Inverse stimuli in perimetric performance reveal larger visual field defects: Implications for vision restoration

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Abstract. *Purpose*: When studying the efficacy of vision restoration training (VRT), near-threshold and super-threshold perimetry revealed visual field enlargements whereas the Scanning Laser Ophthalmoscope (SLO) did not. Because the SLO procedure differs in many parameters from the other perimetric tests (task difficulty, inability to reveal relative defects, inverse stimulus presentation, bright red background) the question arises which of these parameters might be responsible for such discrepancies in outcome. We have therefore simulated with a computer-based campimetry test some of the SLO parameters and compared performance with that in standard perimetry.
Methods: A 46-year old female patient was evaluated with computer-based high resolution perimetry (HRP) using detection tasks of "positive" (bright) stimuli on grey background. Performance was compared with an SLO-like task using "inverse" black target stimuli on red background.
Results: Detection rate was 89% when the stimuli were positive (HRP) but dropped to 79.6% and 80.4% in the SLO-like "inverse" stimulation mode with red background, and striped red background, respectively. The number of false positives increased from 8.5 when a grey background was used, to 9.8 and 9.5 for plain red and striped red background, respectively. Reaction times were prolonged from 384 ms using a grey background to 412 ms and 391 ms using a plain red and striped red background, respectively. Thus, visual fields tested with SLO-like "inverse" stimuli showed larger scotomata and prolonged reaction time.
Conclusions: Inverse stimulus detection on red background is apparently a more difficult task for hemianopic patients than standard perimetric protocols (such as those used in Tuebinger Automatic Perimetry or HRP). The difference in stimulus features might explain why VRT-induced visual field enlargements could not be observed with the SLO. Our findings also suggest that vision restoration training does not improve all aspects of vision, such as inverse, chromatic stimulus detection.

Keywords: Perimetry, vision, visual field, ophthalmoloscope

1. Introduction

Vision restoration training (VRT) has been shown to enlarge the visual field of patients with hemianopias following stroke or trauma. This was repeatedly documented by measuring visual fields with standard near-threshold perimetry (TAP) and superthreshold, high-resolution perimetry (HRP) (e.g.: Zihl & von Cramon, 1985; Kasten & Sabel, 1995; Potthoff, 1995; Kasten et al., 1998; Tegenthoff et al., 1998; Kasten al., 1999; Werth & Moerenschlager, 1999; Poggel et al., 2001; Kenkel et al., 2002; Julkunen et al., 2003; Mueller et al., 2004; Ullrich et al., 2004; Wuest et al., 2004, Müller et al., 2007). However, in one study no such visual field enlargement was seen when a Scanning Laser Ophthalmoscope (SLO) was used (Reinhard et al., 2005). This was surprising because in the very same group of patients, TAP and HRP measurements revealed sig-

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nificant detection improvements (Sabel et al., 2004), comparable to those observed earlier.

A more detailed analysis of these contradictory findings (Sabel et al., 2004, 2005) revealed that the deficit revealed by the SLO-task was significantly larger than when the same patient was studied with standard perimetric tests. This was also evident as a significant visual field "border-mismatch" between HRP and TAP measurements on the one hand and SLO-measurements on the other hand (Sabel et al., 2004). This was true even before VRT was started. Specifically, the visual field borders as defined by SLO were located significantly closer to the vertical midline, i.e. the scotomata were apparently larger in SLO than in TAP or HRP (Sabel et al., 2004). We concluded that perhaps the SLO is a more difficult task to solve for patients and indeed the patients also reported the SLO- required more effort due to the need to discriminate three black stimuli on a red background rather than simply the detection of a single stimulus on grey background. We have speculated earlier that this greater task difficulty of the SLO was the reason why VRT did not improve SLO performance. Thus, when measured by SLO, no restoration was found (the "SLO-null-finding") whereas when measured by TAP or HRP, significant restoration was seen.

To further address this issue, the present single-case study was carried out to determine if methodological differences in stimulus presentations between the SLO and other perimetric measures might have accounted for these contradictory results.

The SLO parameters selected by Reinhard et al. (2005) were different in several respects to standard perimetry tasks. While HRP and standard perimetry (such as TAP) typically use positive stimuli to evaluate visual fields (bright stimuli, dark background), the SLO employed by Reinhard et al. (2005) used "inverse" stimuli (black stimuli on bright, red background). The SLO paradigm also consisted of a bright red background created by a scanning laser beam. The perceptual appearance of the red background is that of many thin, parallel lines (like a television screen viewed at close range). The target stimuli were three black dots created by omissions of this laser illumination ("inverse" stimulus) and the patients had to make a discrimination by stating verbally how many of the three black dots they had seen. In contrast, TAP used a grey background and the target stimulus was a single dot with near detection-threshold but greater luminance than the background (a "positive stimulus"). Like TAP, HRP uses "positive" stimuli but, unlike TAP, they are well above threshold (bright white single dots presented on dark grey background). Both HRP and TAP do not require target discrimination and verbal reporting but rather simple detection (patient just has to push a button with no verbal report).

In summary, several features make the SLO different from TAP and HRP: (i) the perception of an "inverse image" (black stimulus on bright background), (ii) the use of a red color background, (iii) the need to discriminate rather than detect the stimuli, (iv) the simultaneous presentation of three stimuli, (v) the need to express the judgement verbally (with full awareness) rather than by pushing a button without verbalization, and (vi) in the SLO the patients had to view the stimuli through binocular lenses. Any one of these factors - or a combination thereof – may have affected the SLO's level of difficulty.

With the single case study presented here, we wish to focus specifically on the role of two psychophysical features of the SLO: the inverse (black) target and the red background. We accomplished this by simulating these two SLO features in a campimetric setting where the patient had to perform inverse stimulation tasks on a red color background illumination presented on a computer monitor (rather than in the SLO-device). All other interfering factors in which the SLO-task was different from TAP and HRP (laser light, binocular examination, conscious reporting, three dot detection task) were thus eliminated.

We reasoned that if these stimulus characteristics were the cause of the SLO's greater "level of difficulty", then the visual field defect of our single patient should be larger when an "SLO-like" inverse stimulus was presented on a computer monitor. We have therefore re-examined one of the patients four years after partricipating in the original Tübingen study and compared her perimetric performance under conditions of SLO-like "inverse" stimulus paradigms (red background, black target stimuli) with "positive" stimuli (grey dark background, white target stimuli).

2. Methods

2.1. Perimetry

The scanning laser ophthalmoscope (SLO) is an experimental perimetric procedure which permits the observation of the stimulus positions directly on the retina. It has been described in detail elsewhere (see e.g.: Varano & Scassa, 1998). The SLO is a device to investigate the background of the eye; it is not typically used for perimetric investigations. In the Reinhard et al. study (2005), a special perimetry program was used. Briefly, unlike in HRP or TAP, patients had to look at visual stimuli through a binocular-type device through which a laser beam was directly projected onto the retina to create a laser-generated stimulus. Simultaneously, the retina was imaged in real time. The stimulus parameters of the SLO were rather unlike the HRP and TAP stimuli: a solid red background was created by a fast moving laser beam which created perceptually an array of fine flickering red lines. The target stimuli were three black circles created by laser omissions (241 test locations, horizontally 1° in the healthy visual field and 10° in the defective area, vertically ± 8°, 3° stimulus eccentricity, 2° interdot distance; presentation time was 120 ms.). Unlike other perimetric investigations, the SLO-stimulus produces no scattering light. In contrast to HRP and TAP, where the patient had to detect a stimulus by just pressing a button, in SLO a verbal "discrimination" had to be made: the patient was asked by the experimenter how many circles were present (Fig. 4).

Eye movements and fixation were recorded by online video recording of the SLO performance. The responses were displayed in a binary manner (correct or false) for each location so that no "relative defects" were seen in the SLO (for details see Reinhard et al., 2005).

HRP is a campimetric procedure using a computer monitor (for details, see Kasten et al., 1997). The subject has to hit a key on a keyboard whenever a target stimulus is detected. This examination was carried out with established parameters (i.e. 19 × 15 grid, stimuli were very small white dots; size 0.15°, luminance 95 cd/m^2, duration 150 ms); the inter-stimulus interval was randomized between 1,000 and 2,000 ms (see Kasten et al., 1999). As fixation control the patient had to react to slight color changes of the fixation point.

Usually HRP tests were performed on a dark grey background (luminance 7 cd/m^2). In the present study, we compared this background with a plain red background (luminance 20 cd/m^2) and with a striped red background (luminance 11 cd/m^2). The black stripes were 1 pixel wide and had a distance of 1 pixel. The black stimuli were 9 pixel in diameter (i.e. about 1°) and the luminance was 0.35 cd/m^2.

In the original Tuebingen study (Reinhard et al., 2005, Sabel et al., 2004), one of the perimetry methods used the Tübingen Automated Perimeter (TAP-2000). Here, visual stimuli were presented inside a hemispheric dome with a relatively low resolution (191 stimulus positions, presentation time 0.2 sec). The stimuli were presented in different luminance levels to determine the near-threshold value (for details see Lachenmayr & Vivell, 1992). Stimuli presented in TAP were near-threshold with a light grey background. TAP was also equipped with a fixation control procedure using a video-camera for eye monitoring (see Sabel et al., 2004).

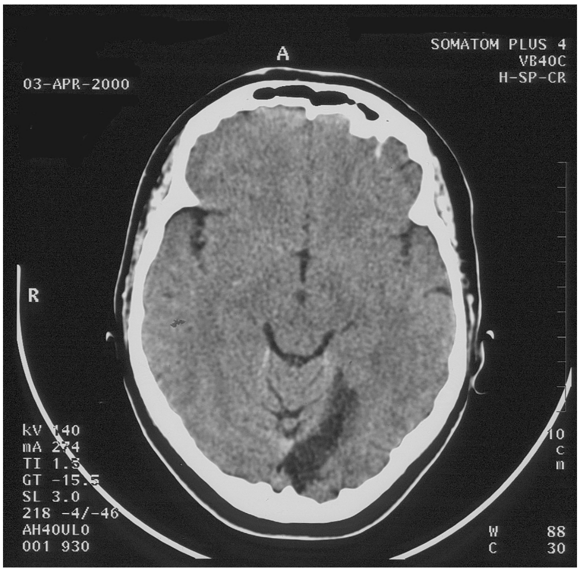

Fig. 1. CT of the brain of patient I.M. from April 2000. The left occipital lobe shows a large defect can be seen.

2.2. Patient description

In July 1998, when our patient, I.M., was 39 years old, she had a stroke in the posterior cerebral artery of the left occipital lobe which led to a quadrantanopia in the upper right sector of her visual field (see Fig. 1). In the patient's anamnesis, typical risk factors were identified including adipositas, nicotine abuse, use of estrogene-contraception and high blood pressure. Four weeks before the stroke, she has had a breast cancer surgery. About one year after the stroke, a hyperthyreosis was found.

I.M. participated in the original clinical trial from January to August 2001 which was conducted as a collaboration between the University of Magdeburg and the University of Tübingen and the results of which were previously published (Reinhard et al., 2005; Sabel et al., 2004). Diagnostic tests at baseline and at final outcome were carried out at the Eye Clinic in Tübingen as part of the original trial. Vision restoration training (VRT) was provided, as well as managed, by Nova Vi-

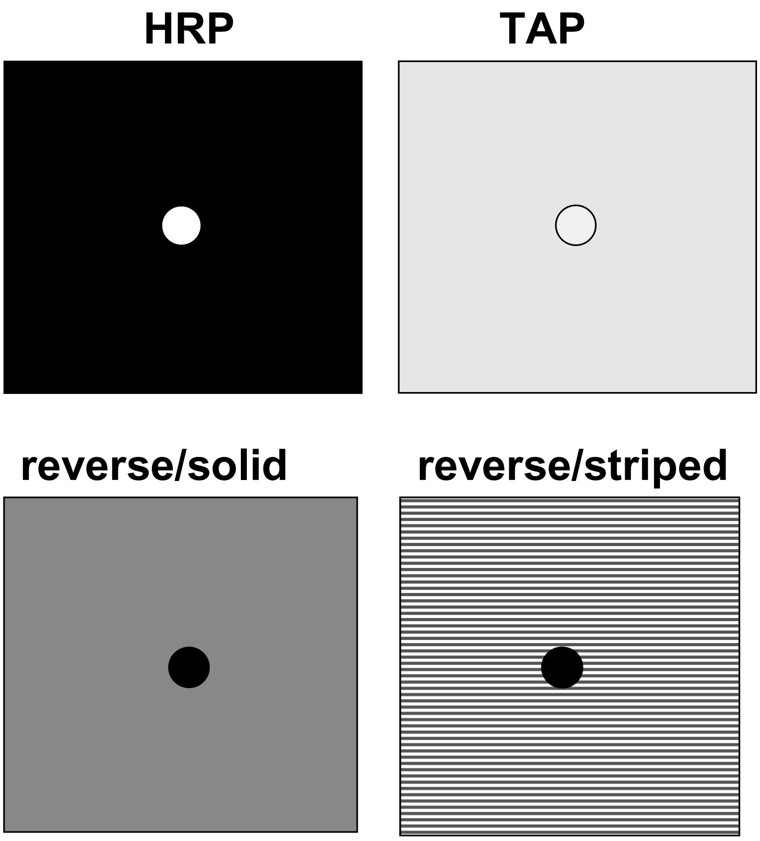

Fig. 2. Cartoon of stimulus target configuration used for perimetric assessment of patient I.M. Upper left panel: High Resolution Perimetry (HRP) using above-threshold stimulus on a black background. Upper right panel: TAP-perimetry (Tuebinger Automated Perimetry) uses near-threshold stimuli on light grey background (presented in a hemisphere). Lower left panel: SLO-like feature of campimetric test stimulus: dark target on solid, red background (red color shown here in grey shade only). Lower right panel: another SLO-like feature; here: dark target on a striped, red background), and (TAP, lower panel).

sion AG (Magdeburg) free of charge. Briefly, the patient's visual field was studied with three different perimetric examinations before and after a 6-months VRT period: high resolution perimetry (HRP), Tübingen Automatic Perimetry (TAP) and Scanning Laser Ophthalmoscope (SLO).

In a previously published study, TAP measurements in our patient, I.M., improved as revealed by decreases of undetected stimuli ("misses") from 21 to 7 for the right eye (OD) and from 26 to 15 for the left eye (OS), respectively. In four baseline and four final outcome investigations with HRP, we found an average decrease of undetected stimulus positions from 19% to 8% for the right eye and from 28% to 14% for the left eye.

The examination of the visual field defect under control of the SLO revealed a decrease from 83.0 to 39.5 blind positions for the right and from 80.0 to 62.5 for the left eye. Our patient was the only case in the earlier trial which had actually improved in SLO performance (Reinhard et al., 2005).

The current case study was carried out 4 years after the original trial was completed. I.M. visited our laboratory in Magdeburg for this follow-up examination in 2005.

2.3. *Subjective vision*

I.M. was interviewed in a semi-standardized fashion with questions addressing subjective impressions of visual impairment, development of the defect and activities of daily living similar to our previous studies (Mueller et al., 2003). The patient testimonials were recorded and then categorized into functional domains.

2.4. *Vision restoration training* (*VRT*)

VRT is a training software which runs on personal computers and is carried out at the patients' home (pro-

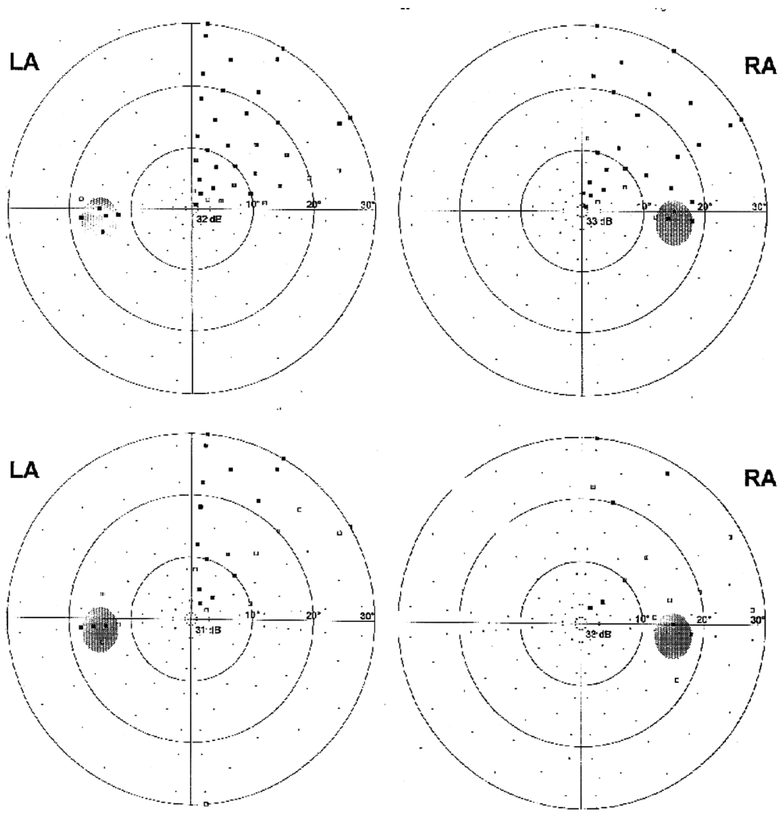

Fig. 3. Results of the Tuebinger Automated Perimetry (TAP-2000), ± 30° visual field, near threshold perimetry; upper panels: before the training, lower panels: after the training. RA = right eye, LA = Left eye; small points indicate detected stimuli positions, black squares are blind areas and grey squares relative defects.

Table 1
Results of campimetric performance under different stimulus conditions: white stimulus on grey background, black stimulus on plain red or striped red background (average ± S.E.). The statistical differences are given as well

Background	Stimulus detection in %	Fixations (%)	No. false positives	Reaction time (ms)
Grey	89.0 ± 2.4	100.0 ± 0.0	8.5 ± 3.0	384.8 ± 11.1
Plain red	79.6 ± 2.3	98.9 ± 1.3	9.8 ± 2.4	412.5 ± 11.8
Striped red	80.4 ± 0.6	99.9 ± 1.3	9.5 ± 6.2	391.5 ± 10.4
Kruskal-Wallis ANOVA	$p = 0.018$	n.s.	n.s.	$p = 0.063$

vided by NovaVision; Magdeburg, Germany). VRT projects stimuli on a computer monitor in areas of residual vision (ARVs, see Kasten et al., 1998), 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 detect the stimulus which is presented in or near areas of residual vision (transition zone). The patients carried out training sessions twice daily for half an hour each within a six-month period. Training 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. Detailed information is provided elsewhere (Kasten & Sabel, 1995; Kasten et al., 1998; Kasten et al., 1999; Wuest et al., 2004). After completing the training program, the patient performed additional training of saccadic eye movements for several months.

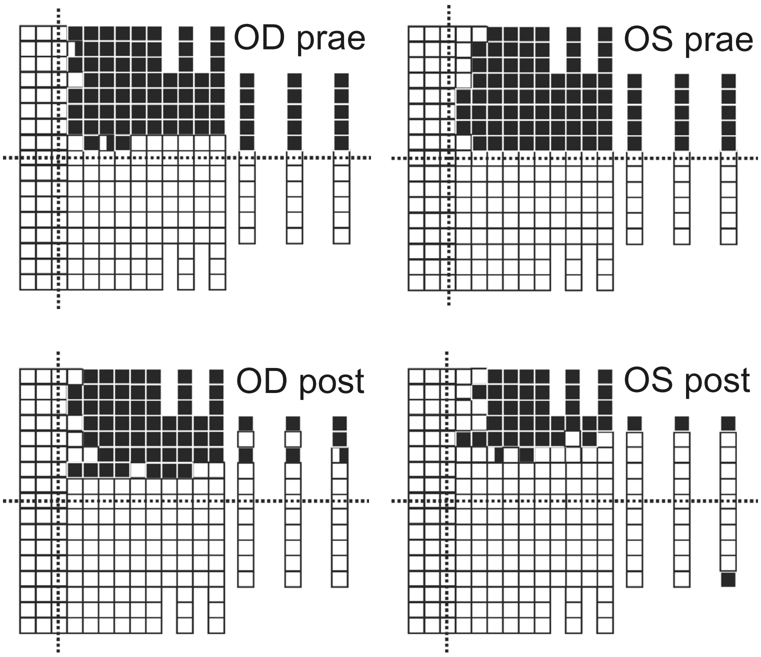

Fig. 4. Result of the Scanning Laser Ophthalmoscope (SLO perimetry), in which the patients had to recognize triplets of black points on red background. (for details see: Reinhard et al., 2005). White squares indicate detected and black squares undetected stimuli. Investigated visual field size was ± 8° vertically and 10° horizontally. Upper panels: before VRT; lower panels: after VRT.

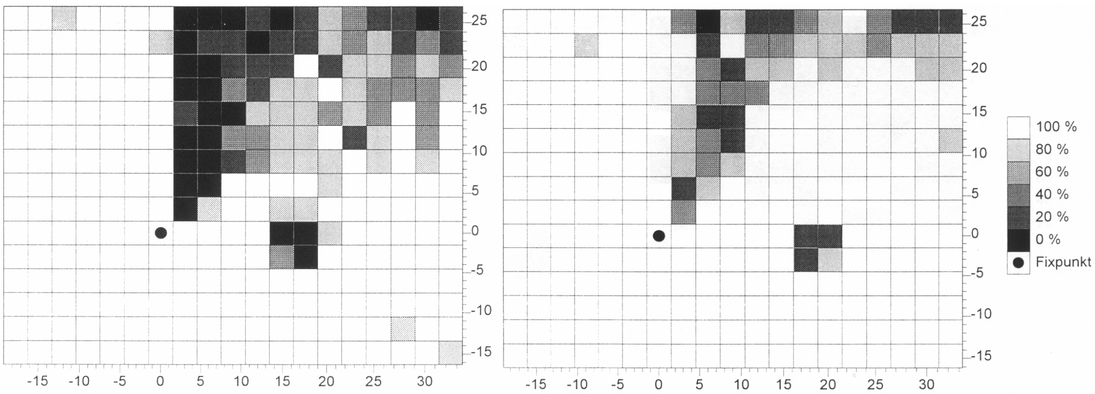

Fig. 5. Results of high resolution perimetry (HRP) of the right eye before (left) and after VRT (right). The graph shows superimposed measurements. White indicates intact areas, black = blind, grey = areas of residual vision.

3. Results

3.1. Perimetric performance

During baseline-investigations (before VRT), I.M. detected an average of 81% and 72% of the stimuli for OD or OS, respectively. In the four repeated HRP examinations after VRT completion, she had detected an average of 92.0% (OD) and 88% (OS) of the stimuli in August 2001, i.e. after the VRT period, her values improved 11% OD and 16% OS. At re-examination in September 2005, four years after completing the trial, the visual field size was nearly unchanged compared with the final outcome in August 2001. The average rate was now 89% (OD) and 86% (OS). The upper graph in Fig. 6 shows the result of this follow-up investigation. Note, however, that she continued to perform VRT for several months after the trial was completed.

At the time of re-examination, we compared the influence of different stimulus characteristics on HRP

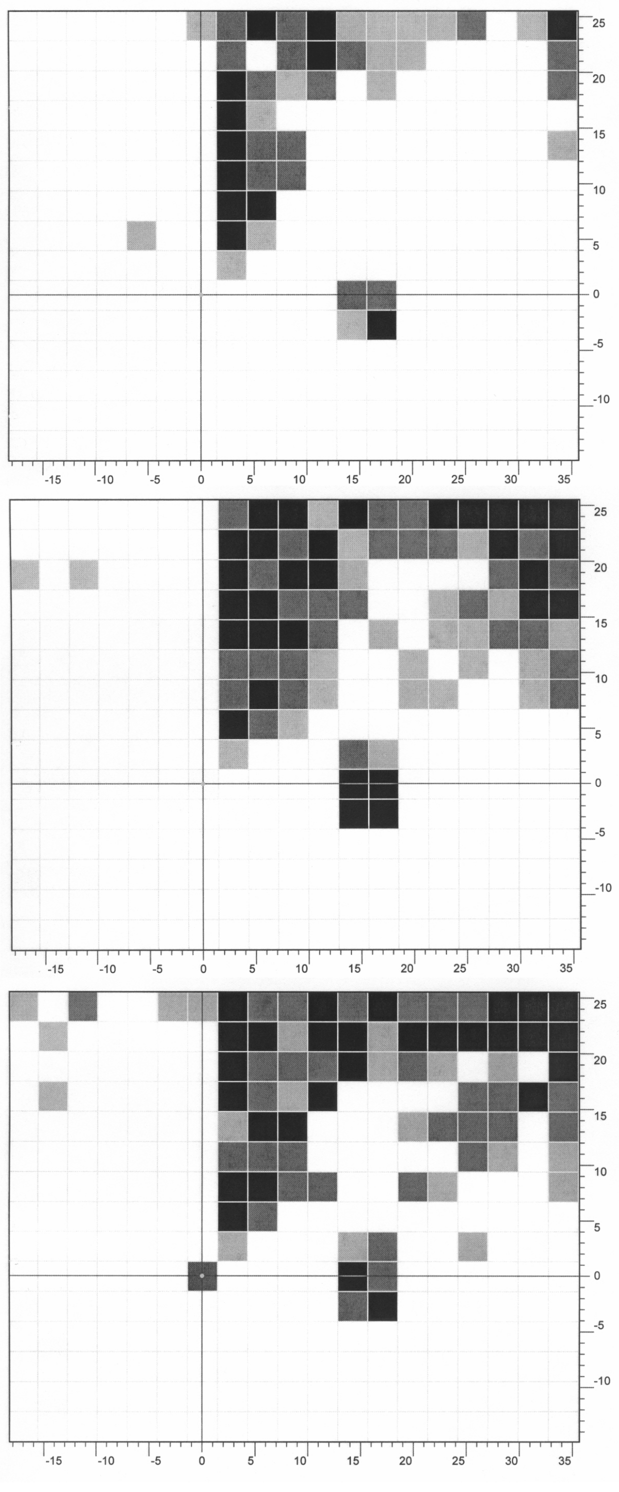

Fig. 6. Results of high resolution perimetry four years after the training. All examinations were made on the right eye. The graphs showes three superimposed measurements. Upper panel: visual field defect with our usual method of measurement, i.e. the detection of a light grey dot (95 cd/m^2) on a dark grey background (positive stimuli). Middle panel: visual field chart obtained with black dots (0.4 cd/m^2) on an even red background (inverse stimuli). Lower panel: inverse, black stimuli (0.4 cd/m^2) on a striped red background (for explanation see Fig. 5).

performance with the right eye (OD) and found the following:

When HRP was carried out with plain red background and black targets ("inverse" stimuli), I.M. detected only an average of 79.6% of the stimuli (as opposed to 89% under positive stimulus conditions) and 80.4% when a *striped* red background was used, i.e. the results with the striped background were almost identical to the solid, red background. There was no change in average fixation behaviour between the three different stimulus characteristics (98.9 up to 100% correctly detected colour changes). The average number of false positives was 8.5 in the positive stimulus condition and 9.8 and 9.5 in both inverse stimulus conditions, the striped red and solid red background, respectively.

Reaction times were 385 ms with positive stimuli (in the grey background) compared to 413 and 392 ms for inverse stimuli, the striped red and solid red background, respectively.

A non-parametric Kruskal-Wallis-ANOVA between the data of the repeated measurements of the three different backgrounds revealed a significant difference for the comparison of the number of detected stimuli ($p < 0.05$); a trend was found for the reaction time ($p = 0.063$; see Table 1 and Fig. 6).

3.2. Subjective report

Before VRT, the patient reported reading difficulties. She held a job as an export sales manager but working with computers all day long made her feel that her visual impairment made reading more difficult, especially in the upper right corner of the monitor (the location corresponding to her scotoma).

Despite her brain damage, she continued driving her automobile but had great difficulties seeing street signs and traffic lights on the right side. She compensated her driving difficulties by frequently moving her head and avoided long distance driving. She generally felt more comfortable driving with someone accompanying her. Despite this, her attending ophthalmologist felt confident that she could continue driving after therapy.

After VRT, she described her field defect as "*smaller than before*" and reported less difficulties in driving. She noticed that when driving straight ahead, she could now more easily see street signs and traffic lights on the right side and that she could recognize them faster than usual. At follow-up examination in Sept. 2005, i.e. 4 yrs. after the initial training, she reported that the subjective visual improvements, which she experienced immediately after VRT in 2002, were maintained even after training was discontinued for at least 3 years. In fact, she had driven all by herself for a distance of more than 500 km to attend the follow-up examination in Magdeburg in 2005 which she had never done before.

When interviewed about her experience with the different perimetric test employed in this study, she reported that the task with the striped, red patterned background was easier to solve than that with the solid red background. During testing with the solid red background, she felt that her view was constricting gradually as if developing tunnel vision. She reported that the field of view became more and more narrow. Both red backgrounds were perceived as being more tiring than standard HRP (grey background). When asked about her subjective experience with the SLO, she remembered that it had been more difficult than TAP and HRP and she thought that she had done worse in the SLO. She reported that the simulated striped pattern resemble the SLO task more so than the simulated plain red background. She also felt that the striped pattern background of the SLO was more tiresome than the striped pattern simulated on the computer monitor.

Subjectively, she reported that the vision she regained back in 2001 was maintained even in 2005, but that under stress she noticed a functional decline.

4. Discussion

Considerable controversy has arisen in the last few years whether or not VRT is able to enlarge visual fields of patients with hemianopia (e.g.: Balliett et al., 1985; Kerkhoff & Schindler, 2000; Kommerell, 2000; Stoerig, 2000). The recent SLO results by Reinhard et al. (2005, see introduction) was taken by some critics (Horton, 2005) as evidence that vision restoration may be an artifact of eye movements. At the time it was not known to these authors that eye tracker recordings document that eye movements are unchanged after VRT (Kasten et al., 2006), but what they have not considered is that while the SLO might have an advantage of controlling eye movements very well, the stimulus characteristics of the target stimuli used during the SLO experiment were very different than those used in all previous perimetric studies. Specifically, the SLO – in which no restoration was found – used black stimuli on bright red background. In contrast, all other perimetric procedures – where vision restoration was found – used bright stimuli on grey or black background.

That the SLO method is more difficult in the mismatch areas may have different reasons: (i) a bright background may increase the probability of a perceptual filling-in which is difficult for brain damaged patients to prevent, (ii) covert attention may fluctuate in these regions, and (iii) a lateral "halo" from the edge of the target stimulus toward the dark inside may reduce the apparent size of the target. In addition, paying attention to 3 black targets rather than one increases the attentional "spot light" and thus increases the detection threshold. We suspect that any one of these or other factors, or a combination of them, makes the task more difficult for patients to perform. It was already suggested by us earlier (Sabel et al., 2004) that hemianopic patients have greater difficulties performing the SLO task as evident by the fact that the apparent size of the visual field was significantly larger than those obtained by standard perimetric test. Our single case study focused on two of the target stimulus characteristics and the results confirm that the visual field defect indeed was larger when defined by detection of "inverse stimuli" (as in SLO) then when defined by "positive stimuli" (as in HRP).

One may argue that bright stimuli on black background produce more stray light than inverse stimuli and that patients respond to the stray light rather than the target itself. With the present study we were not able to address this issue and can not exclude this possibility. If this was true, however, then responding more often to super-threshold stimuli after VRT than before would imply that the patient was able to see the stray light after VRT but not before. This would, in itself, be an improvement of visual perception. We believe, however, that this is not the case because the patient had originally also improved in perimetric performance where near-threshold stimuli were used that produce very little, if any, stray light.

In any event, our single case study is in agreement with our previous conclusion (Sabel et al., 2004) that the greater task difficulty of the inverse stimulus paradigm alone could explain the null-finding in the SLO-study (Reinhard et al., 2005) and that the null findings can not be explained by the superior control of the eye movements. This is well in line with our eye tracker recordings showing that VRT does not change eye movements (Kasten et al., 2006).

What are the mechanisms responsible for the fact that the stimulus characterics have such an impact on whether or not vision restoration can be detected? We see two basic explanations: Firstly, VRT generally uses positive stimuli for training and it may be that the effect of the training is very specific for such stimuli as is seen in other experiments of perceptual learning. Fahle (2004, 2005) has shown that improvements in perceptual learning often is very specific for the task, the stimulus orientation, the position in the visual field, and the eye used during training. For VRT this means that a training of detection of white dots on a black background may not lead to increased abilities to discriminate dark new stimuli on red background. Secondly, the visual field sector which was functionally restored by training remains to be an area of partial, structural damage ("area of residual vision"). Such partially damaged tissue might be sufficiently intact to carry out easier tasks such as simple light detection but insufficient to carry out more difficult tasks such as those requiring discrimination. Perhaps also the luminance difference threshold is elevated in a recovered visual area and a dark (inverse) stimulus may not profit from this. We conclude therefore that differences in stimulus features are sufficient to explain why VRT-induced visual field enlargements could not be observerd with the SLO technique. Our findings also suggest that vision restoration training does not improve all aspects of vision, such as inverse, chromatic stimulus detection. Clearly, more studies are now required to characterize the psychophysical nature of the restored visual fields more fully and based on such knowledge new treatment regimens may be designed to further improve the restoration of vision in hemianopic patients.

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