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Vision Restoration Through Extrastriate Stimulation in Patients With Visual Field Defects: A Double-Blind and Randomized Experimental Study

Sandra Jobke, Erich Kasten, PhD, and Bernhard A. Sabel, PhD

Background. Vision restoration therapy (VRT) to treat visual field defects used single-point visual stimulation in areas of residual vision up to now. The question arises if the efficiency of restoration can be increased when the entire region of blindness is trained by a visual stimulus aimed at activating extrastriate pathways (extrastriate VRT). **Methods.** In this crossover study, 18 patients with visual field defects with prior VRT experience were treated with 2 training paradigms. Group 1 (n = 8) first used extrastriate VRT followed by conventional standard VRT. Group 2 (n = 10) trained in reverse order. Visual field size was assessed with computer-based perimetry and subjective vision with the National Eye Institute Visual Function Questionnaire (NEI-VFQ). **Results.** In group 1, stimulus detection in high-resolution perimetry (HRP) improved by 5.9% ($P < .01$) after extrastriate VRT. After the second training period (standard VRT), detection further improved by 1.8% ($P = .093$). In group 2, detection performance improved after standard VRT by 2.9% ($P < .05$) and after extrastriate VRT by 2.9% ($P < .05$). Detection performance increased twice as much after extrastriate VRT (4.2%) than after standard VRT (2.4%; $P < .05$). All changes in fixation performance were unrelated to detection improvements. NEI-VFQ did not show any significant changes. **Conclusion.** Greater improvement after extrastriate VRT is interpreted as an activation of extrastriate pathways by massive “spiral-like” stimulation. These pathways bypass the damaged visual cortex, stimulating extrastriate cortical regions, and are thought to be involved in blindsight.

Keywords: Vision restoration therapy; Detection performance; High-resolution perimetry; Visual field enlargement; Blindsight

After stroke or traumatic brain injury, many patients suffer from lesions of the visual system and accompanying visual field defects. It was long believed that visual field defects such as scotoma or hemianopia following brain injury were untreatable. However, in the last 2 decades, the concept of plasticity of the visual system has emerged in the neurosciences. Not only during development, but also in adulthood, the visual system shows some modifiability and its potential to adapt to the lesion-induced changes is now well recognized. We have recently shown that specific vision restoration therapy (VRT) can improve such defects.¹⁻³ However, other groups also found an improvement of visual field defects with similar training protocols.⁴⁻⁶

In the search to further improve efficacy of VRT, we explored the possibility to stimulate the visual system more intensely by using a more powerful behavioral stimulation paradigm aimed at activating the extrastriate pathway. This is based on the observation that patients with damaged occipital lobes can often localize the direction of a light without conscious seeing.^{7,8} This phenomenon is described as “blindsight”^{9,10} and it has been proposed that extrastriate pathways provide the physiological substrate for blindsight and their spectral sensitivity has been

established.¹¹⁻¹³ However, Fendrich et al¹⁴ proposed that blindsight is mediated by residual “islands” of vision, which was confirmed by Wüst et al,¹⁵ showing that residual functions are mediated by surviving neurons located within the blind area.

The existence of a second visual system beyond V1 has been described in the animal literature for a long time.¹⁶ There are 2 extrastriate pathways for object and spatial vision, namely the dorsal and the ventral pathway, starting in V1.¹⁷⁻²⁰ The ventral stream, projecting to the inferior temporal lobe, is responsible for detecting objects and has been termed as the “what” pathway. The dorsal stream, called the “where” pathway, projects to the parietal lobe.

Furthermore, in animal studies it was noted that area V5 receives not only projections from V1, V2, V3, and V4, but it is also directly innervated by projections from the lateral geniculate nucleus²¹⁻²⁴ and pulvinar²⁵ nuclei of the thalamus, bypassing V1. In humans, the existence of direct thalamo-V5 connections is currently unclear, but a few studies of patients with lesions in V1, however, have provided some evidence for the existence of such connections²⁶⁻²⁸ and this can explain why perception of motion may remain intact within hemianopic areas (the Riddoch phenomenon).²⁹

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Table 1
Description of Patient Population

| | Patient Number | Age | Sex | Cause of Lesion | Age of Lesion (Months) | Visual Field Defect |
|---------|----------------|-----|-----|---|------------------------|--|
| Group 1 | 1 | 35 | M | CCI in right occipital frontal lobe | 225 | Complete left lower quadrantanopia, no macular sparing |
| | 2 | 58 | M | Ischemia after stroke | 59 | Diffuse, macular sparing |
| | 3 | 57 | M | Brain tumor | 87 | Diffuse, macular sparing |
| | 4 | 49 | M | Ischemia (arteria cerebri posterior) | 103 | Complete HH to the right, macular sparing |
| | 5 | 69 | F | Stroke (arteria cerebri posterior) | 112 | Complete HH to the left, macular sparing |
| | 6 | 32 | M | Surgery because of epilepsy | 67 | Incomplete left upper quadrantanopia, macular sparing |
| | 7 | 34 | M | Ischemia | 55 | Incomplete HH to the left, macular sparing |
| | 8 | 67 | M | Ischemia (arteria cerebri posterior) | 87 | Incomplete quadrantanopia to the right upper quadrant, macular sparing |
| Group 2 | 9 | 51 | F | Meningitis | 236 | Diffuse, macular sparing |
| | 10 | 40 | F | Brain surgery after tumor (left occipital lobe) | 74 | Complete right lower quadrantanopia, macular sparing |
| | 11 | 65 | M | Ischemia (left frontal lobe) | 40 | Diffuse visual field defect in both lower quadrants, macular sparing |
| | 12 | 46 | M | Ischemia (arteria cerebri posterior) | 66 | Complete HH to the left, macular sparing |
| | 13 | 34 | M | CCI | 89 | Complete HH to the right, macular sparing |
| | 14 | 41 | M | Stroke | 60 | Incomplete right upper quadrantanopia, macular sparing |
| | 15 | 38 | M | Brain surgery after tumor (right temporoparietal) | 72 | Diffuse, macular sparing |
| | 16 | 66 | F | Ischemia (arteria cerebri media) | 132 | Incomplete HH to the left, macular sparing |
| | 17 | 63 | F | Ischemia (arteria cerebri posterior) | 82 | Incomplete HH to the left, macular sparing |
| | 18 | 29 | M | CCI (temporal lobe) | 43 | Diffuse, macular sparing |

Abbreviations: CCI, craniocerebral injury; HH, homonymous hemianopia; F, female; M, male.

In the present study, we wished to enhance the previous training paradigm on the basis of these considerations. Our new therapy approach aims at a direct and specific activation of extrastriate cortex structures by a new visual stimulation paradigm. Specifically, we wished to activate these regions by stimulating the entire defective visual field (absolute blind region only) simultaneously with a massive moving spiral to primarily address motion perception. We hypothesized that by engaging the extrastriate system, restoration of the residual functions of the damaged visual system could be further enhanced.

Participants and Methods

Participants

We recruited 21 patients with visual field defects who had prior VRT experience and randomly assigned them to 2 groups. Group 1 consisted of 7 men and 1 woman with an average age of 51.5 ± 14.8 years, and group 2 had 6 men and 4 women with a comparable age of 47.3 ± 13.4 years ($F = 0.288$, $df = 18$, $P = .515$). For detailed information, see Table 1. Three patients had to be excluded from the analysis. One male patient (patient 19) used another vision therapy program not included in this study. Another patient (patient 20) was excluded because he discontinued the training for more than 4 weeks during the trial and a female patient (patient 21) showed poor fixation performance (70% rather than the minimally required 90%).

To eliminate possible influences of spontaneous visual field recovery that typically occur during the first few weeks and

months after the injury,^{30,31} only patients with lesions older than 1 year were included in the trial. The average age of the lesions in group 1 was 89.0 ± 59.9 months (range from 67-225 months) and in group 2, 89.4 ± 57.6 months (range from 40-236 months). Furthermore, all patients had used VRT for at least 6 months (range from 6-36 months) prior to study entry and were therefore experienced participants. We were aware that this might reduce the power of the therapy because of a possible "ceiling effect." To eliminate training bias, no patient carried out VRT during the 6 months preceding the study.

The study has been approved by the ethics commission of the Otto-von-Guericke University of Magdeburg in conjunction with the 1964 Declaration of Helsinki. All participants provided a written informed consent form prior to beginning the training.

Diagnosis

High-resolution perimetry (HRP). The diagnostic procedure is described here only briefly (for a more detailed description, see Kasten et al³²⁻³⁴). The participant's head was positioned in front of a computer monitor with a chin rest. The distance between the patient and the monitor was about 40 cm, the size of the screen was 15 sq in, so that the resulting angle of the measured visual field was about 41 degrees. To ascertain that the patient did not make excessive eye movements, the participant was asked to fixate on a stimulus (diameter 5 mm) located in the middle of the monitor, which occasionally changed color (light green to light yellow) for a brief period

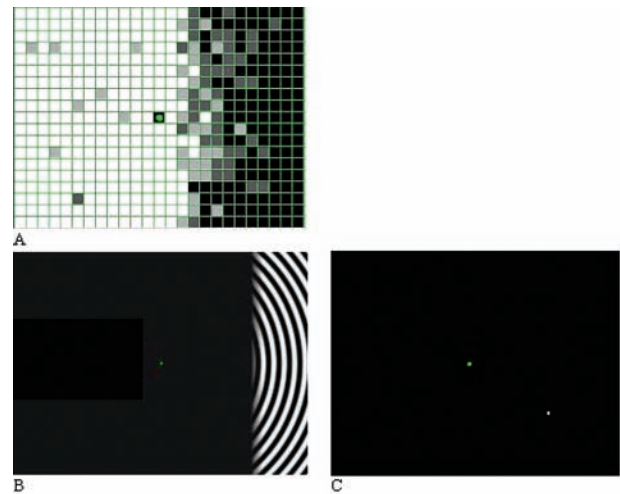
(150 ms) in irregular time intervals (color changes occurred approximately 70 times in each daily session). Eye movements were controlled by the examiner, but an eye tracker was not available for this experiment. The examiner reminded the patients in irregular time intervals, or whenever necessary, to avoid eye movements and to keep their eyes fixated as much as possible to enhance the therapy effect. Therefore, they had no motivation to make eye movements to enhance their training results. As in the HRP, the fixation performance was controlled by the number of detected color changes as described, and in our hands this is a useful and practical method to prevent the eyes from wondering around.

The participant had to respond to each color change by pressing the space bar. The number of such color changes was recorded and served as a useful measure of fixation quality. Furthermore, the participants were also asked to respond by pressing the space bar to additional white “target” stimuli (diameter 5 mm) presented at random locations on a dark gray background anywhere in the visual field. The presentation time of these stimuli was 500 ms and the contrast between stimuli and background was 94%. A total of 474 target stimuli were presented on the computer monitor during each of the tests. The participants were instructed to respond to these and to the color changes of the fixation point as fast as possible, but also as precisely as possible. No catch trials were given. The HRP program recorded both the correct detections of the target stimuli, the fixation color changes, and the reaction times. If participants pressed the space bar in the absence of a stimulus or outside a permissible time window of 1500 ms after stimulus onset, a “false hit” was registered. Detection performance was quantified by counting the number of detected stimuli (hits) in HRP. Before and after VRT, 3 of such visual field tests were carried out, and the detection performance score was defined by the average percentage of hits in these 3 test repetitions.

Although it would be better to carry out all measurements and diagnoses under best refractive correction,³⁵ diagnoses and visual field training were done without glasses. On one hand, many patients had only reading glasses with glasses too small so that spectacle scotoma occurred; other patients had bifocal or progressive lenses that were inapplicable for diagnoses on a computer screen. On the other hand, most of the patients’ glasses were not applied with an antireflection coating so that reflections in the glasses would have been very disturbing during training.

Description of extrastriate VRT. While visual field defects were previously trained with single-point stimulation (standard VRT), in the new training paradigm (extrastriate VRT) the size of the training area was enlarged. We stimulated the entire blind area with a massive moving spiral as shown in Figure 1. The concentric rings moved at a frequency of 2.5 Hz with an increasing width from the fixation point to the periphery to generate the perception of motion. The size of the training area varied from patient to patient according to the size of the visual field defect. It was important that the patients did not feel disturbed by the moving spiral.

Figure 1
A Comparison of Both Training Paradigms
in Patient 13



Note: The upper image (A) shows the results of 3 high-resolution perimetry (HRP) tests (fixation spot at center). The center image (B) demonstrates the training stimulus in extrastriate vision restoration therapy (VRT). The moving spiral is only shown in the blind area (black region). The right panel (C) shows the standard VRT. Target stimuli were only presented in the transition zone (gray).

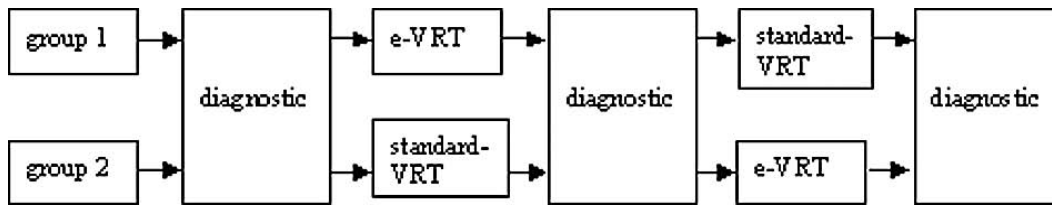
Additionally, areas of residual vision (relative defects) were stimulated by standard VRT, ie, the common single-point stimulation paradigm. Just like in standard VRT, the patient had to respond to the white target stimuli presented at random locations in areas of residual vision.

Perimetry. To obtain independent confirmation with a separate perimeter, the visual field of all patients was evaluated by a common static perimetric diagnosis at their own ophthalmologist’s office before and after the training. The standard white-on-white perimetry determines the visual field by using test objects at fixed positions. Although this is a nonstandardized perimetry evaluation in all patients, it still provides an independent method of measuring the visual fields.

National Eye Institute Visual Function Questionnaire (NEI-VFQ). To evaluate subjective vision, patients were asked to fill out the NEI-VFQ, which assesses some measures of activities of daily living.^{36,37} The NEI-VFQ is divided into 12 subscales recording, for example, social functioning, dependency on others, and mental health. A German translation is available. The higher the score in each subscale, the greater the functionality (minimum score 0, maximum score 100). Impairments in the subscales are shown as negative values.

Additional measurements. We measured visual acuity at a distance of 40 cm using the Radner reading test.³⁸ Patients were instructed to read aloud sentences printed in decreasing font size. The required time and the errors were noted and the

Figure 2
Study Design



Radner reading score was calculated. The worse the visual acuity and the more errors that were made, the worse the Radner reading score was. This test was used binocularly and without the patients' glasses because the training was also done without glasses.

Furthermore, the patients completed the Zahlen-Verbindungs test (ZVT) for measuring the speed of connecting numbers in a paper-pencil test. The patients had to connect 90 numbers sequentially as fast as possible and the time to complete the task was recorded. To improve validity, this test was repeated three times. For analysis, the mean value was calculated. While performing the ZVT the patients were allowed to use their glasses.

Study Design

In this crossover study, all patients first underwent a baseline diagnostic evaluation completing all tests specified above and were then randomly assigned to 1 of the 2 groups. Both groups were comparable in age, gender, and age of lesion (see above).

The patients of group 1 were first treated with extrastriate VRT for 90 days and then with the conventional VRT for 90 days. The patients of group 2 did the training types in reverse order (Figure 2). Each patient trained once a day for half an hour. Training breaks of longer than 2 weeks led to exclusion of the patient. Every week the patients completed a self-administered diagnostic test at home and sent their data to the institute for updating the training region if necessary. This test provides only the basis for updating the training region and not for analysis, and was done just like the diagnostic test described in the HRP section. All patients were instructed to do this test with the highest concentration and they knew that it would make no sense to make eye movements to enhance their training results. The fixation performance was controlled by the number of detected color changes, as described in the HRP section.

Data Analysis

The differences between the 2 training groups were analyzed with the Student's *t* test. If directed hypotheses were made, the 1-tailed *t* test was applied to assess if the means of

both training groups were statistically different from each other. Otherwise, a 2-tailed *t* test was calculated. The measurements were all normally distributed. Analyzing the results of the NEI-VFQ, the Bonferroni correction had to be done because of multiple *t* testing.

Results

HRP

Detection performance. In group 1, the percentage of HRP hits after the first training period (extrastriate VRT) improved from $52.4 \pm 9.9\%$ to $58.3 \pm 11.8\%$, ie, a significant increase of 5.9% ($t = -5.262$, $P = .0005$). After the second training period (standard VRT) the number of detected stimuli further improved by an additional 1.8%, which was also significant ($t = -1.944$, $P = .047$). The patients of group 2 improved their detection performance after the first training period (standard VRT) from $51.8 \pm 14.2\%$ to $54.7 \pm 15.3\%$, which was a significant but smaller increase of 2.9% ($t = -2.373$, $P = .021$). After the extrastriate VRT training period, the percentage of HRP hits further improved by 2.9% to $57.6 \pm 16.6\%$ ($t = -2.480$, $P = .018$).

Reaction times. The reaction times did not change in either group or training period (group 1: 450.9 ± 20.1 ms before training, 446.9 ± 22.3 ms after the first training period, $t = 0.332$, $P = .750$, 458.0 ± 34.9 ms after the second training period, $t = -1.276$, $P = .243$; group 2: 459.9 ± 53.4 ms before training, 446.5 ± 59.8 ms after the first training period, $t = 1.073$, $P = .311$, 446.8 ± 68.1 ms after the second training period, $t = -0.039$, $P = .969$).

Fixation performance. In HRP, the fixation quality is measured by the number of correct responses (in percentage) to an occasional color change of the fixation point. The definition of a "good fixation quality" was 90% or more correct responses. At baseline examination, the patients of group 1 responded to an average of $93.1 \pm 9.3\%$ of the color changes, which declined to $88.0 \pm 9.0\%$ after the first training period, just missing significance ($t = 2.264$, $P = .058$). After standard VRT, the patients responded correctly to $88.5 \pm 7.3\%$ of the color changes ($t = -0.261$, $P = .802$).

Table 2
Study Results by Training Types^a

| | Group 1 | | Group 2 | |
|----------------------|------------------|--------------|--------------|------------------|
| | Extrastriate VRT | Standard VRT | Standard VRT | Extrastriate VRT |
| Detection | +27.8*** | +8.6 (ns) | +13.6* | +13.9* |
| Detection in % | +5.9*** | +1.8 (ns) | +2.9* | +0.3 (ns) |
| Reaction times in ms | -4.0 (ns) | +11.2 (ns) | -13.4 (ns) | +0.3 (ns) |
| Fixation in % | -5.1 (ns) | +0.5 (ns) | +4.1 (ns) | -2.3 (ns) |
| False hits | +2.3 (ns) | +1.6 (ns) | -1.7 (ns) | +2.7 (ns) |
| No reactions | -26.0*** | -8.7 (ns) | +15.9 (ns) | -12.3 (ns) |
| Too early/ too late | +1.8 (ns) | -0.2 (ns) | -0.5 (ns) | +0.3 (ns) |
| Radner visual acuity | -0.09 (ns) | ±0 (ns) | +0.02 (ns) | +0.08 (ns) |
| ZVT(s) | -6.3 (ns) | -9.0*** | -4.4 (ns) | -22.3 (ns) |
| Radner reading score | +0.01 (ns) | -0.05 (ns) | -0.02 (ns) | +0.08 (ns) |

Abbreviations: VRT, vision restoration therapy; ns, nonsignificant; ZVT, Zahlen-Verbindungs test for measuring the speed of connecting numbers in a paper-pencil test.

^aDifferences are given as comparison between pre and post 3-month training. * $P < .05$. ** $P < .025$. *** $P < .01$.

While the fixation performance in group 2 improved slightly from $91.6 \pm 13.8\%$ before training to $95.7 \pm 4.4\%$ after the standard VRT, it was at $93.4 \pm 8.4\%$ after the second training period. Both changes in fixation performance were not significant ($t = -1.257$, $P = .240$; $t = 1.070$, $P = .312$). Fixation performance changes did not correlate with any of the other outcome measures in either training period (such as detection improvements in both training periods, $r = -.68$, $P = .790$; $r = .378$, $P = .122$, respectively).

False hits. The number of false hits is a quality marker of the patient's test performance. Because an increase in the number of hits can be caused by a shift in the participant's decisional criterion, the number of false hits is a useful indicator. Patients of group 1 showed 6.1 ± 6.8 false hits before and 8.4 ± 6.5 after the first training period out of 474 possible responses, which was not significant ($t = -2.142$, $P = .069$). After standard VRT, the number of false hits was 10.0 ± 7.1 , a nonsignificant change ($t = -1.081$, $P = .315$). Patients of group 2 changed from 4.8 ± 2.8 to 3.1 ± 2.4 false hits after the first training period (standard VRT), while in the second training period (extrastriate VRT) the number increased to 5.8 ± 7.4 . Both changes were, however, not significant ($t = 1.600$, $P = .144$; $t = -1.480$, $P = .173$).

No reactions. HRP not only registers the hits but also the stimuli and fixation controls to which the patient did not respond (misses). In group 1, the number of misses decreased from 229.5 ± 49.8 to 203.5 ± 60.9 after the first training period, which is a significant decline of 26.0 misses ($t = 3.919$, $P = .006$). After the second training period, the number of misses further decreased to 194.8 ± 60.7 ($t = 1.594$, $P = .155$).

In group 2, the number of misses declined from 233.1 ± 70.0 to 217.2 ± 73.6 after the first training period, which was significant ($t = 2.529$, $P = .032$). After the second training period, the misses further decreased to 204.8 ± 79.5 , which

just missed significance when compared to the value at the end of training phase I ($t = 1.961$, $P = .081$).

Radner Reading Test

In group 1, only 6 patients could be tested for visual acuity and in group 2, only 8 patients. The Radner visual acuity in group 1 did not change after the first training period (0.43 ± 0.46 vs 0.44 ± 0.40 ; $t = -0.106$, $P = .920$) or after the second training period (0.39 ± 0.39 ; $t = 1.004$, $P = .361$). The Radner visual acuity in group 2 also slightly decreased from 0.30 ± 0.30 before training to 0.27 ± 0.25 after the first training period ($t = 0.438$, $P = .674$), but performance increased in the second training period to 0.35 ± 0.29 , which just missed significance ($t = -2.140$, $P = .070$). The Radner reading scores did not change after the extrastriate VRT or after the standard VRT (see Table 2).

ZVT

The patients in group 1 improved from 109.0 ± 29.5 seconds before training to 102.7 ± 28.9 seconds after the first training period, which comprised a trend toward enhancement by 6.3 seconds ($t = 1.712$, $P = .066$). After the second training period, performance further improved to 93.7 ± 25.7 seconds, which was a significant enhancement of 9.0 seconds in comparison to the end of the first training period ($t = 4.036$, $P = .0025$).

Patients of group 2 slightly improved by 4.4 seconds from 131.7 ± 65.0 seconds before training to 127.3 ± 77.9 seconds after the first training period ($t = 0.195$, $P = .425$). After the second training period, they improved by 22.3 seconds to 104.9 ± 39.9 seconds. However, this did not reach significance ($t = 1.179$, $P = .135$).

The improvements in ZVT are probably due to the training because the patients are allowed to practice the test once before the time is measured. Furthermore, there are 4 parallel versions of the test, so that it is impossible to memorize the arrangement of the numbers.

Perimetry

Since we could not ensure a standardized perimetry in all patients, we analyzed only perimetry charts where precharts versus postcharts were available (7 patients out of group 1 and 4 patients out of group 2). This is a very small number of cases, which clearly limits the power of this measure.

In group 1, after the first training period, the number of detected stimuli in the right eye (oculus dexter [OD]) increased nonsignificantly by 1.8 ($t = -0.725$, $P = .248$) and in the left eye (oculus sinister [OS]) significantly by 3.0 ($t = -2.097$, $P = .04$). Fixation performance was stable. After the second training period, the number of detected stimuli slightly decreased by 1.0 in OS and by 1.1 in OD, which was not significant (OD: $t = 0.467$, $P = .329$; OS: $t = 1.125$, $P = .152$). In group 2, the number of detected stimuli only slightly changed in both training periods, but none of these changes were significant. Fixation performance was stable.

NEI-VFQ and Subjective Reports

After Bonferroni correction we could not detect any significant changes in either of the NEI VFQ subscales. In group 1, after the first training period (extrastriate VRT), there was only a slight improvement in the scale “color vision” (+9.4, nonsignificant [ns]) and a slight impairment in the scale “general health” (-7.2, ns) and “peripheral vision” (-6.3, ns). After the second training period (standard VRT) there was an improvement in the scale “peripheral vision” (+12.5, ns) and “social functioning” (+5.2, ns), which did not reach significance at all. In group 2, there was an improvement in the scales “mental health” (+17.5, ns) and “dependency” (+11.3, ns) after the first training period (standard VRT). Solely, the scale “peripheral vision” (-5.0, ns) slightly impaired, which did not reach significance. After the second training period (extrastriate VRT), there were slight but nonsignificant enhancements in the scales “general health” (+7.0, ns), “ocular pain” (+6.3, ns) and “distance activities” (+5.8, ns). Furthermore, the subscales “social functioning” (+8.3, ns), “role difficulties” (+5.6, ns), and “peripheral vision” (+5.0, ns) nonsignificantly improved.

When the NEI-VFQ scales of all patients were compared before and after both training periods (after 6 months), 6 of 12 scales show significant improvements, eg, “distance activities” ($P = .033$), “social functioning” ($P = .049$), “mental health” ($P = .002$), and “role difficulties” ($P = .007$). Furthermore, the patients reported that they needed less help from others (“dependency,” $P = .036$) and could perceive colors better than before training ($P = .042$).

Extrastriate VRT Versus Standard VRT

We also pooled the training outcomes of all patients for each training type, independent of the order in which the training was given (see Table 3). The detection performance improved significantly in both training types, but it was found to be almost twice as high in the extrastriate VRT period

Table 3
Study Results of all Patients (Both Groups Pooled) by Extrastriate VRT Versus Standard VRT

| | Extrastriate VRT | Standard VRT | Extrastriate VRT vs Standard VRT |
|----------------------|------------------|--------------|----------------------------------|
| Detection | +20.1*** | +11.4*** | $P = .036$ |
| Reaction times in ms | -1.7 (ns) | -2.5 (ns) | ns |
| Fixation in % | -3.5* | +2.5 (ns) | $P = .044$ |
| False hits | +2.5* | -0.2 (ns) | ns |
| No reactions | -22.1*** | -9.1 (ns) | ns |
| Too early/too late | +0.9* | -0.4 (ns) | ns |
| Radner visual acuity | +0.05 (ns) | -0.04 (ns) | ns |
| ZVT(s) | -15.2 (ns) | -6.4 (ns) | ns |

Abbreviations: VRT, vision restoration therapy; ns, nonsignificant; ZVT, Zahlen-Verbindungs test for measuring the speed of connecting numbers in a paper-pencil test.

*Differences are given as comparison between pre and post 3-month training. * $P < .05$. ** $P < .025$. *** $P < .01$.

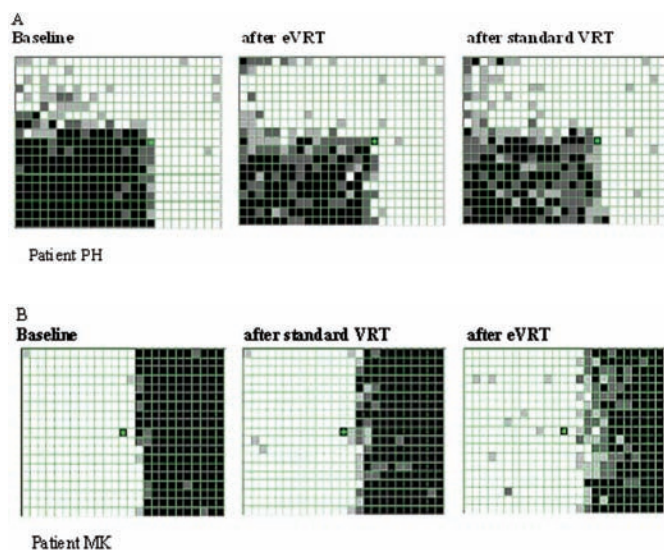
(4.2%, $P < .001$) than in the standard VRT period (2.4%, $P < .01$). This difference between both training paradigms was significant ($t = 1.926$, $P = .036$). Interestingly, in the extrastriate VRT period, fixation performance decreased by 3.5% ($t = 2.283$, $P = .036$), whereas it remained statistically unchanged (+2.5%) in the standard VRT period. Furthermore, the number of false hits significantly increased from 4.4 to 7.0 in the extrastriate VRT period ($t = -2.365$, $P = .03$), but in standard VRT, the number of false hits remained unchanged ($t = 0.211$, $P = .835$). The reaction times did not change in either of the training paradigms.

We also checked the location of the detection performance improvements after extrastriate VRT and found that they occurred primarily in areas where the spiral was presented, ie, in the field of absolute blindness. A total of 8 patients showed marked detection gains in these regions (see Figure 3), 4 patients moderate gains, and 6 patients few gains or none. The average number of detected stimuli in this blind area across all patients improved significantly by 2.6% ($P = .005$). In case of the standard VRT, detection performance did not improve in the total blind visual field.

Only slight changes were found in the NEI-VFQ, which did not reach significance. After extrastriate VRT, the patients rated that distance activities (+5.0, ns) could be performed better and that color vision had improved (+5.6, ns). After the standard VRT period, the patients showed a decrease in general health (-4.5, ns). However, we attribute this to the fact that 3 patients had a long stay in a hospital, a death in the family, or a headache caused by weather conditions at testing, respectively. In contrast, the mental health improved (+9.4, ns) and the dependency on others decreased (+8.0, ns) in the same training period, so that the patients now needed less help from others.

In standard perimetry, no significant changes were found after extrastriate VRT period as well as after standard VRT

Figure 3
Three Repeated HRP-Tests of Patient 1 and Patient 13



Note: Patient 1 (A) was first treated with extrastriate vision restoration therapy (VRT) for 3 months followed by 3 months of conventional VRT. Note extrastriate VRT improved performance primarily in the previously blind field. In patient 1 this happened in the first phase of extrastriate VRT and in patient 13 (B) who trained in reverse order, ie, after extrastriate VRT in the second phase. These 2 patients are typical cases of patients that responded to therapy.

period. The results of the perimetries do not correlate with the results of the HRP tests in fixation or in detected stimuli. The perimetries in this study were all performed at the patients' ophthalmologists so that a real standardization could not be ensured in all patients and this variance may explain the null findings. There were also no significant changes in the ZVT test pre versus post and standard VRT versus extrastriate VRT.

Group 1 Versus Group 2 Comparisons in HRP

The patients of group 1 (sequence extrastriate VRT/standard VRT) showed increased stimulus detection from 52.4% before training to 60.1% after both training periods, which was a significant overall improvement of +7.7% ($t = 3.670$, $P = .002$). The patients of group 2 (standard VRT/extrastriate VRT) reached a total increase of +5.9% from 51.8% to 57.7% ($t = 2.713$, $P = .024$). Since both improvements were significant, group 1 reached a higher increase in detected stimuli than group 2, but this difference between the groups was not significant ($t = 0.673$, $P = .511$).

Discussion

Both training groups showed significant improvements in their ability to perceive small visual stimuli well above detection threshold (HRP) after the training (see Table 3) even

though they only trained half an hour daily. While the patients perceived on average of 4.2% more stimuli after extrastriate VRT, the detection performance improved only by 2.4% after standard VRT. Thus, the improvement was almost twice as good after extrastriate VRT than after standard VRT. While in the extrastriate VRT period 10 of 18 patients (55.6%) showed a visual field enlargement of more than 3%, in the standard VRT period only 5 of 18 patients (27.8%) reached such a magnitude of change. In the standard VRT period, 4 patients (22.2%) even worsened in their detection performance, whereas in the extrastriate VRT period there were only 2 patients (11.1%) who perceived fewer stimuli after the training.

The visual field enlargements during the standard VRT period (2.4%) were only about half the enlargements found in previous studies. In a previous study from our laboratory³⁹ we found a stimulus detection improvement of 3.9% after a 6-month training period in patients with postchiasmatic lesions. These smaller enlargements are probably because of several factors including that our patients trained only half as long as those in prior studies and that our patients had prior training experience, as they had attended at least one 6-month restoration training before this study. In contrast, the visual field enlargements during the extrastriate VRT period of 3 months (4.2%) were even a little higher than those during the 6-month standard training. This indicates that comparable therapeutic effects can be reached in half the time of training. The benefits of extrastriate VRT over standard VRT are mostly attributed to increased detections in the perimetrically blind regions where the spiral stimulus was presented.

Fixation performance in the extrastriate VRT period decreased slightly by 3.5% and therefore the possibility has to be considered that all of the detection gains can be explained by eye movements. Although some eye movements may contribute to the detection changes we believe that the main effect is independent of eye movements. First, we found no correlation between fixation performance changes and detection gains. Second, eye movements during the measurements were controlled by the examiner and found to be small and within the expected range of 1 to 2 degrees of visual angle. Third, improvements in detection performance not only occurred at the border between intact area and visual field defect (so called "areas of residual vision") but also proceeded deep in the blind area where the patient first would have to perceive a stimulus before he or she could make an eye movement into that direction. In another investigation we showed that the detection ratio of isoluminant color changes, as used for fixation control, drops below 90% when the stimuli are presented beyond 2 degrees eccentricity in healthy participants. Surely, it is much harder for patients with a worse visual acuity to make excessive eye movements (greater than 2 degrees) and to show a fixation performance of 90% or more. Thus, we believe that eye movements cannot explain our findings, which is in agreement with Kasten et al⁴⁰ that VRT has no effect on either the direction or the amplitude of horizontal eye movements during visual field testing. These considerations all argue against the

theory that the visual field enlargements are artifacts by eye movements only. Jamara et al⁴¹ also demonstrated that an actual visual field enlargement is distinguishable from scanning eye movements. Furthermore, there were no significant correlations between the increased detection performance and the increasing number of false hits.

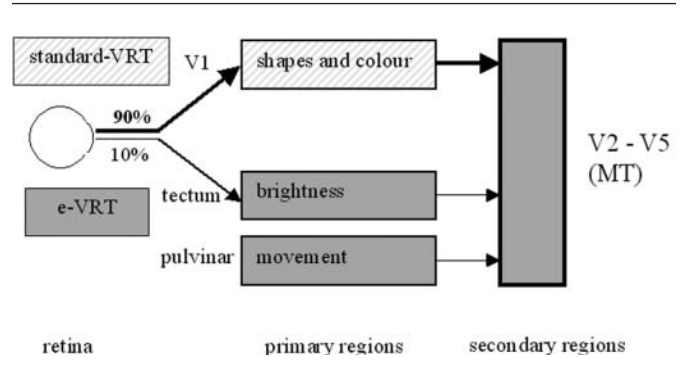
The reaction times in both groups did not differ before or after the training. This might be caused by a ceiling effect because of the prior training experience of the patients, ie, the trainability of the reaction times could have reached their limit. In earlier studies, significant reaction time gains of 31.7 ms were found.^{42,43}

In the previous vision restoration training, which the patients (n = 24) had carried out before participating in the present study, the number of detected stimuli increased from 53.7 ± 14.8 to 62.8 ± 17.1% (*P* < .001) after 6 months of standard VRT. These training results were stable over a period of at least 3.5 years.⁴⁴ Note that not all patients in the study from Gall et al participated in the present study. Thus, the new gains are not the re-establishment of the old gains but are actually on top of the old gains, which did not drop back to baseline after completion of the first training period.

Although we found significant visual field enlargements in HRP, there were no significant improvements in standard perimetry. This could be due to the fact that HRP and standard perimetry differ in their psychophysical features. In HRP, the patients have to detect bright, super-threshold stimuli on a dark gray background. In standard perimetry, a light gray or white, near-threshold stimulus is presented on light gray background. Furthermore, in HRP there are 474 target stimuli while standard perimetry only presents about 150 target stimuli. This implies a lower resolution in standard perimetry, thus possibly reducing sensitivity below a level needed to document visual field enlargements. A major source of this null finding, however, is the lack of standardization in the data collection with standard perimeters. These data were collected by the patients' own physicians, which introduced considerable variability, making this data set less reliable. In addition, the number of cases with complete records was very small.

There were only slight changes in the results of the NEI-VFQ when comparing both training types. When pooling both training types together, some activities in daily life show improvements, eg, social functioning and dependency on others. Maybe the NEI-VFQ is not sensitive enough to reveal changes over one 3-month training period only whereas after 6 months effects emerge. Our findings of some improvements in the NEI-VFQ are compatible with other studies. Mueller et al⁴⁵ studied the effect of vision restoration training on activities of daily life. Here, 88% of the patients reported subjective benefits, especially in carrying out hobbies and general improvements of vision. But these subjective changes were found with patients' testimonials collected during standard interviews, not with questionnaires. Interestingly, in the Mueller study no correlation was found between visual field size improvements and visual confidence/mobility and ability

Figure 4
Proposed Pathways Involved in the Effects of Standard VRT Versus Those Mediating the Effects of Extrastriate VRT



Note: Effects of standard VRT (striped) versus extrastriate VRT (gray). The percentage indicates the estimated number of fibers involved.

to avoid collisions, ie, there was a mismatch between objective and subjective vision parameters.

Our findings of an enhancement by extrastriate VRT can primarily be explained by a 2.6% detection gain deep in the blind field, ie, the area that was stimulated by the spiral pattern. How can such extrastriate VRT specific improvements be explained in the areas of presumed total blindness? The normal neuroanatomy of the visual system already suggests some possibilities. It is well established that there are different, parallel visual pathways processing visual information. Particularly the pathways involved in the perception of motion (which is induced by our spiral stimulus) that include the magnocellular pathway (M pathway) are of interest here. This pathway arises in the magnocellular layers of the lateral geniculate nucleus, travels through the interlobular regions in V1 to the thick stripes of V2, and ends up in the middle temporal area. This cortical area is thought to be the human homologue of the well-studied monkey visual area medial temporal/medial superior temporal cortex, which receives anatomical connections not only from V1, V2, V3, and V4,⁴⁶ but it also receives direct input from the lateral geniculate²¹⁻²⁴ and pulvinar nuclei in the thalamus,²⁵ bypassing the primary visual cortex, V1.

The existence of these direct connections from lateral geniculate nucleus to V5 in humans is currently under investigation. Most neuroimaging studies have failed to provide evidence for activity related to these direct connections. A few studies of patients with lesions in V1, however, have provided some evidence for the existence of such direct connections (see Figure 4).²⁶ Other studies of projections in primates have demonstrated the existence of a pathway from the retina to V5 via the superior colliculus and pulvinar. The findings of Schoenfeld et al^{27,28} also provide evidence for a direct thalamic functional pathway to extrastriate visual cortical motion, processing areas in the human that bypasses the primary visual cortex. Furthermore, it has been suggested that this pathway might play an important role in blindsight, a phenomenon in which patients with V1 lesions can detect motion in their blind

visual field, but often without awareness.⁹ We propose that this direct thalamic functional pathway provides the physiological substrate for the greater improvement after using extrastriate VRT. By stimulating with a moving spiral-like stimulus, this motion-sensitive system is activated and thus enhances vision restoration. The latest findings from Marshall et al⁴⁷ also support an alteration in brain activity. They found a significant time by condition interaction manifested as increased BOLD activity for borderzone detection after VRT. The effect appears to be mediated by the anterior cingulate and dorsolateral frontal cortex in conjunction with other higher order visual areas in the occipitotemporal and middle temporal regions.

Although in our study all patients had used VRT prior to study entry, the majority of the patients still reached a further improvement of visual field defects. This shows that there is additional vision restoration potential even well beyond the initial 6 months of VRT. The extrastriate VRT effects add yet additional benefits. VRT efficacy can be additionally enhanced by using special visual stimulation paradigms aimed at extrastriate activation.

In future studies, the extrastriate VRT training should be applied in patients who had never participated in a restoration program. Furthermore, functional imaging (fMRI) would help delineate the actual areas of the brain involved after standard VRT versus extrastriate VRT. Both studies would help delineate conditions that enhance vision restoration beyond the levels achieved by the current approaches.

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