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Vision restoration therapy (VRT) efficacy as assessed by comparative perimetric analysis and subjective questionnaires

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Abstract. *Purpose*: We wished to evaluate the efficacy of vision restoration therapy (VRT) in patients with post-chiasmatic brain damage using different functional perimetric tests. These were compared with measures of subjective vision and reaction time.
Methods: An open trial was conducted with hemianopia/scotoma (n =16) patients. Before and after 6 months of VRT results of high resolution (HRP) and Tuebingen automated perimetry (TAP) were evaluated and compared to performance in a Scanning Laser Ophthalmoscope (SLO) as previously reported. Whereas TAP and HRP used above-threshold or near-threshold individual target stimuli on grey background, the SLO used a psychophysical task of detection of three black targets (reverse stimulus) on bright red, patterned background. Subjective testimonials of activities of daily living (ADL) were probed with questionnaires and interviews.
Results: Before VRT, the visual field border as assessed by SLO was located significantly closer to the vertical midline than the HRP and TAP border (border mismatch). After VRT the SLO border was still unchanged whereas HRP measurements revealed significant border shifts due to improved stimulus detection ($p < 0.0001$) and improved reaction time ($p < 0.005$) . Fewer misses were also observed in both eyes with TAP ($p < 0.01$) which was primarily due to a significant shift of the absolute borders. Thus, VRT potentiated the mismatch between the SLO borders and the HRP/TAP borders. Fixation performance and the blind spot position remained unchanged after VRT. ADL ratings in the questionnaire improved significantly after VRT which was confirmed by independent patient testimonials.
Conclusions: We replicated earlier findings that VRT improves stimulus detection in HRP and TAP perimetry which were accompanied by subjective, visual improvements. These changes are not caused by fixation or eye movement artifacts. Because the SLO border was located significantly closer to the vertical midline before VRT ("border mismatch") and, in contrast to HRP and TAP, did not change after VRT, we interpret this border mismatch to indicate that the SLO task was too difficult to perform and thus insensitive to VRT effects. Significant reaction time improvements indicate that plasticity of temporal processing might play an important role in vision restoration after brain damage. A further description of the precise psychophysical nature of the restored areas of residual vision is now warranted.

Keywords: Hemianopia, scotoma, visual field defect, computer training, high resolution perimetry, rehabilitation, vision, training, therapy, plasticity

1. Introduction

It was long believed that visual field defects such as scotoma or hemianopia following brain injury are untreatable. In the last two decades, however, 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 [3–5,22,28,29,36–39]. Poeppel et al. [23] showed already in 1978 that training visual functions may alter the visual field. They described a posterior infarct patient which, after repeated testing with a perimeter, showed a visual field expan-

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sion. Zihl et al. [42] observed similar "training" effects of repeatedly measuring incremental thresholds in the same retinal location which resulted in shifts of the visual field border [43,44]. However, Balliet et al. [1] criticized these findings on the grounds that they were unable to replicate the effect and that small eye movements might lead to apparent and not real border shifts. However, as Kasten et al. [8] have pointed out, the Balliet study had serious experimental limitations: the training period for the patients was too short to achieve any training effect and eye movement recordings were also not made.

Almost a decade after the Balliet et al. study the first computer-based vision training was developed, "Vision Restoration Therapy" (VRT). Initially, a pilot trial [8] was carried out and subsequently two independent, prospective placebo-controlled clinical trials [10]. Again, significant visual field enlargements were observed. The regained visual functions were maintained well beyond the 6-months training period [7] and patients with post-chiasmatic, but not pre-chiasmatic, damage also showed improvements in shape and color recognition [13]. Meantime, the principle benefits of visual field training were confirmed (i) by Poggel et al. [24] studying the role of attention in vision restoration, (ii) in a retrospective analysis [21], (iii) by a Finish group using their own training protocol [6] and (iv) by Kelts et al. [14] who trained the perception of moving dots.

Despite this body of evidence, criticisms have been raised that the "apparent" border shift may not be due to real restoration of vision but instead due to an artifact of eye movements or eccentric fixation. Specifically, concerns raised include that (i) the training effect might be explainable by the patients learning to fixate eccentrically, (ii) that the border shift may be an artifact of eye movements towards the blind field, and (iii) that it is unclear if VRT has any benefit to the patients subjective vision or activities of daily life. In addition, it was deemed desirable to conduct an open clinical trial in an independent laboratory setting. The current single-group trial was therefore conducted with the goal to replicate the prior studies with the hope to address these methodological concerns.

The study was carried out using independent methods of perimetry. These were high Resolution Perimetry (HRP) which employs super-threshold stimuli and Tübingen Automated Perimetry (TAP) which employs near-threshold stimuli. Visual field charts thus obtained were compared with the charts obtained by the laser scanning ophthalmoscope (SLO) which involved a three dot detection task of reverse (black) stimuli. This SLO measurement had revealed no border changes after VRT in our prior study [27].

We also wished to determine if VRT has an effect on subjective visual improvement which was studied with subjective vision questionnaires and by recording patient testimonials. This aspect of the study was prompted by the observations in a retrospective study [21] that patient testimonials attested subjective visual improvements.

2. Materials and methods

2.1. Patient recruitment

The trial was conducted at the University of Tuebingen Eye Clinic. Prior to the commencement of the trial, the study design and the definition of the outcome criteria and data analysis were approved by the institutional review board of the University of Magdeburg. No control group was included in this confirmatory study. Rather the patients were subdivided post-hoc into two groups (see below). The reasons for selecting a single group design with a two-group subdivision rather than a placebo vs. treatment design is that several studies have already employed a placebo vs. treatment design and have established that there is no placebo/experimenter bias.

The patients were then selected from the archives of the Eye Clinic of the University of Tuebingen. All diagnostic tests were carried out at the Eye Clinic and VRT was courteously supplied by NovaVision AG (www.novavision.info; Magdeburg), which also carried out the regular training adjustments.

2.2. Patient sample

After selecting the patients from the archives, they were invited to participate in the trial. To eliminate possible influences of spontaneous visual field recovery that typically occur during the first few weeks and months after the injury, only patients with lesions older than one year were included in the trial. The average age of the lesion was 40.8 months (range 15 to 127 months). To be included in the study, the visual field defect had to be homonymous and caused by brain damage. Exclusion criteria were: (1) known seizures or photosensitive epilepsy (2) evidence of spontaneous remission or unstable baseline; (3) total blindness; (4) central scotoma; (5) absence of a visual field defect

within the central 10° area (the reason being that SLO can investigate only the central 10° area); (6) unstable fixation or nystagmus; (7) neglect; (8) age of patients less than 18 or more then 75 years; (9) chronic degenerative illness; (10) serious handicaps such as deficits of motor functions, concentration ability or memory; (11) psychotic or depressive diseases; (12) intellectual deficits (IQ under 85); (13) other severe visual defects such as: vision below 0.4, amblyopia, diplopia, strabism, maculopathy, glaucoma, other retinal disorders (e.g. retinitis pigmentosa, retinopathy).

The trial was started with 19 patients, but three patients had to be excluded after study entry (No. 03, 12 and 15): One female patient did not achieve a total of 6 months of regular training, one male patient had large fluctuations of his visual field border for unknown reason and another male patient began to suffer from seizures due to neurological disease. Thus, complete data sets were obtained from 16 patients (5 male, 11 female, average age: 49.3 ± 12.9 years, range: 24–72 yrs).

After completion of the trial patients were assigned to one of two sub-groups depending on their lesion characteristics: the "complete hemianopia" group "COM" ($n = 9$; patient no. 1, 2, 6, 8, 9, 10, 11, 16 and 19) consisted of patients with a clear (sharp) visual field border with or without macular sparing. The "incomplete" group "INC" ($n = 7$; No. 4, 5, 7, 13, 14, 17 and 18) consisted of patients with incomplete hemianopia/quadrantanopia or paracentral scotoma. With this subdivision we wished to determine to what extent the presence of "areas of residual vision" contributed to outcome. The patient sample is described in Table 1.

2.3. Perimetric evaluation methods

Before and after the 6-months VRT period, all patients were investigated with three perimetric procedures: High resolution perimetry (HRP), Tübingen Automatic Perimeter (TAP) and Scanning Laser Ophthalmoscope (SLO). The SLO findings have already been reported elsewhere [27] and are used only for comparison purposes in the present experiment. Subjective vision was assessed in three ways: (i) by a standardized vision questionnaire before and after VRT, (ii) by a post-VRT questionnaire assessing subjective changes of vision, and (iii) by collecting patient testimonials.

2.3.1. *High resolution perimetry* (*HRP*)

Technically speaking, HRP is a campimetric procedure because visual stimuli are presented only in the central 27-degree visual field on a computer monitor (NovaVision "Status"; Magdeburg, Germany). For a detailed description of these programs and normative data see [11]. The subject has to hit a key on the keyboard whenever a target stimulus is presented. The target stimuli are small, stationary white dots which are presented for 150 ms in a randomized sequence at 474 different positions in a 25×19 grid on a dark monitor screen, a relatively high resolution. The stimuli are presented at random positions on a computer monitor. We presented no acoustic signals prior to the visual stimulus to reduce the likelihood of anticipatory eye movements toward the stimulus. The inter-stimulus interval randomly varied from 1–2 sec. to reduce the probability of false positives.

The target stimuli are well above threshold (suprathreshold) (stimulus size: 0.15°, stimulus luminance: 95 cd/m^2; background luminance: < 1 cd/m^2) and therefore the HRP task is easier than testing at near-threshold (as in TAP). A "hit" was only counted if the subject responded within a time-window of less than 1000 ms. Each diagnostic HRP session lasted 20–25 minutes. Most patients were tested binocularly with the HRP. Patient PD and patient IM were tested and trained monocularly. Patient PD showed strabismus and consequently binocular fixation problems. Patient IM's binocular performance differed so much from monocular performance that effective binocular training was not possible.

In the HRP sessions above-threshold stimuli were presented on the computer monitor. Here, the stimuli are presented five times per visual field position. This was carried out at study entry and at follow-up. The HRP charts show areas of residual vision, where the shades of gray reveal the extent of residual vision, i.e. how often the patient responded. Specifically, if the patient responded correctly fewer than the maximum possible 5 presentations at a given location (i.e. 1–4 times), this was defined as "residual vision" (Fig. 1a). Areas of residual vision (ARVs) could thus be quantified for each patient. In addition to this detection performance, the "NovaVision Status" program also records the reaction time of each response. Patient 14 performed only four binocular sessions at study entry because of fatigue; patient 2 performed five sessions per each eye and patient 5 performed four sessions per each eye.

Fixation control: In HRP, fixation is controlled by a color change of the fixation spot. Patients were in-

Table 1
Patient demographics

No.	Age/sex	cause of lesion	visual field defect
01	72/f	Ischemia	Complete HH to the left with macular sparing
02	24/f	Haemorrhage	Complete HH to the left
04	60/f	Ischemia	Quadrantanopia of the left upper quadrant
05	41/f	Ischemia	Incomplete right upper quadrantanopia
06	30/f	Ischemia	Complete HH to the right with macular sparing
07	57/m	Ischemia	Incomplete HH to the left
08	52/m	Ischemia	Complete HH to the right
09	50/f	Brain surgery	Complete HH to the left
10	40/f	Haemorrhage	Complete HH to the right
11	39/f	Ischemia	Complete HH to the right
13	36/f	Brain surgery	Incomplete HH to the left
14	62/m	Ischemia	Right upper quadrantanopia
16	58/m	Ischemia	Complete HH to the left
17	42/f	Ischemia	Small paracentral scotoma to the right
18	51/m	Ischemia	Right upper quadrantanopia
19	58/f	Brain surgery	Complete HH to the left

Description of patient population (HH = homonymous hemianopia, f = female, m = male).

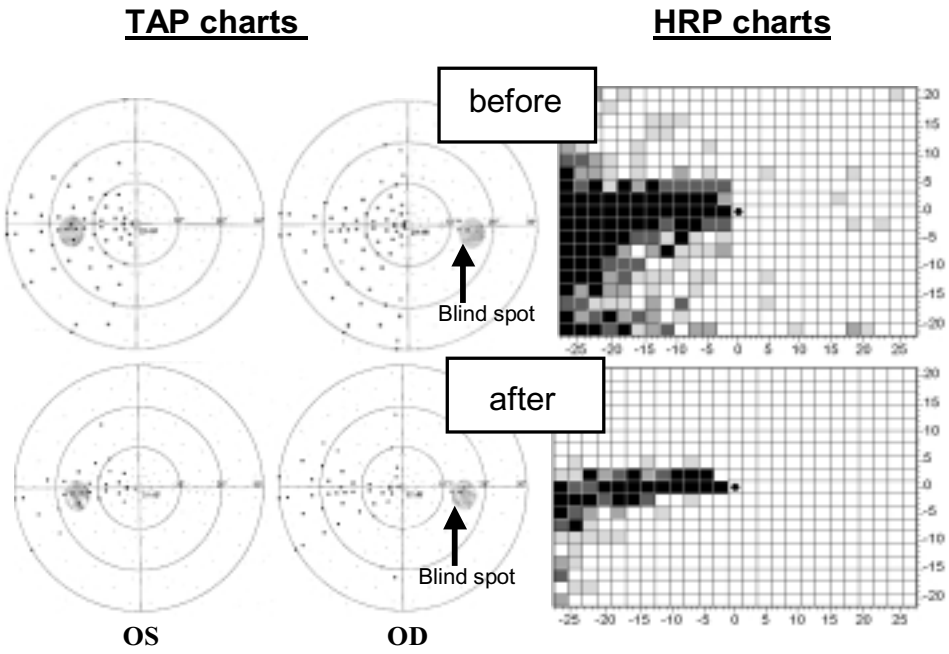

Fig. 1. HRP and TAP performance in a single patient. This graph shows perimetric performance of patient C.H. Left panels: TAP results (30°) are displayed for the left (LA) and right eye (RA). A deficit is present in the left hemifield, shown by black squares (= missed targets). As compared to before VRT (top panel), the patient had fewer misses in both eyes after VRT (bottom panel). VRT did not change the position of the blind spot (arrow). Furthermore, the deficit right next to the fixation spot did not change its location either, confirming that eye movements had not interfered with perimetric testing. Right panels: Binocular HRP results of the same patient. In each square, the target was presented five times in random sequence. Black squares indicate regions where no responses were recorded; white indicates 5 responses (= intact); shades of gray indicates areas where the patient had partial vision, i.e. responded correctly 1–4 times. We termed regions with such gray squares "areas of residual vision".

structed to look at a 0.5° fixation point at the center of the monitor throughout the HRP examination. Whenever the fixation point changed its color from light green to yellow, the patient had to press a key. Patient 2 and patient 4 were tested and trained with a fixation point color change from green to orange, because they had problems to detect at all the green-yellow change. If a subject does not fixate properly, many color changes

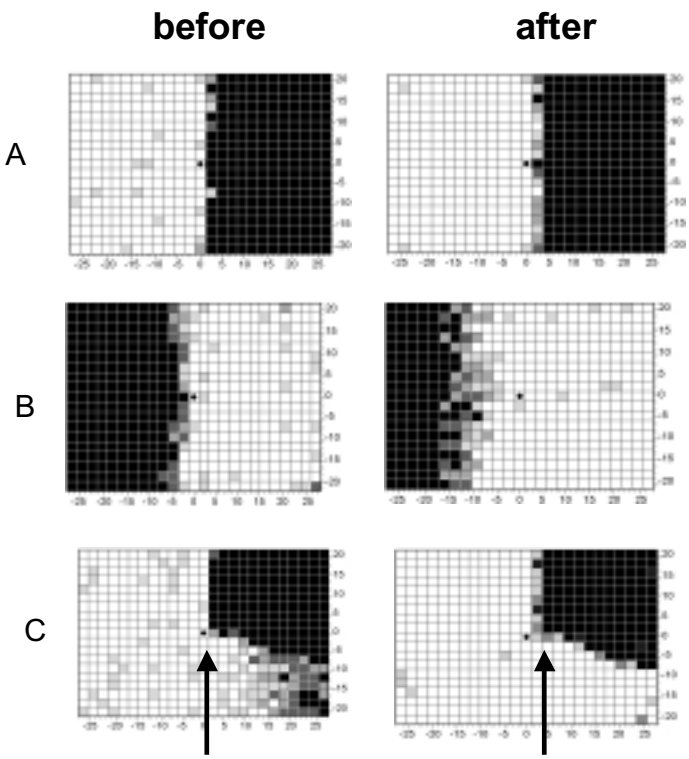

Fig. 2. HRP results of different patients. This graphs shows results of different representative patients in HRP before (left) and after VRT (right). Patient displayed in A started with a clear-cut visual field border without any large-scale area or residual vision and with no border shift after VRT. Patient B experienced a shift of the absolute border by about 10 degrees. Here, areas which were previously blind (at 15° eccentricity) now show some partial function, i.e. the patient is able to respond to some stimuli again. The absolute defect changed to become a relative defect. Patient C showed an enlargement of the visual field only in the lower right quadrant. The border of the upper right quadrant showed only a small change (arrows). If eye movements had occurred, the border in the upper quadrant would have shifted as well. This indicates that eye movements do not explain the visual field enlargement in the lower quadrant.

will be missed. Patients are always instructed by the experimenter to keep stable fixation and that this is important to benefit from VRT. Consequently, patients try their best to fixate properly. If fixation shifts (or large saccades) occur during the testing in any significant way, the number of correct reactions (hits) to color changes of the fixation point decreases. Maintaining performance in color change-detection is thus an indirect measure of fixation performance. Though the precision of this method of fixation is debatable, it is a practical and useful fixation control procedure for home training.

Data analysis: An adequate method to analyse HRP data is to count the number of "hits" (i.e. correct responses) as an outcome measure. Here, "percent"-values rather than absolute values are used to quantify visual functions because this parameter is less influenced by original defect sizes.

Note that the fixation point before and after VRT is always kept at the same position on the monitor, because shifting the position of the fixation point (which may be required during training) would otherwise change the detection rate even if no improvement had taken place. The disadvantage of keeping the position of the fixation point unchanged at follow-up, however, is that areas of improved vision may be lying outside the original testing region and are therefore ignored.

2.3.2. Tübinger automated perimetry (*TAP*)

In TAP, visual stimuli are presented inside a hemispheric dome with a relatively low resolution (191 stimulus positions in a 30 degree radius). The stimuli are presented in different luminance levels to determine the near-threshold value in a stair-case fashion. The near-threshold target stimuli are given only once per location of the visual field, unless the patient fails to respond to them. In this case, the stimulus is given again with greater luminance in a stair-case fashion until the patient responds to it. If the patient does not re-

spond even at the highest luminance level, the location is defined to be blind. TAP does not allow repeated presentations of super-threshold stimuli. Because the stimulus presentation is near-threshold with a gray (and not black) background, the task itself is more difficult than supra-threshold HRP testing. Target stimuli are typically white on light gray background. Unlike HRP, TAP sessions use stimuli of variable luminance in a "stair-case" procedure to determine the detection threshold automatically (Fig. 1b).

Fixation control: During TAP, the patient is instructed to continuously look at the center of a small square formed by red light dots in each corner of the square. At unpredictable intervals a stimulus is presented in the center of the square. Reaction to this presentation is used as a fixation measure. If the patient always reacts correctly to the light stimulus at the fixation point, the value is 100%. If the patients missed the stimulus, the fixation value decreases accordingly.

Data analysis: TAP counts the number of hits and the number of misses. For scientific purposes, an adequate data analysis is to count the number of "misses" because this measure is more useful for several reason: in "areas of residual vision" (ARV) (which are similar to "areas of relative defects") the patient shows more misses depending on the degree of neuronal integrity. Areas with good function have fewer misses than areas with more impaired function. To count the number of "hits" as an outcome measure, areas of relative defects would always be represented by a "1", because the staircase method stops testing in this location as soon as the patient answers correctly, irrespective of the luminance of the stimulus. In conclusion, in contrast to HRP, the number of "misses" in TAP represents the "relative defect" more adequately than the "number of hits".

2.3.3. Scanning laser ophthalmoscope (*SLO*)

The SLO is an experimental method to determine visual field defects by observing the stimulus positions directly on the retina. It has been described in detail elsewhere [27]. Briefly, unlike the HRP or the TAP method, patients have to look at visual stimuli through a binocular-type device with a laser beam projecting images directly onto the retina. Simultaneously, a camera images the retina in real time. Whereas the patient sees the image created by a laser light, the examiner also sees the retina in a quality of an ophthalmoscope. In the SLO setting used in our patients, unlike the HRP and TAP, the solid red background is created by a fast moving laser beam which produces perceptually an array of fine flickering red lines. Within this red background three black circles – the target stimuli – were created by laser omissions. In contrast to HRP, where the patient has to detect a stimulus, in SLO a "discrimination" is required because the patient has to verbally tell the experimenter how many circles were present and where they were located (Fig. 5).

The primary advantage of the SLO is that the retina can be viewed directly on-line, allowing perimetric testing under eye movement and fixation control. If the subject does not properly fixate, the stimulus can be repeated. Unlike HRP or TAP, the SLO responses are video taped and then later analyzed by hand. The responses are displayed in a binary manner (correct or false) for each location so that no "relative defects" can be seen in SLO (Fig. 1c).

2.4. Determination of border positions in HRP, TAP and SLO

Reinhard et al. [27] found that when visual field borders were measured with the SLO, no evidence of visual field enlargements after VRT could be found. Because in the same patients HRP and TAP charts were available, their detailed analysis and comparison to the SLO measurements were of interest. Specifically, the question arose how the HRP and the TAP results compare to the SLO findings. For this purpose we directly compared the visual field border position as determined by TAP and by HRP to that obtained by the SLO (the SLO data have already been published elsewhere [27]).

Specifically, we were interested in the question how a null-finding with the SLO can be reconciled with the findings that HRP and TAP performance as well as subjective vision had improved after VRT (see results section below). We therefore compared the location of the visual field borders between (a) HRP, (b) TAP and (c) Scanning Laser Ophthalmoscope (SLO) to determine if they match. A match would indicate that all three methods measure the same or similar visual function. However, if they do not match one could assume that they likely test different psychophysical functions.

Because the SLO measurement is restricted to the central 10° region of the visual field, direct border position comparisons were possible in this region only. To this end, we first determined the border position of the absolute visual field defect in HRP, TAP and SLO which is defined by the stimulus positions where no responses were recorded ("absolute border"). We next determined also the relative border in HRP and TAP, which is defined by the presence of either less then

perfect hits in HRP or threshold increases in TAP (the "relative border").

The determination of the exact border position is sometimes ambiguous because there are inconsistencies of the border measurements. Thus, predetermined criteria needed to be established to account for such inconsistencies across all cases in a standardized fashion as follows: occasional, single test points which stand alone and are disconnected from any continuous scotoma or deficit regions were ignored. Likewise, single target omissions (misses) within the intact visual field were also ignored. Because the SLO measurements were an "all-or-none" event, areas of relative defects can not be determined in SLO.

For each of these borders, the position was defined by measuring the distance of the visual field border (relative or absolute) in degrees of visual angle from the 0-vertical meridian in degrees of visual angle and in vertical steps of 2°. Note that only vertical visual field borders were included in the analysis; horizontal borders were not considered to avoid introducing artifact caused by the border orientation.

2.5. Subjective evaluations by questionnaire and interview

To quantify subjective vision we asked subjects to fill out a standardized "vision status questionnaire" before and after VRT. The questionnaire was based on the one published elsewhere [16] but truncated to 5 items which are sensitive to visual field defects. The items had to be rated on a scale of 1 ("absolutely not") to 10 ("yes, very much"). One patient answered the questionnaire only after training and therefore her data were excluded from calculating the average scores.

With the additional "change-questionnaire" we evaluated if patients experienced changes in activities of daily living and general satisfaction with the training. The questionnaire was only given after VRT was completed. The individual questions/statements had to be rated on a 6 point scale ranging from -3 (decrease, very dissatisfied) to $+3$ (increased, very satisfied).

In addition, a post-treatment interview was given to collect patient testimonials. The interview was semi-standardized with questions addressing subjective impressions of visual impairment, development of the defect and activities of daily living. The patient testimonials were recorded and then categorized into five functional domains, which had been established in a previous study. Categories are: general visual improvement and/or visual field enlargement; better orientation/ more confidence in mobility; less bumping into objects or people; reading/watching TV/working on a PC; a personally meaningful activity/hobby can be performed again [15].

2.6. Vision restoration therapy

VRT is a training software which runs on personal computers and is carried out at the patients home (courteously provided by NovaVision; Magdeburg, Germany). VRT projects stimuli in areas of residual vision (ARVs), i.e. partially defective areas located typically between the intact and the blind parts of the visual field. Patients have to press a key on the keyboard whenever they detected the stimulus which is presented in or near the areas of residual vision (transition zone). The patients carried out training sessions twice daily for half an hour each during a six months period. Therapy results were stored daily on a disk and compliance and changes in visual field size could thus be recorded. Training parameters were regularly adjusted by NovaVision (usually once or twice a month) so that the level of difficulty could be adjusted to the continuous improvements for each individual patient. The patient transferred the data to NovaVision by regular mail or email.

2.7. Data analysis

Our initial statistical analysis was carried out with the data of all patients (total patient sample) using SPSS and Statistica (t-tests for dependent samples, bivariate correlations and ANOVA). Thereafter, the group was subdivided into two sub-groups, depending on the size of the lesion (see above): group COM (complete hemianopia) and group INC (incomplete hemianopia, quadrantanopia and scotoma). Results are displayed for the pooled data of both groups or for each group, COM and INC., separately as mean $\pm$ S.E.M. Number of hits or misses were always expressed as performance in the entire visual field, not just the damaged side.

3. Results

3.1. High Resolution Perimetry (HRP)

3.1.1. Detection performance

Detection performance was quantified by counting the number of detected stimuli ("hits") in HRP. Before and after VRT five such visual field tests were carried

out, and the detection performance score was defined by the average percent of detected stimuli ("hits") in these five (or – in two cases – four) test repetitions.

In the total patient sample the percentage of HRP-hits improved from 63.04 ± 3.2% mean ± S.E.M. to 69.63 ± 3.4%, i.e. a significant increase of 6.59% of the total visual field (t-test for dependent samples $p < 0.01$). This represents an improvement of 10.45% above baseline. When the data analysis is restricted to stimuli in the central 5° region patients improved 6.6% ± 1.4% and in the more peripheral 6°–10° area 8.4 ± 1.6%. Figure 2 shows HRP charts of three patient before and after VRT. The performance gains in group COM and INC were statistically comparable, though slightly smaller in patients of group COM (5.78 ± 1.38%) than in group INC (7.64 ± 2.22%). For both subgroups, the increase was significant (COM: $p < 0.01$; INC: $p < 0.05$).

3.1.2. False positive reactions

The number of false positive reactions is a marker of the patient's test performance quality. Because an increase in the number of hits can be caused by a shift in the subjects decisional criterion, the number of false positive reactions is a useful indicator of a possible decisional criterion shift. The patients showed 4.1 ± 0.80 false positives before and 5.7 ± 1.28 after VRT out of 474 possible responses ($p = 0.33$, n.s.). Group COM patients showed significantly fewer false positives than group INC before (COM: 3.5 ± 0.57; INC: 4.9 ± 1.05, $p < 0.05$) and after VRT (COM: 4.4 ± 1.05; INC: 7.5 ± 2.57, $p < 0.05$). In both groups the number of false positives did not change due to VRT (COM: $p = 0.462$, INC: $p = 0.492$, n.s.)

3.1.3. Fixation performance

In HRP fixation quality is measured by the number of correct responses (in percent) 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 responded to an average of 96.8 ± 2.1% of the color changes (range of 92.08% to 99.53%) which slightly improved to 98.6 ± 1.9% after VRT (range: 91.92% to 100%) (Fig. 3). In both, group COM and INC, fixation quality increased after VRT, though only for group COM the increase was significant ($p < 0.01$). Fixation performance did not correlate with any of the other outcome measures (such as visual field enlargements).

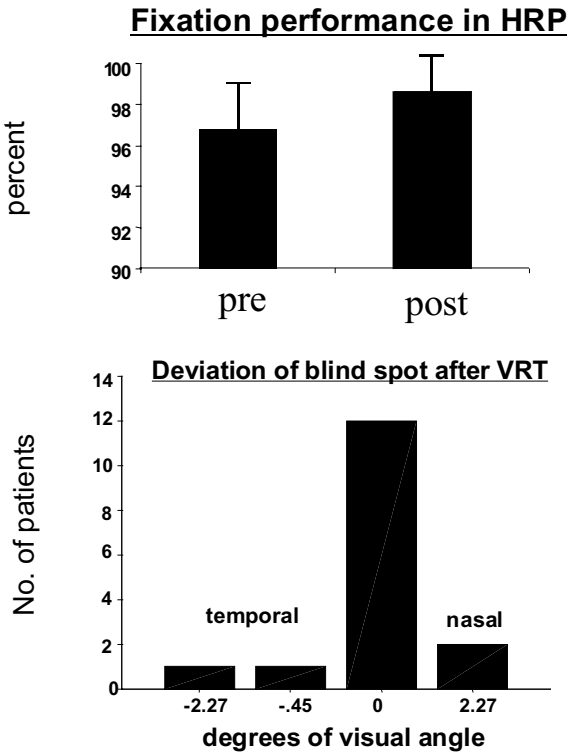

Fig. 3. Fixation behavior The upper panel shows the fixation ability (= correct responses to color changes of the fixation spot) as determined by HRP before and after VRT. Fixation performance slightly improved (not significantly). The lower panel displays the pre-post change of the blind spot position as assessed by monocular TAP assessments. In the majority of the patients the blind spot did not change its position. In two patients it shifted slightly laterally, in two other patients it shifted temporally. The two patients with the nasal shift did not profit from VRT.

3.1.4. Analysis of reaction time

Before commencing with the 6 months VRT period, the average reaction time to hits (valid responses), irrespective of their location, was 434.2 ± 12.3 ms. After VRT, reaction time significantly improved to 402.5 ± 11.7 ms ($p < 0.01$) when all patients were considered. Sub-groups COM and INC, however, differed in the extent of reaction time improvements. For group COM the reaction time before VRT was 446.6 ms and after VRT 422.6 ms (t-test $p = 0.143$, n.s.). In contrast, the average reaction time of group INC was 418.4 ms before and 376.6 ms after VRT, i.e. a significant improvement by about 40 ms (t-test $p < 0.05$). Figure 4 displays a patient that had experienced a reaction time change from 468 ms before VRT to 383 ms after VRT. Note that reaction time also improved in the intact visual field sector and not only in the area of residual vision.

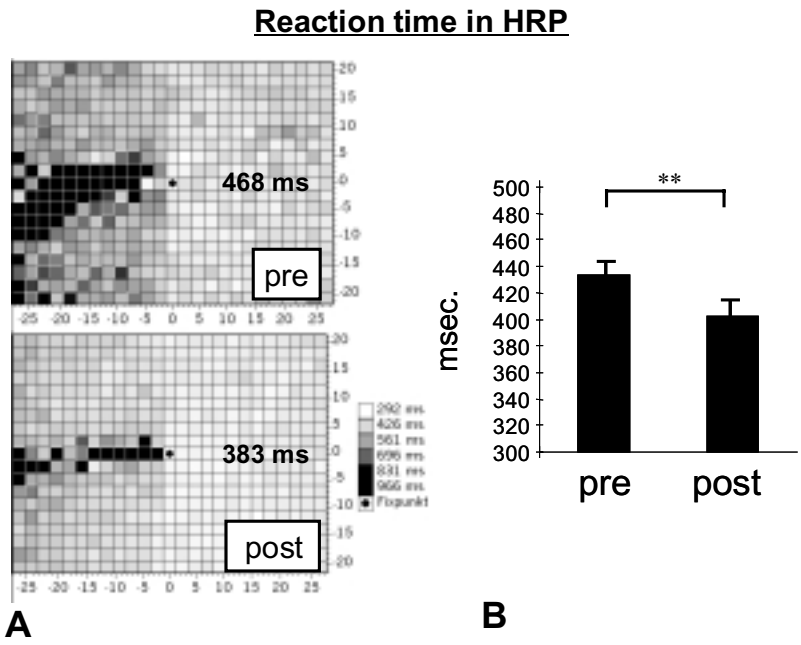

Fig. 4. Reaction time analysis: Reaction times are simultaneously recorded by HRP and can be displayed in gray charts. The graduated gray values represent reaction times: (A) Reaction time charts of patient C.H. before (top panel) and after VRT (bottom panel). Part B shows the average reaction time of all patients. After VRT, the reaction time was significantly shorter compared to before VRT ($p < 0.01$).

There were no significant correlations of individual reaction time gains with gains in any of the other objective or subjective outcome measures such as TAP performance, HRP performance or subjective questionnaire scores.

3.2. Tuebinger Automated Perimetry (*TAP*)

The results of Tuebinger Automated Perimetry (TAP) performance is also described by Schreiber et al. [33]. Because we had disagreements over the method of numeric statistical analysis and the conclusions drawn from it, we have re-analyzed the TAP data. The focus in the present study is that of comparing the TAP data to those obtained by other perimetric measures (HRP and SLO). We were particularly interested to determine the visual field border position as well as fixation performance and the number of false positives.

3.2.1. Detection performance

Before and after VRT the visual field of each eye (OD and OS) was examined by TAP. To determine the extent of the visual field defect, the number of misses (no reaction to presented stimulus) was counted in every stimulus position throughout the entire visual field. When the patient did not respond to a stimulus at threshold luminance, it was presented again at higher luminance in a stair-case fashion. When the patient did not respond to a stimulus at all, not even at highest luminance levels, the position was categorized as “absolute defect”. When the patient did respond at higher luminance, it was categorized as “relative defect”.

In the total patient sample, the number of misses (absolute defects) in TAP decreased from 60.94 before VRT to 52.94 after VRT for the right eye (OD) and from 63.44 to 54.69 for the left eye (OS). This is a significant change of about 8 testing points (OD and OS: $p < 0.01$).

For sub-group COM the decrease in misses was significant for the left eye ($p < 0.05$) but not for the right eye ($p = 0.32$). For group INC the decrease was significant for both eyes (OD: $p < 0.05$, OS: $p < 0.01$).

As expected, group COM had significantly more absolute defects on both eyes pre and post VRT than group INC (pre VRT $p < 0.01$ for each eye, post VRT $p < 0.001$ for each eye). Surprisingly, they did not differ significantly in the number of relative defects for each eye pre and post VRT.

3.2.2. False positive reactions

In TAP, the number of false positives is measured by the function “response control”. Here, the presentation

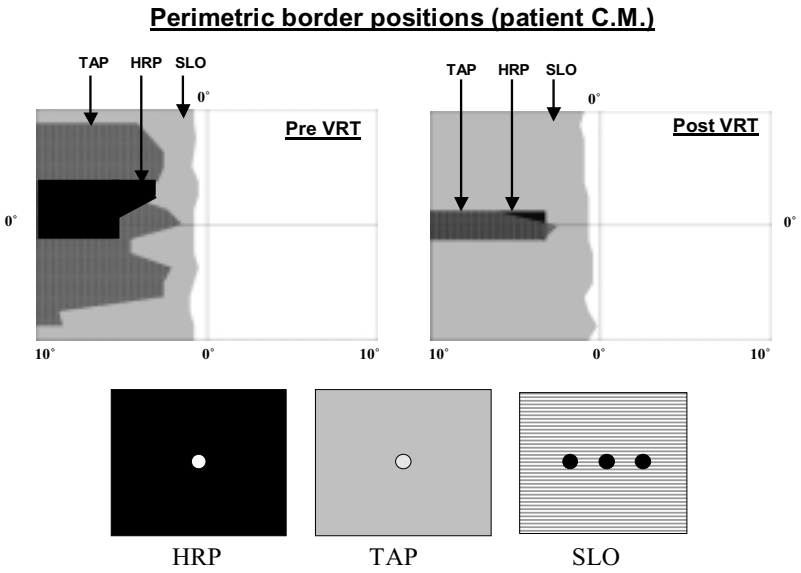

Fig. 5. Comparison of border position as defined by SLO, TAP or HRP. Upper panels: border position as assessed by the three perimetric tests in patient case C.H. The gray areas represent the area of the defect. Before VRT the border position as determined by the three perimetric measures HRP, TAP and SLO showed already a mismatch. After VRT, however, the HRP and TAP border shifted away from the vertical meridian whereas the SLO border remained roughly in the identical position, exaggerating the border mismatch. The lower panels displays the perimetric stimuli used in the study to elucidate the possible cause of the border mismatch. The target stimuli and the background differed in the three procedures. The target and the background were as follows: high threshold/dark background in HRP; near-threshold/light gray background in TAP; black target/red background with parallel line pattern as created by a laser beam in SLO.

of a light stimulus is accompanied by a distinct sound. On occasion, the sound is given without presentation of a light stimulus and a key response in such a case is then considered to be a false positive reaction. Response control is 100% when the patient shows no false positive reaction at all. The response control value decreases with increasing false positive reactions.

Response control performance before VRT was 97.5 $\pm$ 1.16% for the left and 97.4 $\pm$ 1.27% for the right eye. After VRT this decreased to 94.0 $\pm$ 1.92% and 90.7 $\pm$ 3.29%, respectively. The decrease in response control values was not significant for the left eye ($p = 0.102$) and a trend towards significance for the right eye ($p = 0.051$).

3.2.3. Fixation performance

Fixation performance in TAP was 77.56% (OD) and 87.75% (OS) before VRT. After VRT fixation slightly improved to 85.19% (OD) and 84.56% (OS) after VRT, respectively (not significant). There were no significant differences between groups COM and INC. The position of the blind spot as assessed by TAP is an independent measure of fixation performance [35]. It was unchanged in 12 patients. In 2 patients it shifted slightly nasally, and in another 2 patients it shifted slight temporally (Fig. 3). This slight blind spot shift in the 4 patients was unrelated to any improvements in perimetric performance. In fact, the two patients with nasal shift of the blind spot (which could have produced a temporal shift of the visual field border, i.e. an artificial visual field enlargement) were among those who profited the least from VRT.

3.3. Comparison of visual field border position among HRP, TAP and SLO

The determination of the border position is a quantitative method often used to evaluate visual field size. The "absolute" border is that which defines the absolute defect (no visual function at all), excluding the areas of the "relative" defects. In contrast, the "relative" border delineates areas of relative defects where some residual vision is still found (as evident by increased detection threshold or by reduced detection probability in super-threshold testing). We have measured the distance of the visual field border from the 0-vertical meridian (midline) in degrees of visual angle and compared the "absolute" border position in SLO with both "absolute" and "relative" borders in HRP and TAP (Table 2). The isolated SLO finding has already been reported by Reinhard et al. [27]. These data were used here for purposes of comparing them to HRP and TAP performance (Figs 5 and 6).

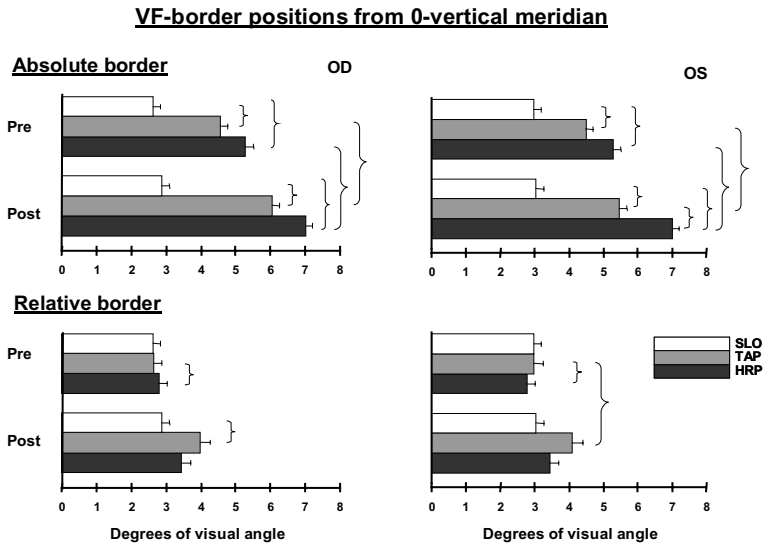

Fig. 6. Group average of border position analysis We measured the visual field border for SLO, TAP and HRP in the central 10° region in degrees of visual angle from the 0-vertical meridian before and after VRT. We thus determined the border position of both the absolute visual field defect (top panel) and of the relative defect (bottom panel). For this analysis the defective region was always displayed to the right and the intact region to the left (Mean ± S.E.M.). Note that HRP-data are binocular. Therefore, for comparison purposes only, the HRP data are identical in the OS and OD graph (the brackets indicate whenever a group difference was significant); see also Table 2.

3.3.1. Position of the absolute visual field border before VRT

Single case description: patient No. 13 (Fig. 5) is female and was 37 years of age when commencing VRT. She suffers from surgery of a parieto-occipital right angioma resulting in an incomplete hemianopia to the left; the visual field defect was 15 months old. In this patient, and in most other patients, the position of the absolute visual field borders depended on which perimetric method was used. In most patients, the SLO border was noticeably closer to the midline than the TAP and the HRP border. This was confirmed by statistical analysis of the group values (Fig. 6). On average, the SLO border was located at 2.61° ± 0.21° (right eye) and 2.98° ± 0.22° (left eye) from the midline, the absolute TAP-border, in contrast, was located at 4.56° ± 0.21° (right eye) and 4.49° ± 0.20° (left eye) and the absolute HRP (binocular) border at 5.28° ± 0.23°. As a consequence, before VRT the absolute visual field defect is significantly greater when measured by SLO than when measured with TAP (t-test right eye: $t = 4.48$, $p < 0.001$; left eye $t = 4.50$, $p < 0.001$) or HRP ($t = 3.73/4.71$; $p < 0.001$; binocular test). Visual field size determined by TAP and HRP were comparable. Thus, we found a mismatch of the border position between SLO on the one hand and TAP and HRP on the other hand. Though in some patients the border position matched rather well, most patients showed such mismatches. Thus, the "apparent" visual field defect is greater when measured with SLO than when measured with TAP or HRP. After VRT this mismatch was even more pronounced (see below)

3.3.2. Position of the relative visual field border before VRT

In the SLO it is impossible to determine areas of "relative defects". These can only be determined with HRP and TAP and then be compared to the absolute defect in the SLO. In contrast to the situation with the absolute visual field defects we found only a minor mismatch between the relative HRP and TAP borders and the absolute SLO border (Fig. 6). Before VRT, the SLO border was located at 2.61° ± 0.21° (right eye) and 2.98° ± 0.22° (left eye) (see above). The relative border in TAP was located at 2.67° ± 0.25° and 2.89° ± 0.25° respectively. The relative HRP border was located at 2.78° ± 0.25°. Thus, when the relative border is used to define the size of the visual field defect, it is roughly comparable among different perimetric method. There was only one mismatch between the SLO border and the relative TAP border in the left eye. T-tests between TAP and SLO and HRP were generally not significant (TAP/SLO right eye: $p = 0.95$, left eye: $p = 0.60$; HRP/SLO right eye: $p = 0.24$, left eye: $p = 0.46$), though the HRP/TAP difference was significant (right eye: $p < 0.04$, left eye $p < 0.05$).

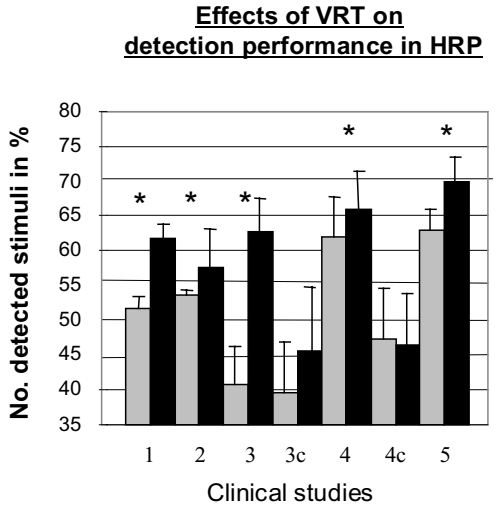

Fig. 7. Comparison of results with other studies To be able to compare the results of the present study with those of prior reports, we calculated the percentage of detection performance in (binocular) HRP as a measure before and after VRT (left and right bar, respectively). The studies are: (1) by Mueller et al. [21]; (2) Poggel et al. 24; (3) optic nerve patients treated with VRT or a placebo condition (c) in the Kasten et al. [10] study; (4) same as in (3), but post-chiasmatic patients (c = control group). The bars shown in (5) are the results of the present trial. Though there are differences in the performance levels before VRT, the degree of improvement in various prior studies was roughly comparable to the results obtained in the present experiment (TAP data not shown).

Thus, a given area of the damaged visual field may show "no function" when measured with the SLO but residual vision (relative defects) when measured by supra-threshold detection performance in HRP or by near-threshold testing as in TAP. From this it may be concluded that the SLO task is insensitive to "relative defects". To put it differently, this particular SLO task is significantly more difficult or impossible to perform in areas of relative defect .

3.3.3. Effects of VRT on the absolute and relative defects

As we have previously reported [27] the SLO border was largely unchanged following VRT, i.e. located at $2.87^\circ \pm 0.22^\circ$ (right eye) and $3.04^\circ \pm 0.22^\circ$ (left eye). Only one patient showed a border shift in the SLO. When measuring the visual field defect with TAP and HRP, in contrast, the situation is quite different and needs to be considered separately for the relative and the absolute border.

As described above, with regard to the absolute defect both borders of HRP and TAP were located significantly more temporally than the SLO border already prior to VRT, i.e. in HRP and TAP the deficit appeared significantly smaller even before training was started (Fig. 6, Table 2). When the data of all 16 patients were averaged, the SLO border was found to be located significantly closer to the vertical midline (at 2.98°/2.61° than the absolute TAP and HRP borders (located at 4.49°/4.56° and 5.28°, respectively).

After VRT, the SLO border was largely unchanged, i.e. located at 2.87° (OD) and 3.04° (OS). The absolute border in both HRP and TAP shifted significantly toward the periphery ($p < 0.05$) from 4.56° to $6.05^\circ \pm 0.20^\circ$ for the right eye and from 4.49° to $5.47^\circ \pm 0.21^\circ$ in the left eye. The absolute HRP border shifted also from 5.28° to $7.01^\circ \pm 0.20^\circ$ which was also a significant change (see Fig. 6 and Table 2).

With regard to the relative border the results were different: the relative HRP border was not different from the SLO and the shift of the border which occurred after VRT was also not significant. In TAP, the relative border position of the left eye was significantly different from the SLO border and this performance also improved significantly after VRT. In the right eye, however, there was no such statistical difference. Thus, the relative border positions in HRP or TAP shift only slightly. The shift of the relative border was significant only for the left eye of the TAP measurements.

To summarize: The "apparent" visual field defect is larger when measured by SLO than for HRP or TAP. The apparent deficit size thus follows the typical relationship of SLO > TAP = HRP. If, on the other hand, the "relative" border is taken as the criterion, then the relationship is roughly SLO = TAP = HRP, i.e. all borders are located at roughly comparable distances from the 0-vertical meridian (Fig. 6). Thus, regions of the "relative" defects in HRP and TAP are more or less identical to the "absolute" SLO defect. After VRT this border mismatch was even more pronounced.

An analysis of variance (one-way ANOVA) supported this result of highly significant differences of the absolute defects ($F = 21.6$; $p > 0.0001$). Post-hoc comparison of means (Scheffe-test) were not significant between HRP and TAP ($p = 0.18$), but between TAP and SLO and between SLO and HRP the difference was significant (both $p < 0.0001$). Comparison of the relative defects of TAP and HRP results with the SLO border showed no significant differences in ANOVA ($F = 0.8$, $p = 0.45$).

From this it can be concluded that the SLO task is more difficult than the HRP and TAP task. This difference in task difficulty may explain why after 6 months of VRT the SLO border remains unaffected whereas both TAP and HRP improved significantly. The patient

Table 2
Visual field border positions

	SLO	TAP absolute	HRP absolute	TAP relative	HRP* relative
OS pre	2.98 ± 0.22	4.49 ± 0.20	5.28 ± 0.23	2.98 ± 0.25	2.78 ± 0.25
OS post	3.04 ± 0.22	$5.47 \pm 0.21^*$	$7.01 \pm 0.20^*$	$4.11 \pm 0.30^*$	3.44 ± 0.27
OD pre	2.61 ± 0.21	4.56 ± 0.21	–	2.64 ± 0.25	–
OD post	2.87 ± 0.22	$6.05 \pm 0.20^*$	–	3.98 ± 0.30	–

Position of visual field border in degrees of visual angle from 0-vertical meridian; HRP was carried out as a binocular test only. * = significant difference between pre-post values.

example displayed in Fig. 5 is an example to illustrate this. Here, visual field borders of the SLO, TAP and HRP have been drawn into the same chart to allow direct comparison of the three border positions. In this patient, as in others, the different borders show a major mismatch well before VRT. After VRT, the absolute TAP and HRP border shifted significantly away from the midline whereas the SLO border remained essentially unchanged. VRT thus amplified the border mismatch.

3.4. Subjective vision

3.4.1. Questionnaires

The "vision status questionnaire" was applied before and after VRT (Table 3). For statistical analysis a "vision function score" (VFS) was calculated for each patient by adding the respective 1–10 scale answers of the 5 questions (5 questions $\times$ 10 scale levels $=$ 50 maximum points). Values of questions with a negative orientation (such as "I have difficulties reading") were reversed. VFS significantly increased from 37.4 ± 2.5 before VRT to 42.2 ± 2.0 points after training ($p < 0.001$); i.e. of the maximum possible score of 50 the patients gained subjectively on average 5 points, i.e. a 10% improvement.

In the "vision change questionnaire" (Table 4) 14/15 patients rated their visual performance as having improved after VRT in one or more of the categories asked. On a -3 to $+3$ rating scale, "General visual functioning" was rated having improved by an average score of $+1.6$, "visual field enlargement" was scored $+1.67$ on average, "activities of daily living" were scored with $+1.6$ improvement and "orientation and mobility" had improved by a $+1.53$ score.

3.4.2. Interviews

The free speech testimonials during the interview closely matched the results of the patient responses in the questionnaire. Observation of "general visual and/or visual field improvement" were noted by ten patients (62.5%). Eight patients (50%) noticed "improved mobility and orientation", 8 patients (50%) reported "better reading", 5 patients (31.3%) reported that "bumping into objects or people" happened less frequently and 5 patients (25%) described having picked up "specific hobbies again after VRT which they were unable to carry out before starting with VRT due to visual problems. Four patients experienced no improvement. Examples of free speech testimonials are displayed in Table 5.

3.5. Correlation analyses

In order to gain insight into factors influencing outcome we carried out a correlation analysis between the extent of visual field changes and other subjective and quantitative measures. The following measures were correlated: (i) number of hits in HRP for visual field size, (ii) percent change in HRP-hits as an indicator of visual field enlargement, (iii) average reaction time in HRP, irrespective of the stimulus location, and (iv) subjective scores (Vision Status Questionnaire, Vision Change Questionnaire, number of categories stated as having improved in the interview.).

HRP and TAP: The percent improvement in (binocular) HRP correlated with the percent change in TAP in the left eye ($r = 0.61$, $p < 0.05$) but not in the right eye ($r = 0.32$, n.s.). This suggests that the VRT effect may be more consistent in the left eye, which, in most patients, is the non-dominant eye. The change of visual field size does not depend at all on the original size of the visual field defect ($r = 0.17$, n.s.). Therefore patients with larger field defects profited as much from the VRT than patients with smaller lesions. Also, as previously observed, age of the patient and age of the lesion did not correlate with outcome.

Objective vs. subjective measures: The patients' subjective improvements as measured by interview or questionnaire did not correlate with HRP improvement. There were also no significant correlations between interview data or questionnaire scores on specific activities of daily living with objective measures of TAP performance. Significant correlations were found between

Table 3
Vision status questionnaire

Questionnaire	Pre (± S.E.)	Post (± S.E.)
1. Coping with the visual defect in every day life	6.47 ± 0.46	7.47 ± 0.62
2. Difficulties in reading	3.80 ± 0.80	2.73 ± 0.49
3. Bumping into objects and people	3.47 ± 0.67	2.80 ± 0.50
4. Acuity and clarity of vision	7.50 ± 0.69	8.13 ± 0.62
5. Difficulties being able to concentrate	3.13 ± 0.59	2.53 ± 0.70

On a scale from 1 to 10 the patients had to rate several visually guided functions pre- and post-VRT. Note that question 2, 3, and 5 are negative questions, i.e. smaller values indicate greater function.

Table 4
Vision change questionnaire

Patients subjective report of changes due to VRT	Decrease (or No)	No change	Increase (or Yes)
1. changes of visual abilities	1 (06.3%)	1 (06.3%)	14 (87.5%)
2. changes of visual field size	1 (06.3%)	1 (06.3%)	14 (87.5%)
3. activities of daily living (reading, use of computer, eating, etc.)	0 (00.0%)	2 (12.5%)	14 (87.5%)
4. confidence in visual orientation and mobility	0 (00.0%)	2 (12.5%)	14 (87.5%)
5. satisfaction with the visual field training	2 (12.5%)	0 (00.0%)	14 (87.5%)
6. training efforts justifies visual improvements	2 (12.5%)	0 (00.0%)	14 (87.5%)
7. Willingness to continue VRT after completion of trial	6 (37.5%)	0 (00.0%)	10 (62.5%)
8. Would recommend VRT to other patients	0 (00.0%)	0 (00.0%)	15 (100%)

Patient responses in the post-VRT interview. In question 8 one patient did not respond.

TAP results and selected items of the two questionnaires. Question 6 of the vision change questionnaire ("given the extent of visual improvements were the training efforts justified?") and the average decrease of absolute defects in TAP perimetry of right and left eye ($r = 0.518$; $p < 0.05$) showed a significant correlation. Also, the following more general vision questions of the vision status questionnaire correlated significantly with an average decrease in TAP absolute defects: a) 'How much did the therapy help you?" $r = 0.727$, $p < 0.001$; b) "How much did your visual functions improve?" $r = 0.562$, $p < 0.024$; c) "How sharp/clear is your vision in general? (difference pre/post VRT)", r= 0.567, $p < 0.28$.

Fixation performance: Neither HRP-improvements (percent change over baseline) nor TAP-improvements correlated with fixation ability pre or post VRT; this finding argues against the criticism that HRP and TAP improvements after VRT can be explained by eye movements or alterations in fixation performance alone.

Reaction time measurements: HRP improvements (percent change) and TAP -improvements did not correlate with reaction time improvements.

The results of the correlation analysis can be summarized as follows: TAP improvements correlated with measures of subjective vision but not with reaction time and fixation performance: Detection performance as measured by HRP showed no statistical relationship to the other functional measures. Because subjective visual improvements correlate well with reaction time changes, improvements processing time may be an additional, important contributor to the overall VRT effect.

4. Discussion

The present confirmatory, small-sample trial used three different perimetric procedures (HRP, TAP and SLO) to evaluate the efficacy of VRT along with questionnaires and interviews probing subjective visual function. Therefore, the study provides an opportunity to compare perimetric measures with each other and to relate them to subjective visual functions.

As in previous studies, patients treated with VRT showed improvements in TAP, i.e. a significant decrease of misses by 8 stimuli for the right eye and 8.75 for the left eye. This magnitude of change was greater than previously reported [8,10]. As in the past, the individual improvements varied considerably between patients. Given that these results are comparable to our previous observations and were accompanied by significant subjective improvements lead us to the interpretation that an average improvement of 8 points is not a marginal change but a relevant and meaningful improvement.

Also HRP measurements showed significant improvements of stimulus detection after VRT (6.59%)

Table 5
Individual patient testimonials after VRT

Visual confidence
• I trust my vision again; can rely on what my vision tells me
• I move about more safely in the environment
• When sitting at the table I do not accidentally spill my glass any more; when eating I no longer push the food off my plate
• I can go out again
• Can orient myself better in places, such as the train station
• I am not afraid anymore to cross the street
• I bump less frequently into objects or people
• Before (VRT) I could not get oriented in the supermarket and had real panic attacks. Now I can go shopping again.
• Can read the price tag again completely (no more "surprises" at the cash register because I did not see the first number on the price tag)
Reading
• Can read faster
• I no longer have the problem that words are missing to the right or left; I do understand the meaning of sentences more easily because words are not missing any longer
• Now I can read not only newspapers with narrow columns but can read books again.
• I can solve crossword puzzles again
• I can fill out forms again and can sign on the signature line
Employment
• I can read on the PC so well now that I can be employed as a journalist again.
• Can carry out calculations with computer tables again, I do not miss tables any longer
Hobbies
• I can do fine handy crafts again, e.g. I carry out embroidery again
• I can carry out tasks requiring fine hand coordination such as soldering
• I can watch a movie again on TV, can follow a soccer game again
• I can follow a soccer game "live" again
• I can play tennis again
• I feel safe skiing again, it actually worked rather well
• I can play golf again
Mobility
• I notice that the visual field expanded, I see more now
• Can drive the car again
• I feel safe riding the bicycle again

Individual patient testimonials are subjective in nature and may be rather general or very specific. Particularly if their content is very specific, they are considered to be credible reports. The patient testimonials are examples only. They were recorded during a semi-structured neuropsychological interview.

which was mainly due to a shift of the absolute visual field border. A closer look at prior studies showed that the results of the present study are rather comparable to other VRT studies (Fig. 7).

The majority of patients in the present study also reported noticeable changes in their subjective visual functions as documented by interviews and questionnaires which confirms our previous observations [10, 21].

In contrast to these findings, however, VRT did not improve SLO performance [27]. This discrepancy of improvements in HRP and TAP on one hand and the absence of a change in SLO on the other hand leads us to conclude that both the original size of the visual field defect and also efficacy of VRT both depend on which method is used to document the visual field borders: when the SLO is used as an outcome measure, the absolute visual field border is located significantly closer to the vertical midline and this border remains also unchanged after VRT. In contrast, when HRP and TAP are used as outcome criteria, the apparent visual field defect is significantly smaller and significant VRT effects can be observed. This discrepancy was unexpected and now raises the question of what may have caused it. To find a clue to this puzzle, let us evaluate the similarities and differences between the three perimetric procedures, HRP, TAP and SLO. Perhaps the different methodologies are the cause of this discrepancy.

4.1. Methodological comparison of HRP, TAP and SLO

The SLO stimulus parameters selected by Reinhard et al. [27] essentially consists of a bright red background created by a laser beam. The perceptual appearance is that of very thin lines (like a TV screen viewed at close range). Unlike in TAP and HRP, the target stimuli to which the patient has to respond are three

black dots created by omissions of this laser illumination (an inverse image as shown in Fig. 5). The task for the patient is to make a discrimination by stating verbally how many of the three dots were seen by the patient. In contrast, TAP presents a grey background and the near detection-threshold stimuli are of greater luminance than the background (a "positive image"). Similarly, in HRP the stimuli are also "positive" but, unlike TAP, they are well above threshold (bright white dots presented on dark grey background). Both HRP and TAP involve a stimulus detection task (patient just has to push a button) and require neither discrimination nor any verbal statements.

It is also conceivable that the laser lines actually produce a somewhat flickering perception which is the result of interferences from lateral interactions when many thin lines are spaced in close proximity. When closely alined, this produces striking after-effects, similar to an effect described by MacKay [20]. In addition, the lines of the background may have caused some filling-in-phenomenon of the black target dots; here the visual cortex may try to "complete" the black holes (the target stimuli) by virtue of perceptual "filling-in", thus attempting to "close" the parallel lines of the laser background. It is conceivable that a partially damaged region of the brain is unable to prevent this filling in from occurring (even if training improved the ability to detect simple, positive targets). This, in turn, renders the SLO task more difficult to perform in the partly damaged region (not the intact regions) than HRP or TAP. In fact, strict fixation at a single location for extended time periods (which was prompted by the experimenter) may enhance the filling-in process (Safran, personal communication).

Thus, several features make the SLO different from TAP and HRP: (i) the perception of an "inverse image" (black stimulus on bright background), (ii) the need to discriminate rather than detect the stimuli, (iii) the simultaneous presentation of three stimuli, (iv) the need to express the judgement verbally (with full awareness) rather than by pushing a button without verbal feedback which might include "blindsight"-like responses where the patient has no conscious awareness [40], and (v) the use of a red color background (note that color was not trained by VRT). We believe that any or all of these 5 features make the SLO task more difficult to perform than TAP and HRP.

The superimposed visual field borders of the three perimetric methods as shown in Fig. 5 illustrate this point. This graph displays visual field maps of a patient with the absolute border positions of HRP, TAP and SLO. Before VRT (left panel), the position of the three absolute borders already showed a mismatch. After VRT, the TAP and HRP border shifted whereas the SLO border remained unchanged (right panel). Calculations of the average border position for all patients confirm that this border-mismatch was significantly different even before any VRT commenced (Fig. 6). This mismatch of the border positions is at variance with earlier findings by Trauzettel-Klosinski et al. [35] who found TAP and SLO to match in most hemianopic patients.

In any event, the mismatch is, indeed, an observation which teaches us an important lesson. It hints at important aspects of residual vision: in areas of "relative defects" vision is affected differentially with regard to the psychphysical characteristic of the functions. Due to a different neurobiological substrate, i.e. different levels of functional loss in partially damaged neuronal network, some (simple?) functions remain intact while others (more difficult tasks?) are deficient. Clearly, a precise psychophysical description of the nature of residual vision would be needed to better understand the restored regions of the visual system (Torsten Wiesel, personal communication).

4.2. The coast-line model of visual field defects

Based on these considerations we wish to propose that visual field borders are not all-or-none events. Rather, just like a "coast-line" varies in altitude, the morphology of the damaged region may be quite different in different patients and different sectors of the visual field. In some places it may be more shallow, in other places it may be steeper. This coast-line model is compatible with the hypothesis of minimal residual function as proposed by Sabel and Kasten [29]. It states that following damage in the visual pathway, the degree of residual vision depends on the number of surviving cells in the injured zone and their activation state. We propose that if a greater number of cells survive the injury in a given brain region, the amount and/or quality of residual function would be superior. In regions at or near the visual field border we would not always expect a sharp drop-off in cell numbers from 100% to 0%. Rather, depending on the extent of local tissue sparing, the cell number would decline gradually from 100% towards zero in a more or less gradual fashion, sometimes more "shallow" and other times more "steep". As rat studies have shown, as little as 10–20% neuronal survival is sufficient to drive some residual visual functions which may recover up to 80% normal levels [30]. Assuming that the degree and quality of residual func-

tions depends (among other factors such as attention) on the (not yet specified) number of surviving neurons, the position of the "apparent" visual field border would therefore also depend on the amount of tissue spared. Like a coast-line that gradually drops in altitude, the functional loss would be gradual as well. Depending on how many residual neurons may be spared by the lesion, performance in the respective region would vary: in a difficult task function may fail whereas with easier tasks it may be intact. Thus, performance in the border region would depend on task difficulty.

Other factors which may influence the performance of residual cells are cognitive/motivational factors such as attention, fatigue etc. Indeed, areas of residual vision by their very nature of being partially injured may vary depending on the time of day or even the time of year [23]. Because patients perform at their "functional threshold" in these regions, any factor influencing visual function would have a much more dramatic impact on the performance in these partially damaged regions than in healthy tissue. In that sense areas of residual vision are particularly sensitive to the nature of the visual task being queried.

Along this line of reasoning, we wish to propose that whether the field borders match depends on the amount of neuronal sparing: when all neurons are lost, there would be a steep functional drop-off with no residual vision and a good border match. This, in turn, results in identical border positions, no matter how the border is measured (a true "absolute defect", like a cliff at the coast line). No matter how easy the task, the patient can not perform the task at or near the border. In contrast, if some neurons survive at the border, they may be sufficient to sustain easier perimetric tasks (such as a simple dot detection task) but are insufficient to perform more difficult tasks, creating a border mismatch. Thus, the respective border positions in relation to the vertical meridian would depend on the degree of tissue sparing. Though several of our patients had a rather "sharp" border at the beginning of the training, most showed a border mismatch even before training commenced. We believe that such border-mismatches can be taken as an indicator of "sub-total" damage (which is functionally a "relative defect"). The surviving subset of neurons would be expected to drive some reduced functionality. As our current data show, in areas of such mismatches easier tasks can still be performed (e.g. supra-threshold, "positive", single stimuli) while more difficult tasks can not (such as inverse, multiple discrimination as in the SLO). Indeed, in many patients we found areas of the visual field which were deficient in the SLO task but (partially) intact in TAP- or HRP-performance (see example in Fig. 5).

What is the consequence of this border-mismatch for the discussion of whether or not VRT is effective in patients with brain damage? From the discussion above it is clear that the null-finding with the SLO does not proof that VRT is ineffective; rather, the null-finding may be caused by the greater task difficulty of the SLO. Whereas in easier tasks (supra-threshold stimulus detection) patients show benefits from VRT, tasks that are more difficult to perform (here: SLO performance) may not benefit. Because VRT typically uses rather simple detection tasks, more difficult tasks, such as the one used for the SLO, were not trained and thus did not improve.

Apparently, when training effects are considered, task difficulty is a critical factor. The following analogy serves to illustrate this point: if students are trained to run a short-distance, one-mile course every day and repeatedly win the race over non-trained students, training must have benefited the students. If subsequently they fail to be faster in a marathon, it is not logical to conclude that training for one-mile races is ineffective. It simply means that training the simple task was of no consequence for performance in the more difficult task. Similarly, if VRT trained simple tasks, more difficult tasks (such as the one used in the SLO) apparently do not profit from VRT.

4.3. Is the border shift caused by insufficient fixation?

One goal of the current trial was to verify VRT-induced border shifts by use of a method which positively can not be influenced by eye movement artifacts, the SLO. The SLO is an excellent method to control eye fixation by permitting simultaneous fundus imaging and observation of the stimulus presentation on the retina which is the reason why we initiated the study. Although the SLO suffers some methodological limitations (a human observer has to decide if the patient fixated properly or not, which renders the SLO prone to subjective bias) our original assumption was that if we were able to confirm the border shift after VRT with the SLO, then fixation and eye movement artifacts could be ruled out as a possible explanation for such apparent border shifts.

However, when using the SLO measurements [27] none except one of the patients showed visual border shifts. One may be tempted to argue this null-finding proves that the "fixation-artifact hypothesis" must be correct since only the SLO provides an optimal method

to control fixation. The logic of such an argument, however, rests on the assumption that SLO-perimetry measures the same functions as TAP and HRP while, at the same time, it provides better fixation control. As discussed above, the border mismatch indicates that this is actually not true. It must therefore be concluded that the SLO measures a different function than TAP and HRP which explains both the border mismatch at study entry and the "null finding" after VRT (see discussion above).

The null-finding with the SLO [27] neither verifies nor rejects the "fixation-artifact" hypothesis. Just because it avoids fixation artifacts better than other methods does not proof that the SLO-null-finding shows that border shifts are an artifact of fixation. To stay with our analogy: if the one-mile race was measured with a stop-watch but the marathon was measured with a more precise laser-timer, the failure to do better in the marathon can not be explained by the measuring device! The task difficulty on one hand and the precision of the measuring instrument on the other hand are two different variables which are not causally linked. Likewise, the task difficulty and the superior fixation control of the SLO are independent variables. The null-finding with the SLO can therefore not be interpreted as confirming the fixation-artifact hypothesis.

The fixation-artifact hypothesis has first been raised by Balliet et al. [1] who claimed that eye movements may have explained the early findings by Zihl [42]. By trying to replicate the original Zihl finding, in their study the vision training was carried out with very small stimuli which were presented monocularly for a short training period only. In spite of these minimized therapy conditions, Balliett et al. actually found changes of the visual field border between -2° and $+4^\circ$; most of the patients actually showed enlargements. When asked about subjective improvements, four patients reported to benefit from the procedure, 2 were not sure and 6 had no subjective improvement of visual functions. No patient reported a decreased function. Interestingly, the authors then compared the results of the trained with the untrained eye and found no difference. If we consider that Ballietts patients had clearly post-chiasmatic lesions and if we further consider that a transfer effect betwee both eyes have been reported [23], the Balliet results are at least ambiguous and inconclusive. They clearly did not present evidence that eye movements explain the visual field enlargements. Neither Balliet et al. nor any other investigators have yet found positive evidence for the "fixation-artifact" hypothesis.

At least in the German clinical literature there has been some debate about the "fixation-artifact" hypothesis. Though not having experimentally studied the problem, some commentators [19] have re-visited the issue raised by Balliet arguing that artifacts of eye movements (such as small saccades toward the blind field) rather than restoration of vision explain the border shifts. Indeed, some hemianopic patients perform eye movements towards the hemianopic field to compensate for the deficit and a few patients even develop stable eccentric fixation to artificially "shift" the border toward the periphery [35]. In fact, these authors stated that such artificial border shifts due to eccentric fixation only occur in patients without macular sparing. Therefore, measuring these parameters is needed to determine if the border shifts are caused by eye movements or whether they represent true restoration of vision. Our previous SLO study [27] had established that none of the patients showed stable, eccentric fixation. In addition, the blind spot position as determined by TAP in the present study (which was unaltered) confirmed this conclusion. Of course, one can not control the eye movements while the patients are training at home. But the color-change of the fixation point is both a useful and practical method to determine in a home setting if eye movements had occurred excessively during training. Though it clearly is an inferior fixation control method compared to the SLO, it is the only currently available method that can be implemented for home-training.

Because the fixation discussion is important to fully understand the effects of VRT, let us consider how well patients perform the fixation control procedure in HRP, TAP and by SLO. If eccentric fixation and eye movements indeed have occurred during follow-up, then this should affect several variables. However, this was clearly not the case as the following observations testify:

1. *Good fixation in SLO*: In the SLO-study [27] some patients tended to make small intermittent saccades (in the order of 0.5-1° of visual angle), which is rather typical. The large majority of patients, in contrast, fixated rather well. None of the patients showed stable eccentric fixation in the SLO.
2. *HRP-fixation performance unchanged*: Using the method of the color change of the fixation spot during HRP (see methods section) it was found that all patients actually displayed good fixation abilities. Without exception, all patients responded to the color change of the fixation spot in

$>$ 90% of the trials. In fact, fixation remained stable throughout the 6 months and fixation performance also did not correlate with any of the outcome measures such as visual field improvements or reaction time gains.

3. *TAP-fixation performance unchanged*: Fixation quality was measured by standard TAP fixation control measures (see methods section) and was found to be unaltered by VRT. As in HRP, TAP fixation performance also did not correlate with any of the outcome measures.
4. *Blind spot position unchanged*: Trauzettel-Klosinski and Reinhard [35] state that lack of a shift in the blind spot position is a good indicator that fixation is not eccentric. Our analysis shows that the position of the blind spot remained identical in 12 of the 16 patients. Only 4 patients showed a small shift of the blind spot; in two patients the blind spot was located more temporally (which should, if anything, have produced an artifactual "shrinkage" of the visual field). However, the two other patients with a slight blind spot shift nasally (which could theoretically produce an artifactual field enlargement), did not belong to the category of patients who improved in TAP or HRP. In other words, the two (of the 16) patients where the "fixation-artifact" could have occurred are patients who did not profit from VRT.

In summary, there is clearly no evidence for the VRT-effect being explainable by altered fixation behavior or eye movements. In contrast, we obtained evidence that these artifacts can be ruled out as an explanation for the VRT-effect.

4.4. Activities of daily living

To date, there has been little information on the effect of VRT on any subjective indicators of activities of daily living (ADL). In all previous studies, perimetric detection tasks were used as outcome measures. In a recent retrospective study Mueller et al. [21] analyzed the data of 69 patients after 6 months of VRT and found that most patients (88%) reported subjective benefits in activities of daily living (ADL) in at least one of the categories. Our study confirms these observations. The standardized questionnaire and the interview revealed improvements in visually guided activities of daily living, including improved visual confidence and mobility (in 50% of the patients), better reading (50%), and fewer instances of bumping into objects or people (31.3%). In the Reinhard et al. study [27], several patients actually had improved reading ability in SLO after VRT. The group difference in an easier reading task were, in fact, significant, though it is debatable whether or not the percent changes are relevant for those patients. Nevertheless, the large majority (87.5%) of the patients were, on the whole, satisfied with VRT (independently confirmed by several clinical observers).

Thus, VRT not only increases detection ability in perimetry, but, as the patient testimonials document, VRT has a beneficial effect on activities of daily living. Despite this finding, more studies are now needed using functional tests of activities of daily living (such as reading, driving performance or navigation in a park of objects) to confirm this.

Despite the positive subjective reports of the patients, a note of caution, however, is necessary. We need to be aware that the current trial was an open, non-randomized "exploratory" study without a blinding procedure. Therefore, some patients may have responded in a biased way. While such a "placebo" effect can not be excluded completely in the current study, our findings are compatible with previous reports: both the randomized clinical trial [10] and the retrospective study of patients seen by the NovaVision Clinic in Magdeburg [21] confirm that about 1/3 of the patients have little or no benefit from VRT, 1/3 have clear-cut, noticeable improvements, and 1/3 have remarkable improvements.

Thus, VRT can help many, but not all, patients to improve their subjective vision. As the null finding with the SLO shows, however, not all aspects of vision improve by the current version of VRT and therefore more effective training algorithms are required to help the patients master also more difficult tasks.

4.5. Correlation of ADL and visual field size improvements

The present study also addressed the issue to what extent perimetric improvement and subjective measures of ADL relate to each other. We found that there was some correlation between these measures. The literature reveals surprisingly little information of how visual field defect size and subjective vision correlates. Though it is obvious that hemianopia impairs subjective vision, there is little knowledge what impact minor or even major changes of defect size have on subjective vision. Most recently, Mueller et al. [21] carried out a correlation analysis between visual field enlargements and subjective patient testimonials after VRT.

Only small correlations were found between visual field enlargement in the categories "carrying out hobbies" ($r = 0.36$) and "general improvement of vision" ($r = 0.24$). No correlation was found between visual field size improvements and "visual confidence/mobility" and "ability to avoid collisions". Mueller et al. concluded that visual field size appears to be one of several factors which impairs subjective vision in brain damaged patients. It was proposed that other factors, such as temporal processing, may be involved as well. The results of the present experiment are therefore generally in agreement with the Mueller et al. findings. If other factors are involved in subjective visual improvements, these factors now need to be determined. The influence of such other factors may also help to explain how a relatively "small" visual field enlargement can have such great subjective effects. It would also explain the rare cases where patients with no visual field enlargements after VRT still reliably report subjective improvements or those cases with visual field enlargements but no subjective improvements [21].

5. General conclusions

The present study thus confirms what has been reported for the last 25 years, namely that training can help patients regain some of their visual field [6,8–10, 14,17,23,25,26,32,34,36,37,41–44]. In fact, the degree of visual field enlargement we found in the present study was roughly comparable to that reported previously (Fig. 7). Yet, the discrepancy between these results and the SLO null-finding teaches us an important new lesson: determining the visual field border with different methods does not always produce the same outcomes. In fact, the discrepancies remind us that the border of the visual field defect has an interesting topography which is probably determined by the number of neurons surviving the injury and their activation state. Probing the function in such areas of "residual vision" is not a trivial task and requires further study. Clearly, several factors determine the degree of residual vision such as attention [24], task difficulty, and temporal processing [21].

Despite the debate over the interpretation of the SLO study [27], the present study generally confirms that restoration of vision is possible, i.e. the brain can adapt to lesion-induced changes in a process of neuronal plasticity. What is new is that in (more difficult) SLO-type tasks, VRT has no effect. This implies that not all functional aspects of the visual system benefit from the current version of the VRT. Advanced versions of the VRT-training are therefore required to help treat more difficult (and more complex) visual functions.

As the border-mismatch discussion above shows, however, the relationship of improvement in some perimetric procedures to subjective vision is more complicated than previously thought. Clearly, the relationship of objective and subjective parameters of vision needs further exploration, a field which has received little attention so far. Visual field enlargements correlate with some subjective visual improvements as assessed by questionnaires or patient testimonials. Perhaps other factors, such as temporal processing, may also be important contributors to vision restoration. Further scientific study is now required to shed more light on such mechanisms. The ultimate goal remains to better understand the neurobiological basis of adult visual system plasticity to help patients to further restore visual field defects and thus improve their quality of life.

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