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Multifactorial predictors and outcome variables of vision restoration training in patients with post-geniculate visual field loss

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Abstract. *Purpose:* Systematic stimulation of the visual field border in patients with visual field loss after cerebral lesions improves visual function even years after the onset of partial blindness. However, computer-based training programs like Vision Restoration Training (VRT) are not equally effective in all patients. We therefore tested which factors determine training outcome and which visual and cognitive functions are changed by VRT.
Methods: Multiple outcome measures were predicted using a multifactorial regression approach. Nineteen patients with post-geniculate visual system lesions performed six months of VRT and underwent extensive testing before and after treatment, including visual field measurements, attention functions, and subjective parameters.
Results: Visual field size increased significantly during training, but a number of cognitive, especially attentional, variables also improved, as did subjective visual function. The size of areas of residual vision was the strongest predictor variable for visual field increase. Demographic and lesion-related variables had little influence on training success.
Conclusions: With multivariate regression models, training outcome on different variables can be accurately predicted. Moreover, visual field increase is sufficiently predictable based on a set of variables readily available to the clinician: age of the patient, time since lesion, number of absolute perimetric defects, eccentricity of the visual field border, size of areas of residual vision, and average reaction time to perimetric stimuli.

Keywords: Visual field loss, restoration of function, rehabilitation, predictor, evaluation

1. Introduction

Designing new rehabilitation strategies and monitoring functional recovery are major challenges of applied clinical neuroscience. Over the last two decades, evidence has accumulated for an amazing capability of the brain to reorganize in response to lesions. This is also true for the visual system as has been demonstrated, for instance, by studies on spontaneous recovery of visual function (Chino et al., 1995; Darian-Smith and Gilbert, 1994; Gilbert and Wiesel, 1992; Kaas et al., 1990; Poggel et al., 2001; Sabel, 1999). But even when the phase of spontaneous recovery is completed after lesions, systematic training of visual function can further improve performance (Julkunen et al., 2003; Kasten et al., 1998; Kasten et al., 1999; Mueller et al., 2003; Pleger et al., 2003; Poggel et al., 2001; Poggel, Kasten et al., 2004; Werth and Moehrenschlager, 1999; Widdig

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et al., 2003; Zihl and von Cramon, 1979, 1985). Moreover, even the healthy visual system can be trained to improve (Fine and Jacobs, 2002; Seitz and Watanabe, 2005).

Vision restoration, like most medical or neuropsychological treatment approaches, is not effective in all patients (Kasten et al., 1998; Pambakian and Kennard, 1997). In those patients where the training has an effect, shifts of the visual field border may vary from a few degrees of visual angle (close to or even below the error rate of perimetric tests) (Balliet et al., 1985) to large shifts of up to 20 or even 30 degrees (Zihl and von Cramon, 1979, 1985; Kasten et al., 1998; Poggel et al., 2004) or even beyond that (Werth and Moehrenschlager, 1999). Looking simply at outcome averages over patient samples and visual field regions does not convey a realistic picture because training success varies considerably in extent and visual field localization between patients. To gain insight into the potential for functional plasticity in an individual patient and to be able to identify candidates who would most likely profit from vision restoration treatment it would be desirable to learn more about possible predictors of restoration success (i.e. finding independent variables at baseline that affect training outcome). The predictability of training outcome would help to make an informed decision about the most adequate form of treatment for a given patient (Kerkhoff, 1999; Kasten et al., 1999). Beyond visual field assessment and the perimetric measurement of visual field size which is clearly the major outcome variable, subjective variables and information about activities of daily living have to be taken into account to evaluate training outcome.

Predictors of vision restoration have been partially investigated in previous studies. Kasten et al. (1998) found that the size of areas of residual vision (or transition zones, see Zihl and von Cramon, 1986) was a major factor predicting visual field improvements, but age, sex, size of the visual field defect and time since lesion were found to play no significant role (see also Mueller et al., 2006). The importance of the form of the visual field border between intact and blind areas had already been mentioned by Zihl and von Cramon (1979) in their early training experiments, but so far this has not been quantified. Zihl and von Cramon (1979, 1985, 1986) also reported subjective improvements in their patients, but Balliet et al. (1985) found no relationship between increase of visual field size and the patients' subjective assessment of improvement. While Kasten et al. (1998) reported a strong subjective training effect (72.2% of patients in the treatment group and only 16.6% in the placebo group noticed an improvement), Mueller et al. (2003) found only low correlations between visual field increase and subjective improvement of activities of daily living.

The primary goal of the study presented here was to identify factors that influence the extent of vision restoration and to clarify their relative prediction value as well as interactions amongst them. Secondly, different variables of treatment outcome were examined to test whether the training procedure affected other functions besides perimetric performance, especially neuropsychological performance measures that could be relevant for activities of daily living. Using such a multivariate approach we then created a model for the prediction of training outcome in patients with postgenicular visual field loss which could serve as a guideline for efficacy prediction and help both patients and clinicians to make a decision if treatment should be recommended for individual patients.

2. Methods

Data for the present study were acquired in the context of a training study evaluating the effects of attentional cueing during VRT (Poggel, 2002; Poggel et al., 2004) to which reference is made concerning some methodological details and results for the sake of brevity. Here we report only those results that were not differentially influenced by attentional cueing. This justifies the pooling of data of all patients who participated in the training with and without attentional cueing.

In this section, we will describe the sample characteristics and the methods of measuring visual field parameters, other variables of visual function, attentional functions, and subjective measures. Note that these variables may be used for the prediction of training outcome (i.e. they can be predictor variables), but the same variables may also be outcome variables when measured after the training period. For example, visual reaction times measured before the training may be an indicator of the patient's attentional level and processing speed and act as a predictor for training outcome (e.g. they may influence visual field restoration, subjective training success etc.). On the other hand, the difference between the post-training and pre-training mean reaction times (i.e. the change) can be used as an outcome measure (e.g. to investigate whether light detection training has an effect on reaction time improvement during training). The function of each variable as predictor and/ or outcome variable is described in the respective section of the Results part. An overview of the variables is shown in Table 1.

Table 1
Overview of outcome variables and predictors

Categories	Specific variables
Outcome variables	
Visual field size	HRP: increase of stimulus detection HRP: shift of visual field border Perimetry: decrease of relative defects Perimetry: decrease of absolute defects Perimetry: shift of visual field border Perimetry: decrease of luminance detection thresholds
Visual field related variables (residual & temporal function)	HRP: decrease of reaction time HRP: decrease of areas of residual vision
Form and color vision	HRP: increase of form discrimination HRP: increase of color discrimination
Visual exploration	HRP: decrease of visual search times (intact/ blind field) Stroop Test: decrease of response time in reading AKT: decrease of response time
Visual acuity and contrast	Landolt near acuity Contrast sensitivity for gratings
Visual attention	TAP Alertness TAP Go-Nogo (selective attention) TAP Vigilance Stroop Test AKT Test
Subjective outcome	Rating scales (improvement, everyday life, satisfaction) Interviews (improvement, everyday life, satisfaction) Subjective visual field size maps
Predictors	
Socio-demographic factors	Age Gender
Lesion-related factors	Etiology Location (cortical/ subcortical) Side/ hemisphere (left/ right) Lesion age/ time since lesion
Size and eccentricity of defect	Size of visual field defect before training Position/ eccentricity of visual field border before training
Residual vision/ plasticity factors	Size of areas of residual vision before training Degree of lesion (detection impairment) before training Amount of spontaneous recovery after lesion
Pre-training attention factors	HRP: Reaction time before training TAP Alertness: Reaction time before training TAP Go Nogo: Reaction time before training TAP Vigilance: Reaction time before training Stroop Test: interference before training
Training-related factors	Duration of vision restoration training Number of training sessions Intensity of training

HRP = high-resolution perimetry; TAP = Test Battery of Attention Performance; AKT = Alters-Konzentrations-Test (attention test for the elderly)

2.1. Patient sample

Nineteen patients with homonymous visual field defects after post-genicular lesions participated in a study on restoration of vision (Table 2; see also Poggel, 2002; Poggel et al., 2004 for a detailed description of the experimental protocol and patient sample). Patients below 18 or above 75 years of age were excluded, as well as volunteers with damage to the retina or optic nerve or other ophthalmic disorders, cognitive deficits, impairment of attentional functions (including neglect, as determined by the conventional subtests of the Behavioral Inattention Test, see Wilson et al., 1987), psychiatric disorders, photosensitive epilepsy, or diseases

bearing an obvious risk of progressive visual and/or cognitive impairment (e.g. dementia, multiple sclerosis). Patients were included only if their visual-field size was stable, i.e. if it increased or decreased by less than 2% over a baseline period of at least four weeks before training.

All subjects gave their written informed consent prior to taking part in the study. The design of the trial was approved by the local ethics committee and was in accordance with the Declaration of Helsinki.

2.2. Visual field testing

Visual field size was measured using standard perimetry (Tübingen Automated Perimeter TAP-2000, or Tübingen Electronic Campimeter, TEC) with a 30° threshold test and a 90° (60° for TEC) overview of absolute/ relative defects. Fixation of the eyes was controlled by means of a video camera. Dependent variables extracted from these tests were the number of absolute and relative defects and the position of the visual field border (distance of the visual field border from the vertical meridian).

To determine the amount of spontaneous recovery in an early phase after the onset of blindness, we obtained, wherever possible, copies of visual field test results from that period from the patients' records. Perimetric data could be collected from 14 patients. A variety of perimetric methods had been used, kinetic as well as static perimetry, with different portions of the visual field covered by the test (30°, 60°, or 90°). The time of the first visual field test after the lesion (i.e. lesion age at the time of taking the first perimetric test) differed considerably between patients, and in most cases perimetry was performed only at a later stage, i.e. after the period of spontaneous recovery had already been over. Despite this variability in method, we decided to use these data because, if anything, this variability would count against us and would not introduce a bias in favor of our hypotheses. For those patients where perimetric tests were available during the first six months after lesion (i.e. during the period of spontaneous recovery), we measured the position of the visual field border (distance to the zero-vertical meridian) at 0°, ±5° , ± 10°, and ± 20°. The difference between the visual field border as determined by the early post-lesion perimetry and the perimetry in our pre-training baseline was taken as an estimate for the amount of spontaneous increase of intact field size.

A high-resolution computer-based campimetric test (HRP, Nova Vision, Magdeburg, Germany) was used to assess visual-field size and to determine areas of residual vision (ARVs). Testing of 474 visual field positions with white light stimuli on a dark computer screen was carried out under standardized conditions. The method has been described in detail elsewhere (Poggel, 2002; Poggel et al., 2004). Pilot testing prior to the start of the training study provided the information for adjusting the contrast between stimulus and background in such a way that scatter of light from blind into intact areas was avoided. Fixation was controlled by a central color detection task and by observing the subject's eye position via a mirror. Pre-training baseline examinations were carried out over at least four weeks. Results of five campimetric tests were superimposed, and the detection probability was calculated for each stimulus position. For each patient, the ARV was defined as the area at the visual field border enclosing stimulus positions with a detection probability between 20% and 80%. Tests were repeated after the period of VRT. Dependent variables were the number of detected stimuli in each trial, the reaction times for detected stimuli, and the position of the visual field border measured at 0°, ± 5°, ± 10°, and ± 20° visual angle (measured as the distance from the vertical meridian to the visual field border in degrees of visual angle).

Identification of form stimuli and color discrimination were perimetrically examined with two subtests of the HRP program. Examination procedures were essentially identical to that of the HRP visual field test (see above). In the form test, the stimulus was one of three shapes (square, circle, diamond), and upon identification the subject pressed a response key assigned to that particular shape. Similarly, the patient had to identify and to respond to three different color stimuli (red, green, and blue) in the campimetric color test. Both programs registered detection and identification of each stimulus as well as reaction times. Each test was performed four times during the baseline period before training. Results from the first test were discarded to avoid a possible bias introduced by a learning effect. After training, the patients underwent three repetitions each of the color and form test.

2.3. Saccades/search field

The search field subroutine of HRP was used to assess how fast and how accurately peripheral stimuli are reached by eye movements. Instead of white light dots, the figures "2", "3", or "8", respectively, were presented on the screen simultaneously with an acoustic signal. The patient's task was to search for the stimulus

Table 2
Description of patient sample

	Age	Sex	Lesion age (months)	Side of lesion (hemisphere)	Location of lesion	Cause
1	31	f	18.9	left	Cort. + Rad.	Inf.
2	59	m	31.0	right	Cort. + Rad.	Inf.
3	36	m	12.0	right	Cort. + Rad.	Vasc.
4	39	m	31.0	left	Cort. + Rad.	Inf.
5	36	m	43.4	right	cortical	Inf.
6	67	m	28.0	left	cortical	Inf.
7	40	f	189.9	right	Cort. + Rad.	Inf.
8	60	f	83.2	left	Cort. + Rad.	Inf.
9	20	m	18.3	left	cortical	Inf.
10	61	m	6.8	left	Cortical	Inf.
11	40	f	35.8	left	cortical	Inf.
12	30	f	58.3	right	Cort. + Rad.	TBI
13	33	f	11.8	right	radiatio	Vasc.
14	35	m	17.8	right	radiatio	Vasc.
15	36	f	39.4	right	Cort. + Rad.	Inf.
16	58	m	15.5	left	cortical	Inf.
17	50	m	10.6	left	cortical	Inf.
18	37	m	24.4	right	cortical	Inf.
19	41	m	6.7	left	Cort. + Rad.	Inf.

Group: sex: f = female, m = male; Location of lesion: Cort. + Rad. = cortical and optic radiation; Cause (of lesion): Inf. = infarction, Vasc. = vascular (ruptured aneurysm or aneurysm surgery), TBI = traumatic brain injury.

with eye movements, identify it, and press the response key assigned to the respective stimulus as quickly as possible. Reaction times and correct identification of stimuli were registered by the program. Additionally, qualitative information on eye movement strategies was entered into a protocol by the investigator who observed the subject's fixation behavior in a mirror.

2.4. Visual acuity and contrast vision

Patients were tested monocularly for near-visual acuity with Landolt-stimuli at a distance of $d = 40$ cm (Oculus Nahleseprobe, Oculus Optikgeräte GmbH, Wetzlar, Germany). Additionally, contrast sensitivity was determined at a distance of 40 cm for sine wave gratings of five different spatial frequencies (Series A-E with increasing spatial frequencies; Vistech Consultants Inc., Dayton, Ohio, USA).

2.5. Attentional functions

The computer-based test-battery for attentional performance (TAP; Zimmermann and Fimm, 1995) was applied to examine different attentional functions. In the alertness subtest (TAP Alertness), subjects had to press a key as fast as possible after presentation of a central visual stimulus with vs. without an acoustic cue preceding the visual presentation. Four runs were performed with and without the acoustic cue in an A-B-B-A design. The total test time was approximately five minutes. Reaction times were registered as the dependent variable.

In a subtest of selective visual attention (TAP Go-Nogo), subjects were instructed to press a response button when one of two possible targets was detected in a series of five different, high-contrast visual patterns presented in rapid order over a period of three minutes in the center of the screen, and to inhibit the response to three distracter stimuli. The number of misses and false positives, as well as reaction times, were registered by the program.

Visual vigilance (TAP Vigilanz) was examined by having the subjects observe a light bar moving up and down in irregular intervals over a period of 30 minutes and react by pressing a button at critical upward movements of the stimulus that occurred on average once or twice every minute in random intervals. Misses, false positives, and reaction times were recorded as dependent variables.

In a paper-pencil form of the Stroop test, subjects read color words (black ink on white background) in the first part, named color plates in the second part, and named the color of color words printed in a different ink than was indicated by the word in a third condition (Oswald and Fleischmann, 1997). Time to perform each trial was measured, and the difference between the second and third trial was calculated as a measure of attentional interference.

In a simple paper-pencil visual search test (AKT, Gatterer, 1990), subjects marked target patterns in an array of distracter stimuli (semi-circles in different orientations, subdivided into black and white areas). Time to perform the test and the number of missed stimuli and errors were measured.

2.6. Subjective measures

Before and after the training procedure, patients were interviewed with a semi-structured questionnaire addressing their subjective visual performance and evaluation of the training program. Subjects were asked to describe their current visual symptoms (including the visual field defect, visual illusions, and visual capacity in the intact field) and any changes of visual function observed before or during training, respectively. Other questions in the interview concerned activities of daily living (ADL), in particular reading difficulties and impairment of visually guided navigation. At the end of each interview (i.e. before and after training), the patient gave a quantitative estimate on selected questions from the interview on visual analogue scales in a self-developed questionnaire. Subjects rated how much the visual field defect had improved since the time of lesion, how well they were able to cope with everyday tasks, how much they felt impaired in reading and in navigating, how good the quality of vision was in general, and to what degree they felt that their attentional capacity was reduced. Visual analogue scales ranged from 1 to 10 in arbitrary units, and the end points were marked with verbal statements, e.g. for the question how well the patient was able to cope with ADL, the negative end point was marked "not at all", and the positive end point "extremely well". After the training, patients were also asked to rate if the training had been helpful, how much the visual field defect had decreased subjectively during the training period, and if they had been satisfied with training procedure (see Poggel, 2002, for interview and questionnaire forms in German).

In the results section below, we report data from the patient interviews and subjective ratings of the training effects. Data are either frequency values derived from counting the number of patients who made a specific statement, rating scale values regarding the evaluation of certain training aspects, or original quotations from the interviews that provide a typical view patients expressed on the training and its effects. We followed a purely descriptive approach with respect to the subjective data and refrained from interpretation as far as possible.

Additionally, subjects were asked to create drawings of their visual field defect in a standard template depicting the visual fields of the right and left eye before and after training (see Poggel, 2002; Poggel et al., 2007). Data from the interview were analyzed qualitatively and categorized, and the frequency of selected answers was counted (e.g. the number of patients indicating that training had been helpful) to obtain quantitative data for further statistical analysis. Additionally, raw data from the rating scales were used for statistical analysis. The subjective drawings of the visual field defects were quantified by determining the area of the subjective visual field defect in mm^2.

2.7. Training procedure

The training area was adjusted individually to the patient's visual-field border based on the five HRP-tests used to define the ARVs. The training procedure has been described in detail elsewhere (Poggel, 2002; Poggel et al., 2004). Briefly, training stimuli appeared on a dark computer screen, each target increasing in brightness in four steps from dark gray to bright white over 2000 ms. Stimulus size, fixation control, mode of response, and viewing distance were identical to those used for HRP. Depending on the percentage of stimuli detected, the duration of each training session was approximately 30-35 minutes.

Training was done at home in six training units of 56 sessions each (approximately one month when two sessions per day were performed). Data from each session were saved on a disk, and patients received feedback on the number of stimuli detected after the end of each session. At the end of each training unit, patients returned to the laboratory for control examinations (HRP tests), analysis of training results, and adjustment of the training area to the current visual field border. After the sixth training unit, post-training measurements were performed which were identical to pre-training baseline examinations.

2.8. Data analysis

Data from the left and right hemifields of different patients were collapsed for the comparison between intact and blind field regions.

Data were analyzed using the SPSS program (Version 12, SPSS Inc., Chicago, IL, USA) to perform the Wilcoxon Test, Spearman's Rho correlation, and linear

regression analysis. A two-tailed alpha of 0.05 was applied for all tests with appropriate alpha-adjustment whenever multiple comparisons were made (Bonferroni correction integrated in SPSS).

3. Results

We will first present different outcome variables and the generalization of training effects to various neuropsychological and visual functions. In the second section, we will describe the effects of different independent variables on training outcome. Finally, a regression model is established to connect the sets of independent and dependent variables and predict training outcome based on independent variables.

3.1. Outcome measures

3.1.1. Visual field size

Stimulus detection in the visual field tests (HRP) increased significantly over the period of vision restoration training: Average detection rates in the complete visual field increased from 254.3 ± 3.1 (mean ± S.E.M.) stimuli before to 272.8 ± 6.1 after training ($Z = 3.823$, $p < 0.001$). In terms of absolute numbers, the gain was largest in blind areas (mostly adjacent to the visual field border or ARV) with an average increase of 50.5 detected stimuli (mean difference post-pre training detection in HRP tests, over all patients), as compared to a range of 7.8 to 14.7 stimuli in partially defective areas (between 80% and 20% intact before training). However, this apparently enormous difference disappeared when the size of the blind area and of each ARV region from 20% to 80% intact was taken into account and an improvement index relative to the region size was computed: The ratio of improvement per test location was best in those regions that were 20% intact (improvement index = 1.0), 40% intact (improvement index = 1.1), and 60% intact (improvement index = 1.0), as compared to an index of 0.3 in the blind field.

Moreover, the mean shift of the visual field border towards the blind area (averaged over all measured positions of vertical eccentricity) was highly significant; and the shift at each vertical eccentricity was also significant (see Table 3).

Performance in the fixation task and the number of false positives were used as validation criteria. Fixation was extremely stable; in fact, a slight increase was noted (98.5% correct fixation before vs. 99.3% after training). Although the number of false positives increased after training, detailed analysis showed that this was due to the results of two patients: No. 12 who showed only a slight increase of HRP performance and performed worse on attention parameters after the training period, and No. 8 who showed a massive increase of intact visual field size and had a very large area of residual vision. In both patients, the increased number of "false positives" was an increase of delayed responses – due to attention problems in patient No. 113 and due to delayed detection of stimuli in ARVs in patient No. 109.

Perimetric testing covering the entire visual field (90° for TAP-2000, and 60° for TEC, respectively), i.e. including mainly regions outside the training zone, showed a non-significant decrease of relative and absolute defects in both eyes. In contrast, perimetry of the central 30° mostly included the trained visual field areas and showed a significant decrease of the number of absolute defects (Right eye pre-training: 54.3 ± 4.4, post-training: 51.2 ± 5.0; Wilcoxon Test: $Z = 2.618$; $p = 0.009$; Left eye pre-training: 57.5 ± 5.2, post-training: 52.3 ± 5.4; Wilcoxon Test: $Z = 2.402$; $p = 0.016$). The decrease of relative defects did not reach significance, however. The average shift of the visual field border in perimetric results was highly significant, and the shift at almost all eccentricities was significant or close to significance (Table 3).

Luminance detection thresholds in 30°-perimetry tests showed a highly significant overall increase in the ARV of both eyes combined (mean luminance detection threshold before training: 14.9 dB ± 0.3 dB, after training: 18.3 dB ± 0.2 dB, Wilcoxon Test: $Z = 11.280$; $p < 0.001$). The same was true for each eye separately (OD_{pre}: 14.7 ± 0.4 dB; OD_{post}: 17.6 ± 0.3 dB; $Z = 8.878$; $p < 0.001$; OS_{pre}: 15.1 ± 0.4; OS_{post}: 19.0 ± 0.3; $Z = 6.958$; $p < 0.001$)

3.1.2. Other visual field related variables

Reaction times in HRP tests decreased, i.e. patients reacted faster to light stimuli after training, especially within the ARVs (mean RT ± S.E.M.; before training: 509.6 ms ± 10.4 ms; after training: 460.8 ms ± 8.6 ms; Wilcoxon Test: $Z = 3.300$; $p = 0.001$). The size of the ARV increased significantly during training (mean size in number of stimulus positions (± S.E.M.) before training: 32.9 ± 5.2; after training: 41.4 ± 6.5; Wilcoxon Test: $Z = 2.156$; $p = 0.031$).

Table 3
Shift of visual field border in horizontal degrees of visual angle at different vertical eccentricity positions (single positions and averaged over all eccentricities) in HRP and conventional perimetry within 30° visual angle. Perimetric results are presented only for the right eye (OD) because visual field loss was homonymous in all patients and results of the left and right eye comparable.

Position of measurement (vert. ecc., deg. vis. angle)	HRP			Perimetry OD 30°		
	Position of visual field border (deg)		Wilcoxon - Test Z p	Position of visual field border (deg)		Wilcoxon-Test Z p
	before training	after training		before training	after training	
+20	3.97	5.38	2.744	6.55	9.72	2.510
	± 0.90	± 1.39	0.006	± 1.48	± 1.88	0.012
+10	3.07	3.77	2.582	6.71	8.18	2.629
	± 0.66	± 0.90	0.010	± 1.68	± 1.75	0.009
+5	2.94	3.79	2.734	7.01	7.88	1.649
	± 0.70	± 1.00	0.006	± 1.57	± 1.74	0.099
0	3.92	4.61	2.513	9.06	9.72	1.376
	± 0.83	±1.04	0.012	± 1.80	± 1.89	0.169
−5	4.07	6.16	3.130	9.37	10.23	0.454
	± 0.88	± 1.35	0.002	± 1.86	± 2.12	0.650
−10	4.02	6.10	3.223	8.58	10.15	1.889
	± 0.77	± 1.17	0.001	± 1.65	± 1.90	0.059
−20	4.22	6.17	3.724	8.72	9.28	1.399
	± 1.05	± 1.19	< 0.001	± 1.65	± 1.90	0.059
MEAN	3.74	5.14	3.823	8.00	9.31	2.878
	± 0.62	± 0.88	< 0.001	± 1.26	± 1.43	0.004

3.1.3. Form recognition and color discrimination

In the campimetric form test, the number of correctly identified stimuli remained almost constant over the training period (Table 4). However, the number of incorrectly detected stimuli increased significantly while the number of null responses (no reaction to a stimulus) decreased. Moreover, reaction times for all trials as well as for correctly identified stimuli were significantly faster after training.

Likewise, there was no improvement in the number of correctly identified color stimuli in the HRP color campimetric test, but again, we observed a highly significant increase of incorrectly identified stimuli, i.e. the detection performance improved markedly. In addition, a highly significant decrease of null reactions and faster reaction times was noted after training (Table 4).

3.1.4. Visual exploration

In the HRP search field test, overall saccadic search times became significantly faster (see Table 5). This improvement was mainly due to a significant decrease of reaction times to stimuli presented in the *intact* visual field, but there was also an acceleration of visual search in the blind areas that just missed significance. However, the difference of reaction times between the blind and the intact visual field areas did not change during treatment, i.e. search in the blind field did not become disproportionately better as compared to the intact field. Qualitatively, we observed more efficient and target-directed search patterns after training, i.e. after the presence of the target had been indicated by the acoustic signal, many patients were able to make saccades directly toward the stimulus without systematically searching the blind visual field region (see Poggel, 2002).

The paper-pencil tests also provided evidence of improved visual exploration. In the first condition of the Stroop-test (reading of color words), performance improved significantly (see Table 5).

3.1.5. Visual acuity and contrast sensitivity

Visual acuity in both eyes remained unchanged after training. Contrast sensitivity did not change for coarse grating stimuli (i.e. with a lower spatial frequency, test pattern series A-C), but there was a trend towards improvement of contrast sensitivity for gratings with a higher spatial frequency ("D" series; Table 5).

3.1.6. Visual attention

In the computer-based alertness test (TAP Alertness) reaction times improved slightly, but not significantly (Table 5). In the selective attention subtest of the TAP (Go-Nogo), choice reaction time decreased highly significantly (Table 5). The vigilance subtest of the TAP showed a significant decrease of reaction times (Table 5). In none of the TAP subtests there was a significant change of the number of errors. In the Stroop-test, attentional interference was reduced, i.e. the difference

Table 4
Effect of VRT on perimetric form recognition and color discrimination

Parameter Mean ± S.E.M.	Form test before training	Form test after training	Form test Wilcoxon-Test Z p	Color test before training	Color test after training	Color test Wilcoxon-Test Z p
Number of detected stimuli (all trials)	143.9 ± 3.2	146.3 ± 3.4	0.362 0.717	145.2 ± 3.1	150.1 ± 4.09	1.449 0.147
Reaction time (all trials)	799 ± 19	744 ± 20	3.421 0.001	792 ± 18	753 ± 20	2.736 0.006
Null reactions	121.4 ± 2.8	111.8 ± 4.2	3.354 0.001	124.9 ± 2.6	114.4 ± 4.2	3.461 0.001

Table 5
Effect of VRT on visual exploration, acuity, and attention

Performance measure	Before training Mean ± S.E.M.	After training Mean ± S.E.M.	Wilcoxon Test Z	Signi-ficance p
Search field test complete field (RT in ms)	1029 ± 32	972 ± 35	2.093	0.036
Search field test intact field (RT in ms)	863 ± 34	801 ± 28	2.535	0.011
Search field test blind field (RT in ms)	1191 ± 33	1141 ± 45	1.650	0.099
Stroop reading (RT in s)	16.1 ± 1.3	14.4 ± 1.1	2.126	0.034
AKT (mean over 3 trials, RT in s)	27.0 ± 2.0	26.2 ± 1.8	1.007	0.314
Contrast "D" series right eye (number of correctly identified targets)	3.5 ± 0.6	4.5 ± 0.6	2.219	0.026
Contrast "D" series left eye (number of correctly identified targets)	3.7 ± 0.5	4.5 ± 0.5	2.581	0.010
TAP Alertness (mean over 4 trials, RT in ms)	237 ± 9	231 ± 8	1.288	0.198
TAP Go-Nogo (RT in ms)	563 ± 28	496 ± 15	3.783	< 0.001
TAP Vigilance (RT in ms)	528 ± 25	497 ± 24	2.012	0.044
Stroop interference (RT in s)	13.6 ±1.5	10.4 ±1.2	2.166	0.030

of performance times between the third and second test condition became significantly smaller over the course of training (Table 5).

3.1.7. Subjective outcome

In the post-training interviews, eleven patients (58%) described the training as generally helpful while five patients (26%) stated that the treatment had not helped them. Three patients (16%) were undecided or did not comment. Moreover, eleven patients (58%) - not in all cases the same subjects who had rated the training as helpful with regard to improvement of visual functions - reported that they had been content with the training procedure, only two (11%) had not been content.

The variability in the patients' qualitative descriptions of visual field improvement was large: statements ranged from generalized descriptions of visual field increase (e.g. "a better overview") or a direction where the field of vision was perceived as expanded or less limited after the treatment (e.g. "to the left", "in the upper right quadrant") to detailed reports where in their visual field a change had taken place. However, quantitative measures of visual field size did not always correspond with the subjective statements the patients made. Closer analysis showed that the evaluation of improvement depended on the location of visual field increase: even small shifts of the visual field border in the centre were experienced as a large benefit, but shifts of equal or even greater size in the periphery of the visual field remained unnoticed (see Poggel, 2002; Poggel et al., 2007).

From the patients' perspective, the training had beneficial effects on everyday life (as indicated by their statements in the post-treatment interviews). Seven patients (38%) stated that they felt much more secure in traffic situations, either as a pedestrian, riding a bike, or driving a car. Seven subjects (38%) indicated that reading had become easier, i.e. the speed and fluency of reading had increased, reading was less effortful and was experienced as more relaxing and enjoyable. Fourteen subjects (74%) mentioned that they had improved in visually-guided navigation, i.e. they felt safer in traffic situations, collided less frequently with people or objects hidden in their blind fields, and were more efficient in visual search tasks. Seven subjects (38%) had noticed an improvement with respect to visual attention and selection of relevant information from complex visual scenes.

In the interviews before the control measurements during the training phase and in the final interview after

training, patients stated that progress took place mainly in the first part of the treatment period, i.e. in the first three months. In this early stage of treatment, patients also spontaneously reported effects on everyday life in the monthly interviews and remarked that visual perception became more salient and reliable in the regained areas of the visual field.

The subjective size of the blind area as depicted in the patients' drawings decreased over the training period (mean size of subjectively blind area ($\pm$ S.E.M.) right eye: before training: 2466 mm^2 $\pm$ 412; after training: 2210 mm^2 $\pm$ 343 Wilcoxon Test: $Z = 1.112$; $p = 0.266$; left eye: before training: 2793 mm^2 $\pm$ 272; after training: 2273 mm^2 $\pm$ 274; $Z = 2.012$; $p = 0.044$). Those patients who had regained so much of their visual field that they were able to notice a difference to the pre-training status were also able to draw the location of improvement with relatively high topographical exactness, although central parts which recovered were somewhat larger in the subjective representation of change than in "reality" (i.e. perimetric measurements; see Poggel et al., 2007).

3.2. Predictors

3.2.1. Socio-demographic variables

Unexpectedly, the patient's age was significantly and positively correlated with the improvement of stimulus detection in the HRP visual field test (Spearman's Rho $= 0.524$; $p = 0.021$) and also with the average shift of the visual field border (Rho $= 0.500$; $p = 0.029$). Similarly, the patient's age correlated negatively with the decrease of null responses in the form recognition (Rho $= -0.337$; $p = 0.158$) and color discrimination (Rho $= -0.495$; $p = 0.031$); i.e. improvement on these outcome variables was better with increasing age. This effect could not be explained by a higher number of training sessions or a higher training density (number of training session per time unit), or the size of ARVs in older participants as compared to younger patients.

There were no significant differences between male and female patients with regards to any of the visual or attentional outcome variables (see section on outcome variables above).

3.2.2. Lesion-related variables

Patients with stroke did not show a different training outcome from that of patients with vascular malformations/aneurysm surgery (results from only one trauma patient could not be statistically compared to the other two groups). The side of the brain lesion had no significant effect on training outcome, although patients with damage to the left hemisphere of the brain showed a non-significantly larger benefit on some outcome variables.

The lesion age had no predictive value for treatment results. The correlation values of time since lesion (= lesion age) with important outcome variables, e.g. improvement of stimulus detection in HRP (Spearman's Rho: $\rho = 0.11$; $p = 0.652$), improvement of reaction times ($\rho = 0.219$; $p = 0.369$), and with the average shift of the visual field border ($\rho = -0.102$; $p = 0.678$), respectively, were low and did not reach significance; nor were there any other substantial or significant correlations with other visual, attentional, or subjective outcome variables.

3.2.3. Size and eccentricity of visual field defect

Perimetric threshold measurements (TAP, TEC) within the 30°-area showed that the pre-training number of absolute defects was negatively correlated with increase of visual field size in HRP, i.e. the smaller the visual field defect as determined by central perimetric measurement before training, the more pronounced the increase (right eye: $\rho = -0.544$; $p = 0.016$; left eye: $\rho = -0.639$; $p = 0.004$). Similarly, the number of absolute defects in 30° perimetry correlated significantly with the shift of the visual field border as measured by HRP (right eye: $\rho = -0.499$, $p = 0.030$; left eye: $\rho = -0.563$, $p = 0.015$). We found no significant correlation for the lower resolution perimetric tests of the entire visual field (60° TEC, 90° TAP). The initial size of the intact visual field area as measured by HRP (number of detected stimuli before training) was not significantly correlated with the increase of detection performance after training ($\rho = 0.186$, $p = 0.446$) or with the shift of visual field borders as measured by HRP ($\rho = 0.240$, $p = 0.322$).

The original mean position of the visual field border (i.e. the eccentricity of the visual field defect before training) had some predictive value for the improvement of HRP stimulus detection performance, just missing significance ($\rho = 0.363$, $p = 0.063$). More specifically, the pre-training position of the visual field border at a particular vertical eccentricity in the HRP test ($\pm$ 20°, $\pm$ 10°, $\pm$ 5°, and 0° vertical eccentricity, respectively) was correlated with the shift of the visual field border at that specific eccentricity. For example, the more peripheral the visual field border at 10° above the fixation point, the larger the shift of the defect border at 10° ($\rho = 0.415$, $p = 0.038$).

3.2.4. Residual vision/ Indicators of neuronal plasticity

The size of the area of residual vision (ARV) as determined by HRP was significantly correlated with many outcome variables. In fact, this factor was the most general and also most important predictor of successful restoration of function. The larger the ARV before training, the more pronounced the improvement of stimulus detection in HRP ($\rho = 0.684$; $p = 0.001$) and the greater the shift of the visual field border ($\rho = 0.457$; $p = 0.049$). Patients with a larger ARV before training tended to show a more pronounced decrease of null reactions in the campimetric tests of form recognition ($\rho = -0.438$; $p = 0.061$), for the color discrimination test this was significant ($\rho = -0.580$; $p = 0.009$). In standard perimetry, the correlation between the size of the ARV and the decrease of absolute/ relative defects was in the range of $\rho = 0.4$ to $\rho = 0.5$, but did not become significant.

A more detailed analysis revealed that there was a topographically specific effect of the ARV on functional improvement. The size of the ARV in the upper visual field before VRT was substantially correlated with the improvement of stimulus detection in that area ($\rho = 0.636$; $p = 0.003$). This was confirmed by correlations between the local size of ARVs and the extent of visual border shift at that specific location: the larger the ARV in the upper visual field, the more pronounced was the shift of the upper visual field border in HRP (+20° vertical eccentricity: $\rho = 0.475$; $p = 0.040$; +10°: $\rho = 0.741$; $p < 0.001$; +5°: $\rho = 0.521$; $p = 0.022$); while in the lower visual field, ARV size influenced the shift of the visual field border specifically in the lower hemifield (-5° vertical eccentricity: $\rho = 0.444$; $p = 0.057$; -10°: $\rho = 0.297$; $p = 0.217$; -20°: $\rho = 0.499$; $p = 0.030$). However, the size of ARVs in the upper visual field did not predict improvement in the lower visual field and vice versa. This topographic specificity was also observed for the color and form tests (see Poggel, 2002 for detailed results).

Spontaneous increase of visual field size after lesion (which could be a general indicator for the brain's capability for functional recovery), as determined by a very limited set of perimetric data measured with different techniques before study entry (see Methods section), was not correlated with training-induced recovery.

3.2.5. Attention level before training

The average reaction time in pre-training HRP testing did not affect any measure of improvement of stimulus detection performance, but outcome variables related to attention and processing speed were correlated with this predictor. Patients who had reacted faster to simple white light stimuli in HRP before training showed a more pronounced improvement of reaction times in HRP over the training period (Table 6).

Consistent with these findings, we observed that pre-training reaction times in the TAP Alertness test were significantly correlated with improvement of response speed in HRP (Table 6). However, similar effects on reaction time improvement could not be confirmed for the vigilance test (Table 6). Neither the pre-training performance in the alertness nor in the vigilance test had any predictive value for the improvement of stimulus detection performance.

Although we had hypothesized that attentional interference as measured by the Stroop-test would be negatively correlated with improvements of stimulus detection, HRP performance increased more strongly in patients with high levels of pre-training interference ($\rho = 0.514$; $p = 0.024$). Similarly, the average shift of the visual field border was larger in patients with higher interference scores before VRT ($\rho = 0.646$; $p = 0.003$).

3.2.6. Training-related variables

Total duration of the therapy did not influence training success, and the total number of training sessions was not correlated significantly with any outcome variables. However, when the intensity of the training, defined as the total number of training sessions divided by the total duration of the training period, was taken into account, there was some correlation with training-induced improvement of visual performance. The correlation of training intensity with the average shift of the visual field border in HRP amounted to 0.327, but this did not reach significance ($p = 0.172$). Similarly, correlations between training intensity and border shifts as determined by perimetry were in the medium range but with a statistical trend only (0° eccentricity: $\rho = 0.421$; $p = 0.072$; -20°: $\rho = 0.372$; $p = 0.116$; +20°: $\rho = 0.388$; $p = 0.100$).

3.3. Regression analysis

3.3.1. Multivariate prediction of specific outcome variables

For a selection of the most important outcome variables, we performed a regression analysis using the main predictors of training outcome (variables on interval level of measurement only) and determined linear regression equations for each outcome variables us-

Table 6
Correlations of pre-training reaction time levels with outcome variables in HRP visual field tests (stimulus detection and reaction time).

		HRP Mean RT before training	TAP Alertness Mean RT before training	TAP Vigilanz Mean RT before training
HRP Improvement of stimulus detection pre vs. post training	Spearman's Rho	−0.54	−0.204	−0.037
	p (2-tailed)	0.828	0.401	0.881
HRP Improvement of reaction time pre vs. post training	Spearman's Rho	−0.504	−0.614	−0.104
	p (2-tailed)	0.028	0.005	0.673

ing the beta weights for each predictor. Table 7 lists the R^2 values for a selection of predictors with respect to different outcome variables. Note that all predictor variables were measured at the pre-training baseline or are directly associated with the training procedure (e.g. number of training sessions). All outcome variables are difference values of performance before vs. after training or post-training baseline measures. Specifically, the variables were as follows:

a) *Improvement of stimulus detection in HRP*
$\mathrm{Pred}_{\mathrm{HRP\ improvement}}$ = 0.524*(age) + 0.060*(time since lesion) − 0.455*(size of defect) − 0.215*(eccentricity of defect) + 0.443*(size ARV) − 0.192*(HRP reaction time) − 0.005*(Alertness reaction time) − 0.364*(Vigilance reaction time) + 0.089*(Stroop interference) + 0.120*(number of training sessions) − 0.009*(training intensity)

b) *Improvement of stimulus detection in perimetry* (*average OD and OS, absolute defects*)
$\mathrm{Pred}_{\mathrm{Perimetry\ improvement}}$ = 0.411* (age) − 0.202* (time since lesion) − 0.110*(size of defect) + 0.156*(eccentricity of defect) + 0.181*(size of ARV) + 0.040*(HRP reaction time) − 0.260*(Alertness reaction time) − 0.390*(GoNogo reaction time) − 0.002*(vigilance reaction time) + 0.286(Stroop interference) − 0.136*(AKT reaction time) − 0.073*(number of training sessions) − 0.029*(training intensity)

c) *Improvement of reaction times in HRP*
$\mathrm{Pred}_{\mathrm{HRP\ reaction\ times}}$ = 0.228*(age) + 0.222*(time since lesion) − 0.155*(size of defect) + 0.250*(eccentricity of defect) + 0.034*(size of ARV) − 0.655*(HRP reaction time) − 0.282*(Alertness reaction time) − 0.390*(GoNogo reaction time) − 0.092*(Vigilance reaction time) − 0.228*(Stroop interference) − 0.343*(AKT reaction time) − 0.251*(number of training sessions) − 0.136*(training intensity)

Using all predictors available in this study, training outcome as measured by HRP detection performance could be almost perfectly predicted (R^2 = 0.925). Fig. 1a shows the scatter plot for this multivariate prediction of visual field enlargement. With the same set of predictors, the variance of perimetric improvement (decrease of the number of absolute defects) could be explained to a large degree (R^2 = 0.820); Fig. 1b shows the scatter plot for this outcome variable.

The improvement of reaction times in HRP could also be accurately predicted based on the full set of variables (R^2 = 0.929, Fig. 1c). For this outcome variable the weight of predictors related to speed of processing (e.g. pre-training average reaction time in HRP, reaction times in the TAP subtest, Stroop interference) was considerably larger than for the prediction of increased detection performance (see also Table 6). However, the variables used to predict these objective variables of improvement did not predict the subjective evaluation of the training as helpful or satisfactory in an equally reliable manner (helpfulness: R^2 = 0.688; satisfaction: R^2 = 0.559).

3.3.2. Prediction of visual field increase with a set of variables available in clinical settings

While the "near-perfect" prediction of different outcome variables is theoretically desirable to explain mechanisms and interactions determining a successful restoration of visual functions, in a clinical setting, a more practical approach would be useful so that training outcome would be predictable with sufficient reliability based on a set of variables that are readily available during pre-training examinations. We used the age of the patient, the time since lesion, the average number of absolute perimetric defects (left and right eye combined), the average eccentricity of the visual field border in standard perimetry and in HRP, the size of the ARV, and the average reaction time in HRP tests as predictors for increased detection performance in HRP. The variance explained by this set of predictors was

Table 7
R^2 values for combinations of predictors and outcome variables

Predictor	Outcome					
	HRP detection gains	HRP detection gains	HRP border shift	HRP reaction times gains	Interview: Subjective help gains	Interview: Satisfaction
Age of patient	0.404**	0.169	0.107	0.052	0.023	0.012
Time since lesion	0.009	0.041	0.003	0.049	0.031	0.004
Size of blind area	0.361**	0.012	0.291*	0.024	0.028	0.035
Eccentricity of blind area	0.284*	0.024	0.069	0.063	0.015	0.021
Size of ARV	0.196*	0.033	0.227*	0.001	0.041	0.014
HRP reaction time	0.037	0.002	0.010	0.430**	0.094	0.000
Alertness test reaction time	0.000	0.068	0.003	0.079	0.027	0.053
Go-Nogo reaction time	0.005	0.152	0.011	0.152	0.153	0.028
Vigilance reaction time	0.061	0.000	0.000	0.009	0.160	0.008
Stroop interference	0.086	0.082	0.163	0.052	0.031	0.002
AKT reaction time	0.008	0.019	0.038	0.118	0.058	0.012
Number of training sessions	0.013	0.005	0.040	0.063	0.000	0.055
Training intensity	0.015	0.001	0.105	0.019	0.002	0.024

$R^2 = 0.794$ (see also Fig. 2). This is shown in the following equation:

$\text{Pred}_{\text{HRP improvement}} = 0.323$*(age) $- 0.454$*(time since lesion) $- 0.012$*(absolute defects perimetry) +3.059*(eccentricity visual field border perimetry) $- 2.527$*(eccentricity visual field border HRP) $+ 0.394$*(size ARV) $- 0.057$*(HRP reaction time)

When using only this limited set of predictors, the clinician can extract the variables from the available patient data in a short time, enter the specific values for a patient into some commonly available software for spreadsheet calculation, and obtain as a result of this computation the expected increase of overall HRP detection performance within minutes. This would indicate the approximate number of stimuli in HRP testing that a patient with a post-geniculate lesion of the visual system would gain over a training period, provided that the training is comparable in its duration and intensity to the settings described here. For other lesion locations and types as well as for other training regimes, other formulae would have to be established to get a valid prediction of visual field increase. Note that this equation does not predict the location where the improvement is likely to occur. This would require a detailed topographic analysis as indicated above and in another study on VRT.

4. Discussion

The results and predictor models presented here are necessarily limited to patients with post-genicular visual system lesions because our sample consisted exclusively of such patients. While it is possible that training outcomes and predictor relationships might be generalized from our sample to other types of visual system lesions (e.g. damage to the optic nerve), the specific pattern of outcome and predictor variables should first be investigated in those populations before a valid prediction of training success is possible.

Another factor that may limit the generalization of our results to the population of patients with post-genicular visual system lesions is the relatively small sample size. However, the replication of training effects shown in earlier studies and the stable predictor structure we found in our patient data speak for the good predictive value and for the usefulness of our results for other patients.

4.1. Outcome measures

Vision restoration training significantly improved light detection in standard perimetric tests but also detection performance in high-resolution computer-based campimetric measurements (HRP) in patients with post-genicular visual system lesions. The extent of the training effect was comparable to that achieved in patients with post-genicular lesions in an earlier placebo-controlled training study with a similar training regime and patient sample (Kasten et al., 1998) and in the range of other studies on vision restoration using different methods and patient populations (e.g. Wüst, 1997; Zihl and von Cramon, 1985; Zihl and von Cramon, 1986). In the study reported here, a visuo-spatial cue was integrated into the conventional VRT procedure to investigate effects of attention on vision restoration (Poggel et al., 2004). Since the effects of the attention cue were local in nature, the results of patients who trained with and without the cue were collapsed when calculating the results.

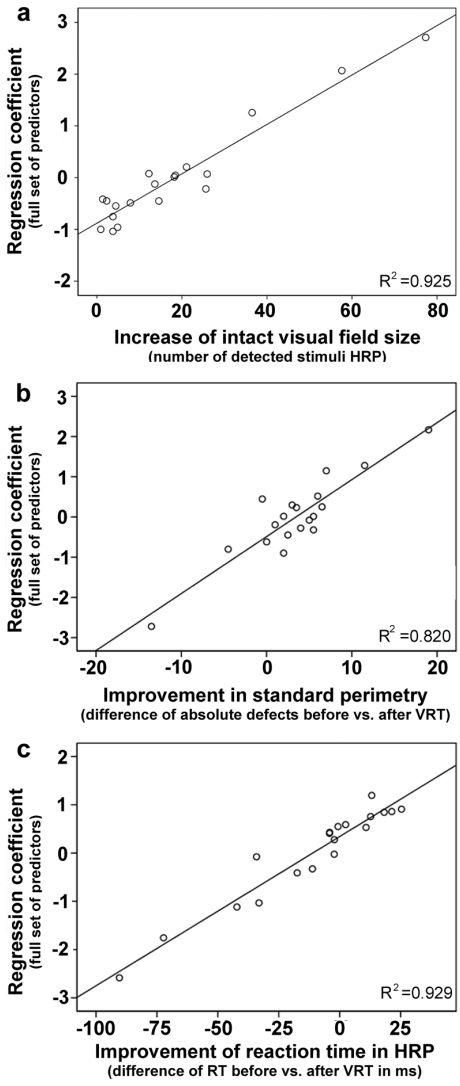

Fig. 1. Scatter plots and regression lines for main outcome variables (stimulus detection in HRP and standard perimetry, reaction times in HRP) using all available predictors. Each point in the scatter plots shows results of one patient in the sample. Individual R^2-values were determined according to the regression models detailed in the text.

Improvement of light detection performance progressed systematically and in a topographically predictable manner: vision was improved mainly along the visual field border, and we did not observe a spatially diffuse increase of detection performance that would have been predicted by a general change of the patient's reaction criterion. The increased performance in visual field tests could not be explained by the patient's error rate because it remained constant throughout the training period. The amount as well as the location of visual field increase during VRT could be predicted to a large extent by the size and location of areas of residual vision (ARV).

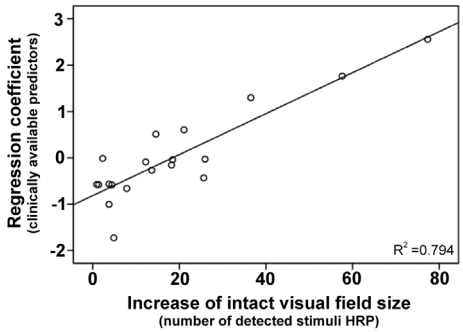

Fig. 2. Scatter plot and regression line of clinically available set of variables predicting visual field increase as measured by HRP detection performance. Each point in the scatter plot shows the result of one patient in the sample. Individual R^2-values were determined according to the regression model detailed in the text.

The topography of the border shift was in accordance with the expectation of visual field increase based upon the architecture of the visual cortex: the pattern of recovery we found in our patients can be explained by the cortical magnification factor, but it could not be easily achieved by eye movements (Poggel et al., 2004; Poggel et al., 2007) because eye movements (or peripheral fixation, respectively) would result in either a parallel shift of the visual field border towards the blind field or a larger (though artefactual) "improvement" in the center which can be monitored much better with small saccades. Clearly, a limitation of this study is the absence of "objective" eye tracker data. However, the characteristics of recovery as described above and the similarity of our data with other studies which included eye-tracking (Kasten et al., 2006) suggest that the effects reported here cannot be regarded as an artifact of eye movements or eccentric fixation. Improvements of detection were slow and gradual; they systematically progressed from slightly impaired to more severely impaired regions at the visual field border. Such a pattern of recovery would be almost impossible to "simulate" by a criterion change or modification of saccadic eye movements.

Training effects partly generalized to other performance variables beyond simple light detection improvement: visual exploration became faster in computer-based and paper-pencil tasks after VRT. On the one hand, this means that the continued demand to keep fixation constant throughout the training did not have any negative effects on visual exploration. On the other hand, the fact that the patients' saccades into the blind field were more often directly aimed at the stimu-

lus may be an indicator of improved unconscious residual vision, e.g. blindsight (Stoerig and Cowey, 2007) or Riddoch phenomena (Schoenfeld et al., 2002). Measures of visual attention (particularly selective attention and vigilance) also improved. Recently, it has been shown that specific training of attentional functions results in plastic changes in the underlying functional architecture of the brain (Sturm et al., 2005; Thimm et al., 2005). The improvement of selective attention and vigilance in our study may be a positive "side effect" of the training procedure because VRT requires constant and high levels of attention especially on these dimensions. From the patients' verbal descriptions as well as based on improvements in attention tests measuring interference (e.g. the Stroop test), it appears that the signal-to-noise ratio was enhanced during the training phase and thus training resulted in more stable and reliable percepts than were possible before treatment.

Simple reaction times (RT) became significantly faster, e.g. in the HRP test across the entire visual field or for a centrally presented visual stimulus in the TAP Alertness test. RTs do not only reflect the duration of visual information processing, but also the motor component of the response. Since patients started the training well after the phase of spontaneous recovery, the influence of any (spontaneous) motor improvement on RTs during treatment should have been negligible. Therefore we hypothesize that VRT improved the speed of visual information processing, which is also confirmed by other reports from our laboratory (Mueller et al., 2003; Sabel et al., 2004). While an influence of the motor component cannot be fully excluded based on our study design, a spontaneous decrease of motor RTs could certainly not explain the topographically selective improvement of RTs in ARVs along the visual field border.

In contrast, VRT did not induce improvement of higher-order visual functions like color recognition or form discrimination. This is in contrast also to previous findings from our group showing a generalization to these variables (Kasten et al., 2000) and to earlier reports from Zihl and von Cramon (1985) with saccadic localization training. In the present study, the psychophysical parameters of testing were more rigorously controlled so that it was not possible to discriminate between the color or form stimuli based on contrast or size differences. We therefore suggest that higher-order visual functions need to be addressed by specific training procedures activating not just the basic (i.e. light detection) but the more complex (color perception, form recognition) functions of the visual system. In fact, Kasten et al. (2000) showed that specific color or form training had a more pronounced effect on performance in color and form discrimination than simple light detection training.

Although the training procedure required stable fixation throughout the training sessions, visual search in the blind as well as in the intact field did not deteriorate but became faster and more efficient over the training period, an effect that has also been found in another study on VRT outcome (Mueller et al., 2002). The difference between pre- and post-training performance in the AKT did not reach significance because of a ceiling effect, i.e. patients had already shown very good performance before training. Hence, although VRT – in contrast to compensatory training programs for partially blind patients (Kerkhoff, 1999) – does not aim at improving saccadic exploration it does not lead to the loss of explorative abilities either which has been a concern of clinicians.

There was no noticeable improvement of visual acuity or contrast after VRT. In fact, for patients with postgeniculate lesions as in the present study, increased visual acuity was not to be expected (Kasten et al., 1998). Such a result should be more common in patients with diffuse visual field defects induced by lesions anterior to the optic chiasma (Wüst, 1997; Wüst et al., 2004) because vision would become clearer if the widespread, especially central, partial defects would be turned into intact areas.

Both, the spatial specificity (improvement in ARVs along the visual field border) and the functional specificity (improvement of white light detection but hardly any generalization beyond that) suggest that the training-induced plasticity takes place in the primary visual cortex, possibly in combination with the thalamus (lateral geniculate). More specifically, partially defective areas at the lesion border representing ARVs may be reactivated or hyperactivated by the systematic stimulation during VRT. With the present set of predictor variables which mainly rely on behavioral observations and some information from the patient files, it is difficult to elucidate the exact location of plastic processes in the brain and the role of partially intact neural tissue in recovery (Werth and Seelos, 2005; Sabel, 1997). While it is very likely that the existence of functional brain tissue in the visual pathway would have some predictive value for training success, this could only be determined with relatively elaborate methods of neuroimaging, e.g. functional MRI. Rather, the goal of our study was to provide a set of predictor variables of immediate practical value that are easy to obtain from

the patient file and behavioral tests with low technical demands. Potential neuronal mechanisms underlying the training-induced restoration of visual functions have been discussed in detail elsewhere (Chino et al., 1995; Eysel et al., 1999; Sabel, 1997, 1999).

The majority of patients rated the training as helpful, and they were content with the procedure. While we cannot fully exclude the possibility that the patient testimonials may have been biased by different motivations, e.g. pleasing the experimenter, or regarding the training as positive because of the high investment of time and effort and the hope of getting help from the procedure, the subjective rating was overall in accordance with training success as measured by visual field tests. Those patients who experienced an improvement were able to describe and draw the changes accurately (Poggel et al. 2007), weighted by the functional importance of different visual field regions. The dependence of noticing the visual field increase on the eccentricity of the improvement had been reported earlier by Zihl and von Cramon (1985). Although subjective and objective training outcome were not perfectly matching, the correlation between both measures in the study reported here was much higher than those previously described (Mueller et al., 2003). The patients in the study by Mueller et al. (2003) were examined retrospectively, the sample was more heterogeneous with respect to visual field loss and possible cognitive impairment (exclusion criteria were less rigorous than in the present study), and the subjective evaluation of training outcome was based exclusively on questions from an interview. Therefore, the relationship between subjective and objective treatment outcome may have been more difficult to determine than in the prospective study reported here. Further investigations with patients with different types of lesions and visual field loss will have to be carried out to test whether our results can be generalized to populations other than the patients with post-geniculate visual system lesions reported here.

The patients' descriptions of training effects on activities of daily life was realistic given the size of the regained area. Thus, although the subjective evaluation of the training procedure alone is not necessarily a valid (but nevertheless important!) indicator of training outcome, the good correlation of objective and subjective outcome measures points at a close relationship between these variables in our sample.

4.2. Predictors

Early concepts of visual system plasticity stated that reorganization is limited to sensitive periods early in life (Hubel and Wiesel, 1970, see Boothe et al., 1985 for a review). However, more recent evidence suggests that the visual system retains a lifelong ability to reorganize and that its architecture is constantly shaped by experience (e.g. Fahle, 2005; Levi, 2005; Sagi and Tanne, 1994). Theories of aging of the nervous systems unanimously state a reduced capacity of the brain to repair and adapt to new situations with increasing age (Godde et al., 2002; Sowell et al., 2004). However, our results did not show such a limitation, because older patients actually profited even more from the training than younger ones. Similarly, Zihl and von Cramon (1985) did not observe any effect of patient age, and Mueller et al. (2007) showed better results in patients over 65 years of age. With the present data, this effect cannot be fully explained, but we speculate that there may be more complex interactions between the visual system and attentional networks in the brain so that training effects may be caused by slightly different mechanisms in younger and older subjects.

After brain lesions, the initiation of treatment as early as possible is considered essential, especially to avoid secondary functional impairment or maladaptive behavior induced by the lesion and by the primary loss of function. While this is certainly true for the acute post-lesion phase (which we could not study in our experiment due to the exclusion of spontaneous recovery early after the onset of partial blindness), our results suggest that the visual brain does not lose the capacity to recover once spontaneous plasticity is complete and the visual field defect has become chronic. Our data confirmed Zihl and von Cramon's (1985) and Mueller et al.'s (2007) earlier observations who did not find a correlation of visual field increase with time since lesion. Thus, VRT can be equally successful at any time after lesion, even decades after the incident that caused the blindness.

None of the other socio-demographic or lesion-related variables assessed in our study reliably correlated with training outcome. Similarly, Zihl & von Cramon (1985) did not find an effect of gender on visual field increase. Thus, it seems that visual system plasticity is a more general and more permanent capacity of the brain than had been previously assumed.

Indeed, the main factors predicting training outcome were indicators of the general level of function rather than demographic characteristics of a patient. Residual visual function, i.e. the presence of ARVs, is the main and most reliable predictor of training success (see also Kasten et al., 1998; Mueller et al., 2002; Sabel et al., 2004; Zihl and von Cramon, 1985). This is true in a

general, quantitative sense as well as in a more specific sense, i.e. with respect to local changes of visual field topography. The systematic progression of recovery along the ARVs at the visual field borders from slightly impaired to more severely impaired areas suggest that VRT gradually reduces the thresholds of visual perception. Presumably, ARVs are the functional expression of partially defective neuronal areas in the brain, e.g. penumbra zones along the border of a stroke region (Sabel, 1999, 1997). Under everyday life circumstances, neurons representing ARVs in visual cortex are inhibited by the much stronger input from intact visual field regions. During vision restoration training, ARVs are specifically stimulated while at the same time input from intact visual field areas is reduced (dark background, darkened room). Such a training regime can successfully activate partially defective neuronal areas even many years after the brain lesion had occurred (Sabel, 1999; Kasten et al., 1999). The neural mechanisms underlying the recovery of function induced by VRT are not entirely clear and can only be speculated on in a human study like the one presented here. But the patterns of visual border shift agree with observations from the animal literature about the topography of receptive field size increase and activation of long-range horizontal connections in the visual cortex as well as thalamo-cortical feedback loops (Gilbert and Wiesel, 1992).

The degree of spontaneous recovery of vision in the early phase after the lesion did not predict training-induced plasticity in our study. The variability of different examination methods and the fact that the "post-lesion" measurement had often been performed several months after the lesion possibly underestimated the amount of spontaneous recovery and induced a high variability of the data to begin with. Hence, this possible predictor should not be discarded from future research but re-investigated with more adequate (i.e. standardized) methods, ideally in longitudinal studies, observing patients over the period of spontaneous and training-induced recovery.

Initial levels of attention and sensory processing speed affected improvement of reaction times in campimetric testing but did not influence the increase of detection performance which was the main outcome variable in our study. Thus, attentional functions appear to exert a more specific effect on information processing speed and problems of signal-noise-interference and may thus support the training process. However, our results suggest that the improved detection of light stimuli cannot be interpreted solely as an attention effect.

While the total duration of training and the absolute number of training sessions did not predict training success, the intensity of the training had some effect on visual field increase. Patients with a regular, uninterrupted schedule of training and a high number of training sessions per time unit had a better chance of regaining vision. Thus, the partially defective neurons representing ARVs presumably need to be activated continuously and regularly to induce the shift of perceptual thresholds in these areas. In contrast to our findings, Zihl and von Cramon (1985) reported that the increase of visual field size depended on the number of training periods, but since the type of training was different (saccadic localization) and the training regime in the hospital was providing a dense training schedule, differences in training intensity did not occur in their sample, so that the only variation was in the duration of training (which was constant for our group).

4.3. Multifactorial predictions

Prediction of different variables measuring training outcome – especially detection performance and reaction times – could be performed with high accuracy using the complete set of predictors available in this study. Thus, with a sufficiently large data base, the post-training performance of patients with post-genicular visual system lesions can be reliably estimated. In a clinical setting it is not possible to acquire such large data sets and to perform hours of testing with patients. Therefore, for practical reasons, a subset of the predictor variables can be used that are readily available for the clinician (see Results section). Even with the limited set of predictors that is easily accessible to the clinician based on patient files and visual field examinations, it is possible to get a relatively good prediction of training-induced visual field recovery for comparable training regimes and patient samples. Although the reliability of the prediction is somewhat reduced as compared to the full data base, still almost 80% of variability in visual field recovery can be explained by this predictor set. In a clinical setting, this approach might be useful to estimate clinical effect size for individual patients to help determine if they should receive VRT or a different form of visual rehabilitation. This will help patients and clinicians to make a rational estimate of the probability if and to what extent vision restoration can be achieved.

Author note

B.A. Sabel is a shareholder in NovaVision, Inc. and E. Kasten is consultant. All other authors have no conflict of interest.

Appendix: Additional regression equations

Shift of visual field border in HRP

$\text{Pred}_{\text{HRP border shift}} = 0.327$*(age) $+ 0.051$*(time since lesion) $- 0.539$*(size of defect) $+ 0.262$*(eccentricity of defect)* $+ 0.477$*(size of ARV) $+ 0.101$*(HRP reaction time) $+ 0.056$*(Alertness reaction time) $- 0.106$*(GoNogo reaction time) $- 0.011$*(Vigilance reaction time) $+ 0.404$*(Stroop interference) $+ 0.195$*(AKT reaction time) $+ 0.200$*(Number of training sessions) $+ 0.325$*(training intensity)

Subjective evaluation of training as helpful

$\text{Pred}_{\text{subjective help}} = 0.152$*(age) $- 0.176$*(time since lesion) $- 0.166$*(size of defect) $+ 0.124$*(eccentricity of defect) $+ 0.202$*(size of ARV) $+ 0.306$*(HRP reaction time) $+ 0.163$*(Alertness reaction time) $+ 0.391$*(GoNogo reaction time) $- 0.400$*(Vigilance reaction time) $+ 0.175$*(Stroop interference) $+ 0.240$*(AKT reaction time) $+ 0.011$*(number of training sessions) $- 0.047$*(training intensity)

General satisfaction with training

$\text{Pred}_{\text{satisfaction}} = 0.109$*(age) $+ 0.064$*(time since lesion) $- 0.186$*(size of defect) $+ 0.147$*(eccentricity of defect) $+ 0.119$*(size of ARV) $+ 0.008$*(HRP reaction time) $+ 0.231$*(Alertness reaction time) $+ 0.166$*(GoNogo reaction time) $- 0.089$*(Vigilance reaction time) $- 0.050$*(Stroop interference) $- 0.109$*(AKT reaction time) $- 0.235$*(number of training sessions) $- 0.155$*(training intensity)

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