of 20 minutes each, according to 8 cases treated in our service.

Study hypothesis

The visual and audio parts of the BT program improve in a synergistic way oculomotor control through attention improvement and volitional eye movements towards pre-designated targets. Improved oculomotor control results in better fixation stability of eyes. Better fixation stability in turn results in better navigation for distance and near vision reading. Dual sensory BT is a therapy used in low vision for more than ten years, showing good results for near and distance vision in cases with macular degeneration and other pathologies. The study hypothesis, never tested before, is that BT in cases with hemianopia will positively impact oculomotor control and visual acuity as it was proven to do in cases with macular degeneration.

Significance of the study

Vision is a major sensory input to the human brain. Half of the afferent neuronal fibers projecting to the brain originate from the eyes. Intact visual abilities are an important condition enabling us to orient ourselves in our world. Pambakian and Kennard [20] reported that 50% of all neurological admissions into hospitals in the United Kingdom are due to a stroke and 30% percent of them are reported to have hemianopia.
Numbers of hemianopic patients reported in the Czech Republic are similar and somewhat lower due to differences in diagnostics and classification of nosological units.[21] Visual impairments are present in 20 to 40% of patients in neurological rehabilitation centers.

If brain visual plasticity is possible to be achieved from conventional vision training methods, specialized training with BT needs to be investigated as a tool for improving a cortical visual disorder. There is a need for simple and more effective visual training which could be used in LVR in large scale for hemianopia cases. Furthermore, BT needs to be evaluated in terms of quality of life (QoL) improvement to the patients.

Clinical trial design

This is a prospective clinical randomized trial to include a control group and take place over a period of up to 24 months. 35 patients will be randomized to the treated group (BT) and 35 patients to the control group.

The objectives set for this trial is to verify if BT impacts on oculomotor control in cases with hemianopia and results in better fixation stability, reading speed and QoL in those trained with BT.

Primary endpoints selected for this trial are retinal sensitivity, fixation stability (FS) estimates as tested with the MAIA C 10-2 Microperimetry (Centervue, Padova, Italy), Compass 30-2 perimetry (iCare, Centervue, Padova, Itay), Humphrey Full Field 120 perimetry (Carl Zeiss, Germany), reading speed as tested with the MNRead test, and QoL assessed with the Massof 48 questions LVR questionnaire.

Secondary endpoints are preferred retinal locus (PRL) topographic coordinates, as tested with the MAIA Microperimeter (Centervue, Padova, Italy), contrast sensitivity measured with the Vistech charts, and Best Corrected Visual Acuity (BCVA) scores for distance and near vision tested with ETDRS charts at 4 meters and 33 cm.

Clinical trial population:
The intended population for this clinical trial is to be found among our own practice patients or among patients referred to our low vision rehabilitation practice. We will consider inclusion into the trial patients that meet the trial entry criteria defined below.

Inclusion criteria: **hemianopia** cases with more than 6 months from the date of the lesion, previously diagnosed accordingly by microperimetry and other tests as needed, 18-90 years old, ability to follow the visual and auditory stimuli and training instructions.
Exclusion criteria: **previous or current treatment for low vision rehabilitation,** ocular diseases, other serious clinical conditions not related to the hemianopia physiopathology, both eyes with media opacity that impairs microperimetry testing, lack of ability to perform the tests and training.

Clinical trial procedures
All parties involved in the conduct of this clinical trial will be qualified by education, training, or experience to perform their tasks, and this training will be documented appropriately. The investigation will not commence after receiving written approval from the UHN REB. All trial staff will be required to undergo training prior to performing any trial-related activities.

The following is an overview of the study procedures: following obtaining consent from study participants, confirmation of eligibility, and baseline visit assessments, patients will be randomized in 2 groups: BT and control. Treated group participants will undergo 5 BT sessions. 30 days after completion of the 5 BT sessions, participants will return for the first follow up visit, followed by follow up visits at 6 months and 1 year post-BT. The control group of participants in the randomized arm will perform the same tests as in the baseline visit at 30 days post-BT and end the participation in the study. After that, the control group will be provided the option to perform the 5 BT sessions. Following completion of the study visits, participants will return to regular clinical care, that includes BT when needed.

The following is a detailed description of the study procedures:

Screening
The following information will be evaluated from medical records and documented, to ensure each subject meets entry criteria prior to consent: diagnosis, age, visual impairment, disabilities related to visual impairments and impact of disabilities on quality of life.

Informed consent
Informed Consent Forms will be utilized detailing requirements and considerations for patient consent or legal representative. An authorized designee will conduct the informed consent process. This process will include a verbal discussion with the patient / legal representative on all aspects of the clinical trial that are relevant to the participant's decision to participate such as details of the procedures, anticipated benefits, and potential risks of clinical trial participation. During the discussion, the authorized designee will avoid any improper influence on the subject and will respect the subject's legal rights. The patient / representative will be provided with Informed Consent Form approved by the UHN REB and written in a language that is understandable to the patient / representative. The participant will have adequate time to review, ask questions and consider participation. If the patient agrees to participate, the Informed Consent Forms will be signed and dated by the patient / legal representative and by the person obtaining the consent. The signed

original will be filed in the subject's research charts, and copies will be provided to the participant.
Standard of care procedures: All clinical trial procedures described below are part of the standard of care procedures experienced by patients with the exception of randomization and the following procedure used in the control group: The procedure involves presentation of a standard LED fixation target (FT) consisting of a small red circle of about 0.76° diameter. Initially the participant will be instructed to stare at the FT circle. Following this stage, the participant will be guided to look at the FT and simultaneously to be aware of any flashing lights in the periphery of vision. As performing this task, the participant will actively control the eye movements and similar to computer games, the patient has to identify targets in the peripheral field of vision and respond by pressing a button.
Baseline procedures

Visit 1: If the patient accepts to take part in this study and signs the consent form, there will be a low vision baseline assessment. This may take about 1 hour. At the time the patient books this assessment, all the procedures for coronavirus screening will be done normally by phone. Before the patient enters the clinic, the screening questions will be repeated, and they should wear a mask all the time during the consultation. Hands hygiene will be facilitated all the way in the clinic, and all the equipment, charts and surfaces will be disinfected pre- and post- examinations. No patients with COVID 19 symptoms will be allowed in our facilities. If the patients have symptoms, contact with persons with COVID 19 or recent travels, they will be instructed to rebook the appointment and go to an emergency service if appropriate. **Demographics and medical history will be collected at this time.**

During the baseline visit (Visit 1) participants will be assessed for Best Corrected Visual Acuity (BCVA) for distance vision with ETDRS charts at 4 meters, retinal sensitivity and fixation stability (FS) estimates from microperimetry C 10-2 with the MAIA microperimeter (Centervue, Padova, Italy), 30-2 perimetry with the Compass (Centervue), Esterman perimetry with the Humphrey perimeter (Carl Zeiss, Germany) , and eye movement scanning with the RightEye device (pupil tracker, Bethesda, MD). Participants will be assessed also for near vision with the Colenbrander chart and contrast sensitivity measured with the Vistech chart. Quality of Life estimates will be assessed with the Massof questionnaire.[16] This visit may take up to an hour in total.

Randomization
Following the baseline assessment participants will then be randomized in a ratio 1:1 between BT Treatment and Control groups. For this purpose, we will use for all study participants one of the freely available Clinical Trial Randomization Tools by The National Cancer Institute's Division of Cancer Prevention (https://ctrandomization.cancer.gov/tool/) randomization generator.
Study participants will be randomized to:

- Group A (Treatment with BT) will receive the audio biofeedback training and follow up visits at 9 weeks, 6 months, 12 months, and 24 months after baseline visit.

- Group B (Control) will perform a follow up visit at 9 weeks, 6 months, 12 months, and 24 months after baseline visit.

Training procedure
BT will take place during a 20 minutes weekly visit to the office. During training procedure visits (Visits 2-6) the participant is seated in front of the instrument. The procedure involves presentation of a standard LED fixation target (FT) consisting of a small red circle of about 0.76° diameter. A fixation training target (FTT) will be selected by the trainer at a perceived better fixation point. Initially the participant will be instructed to stare at the FT circle. Following this stage, the participant will be guided to look in the direction of the FTT and listen simultaneously to the audio feedback. As performing this task, the participant will actively control the eye movements until the audio feedback becomes more frequent and then becomes a continuous sound pattern. This continuous sound will signalize to the patient that the FTT location was reached.

Group A schedule:

Group A	Biofeedback	Microperimetry	Visual Acuity	Reading	Contrast	Perimetry/ Eye Tracking	Questionnaire
V1-1h		X	X	X	X	X	X
V2-20'	X						
V3- 20'	X						
V4-20'	X						
V5-20'	X						
V6-20'	X						
V7-1h -9 weeks		X	X	X	X	X	X
V8-6 months		X	X	X	X	X	X
V9-12 months		X	X	X	X	X	X
V10-24 months		X	X	X	X	X	X

Group B schedule:

After the follow up visit, the same procedures will be repeated on the following visits as shown in the table below.

After completion of study visit at 6 months, the patients will be offered the option to benefit from the biofeedback treatment if desired.

Group B Schedule:

End of study procedures
The final follow up Visit 7 visit will take place at 45 days following visit 6. This visit may take an hour time. At visit 7, repeat assessments will take place for Best Corrected Visual Acuity (BCVA) for distance vision with ETDRS charts at 4 meters, preferred retinal locus (PRL) characteristics, retinal sensitivity and fixation stability (FS) estimates with the MAIA microperimeter (Centervue, Padova, Italy). Participants will be assessed also for near vision, reading speed and contrast sensitivity measured with the MARS charts, stereopsis will be assessed with the Frisby Stereo Test, and Quality of Life estimates will be assessed with the Massof questionnaire. After the participation in the study, the patients will continue to be followed in the regular LVR clinic at the same service.

Follow-up duration

Following the completion of biofeedback treatment visits, patients will be followed for 6 months since their initial recruitment for the primary study time-point. Additionally, patients will be followed for up to 2 years for long-term outcomes of the biofeedback treatment. Visits 8, 9 and 10 will follow the same procedures as visit 7 for assessments.

Data collection

Source documents will be created and maintained by the investigational site team throughout the clinical trial. The data reported on the CRFs will be derived from, and be consistent with, these source documents, and any discrepancies will be explained in writing. The personal information from the participants and source data will be kept separately from the CRFs.

CRF files will include visit dates (including date of enrollment), number of the subject, date of birth, medical history, any adverse events, details of the trial, evidence that the participant met the inclusion/exclusion criteria, date/time of study visits, original informed consent form and record of informed consent process, and other notes as appropriate. These files constitute “source data” and will be signed and dated by the study site research personnel who recorded the data. All entries in the CRFs will be supported by source data. The CRFs will be kept up to date so that they reflect the latest observations on the subjects enrolled in the study. All paper source documentation will be completed using a black or blue ballpoint pen and will be legible. Errors will be corrected by a single line through the error, and the correction written in black or blue ink initialed and dated by the appropriate study site personnel, authorized by the Principal Investigator. Where information is not applicable, “N/A” will be inserted.

Statistical considerations

We have previously observed an increase in retinal sensitivity from 17.2 ± 5.06 dB pre-treatment to 18.3 ± 5.71 dB post-treatment. Based on sample size calculations, using a treatment effect size of 1.1, a population variance of 1.2 dB, a conservative alpha of 1% (0.01) with a power 80%, the minimum number of subjects for adequate study power would be 56 (28 in each arm). When considering a 20% drop out rate, the final sample size is calculated to be 70, with 35 patients in each arm.

Given the volume of the PI’s clinic, it is estimated that there will be 8 eligible patients available for study recruitment per month. As such, we anticipate all study recruitment to be completed within 9 months.
Data analysis will be based on descriptive statistics that include frequency distributions, a measure of central tendency (mean) and a measure of dispersion (standard deviation).
All analyses will be conducted as intention-to-treat (ITT) and therefore will be based on the initial treatment assignment and not on the treatment eventually received.
The primary study time-point is 6 months post-recruitment and additional analyses will be conducted at the completion of 1 year and 2-year study visits.
Statistical comparison between populations will be made by the Wilcox rank sum and t-tests. Differences were considered to be statistically significant at a p-value of less than 0.01. A conservative p value will be used to minimize the chance of a type I error.

Risk and benefits

There are no known risks or side effects known from using biofeedback training. In some cases, the patient may fatigue or get tired due to the effort required to complete the training. The patient may experience some, discomfort or eye strain.

Risks of Vision Testing:

There is a small risk of eye infection using the microperimeters, other perimeters, stereopsis charts, contrast sensitivity charts, and reading speed charts.

Subject withdrawal
Participation in this study is voluntary. Patient/legal representative participant may decide not to be in this study, or to be in the study now, and then change their mind later. Patient/legal representative may leave the study at any time.
During any study visits testing and / or training may be interrupted or terminated if participants experiences and reports symptoms deemed by the participant to be not tolerable. Under such circumstances testing and / or training may be interrupted or terminated.
The investigator may decide also to remove participants from this study without patient/legal representative participant consent at any time and for any reason or if patient/legal representative is unable or unwilling to follow the study procedures.
If the participant decides to withdraw from the study, the information that was collected before he/she leaves the study will still be used in order to help answer the research question. No new information will be collected without the participant's permission.

Publication
Publications or presentations of clinical trial methods or results will be done, adhering to the Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines. Publications will be attempted in peer reviewed scientific journals with an interest in Low Vision Rehabilitation and Neurology.

Confidentiality

Any information and data generated during this clinical trial in reference to any subject's participation in this investigation will be considered confidential. The Investigators will ensure that all subjects' anonymity will be maintained on all documentation kept in the participant study file by completely redacting (eliminating or "blacking out") each subject's name and/or other identifying information. The identifying information will be replaced with the subject's study number. The "source data" will be kept separately from the CRFs so that patient's ID will not be included within the source data. In addition, PHI will not be included within the CRFs.

All information collected during this study, including personal health information, will be kept confidential and will not be shared with anyone outside the study unless required by law. Only the study team or the people or groups listed below will be allowed to look at study records. Representatives of the University Health Network (UHN) including the UHN Research Ethics Board may look at the study records and at personal health information to check that the information collected for the study is correct and to make sure the study is following proper laws and guidelines.

In the event of inappropriate release of personal health information, further release of information will be stopped, any information that can be retrieved will be retrieved, the UHN

Privacy Office and REB will be notified, and actions according to recommendations from the UHN Privacy Office and REB will be taken.

Records

Principal Investigators will maintain the clinical trial documents as required by law and regulations in a secure and safe place. Measures will be taken to prevent accidental or premature destruction of these documents. The Principal Investigator may transfer custody of records to another person/party and document the transfer at the investigational site as appropriate.

These documents must be retained by the investigational site for a period of 10 years after the conclusion of the clinical trial and made available for monitoring or auditing by representatives of the applicable regulatory agencies.

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