Vision Restoration Training for Glaucoma: A Randomized Clinical Trial

Bernhard A. Sabel, PhD; Julia Gudlin, PhD

IMPORTANCE Visual field loss due to retinal damage is considered irreversible, and methods are needed to achieve vision restoration. Behavioral vision training, shown to improve visual fields in hemianopia and optic nerve damage, might comprise such a method.

OBJECTIVE To determine if behavioral activation of areas of residual vision using daily 1-hour vision restoration training for glaucoma for 3 months improves detection accuracy compared with placebo.

DESIGN AND SETTING Prospective, double-blind, randomized, placebo-controlled clinical trial in an ambulatory care and home training setting.

PARTICIPANTS Volunteer sample of patients with glaucoma (mean age, 61.7 years; age range, 39-79 years) with stable visual fields and well-controlled intraocular pressure. After randomization, 4 patients withdrew from the trial because of mild headaches (n = 2) or lack of time to complete the schedule (n = 2).

INTERVENTIONS Computer-based vision restoration training for glaucoma (n = 15) or visual discrimination placebo training in the intact visual field (n = 15).

MAIN OUTCOMES AND MEASURES The primary end point was change in detection accuracy in high-resolution perimetry. Secondary end points were 30° white-on-white and 30° blue-on-yellow near-threshold perimetry, as well as reaction time, eye movements, and vision-related and health-related quality of life.

RESULTS Vision restoration training for glaucoma led to significant detection accuracy gains in high-resolution perimetry (P = .007), which were not found with white-on-white or blue-on-yellow perimetry. Furthermore, the pre-post differences after vision restoration training for glaucoma were greater compared with placebo in all perimetry tests (P = .02 for high-resolution perimetry, P = .04 for white on white, and P = .04 for blue on yellow), and these results were independent of eye movements. Vision restoration training for glaucoma (but not placebo) also led to faster reaction time (P = .009). Vision-related quality of life was unaffected, but the health-related quality-of-life mental health domain increased in both groups.

CONCLUSIONS AND RELEVANCE Visual field defects caused by glaucoma can be improved by repetitively activating residual vision through training the visual field borders and areas of residual vision, thereby increasing their detection sensitivity. Our randomized clinical trial revealed evidence that visual field loss is in part reversible by behavioral, computer-based, online controlled vision training, comprising a new rehabilitation treatment option in glaucoma. Neuroplasticity of the visual cortex or higher cortical areas is the proposed mechanism of action.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01799707.
Glaucoma is a progressive optic neuropathy caused by a pathologic optic nerve head with slow degeneration of retinal ganglion cells. The resulting vision loss is considered irreversible, with no chance of recovery. Because of neuroplasticity, or the ability of the brain to adapt to change, visual system structures are modifiable even in adulthood and old age by the following means: (1) in adult visual cortex, receptive fields can change in size and location after retinal injury; (2) training eccentric (peripheral) viewing in macular degeneration activates cortical regions normally representing central visual areas; (3) visual training in hemianopia activates visual cortex at the lesion border; (4) training-induced vision restoration is greater in cases in which the cortical regions are not directly injured, as in after optic nerve damage; and (5) noninvasive transorbital alternating current stimulation can improve visual fields in optic neuropathy, with corresponding electrophysiological changes.

Evidence exists that visual system plasticity is behaviorally meaningful: regular practice in normal perceptual learning can improve visual acuity and contrast sensitivity. Furthermore, vision loss after visual system damage can spontaneously recover in animals and patients, and stimulating visual field borders in patients with cortical or optic nerve lesions improves detection accuracy and enlarges visual fields, which are stable and improve activities of daily living.

Evidence also indicates that areas of residual vision (ARVs) contain fibers spared by the lesion that can activate the plastic cortex as suggested by the following observations: (1) 10% to 20% retinal ganglion cell survival in animals with optic nerve damage is sufficient to achieve recovery of visually guided behavior up to 80% detection in animals and becoming hyperactive; (3) training-induced vision improvement in patients following stroke is directly related to ARV size, and (4) vision restoration is a function of residual activity locally and in the immediate surrounding area. A pilot trial also showed that training improved detection accuracy in 4 of 5 patients with glaucoma, but definitive evidence of vision restoration training efficacy in glaucoma is still lacking.

**Methods**

**Study Design**

A prospective, double-blind, randomized, placebo-controlled clinical trial was approved by the local ethics committee and was carried out from March 2004 to August 2007. After informed consent, patients were randomly assigned by lot in numbered containers to a vision restoration training for glaucoma (gVRT) group (n = 15) or to a placebo group (n = 15).

Participants and outcome assessors were masked with respect to group identities. Patient recruitment identified 93 potential patients with glaucoma, 43 of whom were enrolled in the study. Nine patients dropped out during the baseline assessments, and 4 patients dropped out after randomization (Figure 1).

Inclusion criteria for study entry were (1) visual field defects due to glaucoma, (2) a stable visual field defect inside 30° eccentricity in at least 1 eye at 2 consecutive examinations during the past 12 months, (3) well-controlled intraocular pressure, and (4) age between 25 and 80 years. Exclusion criteria were a history of the following: (1) medical condition precluding scheduled study visits, (2) chronic degenerative or inflammatory disease affecting the visual field (eg, multiple sclerosis or tumor), (3) trauma or any nonglaucoma ocular disease (eg, diabetic retinopathy, age-related macular degeneration, macular detachment, or vascular occlusion), (4) severe cognitive or motor impairment, (5) insufficient fixation ability, (6) photosensitivity, (7) intraocular surgery or laser treatment during the past 12 months, or (8) scheduled intraocular surgery.

**Patient Sample Description**

The study sample comprised 14 men and 16 women (mean [SD] age, 61.7 [10.1] years; age range, 39-79 years) with primary chronic open-angle glaucoma (n = 20), normal-tension glaucoma (n = 5), or other types of chronic glaucoma (1 angle-closure glaucoma and 4 secondary glaucoma). Groups did not statistically differ with respect to age, time of first glaucoma diagnosis, or intraocular pressure and visual acuity (patient characteristics are summarized in eTable 1 in the Supplement).

**Visual Field Characteristics**

Both eyes were affected in 26 patients, and 1 eye was affected in 4 patients. In 10 patients each, vision loss classification of...
visual field defects was mild (ie, monocular loss of less than half of the visual field), moderate (ie, monocular loss of greater than half of the visual field or binocular loss of less than half of the visual field), or severe (binocular loss of greater than half of the visual field in either eye). In binocular loss, the field defect was always asymmetric. Herein, the more affected eye that had a significantly greater percentage of absolute defects in both conventional white-on-white (W/W) and blue-on-yellow (B/Y) perimetry received training. The mean (SE) values for W/W were 34.49 (19.36) for the trained eye and 23.06 (27.68) for the untrained eye (z = -2.32, P = .02). The mean (SE) values for B/Y were 31.42 (21.89) for the trained eye and 19.70 (25.87) for the untrained eye (z = -2.20, P = .02).

Outcome Measures
During baseline examinations and after training, we assessed different vision tests and used vision-related quality-of-life (25-Item National Eye Institute Visual Function Questionnaire [NEI-VFQ-25]) and health-related quality-of-life (36-Item Short Form Health Survey) questionnaires. The primary outcome criterion was detection accuracy in high-resolution perimetry (HRP) visual field tests. Visual field diagnostic procedures were performed on 2 consecutive days and under the supervision of 2 technicians who were masked with respect to group identities. To minimize the effect of fatigue, patients were given sufficient time to rest between visual field examinations. To reduce variance, the order of the tests was kept constant among all patients in baseline and posttraining assessments.

Visual Field Examinations
Visual fields were measured monocularly with automated perimetry (Twinfield model 56900; Oculus) and HRP. Automated perimetry was performed by an automated testing strategy according to the manufacturer’s manual. For 30° W/W and 30° B/Y perimetry, Goldmann III (but not V) was selected, and detection values rather than sensitivity values were used as outcomes to be able to compare them directly with HRP detection accuracy results. Luminance class determinations were made to identify absolute defects (no response even to the highest luminance intensity), relative defects (elevated luminance intensity), or intact spots (initial luminance intensity).

To assess the visual field, computer-based HRP was used, which is a valid and reliable testing method with suprathreshold stimuli (up to ±27° horizontal and ±20° vertical eccentricity). Responses within 150 to 1000 milliseconds were considered correct detections (hits) and outside this time window were considered delayed responses. To determine a stable baseline before training, 5 HRP repeated visual field charts were obtained. Visual field tests were considered valid if they had less than 10% fixation errors. Visual field was measured without refractive correction because acuity was of minor concern given the large stimulus sizes we used and because wearing spectacles during perimetry interfered with the head holder and eye tracking.

Assessment of Visual Field Fluctuations
Because patients with glaucoma typically experience some variability in their visual fields, we measured natural visual field variability for 2 days before training. Variability was then analyzed (1) as repeated measures and (2) as range variability (ie, the absolute difference between the lowest and highest detection rates) by first determining the range variability for each patient and then calculating group differences.

Quality-of-Life Assessment
Vision-related quality of life was assessed with a German version of the NEI-VFQ-25 survey. We also administered the 36-Item Short Form Health Survey before and after the training, which is a test that is not disease specific but can probe generic physical and mental health status (health-related quality of life) in patients with glaucoma. After all other tests were completed, satisfaction with the training was assessed using a Likert-type scale ranging from 1 to 10. Only then were patients informed of the group to which they belonged. Patients in the placebo group were subsequently offered gVRT.

Eye Movement Recordings
One may argue that detection accuracy gains are an artifact of eye movements. Therefore, we measured eye movements monocularly during HRP to determine the stability of fixation before and after training using an eye tracker (Tobii 1750; Tobii Technology AB) with an eye gaze frame rate of 50 Hz, 0.5° accuracy, and 1° drift rate. Data were not considered for further analysis if the eye-tracking period was shorter than 75% of the HRP testing time. Therefore, only 26 patients were included in the pre-post eye tracker analysis. Eye movements and stability of fixation were quantified using (1) the number of horizontal saccades per minute, (2) the mean gaze position, and (3) gaze position variability (standard deviation).

Interventions
Training was performed 6 days a week for 3 months; the duration was 30 minutes twice daily. After completing the baseline assessments, patients performed the training at home on a commercially available personal PC as previously described with adaptive parameter adjustments online. Seventeen patients trained with the right eye, and 13 patients trained with the left eye.

Vision Restoration Training for Glaucoma
The gVRT group performed a variant of the classic vision restoration training developed in our laboratory whereby visual stimuli are presented in ARVs. The training consisted of luminance increment stimuli similar to perimetry, and the task was simple detection (pressing a key whenever a target stimulus was detected). The training parameters were adaptive using online adjustments of levels of difficulty on a monthly basis (a mean [SD] of 500 [25] stimuli were delivered twice daily, 80% were presented in ARVs, and 20% were administered in the seeing visual field) (Figure 2).

Stimulus Discrimination Training
The placebo group trained with a discrimination paradigm using a line segment (bar), which was always presented within the central ±5° visual field in 1 of 4 possible random orientations (horizontal, vertical, oblique to the right, or oblique to
the left). If the patient had visual field defects in this central area, 80% of the stimuli were presented in the intact part of the training region. The task was to identify line orientations by pressing 1 of 4 assigned keyboard buttons as fast as possible. The number of stimulus presentations was a mean (SD) of 350 (25) sessions twice daily (700 per day), so that training time was the same as in the gVRT group, and this training was also adjusted monthly.

**Statistical Analysis**

The primary outcome measure was detection accuracy (ie, the number of detected stimuli in the HRP visual field tests). Secondary outcome measures were quality-of-life scores, reaction time, eye movements, and reliability parameters in the perimetric measurements (fixation rate and delayed responses). For comparison of test results before and after training, Wilcoxon z test for paired samples was used. Comparisons of training-induced changes between gVRT and placebo were performed with the Mann-Whitney test. To determine the factors that were associated with the changed stimulus detection rate after training, Spearman rank correlation coefficients were calculated. Because the number of delayed responses significantly correlated with the detection performance changes, analysis of covariance was performed. Spearman rank correlation was used to examine the association between the size of binocular visual field loss and the NEI-VFQ-25 subscale scores. The binocular visual field was simulated using the best location model for the summation of the monocular visual fields.57,58 Herein, the higher sensitivity from each of the 2 corresponding visual field locations in the perimetry is determined to give an estimate of the sensitivity of overall vision at that visual field position as if viewing binocularly. The multiple visual field test comparisons were assessed by Friedman test. Data are expressed as means (SDs), and \( P < .05 \) was considered significant using statistical software (SPSS, version 13.0; SPSS Inc).

**Results**

We conducted a prospective, double-blind, randomized, placebo-controlled clinical trial. We show that computer-controlled vision training significantly improves visual detection accuracy and temporal processing in glaucoma.

**Visual Field Variability**

At baseline, the stimulus detections across the 5 repeated HRP examinations fluctuated significantly in the gVRT group \( (\chi^2 = 10.98, P = .03) \), whereas in the placebo group they did not. Expectedly, the detection rate improved during the course of the 5 baseline sessions in both groups. Using the range-based calculation, the mean variability was 8.55% (5.39%) in the gVRT group and 9.54% (4.54%) in the placebo group. The range-based variability was not significantly different between the groups.

**Within-Group Analysis of Detection Performance**

The Table summarizes the mean detection performance of the trained eye before vs after training for both groups as mea-
Table. Pre-Post Comparison of Mean Detection Performance Results Measured by HRP, 30° W/W and B/Y Perimetry in the gVRT and Placebo Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>HRP, Mean (SD)</th>
<th>30° W/W, Mean (SD)</th>
<th>30° B/Y, Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre z P Value</td>
<td>Post z P Value</td>
<td>Pre z P Value</td>
</tr>
<tr>
<td>gVRT (n = 15)</td>
<td>37.45 (21.85)</td>
<td>44.17 (24.39)</td>
<td>-2.69 .007</td>
</tr>
<tr>
<td>Placebo (n = 15)</td>
<td>38.69 (27.03)</td>
<td>39.84 (29.15)</td>
<td>-0.71 .48</td>
</tr>
</tbody>
</table>

Abbreviations: B/Y, blue on yellow; gVRT, vision restoration training for glaucoma; HRP, high-resolution perimetry; W/W, white on white.

In HRP, suprathreshold stimuli (size, 0.43°; luminance, 83 candela [cd]/m²) were presented on a dark screen (background luminance, 20 cd/m²) and with blue light stimuli (size, Goldmann III 0.86° diameter; presentation time, 200 milliseconds; and interval time, 600 milliseconds) on a white background. Detection accuracy was analyzed by detecting relative defects (ie, positions in the visual field with decreased light sensitivity) were defined by stimulus detections. Results are shown only for the trained eye. The statistical pre-post comparison shows that the gVRT group significantly improved in all perimetric tests compared with the placebo group.

However, the detection accuracy gains were not greater in cases with greater visual field variability at baseline ($r = 0.49, P = .32$).

The HRP reaction time was significantly faster after training in the gVRT group than in the placebo group. In the gVRT group, the mean values were 579.73 (72.97) milliseconds (pre) and 541.67 (74.78) milliseconds (post) ($z = -2.61, P = .009$).

In the placebo group, the mean values were 558.53 (71.28) milliseconds (pre) and 559.53 (61.1) milliseconds (post) ($z = 0.00, P > .99$).

Between-Group Analysis of Detection Performance

Nieuwenhuis et al emphasized that statistical evidence of between-group comparison is superior to within-group comparison. Our between-group comparison of the pre-post detec-
tion changes showed significantly greater improvement in all 3 visual field test procedures in the gVRT group compared with the placebo group: HRP ($z = -2.03, P = .02$), W/W ($z = -1.68, P = .04$), and B/Y ($z = -1.74, P = .04$) (Figure 4). Furthermore, the gVRT had significantly faster reaction time in HRP ($z = -2.32, P = .01$).

Eye Movements and Fixation Performance

Neither the mean gaze position nor the mean gaze position variability (standard deviation) changed significantly after training compared with baseline in either group. In fact, the groups did not differ in fixation test results, and no statistical differences were observed in the blind spot positions before vs after treatment (eTable 2 in the Supplement).

The Role of Delayed Responses

In the gVRT group, the mean rate of delayed responses increased in all 3 visual field test methods after training, but this improvement was significant only in B/Y perimetry: 99.07 (2.46) (pre) and 97.33 (3.51) (post) ($z = -2.03, P = .04$). In the placebo group, the mean percentage of delayed responses decreased slightly in HRP. Nevertheless, no significant differences were observed between the 2 groups regarding the delayed response rate changes in any of the visual field tests. In the gVRT group, we found significant correlations between the increased number of delayed responses and HRP detection accuracy ($r = 0.68, P = .005$) and W/W perimetry ($r = -0.53, P = .04$) but not B/Y perimetry ($r = -0.20, P = .11$). In the placebo group, no such correlations were found. To rule out that delayed responses explain the main effect, we used them as covariates. In this analysis of covariance, a significant main effect for training was seen ($F_{1,13} = 14.01, P = .002$) as well as a significant interaction between the detection accuracy improvement and delayed responses ($F_{1,13} = 7.06, P = .02$). Therefore, the training effect was greater than the interaction effect, showing that the detection accuracy improvement cannot be explained by delayed responses alone.

Vision-Related and Health-Related Quality of Life

The baseline NEI-VFQ-25 scores were moderate or high (>65) on all dimensions except general health. Therefore, our patients had few everyday vision deficits at baseline, and none of the subscales showed training effects. The baseline 36-Item Short Form Health Survey showed deficits only in the physical functioning domain, which correlated with severity of binocular visual field defect ($r = 0.41, P = .02$); significant mean improvement was only seen in the gVRT group in the mental health subscale: 69.33 (18.98) (pre) and 77.60 (12.98) (post) ($z = -2.30, P = .02$). Both groups reported a high mean level of satisfaction with the training: 6.93 (2.40) for the gVRT group and 7.53 (2.87) for the placebo group ($z = -0.95, P = .44$). Therefore, our masking procedure was validated. Only the gVRT group reported noticing mean subjective visual improvement: 4.47 (1.95) for the gVRT group and 2.80 (1.93) for the placebo group ($z = -2.35, P = .02$). However, this finding did not correlate with improved detection accuracy ($r = 0.12, P = .37$).

Discussion

Daily training with gVRT significantly improved vision-related performance in patients with glaucoma without affecting eye movements. Compared with placebo patients, gVRT-treated patients had detection accuracy improvement
and reaction time gains, which is evidence of sensitivity improvement in residual vision. Specifically, between-group comparisons of pre-post changes showed that gVRT compared with placebo led to significantly improved detection in HRP and W/W and B/Y perimetry, which was confirmed by the patients’ subjective reports that training improved their vision. As in a previous pilot study by our group and in other studies of vision restoration training, approximately one-third of the patients were nonresponders, one-third achieved moderate improvement, and one-third achieved substantial improvement.

The gVRT group also had significantly faster reaction time. This observation confirms the conclusion of improved temporal processing as noted in earlier studies and may result from increased synchronization of neuronal firing. That genuine sensitivity can improve is supported by the observation that reaction time and suprathreshold contrast are associated.

It is well known that visual fields often fluctuate in glaucoma, which could mask or mimic true visual field changes. However, the changes we observed cannot be explained by natural fluctuations: if one counts only the detection accuracy improvement greater than baseline fluctuations as valid, then 7 patients in the gVRT group and 2 patients in the placebo group showed such improvement. Furthermore, visual field improvement did not correlate with visual field variability at baseline. Therefore, visual field fluctuation cannot explain the detection accuracy improvement after gVRT.

Visual improvement also cannot be explained by eye movement artifacts because eye tracker recordings showed neither signs of shifted gaze positions nor more frequent saccades. Fixation actually improved with vision training indicating more stable eye position, and when fixation inaccuracies occur, they do not correlate with detection improvement, confirming prior observations.

Nevertheless, we found that significant visual field improvement correlated with increases in delayed responses as noted earlier. While such delayed reactions could comprise random responses, we believe they are true hits but that patients respond to the stimulus presentations too slowly. In fact, reaction time impairment is seen in patients with optic nerve damage not only near or inside the scotoma but also in the presumably intact sectors of the visual field, a phenomenon termed sightblindness. Therefore, more delayed reactions may be explained by recovering vision that is still too slow to reach the minimum reaction time criterion (<1000 milliseconds). However, it is also conceivable that patients responded to hallucinations, which are perceptions of light flashes that start emerging during or after spontaneous or training-induced visual field recovery without stimulus presentations. In any event, increased numbers of delayed reactions are interpreted by us as signs of vision recovery, which is why they correlate with detection improvement.

A further goal of the present study was to assess the subjective outcome using vision-related and health-related quality-of-life questionnaires, but training did not lead to robust changes. Only mental health was found to have improved in both training groups, which may be caused by nonspecific training effects such as attention, alertness, or expectation. The general lack of subjective changes as probed by the NEI VFQ-25 may be explained by a ceiling effect: at baseline, patients already had few difficulties in everyday life because most had asymmetrical field loss, which often goes unnoticed during binocular viewing, thus leaving little room for improvement. Nevertheless, gVRT patients in the posttraining interview reported significantly greater subjective improvement, and placebo patients did not.

Possible mechanisms of action for gVRT are as follows: (1) plasticity in the retina; (2) changes at higher processing levels in the geniculate or the primary visual cortex, such as receptive field changes; (3) improved visual attention; (4) normal perceptual learning; or (5) a combination thereof. The fact that detection accuracy gains in glaucoma were not predominantly found in ARVs (as was seen in hemianopia) suggests that surviving retinal ganglion cells deep in the damaged zones might contribute to vision restoration or changes in intact visual field sectors. To clearly delineate the mechanisms of vision restoration requires further study using an electroencephalogram or magnetic resonance imaging recordings.

Conclusions

In summary, our study confirms that visual system plasticity is maintained into adulthood and even old age despite widespread visual system degeneration. Our findings are compatible with the theory of activating residual vision following retina or brain lesions. Vision loss in glaucoma may not be permanent: it is partially reversible through brain plasticity and cortical reorganization, and this finding is clinically useful. Whatever the mechanism, we can now be more optimistic that the course of vision loss in glaucoma is not simply pointed downhill but has considerable uphill potential. This new understanding justifies additional research and provides evidence to support routine use of gVRT in the clinical setting. Our results show that vision restoration and rehabilitation are possible by means of activating residual vision through training-induced brain plasticity.
Conflict of Interest Disclosures: None reported.

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Additional Contributions: Nicole Mäter and Sandra Heinrich assisted in examining the patients.

REFERENCES


