Transfer Effects of Training-induced Visual Field Recovery in Chronic Stroke Patients

DP Bergsma [1,2]; JA Elshout [1]; GJ van der Wildt [1,2]; AV van den Berg [1,3]

[1]Utrecht University, Faculty of Science, dept. of Functional Neurobiology,
H.R. Kruytgebouw, P.O. Box 80058,
3584 TB Utrecht, The Netherlands.
[2]The Helmholtz Research School, P.O. Box 80125,
3508 TC Utrecht, The Netherlands.
[3]Radboud University, dept. of Medical Physics and Biophysics,
Geert Grooteplein 21, 6526 EZ Nijmegen, The Netherlands.

Abstract

Visual training of light detection in the transition zone between blind and healthy visual fields in hemianopes leads to improvement of color and simple pattern recognition (Kasten et al 2000). Recently, we demonstrated that training enlarges the visual field also when stimulating an area just *beyond* the transition zone (Bergsma & vd Wildt 2010). In the current study, we studied if training in this peripheral area also causes transfer to colour- and shape perception and improves reading speed. Further, we studied what measure of visual field enlargement (VFE) relates best to improvements in performance: the average border shift (degrees) or the associated cortical surface gain estimation (mm). 12 patients received forty sessions of 1-hour RFT. Before and after training we measured visual field size and reading speed. Additionally, colour and shape perception in the trained visual field area was measured in 7 patients. VFE was found for 9 of 12 patients. Significant improvements were observed in reading speed for 8 of 12 patients and in colour and shape perception for 3 of 7 patients. When field enlargement is expressed in terms of expected mm cortical surface gain (ECSG_mm), using the Cortical Magnification Factor (CMF), our data indicate that the minimum amount of cortex that is needed for significant changes in colour- and shape perception and reading speed is about 6 mm cortex. This means that white stimulus training-induced VFE can lead to improved colour- and shape perception and to increased reading speed in *and beyond* the pre-training transition zone *if* ECSG_mm is sufficiently large.

Key words: CVA; cortical blindness; recovery; restorative function training; perimetry.

Abbreviations: VFE = Visual Field Enlargement; VFD = Visual Field Defect; RFT = Restorative Function Training; ECSG_mm = estimated cortical surface gain (in mm); CMF = Cortical Magnification Factor; ISI = Inter stimulus Interval

Introduction

Our modern society puts increasing demand on visual information processing. Visual field defects (VFDs) after stroke can pose major limitations on daily life activities such as driving, detecting, recognizing and avoiding obstacles, reading and TV/PC screen use. Because visual processing takes place in many areas of the brain, up to 25% of all stroke patients have visual field defects (Zihl, 2000). One method to treat VFDs is visual Restorative Function Training (RFT*), which consists of visual stimulation of the border area between the blind and the intact visual field. Several studies report that this method can lead to visual field enlargement (Bergsma, 2010, 2008; Julkunen, 2003; Kasten, 2006, 2000, 1999, 1998b; Kerkhof, 1999; Mueller, 2007; Poggel, 2001; Sabel, 2006, 2005, 2000; Van der Wildt, 1998; Werth, 1999; Zihl, 1985, 1981, 1979) although these findings were questioned by others (Balliet, 1985; Horton ,2005a+b; Plant, 2005; Reinhard, 2005; Roth, 2009). The methods of the training are still debated to define better standards (Bouwmeester, 2007; Pelak, 2007). For example, increasingly larger eye movements towards the visual field defect have been suggested to cause the enlargements (Horton, 2005; Reinhard, 2005), but other reports conclude that the observed visual field enlargements are not correlated with eye movements (Kasten, 2006; Muelle,r 2007). Recently, we showed that visual field enlargements after training are not a consequence of saccades towards the presented perimetry stimuli by rejecting all trials with inadequate fixation (Bergsma, 2010).

In an earlier study, we found that colour recognition, temporal properties (critical flicker fusion) and spatial properties (acuity) of the recovered visual field are comparable to normal values in the contralateral, unaffected visual field (Bergsma, 2008). Because these visual faculties were not trained for, one may ask to what extent changes in visual perception and behaviour are induced by RFT? Does VFE after training result in transfer effects to the perception of other stimuli such as Kasten et al. reported (2000) and to higher behavioural functions? If the latter is not the case, one could ask if current practises to train with simple light stimuli should be replaced by stimuli that provide better opportunities for transfer. Second, a visual field area (and VFE) near the fovea involves a larger cortical area than the same enlargement at a more peripheral location. It is conceivable then that a threshold amount of cortical restoration is required to allow transfer from visual training stimuli to non-trained visual functions. Thus, we studied whether possible transfer effects are determined by the average border shift (ABS) in degrees or by the amount of cortical tissue that is involved in the VFE. We use the cortical magnification factor (CMF) as described by Cowey to calculate the estimated cortical surface gain (ECSG _mm) that corresponds to the extent of the regained visual field. We then investigate the relation between the ECSG _mm and the behavioural performance. On the assumption that a regained visual function would require the same amount of visual cortex as in normal subjects one may expect that the ECSG_mm -rather than the ABS- as a result of training- determines behavioural/perceptual changes. For studying untrained perceptual and behavioral improvement after RFT, we

* We use the term RFT instead of VRT (Vision Restoration Therapy), because VRT is a registered trademark. RFT follows the same training procedure as VRT: it stimulates a defective visual field area. RFT is a custom made program and thus, it is not VRT.

measured colour and shape perception in the trained visual field area and reading speed before and after training.

Methods

Training. Training comprised 40 sessions of 1 hour during 10 weeks. Twelve patients were trained monocularly in both eyes by repeated presentation of a white stimulus (Goldmann IVe) for detection, comparable to static perimetry in a Goldmann perimeter. Approximately 90% of the stimuli were presented in the absolute VFD. Locations extended 10°-15° into the defect. Stimulus luminance was increased stepwise with a 0.1 log unit change from ≈4 cd/m2 up to ≈318 cd/m2. During training, fixation was monitored visually. Occasionally, the blind spot was probed as fixation check, which yields no response when fixation is accurate. A more elaborate description of the training is given in Bergsma & van der Wildt (2008).

Perimetry. Visual fields were measured monocularly with dynamic Goldmann perimetry before training. This measurement was repeated after every 10 trainingsessions, according to the guidelines laid out by Frisèn (Frisén, 1990). Gaze directions were measured using an Eyelink II eye-tracker (SR Research Ltd., Mississauga, Ontario, Canada), with a sampling rate of 250 Hz and a spatial resolution of 6 minutes of arc. A customised chin- and headrest stabilized the patient's head and Eyelink headset. Prior to each monocular measurement, the Eyelink system was calibrated and the blind spot was mapped to check for a possible developing pseudofovea during training. During perimetry, the blind spot was probed (Heijl-Krakau method) at random intervals for intermediate assessment of fixation (Heijl, 1975). A more elaborate description of our perimetry method can be found in Bergsma & van der Wildt (2010).

VFE usually concerns both an eccentricity and a polar angle shift. VFE can be expressed as the average border shift (ABS) in degrees, which averages the eccentricity change of the border over all trained angles. However, this does not take eccentricity of the VFE itself into account. VFE eccentricity is taken into account when VFE is expressed in the estimated cortical surface gain (ECSG_mm) that is involved in the VFE. To calculate ECSG_mm we use the cortical magnification factor (CMF) of Cowey (Cowey, 1974). The CMF is a one-dimensional measure that describes the non-linear relationship between eccentricity in the visual field and the cortical area that represents 1° of the visual field. The other dimension (polar angle) of the visual field and its cortical representation are approximately linearly related. We calculated ECSG_mm as follows: the trained visual field area is divided in sectors like a pie-chart with angular segments of 2½°. Of each sector the border shift in the radial direction is established and transformed into the amount of mm cortex involved, using the CMF. The average value of all radial sectors is used as the measure of ECSG_mm.

In hemianopia, the visual field border is oriented vertically, but the border typically shifts in a horizontal direction. This means that in many sectors the shift of the border is not a pure shift in eccentricity but a combination of a shift in eccentricity and a shift in the polar angle direction. To appropriately compute the eccentricity related cortical gain in mm, one must therefore take into account only the component of the shift that runs in the direction of the eccentricity. This is done by multiplication of the border shift by the sine of the angle (θ) between the border and the direction of the eccentricity (figure 1) according to equation (1):

Equation (1): $$ECTG\_mm = (CMF_B - CMF_A) * \sin(\theta)$$

CMFA and CMFB represent converted eccentricity values at locations 'A' and 'B', denoting the cortical distances from the foveal representation according to the data of Cowey.

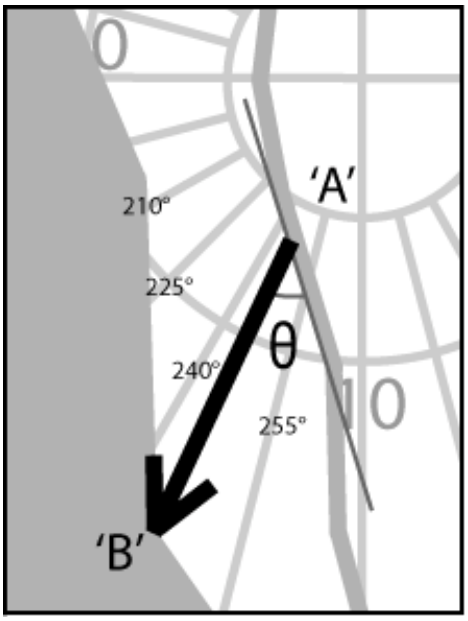

Fig 1. Example of ECSG_mm calculation: The grey line depicts the pre-training visual field defect border. The grey area represents the post-training absolute field defect. The black arrow indicates the border shift in the 2½° wide sector between angles 242.5° and 245°. Because the border is not perpendicular to the radial sector, the growth of the visual field within the sector is partly in the polar angle direction. The part that occurs in the eccentricity direction is found by multiplication with the sine of the angle between the border and the direction of the sector. CMF-values are established using the Cortical Magnification Factor of Cowey. Average border shift is the average across all sectors, after application of the sine corrections in each sector.

Colour and Shape Perception. Before and after training, 7 patients were presented colour- and shape stimuli at locations where we expected visual field enlargement a priori. Stimuli were presented on a screen, 250 cm wide and 235 cm high. Patients were seated at a distance of 165 cm with their head stabilized on a chin-rest. Using Microsoft Powerpoint we presented stimuli with a diameter of 1° for the duration of 1 second and an interstimulus interval (ISI) varying from 1 to 3 seconds. Not known to the patients, shape stimuli were always black and white (open circles, squares and triangles) and coloured stimuli (red, green and blue) were always filled circles. All stimuli (3 colours, 3 shapes) were presented binocularly in random order at each location. This presentation was repeated 1 time binocularly and 1 time in a monocular presentation, so that each location was tested 18 times. Subject responses were classified in one of three categories: (1) Recognition (of either or both of the presented colour or shape) (2) Detection (something is seen) or (3) No Detection (nothing is perceived). We did not use a forced-choice paradigm. To estimate colour- and shape discrimination performance from our data, we treated the no-detection response as if patients responded at chance-level. Therefore, the performance is determined by the proportion of correct responses relative to the total number of responses at that location plus the proportion responses at chance level relative to the total number of non-responses at that location. So, the performance at each tested location can then be calculated by:

Equation (2):

$$\frac{(p*n)+\left((N-n)*c\right)}{N}$$

Where N is the number of trials at a location (9 at all locations for each patient); n is the number of responses at that location; p is percentage of correct responses at that location and c is the percentage correct response by shear guessing (.33 for both the colour and the shape task).

The verbal response of patients often temporally coincided with stimulus presentation, which caused head movement artefacts. Because we were unable to measure these head-movements, the eye tracker could not be used during the perceptual judgements. Therefore, we monitored eye fixation visually during the measurements. When inaccurate fixations were observed, feedback was given in order to maximise the number of adequate fixations. Also, we probed the blind spot during the monocular presentation with a 1° white stimulus just before every stimulus presentation (48-72 stimuli, depending on number of test locations, see figure 1). A positive response during blind spot probing meant inadequate fixation and in that case, the following test trial was removed from data-analysis. The number of inadequate fixations during monocular presentation was considered illustrative of fixation behaviour for the 2 binocular presentations. We hold this because the order of the presentation was the same for the binocular and monocular conditions. Thus removal of the corresponding trials of the 2 binocular measurements removed those conditions from the analysis that were most likely to have also been affected by eye movements. A minority of trials were discarded from analysis for patients RQ (8.3%) and AM (11.8%) following this procedure. Patients HBr, HBo, PP, GL and IT never responded during blind spot probing and all test trials were included in the analysis.

Reading. Twelve patients silently read 2 standardized texts (Arial 14 pt.) with 15 lines (152 words) and 18 lines (168 words), respectively. Reading eye movements were measured using the Eyelink II headset and a chinrest stabilizing the subject's head 30-50 cm away from the texts (depending on favoured reading distance). Dependent variables were reading speed (words/minute) and the average number of forward saccades and regressions (reading errors).

Subjects. Twelve chronic stroke patients (7 females, 5 males) volunteered as subjects. They suffered a first supratentorial stroke in the optic radiation or visual cortex resulting in a visual field defect without visual neglect. The average subject age was 58.9 (± 8.8) years; post-onset time ranged from 6 to 102 months, averaging 23.2 (± 27.4) months. For subjects AM, HBr and RQ the post-onset time ranged from 6 to 9 months. In these cases some residual spontaneous recovery can not completely be ruled out, but it is not expected. All others had lesion-ages ranging from 12 to 102 months (see table 1)

Patient	Age	Gender	Stroke	Visual Field Defect	Post Onset Time
AM	61	F	Inf occipital L	Hemi-R	9 months
HBr	48	F	Inf occipital R	Hemi-L	6 months
PP	65	M	Inf occipital R	Incomplete Hemi-L	1 year
RQ	53	M	Inf occipital R	Incomplete Hemi-L	9 months
GL	59	F	Hm parietal/occipital R	Quadr-LL	1 year
IT	49	F	Inf temporal/occipital R	Scotoma-UL	1 year
HBo	65	F	Inf temporal R	Quadr-UL	3 years, 2 months
EG	67	F	Inf temporal/occipital R	Incomplete Hemi-L	1 year
PK	73	M	Inf occipital R	Hemi-L	1 year
WD	54	M	Inf temporal/occipital R	Hemi-L	3 years, 6 months
IW	46	F	Inf temporal/occipital R	Hemi-R	1 year
PV	67	M	Hm parietal/temporal/occipital R	Hemi-L	8 years, 6 months

Table 1. Subject description. Inf = infarction; Hm = haemorrhage; Hemi=hemianopia; Quadr=quadrantanopia; R=Right; L=Left; LL=Lower Left; UL=Upper Left.

Figure 2 shows the lesions (dark areas) in neurological convention (left=left, right=right) in the anatomical T1-weighted MRI-scans. For subject PK, a T2-weighted scan in radiological convention (left=right, right=left) is shown.

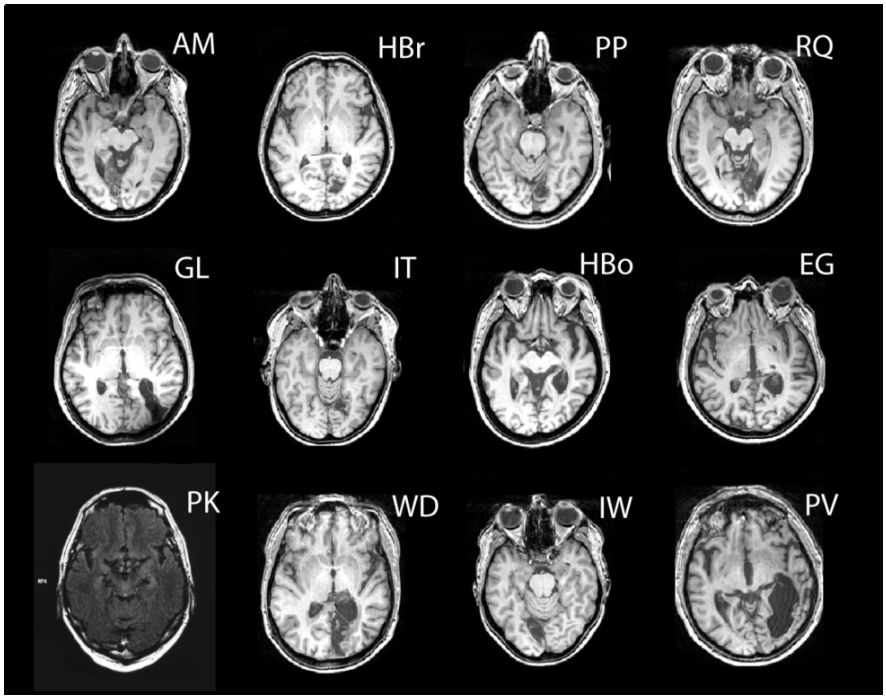

Figure 2. Anatomical T1-weighted MRI-scan slices that optimally show the lesions of the patients. Scans are shown in neurological convention (L=L; R=R). For PK, the slice is a T2-weighted MRI-scan, shown in radiological convention (L=R; R=L).

Results

Visual Fields. The graphics in figure 3 show the results of Goldmann perimetry in 12 patients: the grey line depicts the visual field defect border before training and the grey area shows the remaining defect after training; the recovered visual field lies in between. Also shown is the average border shift (ABS) in degrees. Visual fields are based on trials with accurate fixation only. As can be seen, 9 patients show VFE and 3 patients show no or negligible VFE (WD, HBo and IW).

Colour and Shape Perception. In figure 3, the test locations –selected a priori- of colour and shape stimulus presentation of 7 patients are shown, represented by squares. Most stimuli were presented in an area that was an absolute defect before training and that became responsive visual field areas after training. We did not use a forced-choice paradigm, so patients did not respond when a stimulus was not detected. Therefore, fewer responses were given at certain test locations than at others. However, we treated the tests as if a forced-choice paradigm was used and because 3 colours and 3 shapes are used, the chance-level of performance is 33% in both tasks. The threshold above which performance is considered to have changed significantly lies halfway the remaining 67% which adds up to (33 + (67/2) = 67%. Using the equation on page 5 (the proportion of correct responses relative to the total number of responses at that location plus the proportion responses at chance level relative to the total number of non-responses at that location), we found that 3 patients (AM, PP and RQ) significantly improved performance (correctly discriminated stimuli in ≥ 67% of the cases) and 4 patients did not.

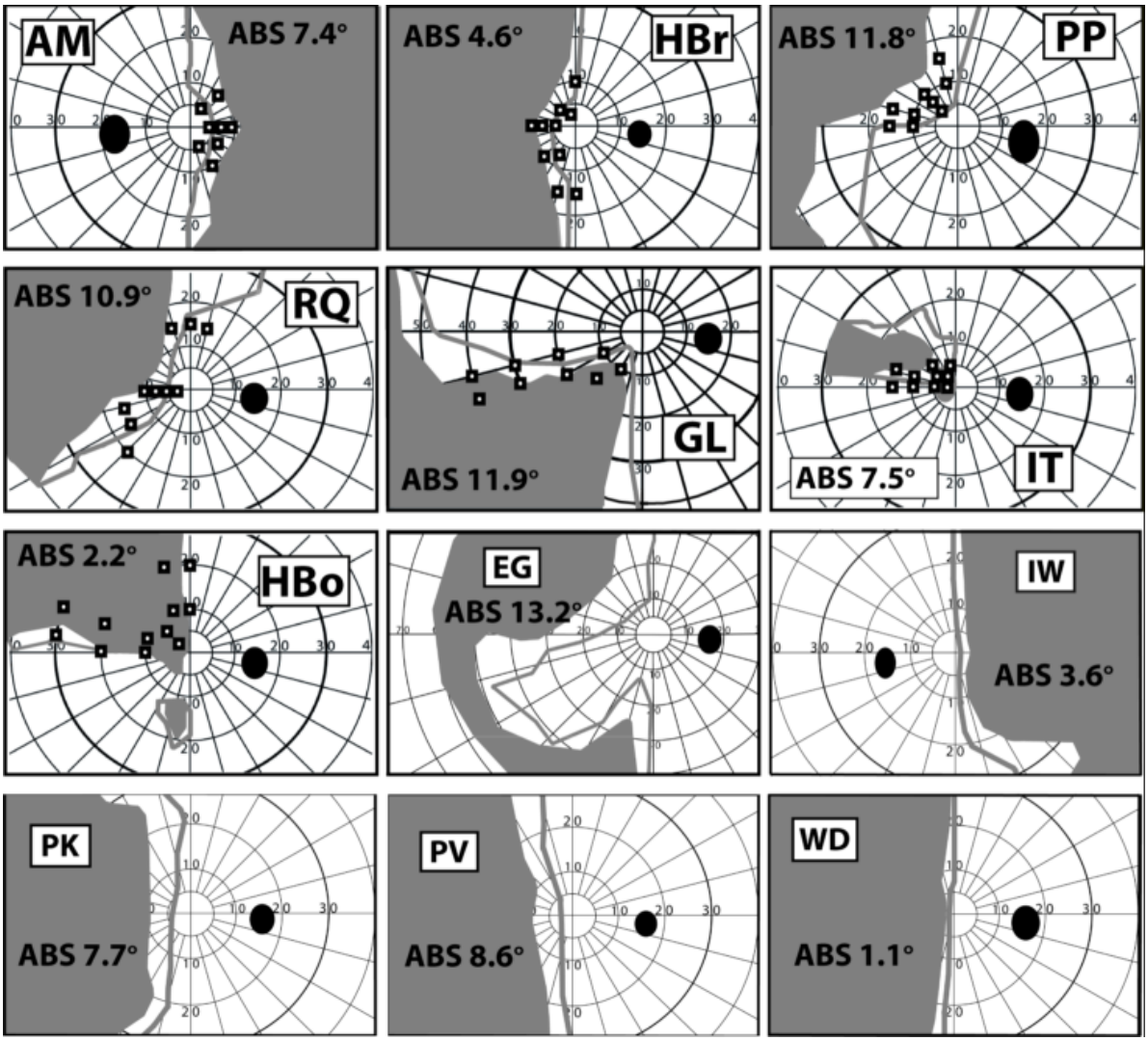

Figure 3. Average border shift (ABS) of 12 patients and colour- and shape test locations in 7 patients (black squares). The grey line depicts the pre-training visual field defect border. The grey area represents the post-training absolute field defect area. The region in between is the recovered visual field. ABS is calculated by averaging the eccentricity shifts in all trained 2½° wide sectors.

Figure 4 shows the percentage of responses on a total of 9 presentations at each location for each patient. Only the visual field area around the test locations is shown. Each circle represents a test location.

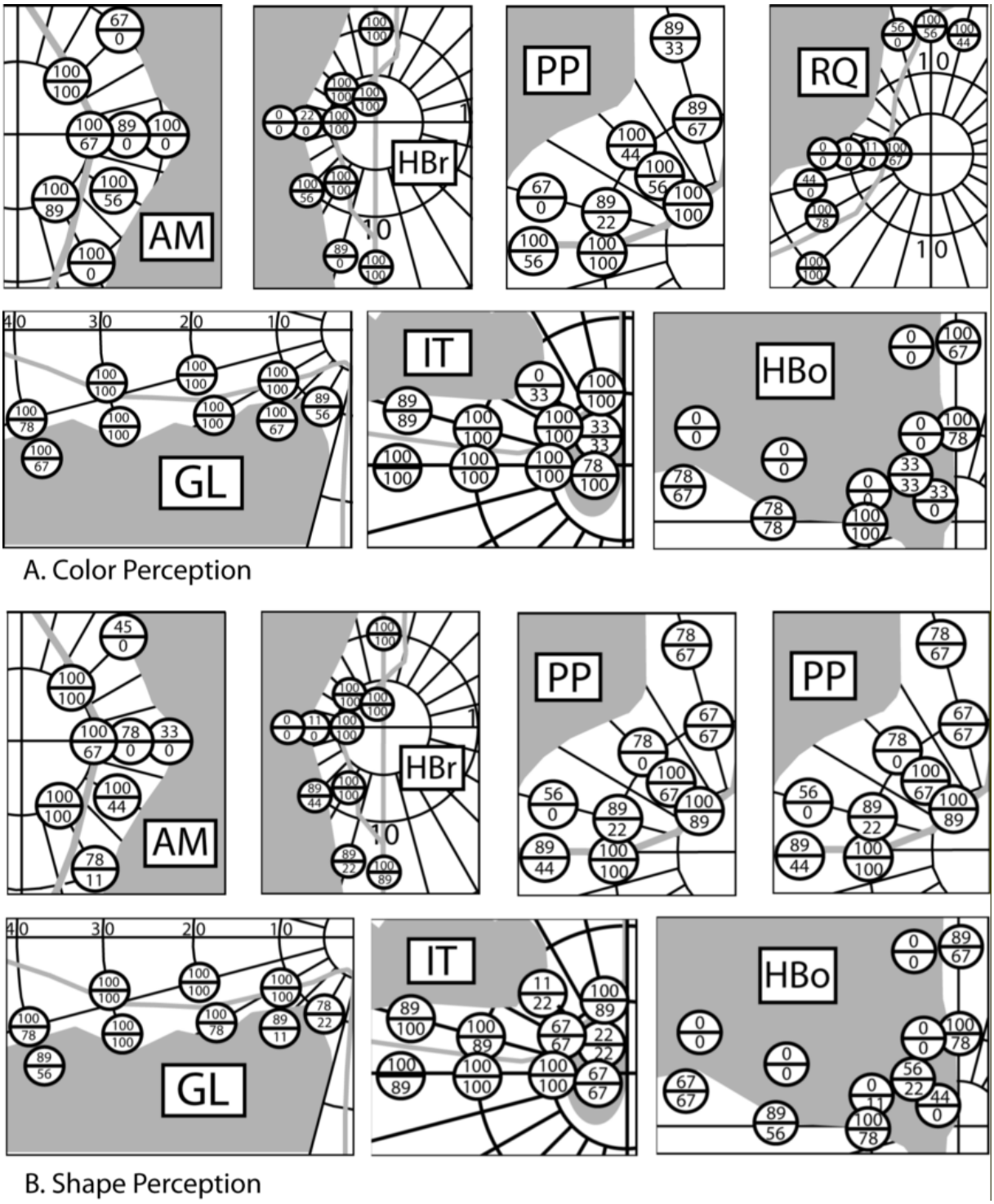

*Figure 4. The **percentage of responses** on a total of 9 presentations at each location for each patient before (lower number) and after training (upper number).*

Figure 5 shows the percentage correctly identified colours or shapes (the lower numbers reflect the percentages before training; the upper numbers correspond to those after training). As can be seen, at almost all locations the post-training scores are equal to or higher than pre-training test scores. Also, near the unaffected visual field, both pre- and post-training scores are higher than near the scotoma. This indicates that recovery of the visual field follows a gradient that is oriented perpendicular to the visual field border. This

supports our previous findings that the visual field is enlarged gradually during training (Bergsma 2010).

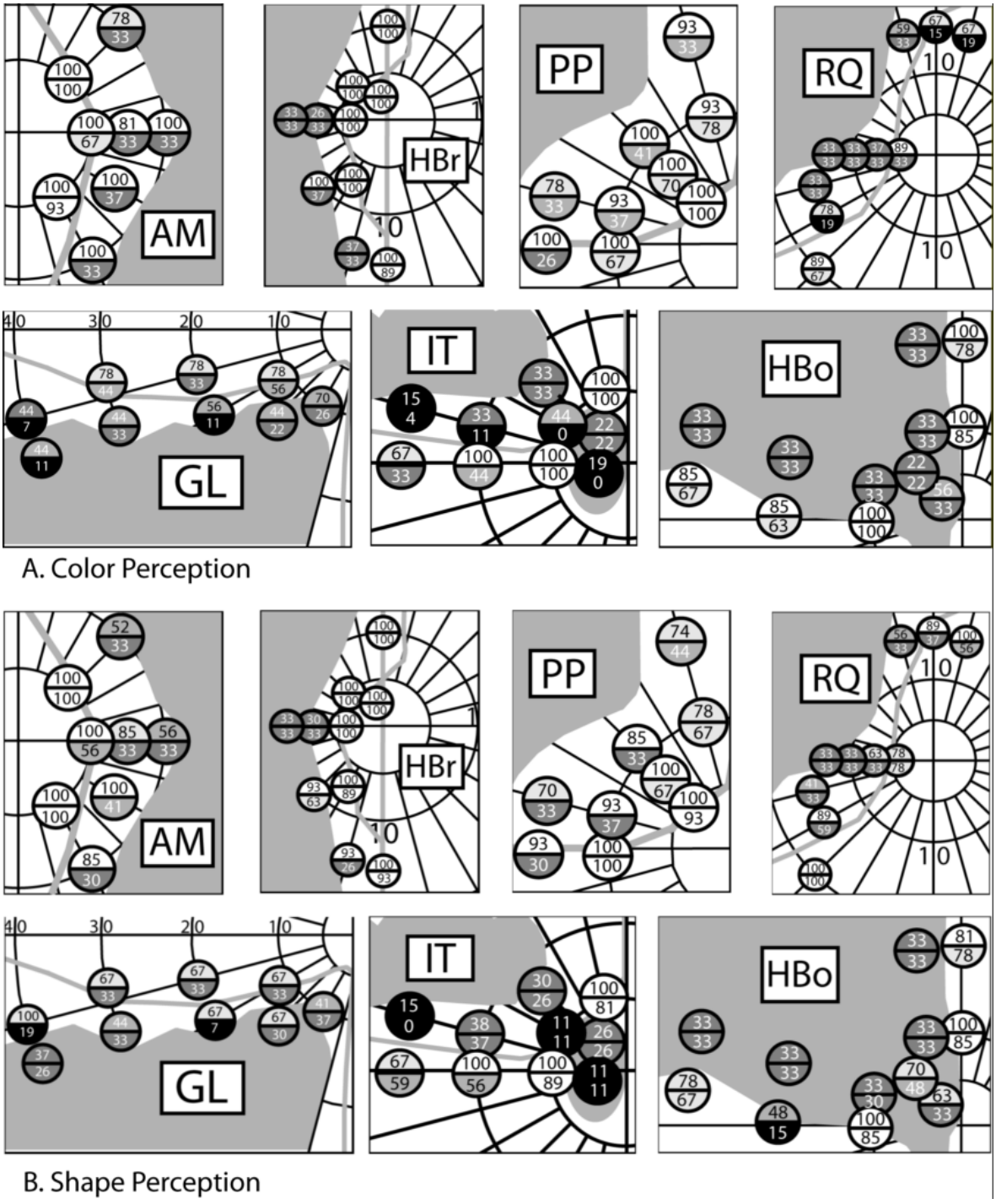

Figure 5. Each circle shows the pre-training (lower number) and post-training (upper number) percentage ***correctly identified stimuli*** *for that location. Performance values are corrected for forced-choice probability. The half-circle greyscales correspond to those percentages and serve to indicate improvement at a quick glance (dark → light).*

Reading. Table 2 shows the results of the reading test of 12 patients. Average number of saccades and regressions (reading errors) are calculated per line and pre-post differences are determined using a t-test. 7 patients significantly improved their reading speed after training. First, the number of saccades per line decreased which indicates that saccade amplitudes are larger, enabling a line of text to be read faster. This is likely supported by an enlarged parafoveal visual field through training. Also, less regressions ("back-jumps") were made, which improves reading speed directly. It also indicates better text comprehension. These results are in line with an earlier report by Zihl & von Cramon (1985). 3 patients showed no change and 2 subjects significantly deteriorated in their reading speed (HBo and PP). HBo made more saccades and regressions during the post-training measurement. Before training, reading speed was already very low, probably due to the parafoveal defect interfering with reading. After training, this parafoveal defect remained unchanged and HBo even showed more regressions than before training. Also subject PP showed pronounced deterioration of reading speed, although he showed fewer regressions, more or less unchanged number of fixations and an enlarged field. PP reported that he experienced distracting visual sensations in the enlarged field after training. This may have interfered with reading performance. Field enlargement may thus be of poor quality in subject PP: useful for stimulus detection, but not for something more complex such as reading.

Patient	Pre training Reading speed (words/minute)	Post training Reading speed (words/minute)	Pre-Post difference (words/minute)	Pre-Post difference Average saccades and regressions
AM	313	391	+77 (+25%) **	AvSac - 0.4 AvReg - 0.3
HBr	315	358	+42 (+13%) **	AvSac - 1.3 AvReg - 0.6
PP	229	167	-61 (-27%) **	AvSac + 0.1 AvReg - 0.5
RQ	243	318	+75 (+31%) **	AvSac - 1.0 AvReg - 0.3
GL	178	215	+37 (+21%) **	AvSac - 0.8 AvReg - 0.4
IT	169	203	+34 (+20%) **	AvSac - 1.2 AvReg - 0.9
HBo	120	83	-37 (-31%) **	AvSac + 6.5 AvReg + 3.3
EG	259	304	+45 (+17%) **	AvSac – 1.3 AvReg - 0.5
PK	282	281	-1 (0%)	AvSac -1.2 AvReg - 0.6
WD	393	392	-1 (0%)	AvSac -0.1 AvReg 0
IW	154	158	+4 (+3%)	AvSac -0.5 AvReg -0.1
PV	150	233	+83 (+55%) **	AvSac -4.2 AvReg -3.2

*Table 2. Reading speed before and after training. Pre-post difference: ** = p ≤ .005, using t-tests. AvSac = average number of saccades per line; AvReg = average number of regressions per line.*

Significance. VFE is usually expressed as the average border shift (ABS) in degrees, which is shown in figure 3. As can be seen in figure 3, VFE takes place at different eccentricities for different subjects. Because we want to study the relationship between VFE at different eccentricities on the one hand and colour- and shape perception and reading on the other,

we calculated the ECSG_mm that is associated with the VFE of each patient and summarized the outcome in table 3.

Patient	AM	HBr	PP	RQ	GL	IT	HBo	EG	PK	WD	IW	PV
ABS	7.4°	4.6°	11.8°	10.9°	11.9°	7.5°	2.2°	13.2°	7.7°	1.1°	3.6°	8.6°
ESCG_mm	8.29	6.29	7.31	6.59	6.06	5.16	0.17	6.08	6.59	0.16	3.44	8.47

Table 3. Visual Field Enlargement of all patients in degrees (ABS) and in estimated amount of cortical surface gain in mm (ESCG_mm).

When does VFE lead to significant perceptual and behavioural improvement? To find out, we compare both ABS and ECSG_mm with performance in the perceptual and the behavioural task. The reading speed data of 12 patients showed that 7 patients had significantly increased their reading speed after RFT and 5 patients did not; the colour-and shape discrimination data of 7 patients showed that 3 patients improved performance significantly and 4 patients did not. Although the patient numbers are low, we can make some inferences about the relationship between VFE and performance by combining the results of both the reading task and the colour-and shape discrimination task, resulting in 19 observations. Figure 6 shows the cumulative graphs of all performance observations as a function of ABS. Dark grey markers represent significantly improved patients; light grey markers represent patients that did not improve. The dark grey curve shows the probability that a patient's performance will improve significantly when the VFE is smaller than or equal to the indicated criterion value on the abscissa. The light grey curve indicates the probability that for VFE larger than or equal to the same criterion the patient's performance will not improve.
The VFE value at which the two curves cross is taken as a threshold value because it offers the best criterion value to distinguish the populations of improved and not-improved patients. As can be seen in figure 6, this value appears to be about 7°.

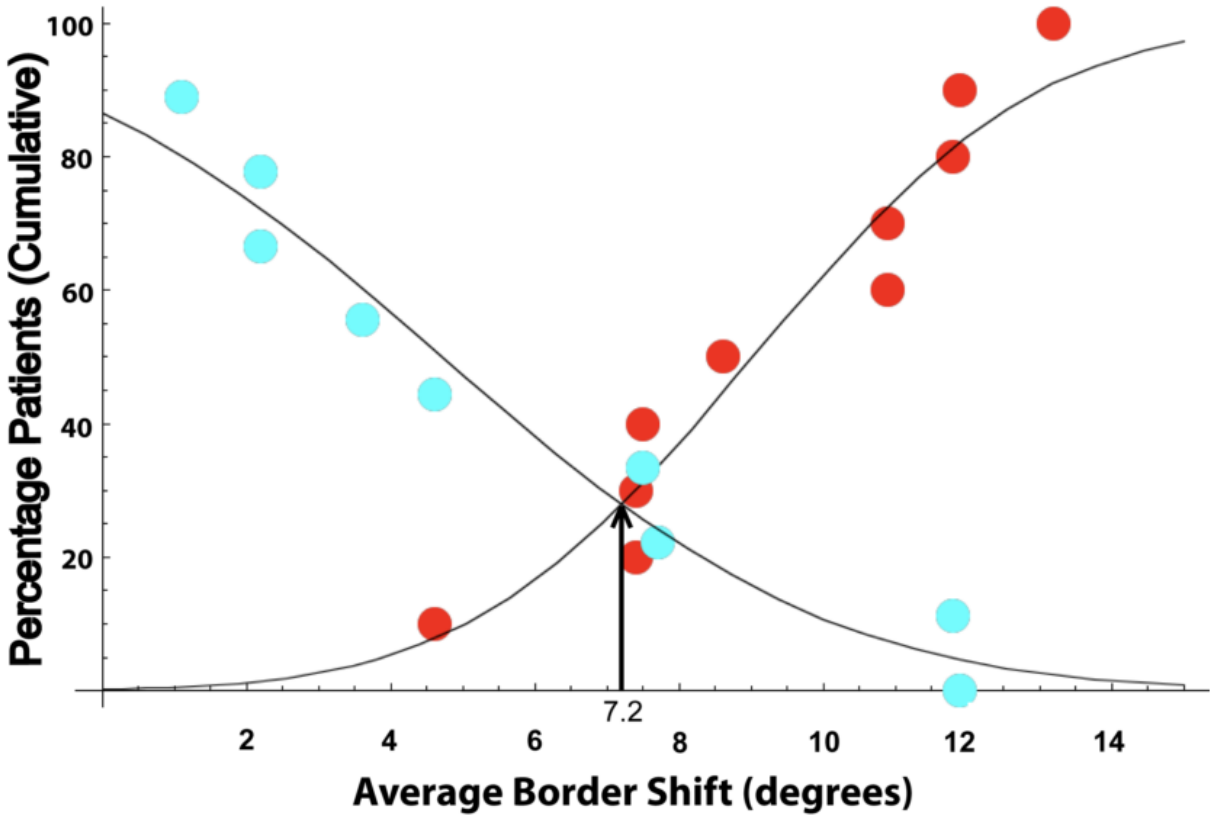

Figure 6. Cumulative data of patients with significant performance improvement (red) and without significant performance improvement (blue) ordered as a function of the average border shift in degrees. The value where the fitted cumulative distributions cross is taken as threshold value, beyond which significant improvement may be expected. The threshold here is 7.2 degrees.

Figure 7 shows the cumulative graphs of the same 19 observations as a function of ECSG_mm. Again, the value at which the two curves cross is taken as a threshold, which in the case of ECSG_mm amounts to about 6 mm cortex. There is slightly less overlap between the two curves in Fig 7, indicating that ECSG_mm can better distinguish improved patients from the not improved patients than ABS. This is also supported by a significant correlation between ECSG_mm and performance (rMMC/PERF =.57; p=.01), but not between ABS and performance (rABS/PERF =.41; p=.08). We therefore conclude that ECSG_mm is the preferred measure to describe the effect of the training on visual field extension and its relation to perceptual and behavioural improvement. We estimate from our admittedly limited sample of patients that a criterion ECSG_mm is about 6 mm cortex.

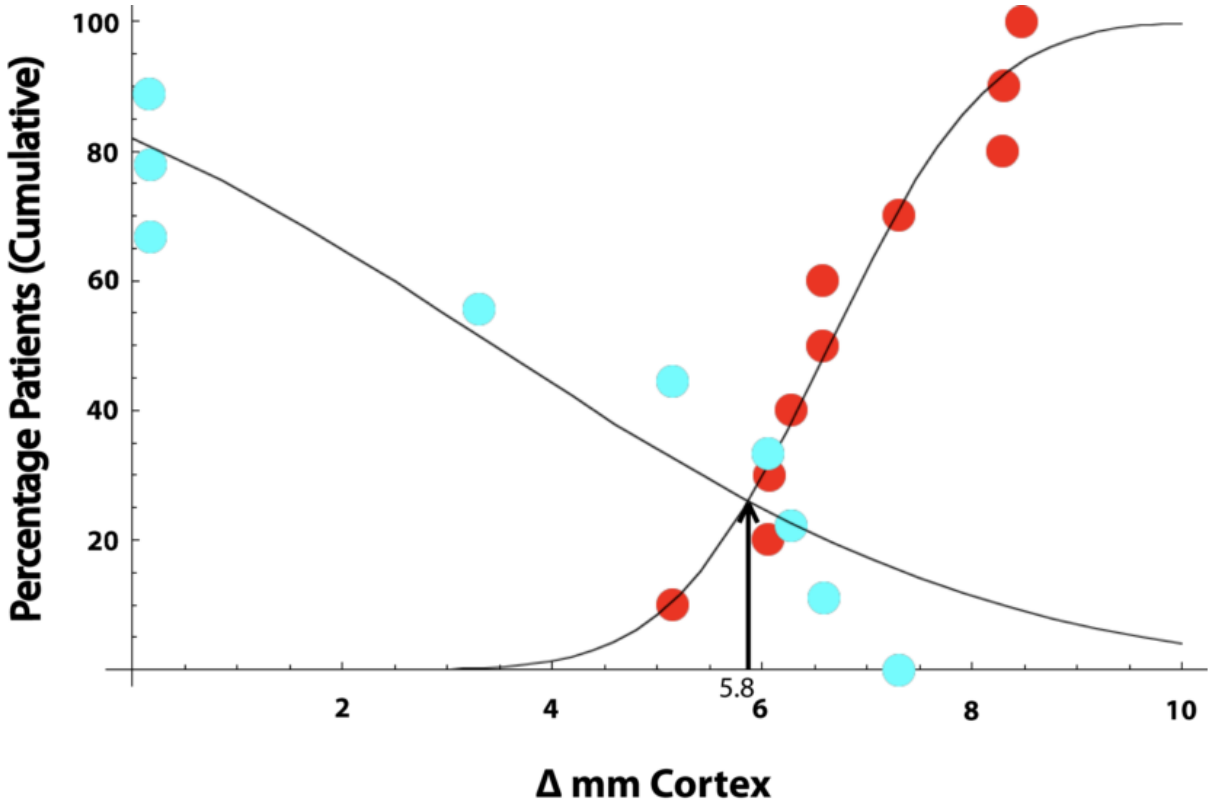

Figure 7. Cumulative data of patients with significant performance improvement (dark grey) and without significant performance improvement (light grey) ordered as a function of ECSG_mm. The value where the fitted cumulative distributions cross is taken as threshold value, beyond which significant improvement may be expected. The threshold here is 5.8 mm.

Discussion

In this study, visual restorative function training was administered to chronic CVA patients with partial cortical blindness, using a Goldmann perimeter. Zihl & Von Cramon and Kasten et al. trained patients in the transition zone between the blind and the seeing field (at least at the start of training). In our study, we trained patients in an area that was located for the larger part within the absolute VFD as measured with Goldmann dynamic perimetry, extending 10°-15° into the defect. This training results in enlarged visual fields in a majority of the patients. In this enlarged area, transfer to other visual functions can occur. Thus, our training with simple white stimuli beyond the border area of the defect had three effects: (1) it reduced the field defect in 9 out of 12 patients, (2) it improved brightness perception, but also improved colour- and shape discrimination in 3 out of 7 patients and (3) it improved reading speed in 7 out of 12 patients. Zihl & von Cramon (1985) mention that a minimum VFE (or central field sparing) is necessary for a patient to even notice it. We also found that for a significant improvement on the perceptual or reading tasks a minimum field enlargement was required that depended on the eccentricity of the defect. This minimum VFE becomes larger as eccentricity increases, which indicates the importance of taking eccentricity into account. This is reinforced by the fact that, in contrast to the average border shift in degrees (ABS), the estimated cortical surface gain in millimetres (ECSG_mm)

correlates well with the improvements in reading and /or shape-colour perception. Therefore, we express VFE in terms of ECSG_mm, which takes eccentricity into account, instead of (ABS) which does not take eccentricity into account. Thus our study indicates a threshold ECSG_mm of 6 mm beyond which significant behavioural and perceptual improvements occur.

Kasten suggested that results like these indicate that actual restitution of cortical functions has taken place which partially resolves a “bottleneck” in the retino-geniculo-cortical pathway. However, the “bottleneck” location is not known and to the present day it can only be speculated as to how cortical functions return. For example, it has been hypothesized that VFE is based on receptive fields enlargement encroaching into the the blind field (Kasten, 1999). This should lead to decreased acuity in that area (because receptive field size and acuity are inversely related) and a decremental effect on reading (speed). Instead, we found that 7 patients increased their reading speed. Another hypothesis says that relative field defects are probably a result of reduced neuronal activity after a subtotal lesion (Sabel, 2000). Stimulation (training) of the defect can lead to increased sensitivity or refinement of spared, but inactive neurones, so that less light energy is needed for detection and detection thresholds decrease. Before training, neuronal sensitivity may not reach the critical level that is needed to achieve conscious vision; during training, neuronal sensitivity is enhanced which can lead to conscious detection of stimuli during perimetryand visual field enlargement. Recently, Das & Huxlin (2010) provided an overview of hypothetical mechanisms for training-induced improvements of perception in cases of (partial) cortical blindness: training (1) stimulates spared islands of cortex within V1, (2) induces plasticity in spared perilesional V1, (3) reactivates damaged V1, (4) strenghtens extrastriatal pathways or (5) recruits or inhibits visual areas in the intact hemisphere. All variants point to changed neuronal activity by training. The increased neuronal activity may be a result of attentional effects on neuronal excitability, brought about by training. This was suggested by Zihl, who showed that attention modulates light-difference thresholds in the visual field (Zihl, 1979) and Poggel et al. who described how directed visual attention decreases detection thresholds in the visual field area that is attended (Poggel, 2004). In another study, Büchel & Friston showed that directing attention to visual motion led to increased connectivity which in turn led to increased neuronal activity (Büchel, 1997). Also, Marshall et al. observed that “(restorative) training appears to induce an alteration in brain activity associated with a shift of attention from the nontrained seeing field to the trained borderzone” (Marshall, 2008). These studies suggest that RFT teaches patients to successfully pay attention to a spared visual capacity, of which he/she was unaware before that moment. Sometimes, spared capacity is absent (patients HBo, WD) which means that no or too little spared neurones are present and which explains why some subjects show no recovery.

Some additional remarks regarding improvement can be made. First, our data show that before training less coloured stimuli and shapes are perceived beyond the visual field border than after training. This improvement happens in a gradual manner: closer to the unaffected field, both pre- and post-training scores are higher than near the absolute defect, which means that the first improve before the latter. This confirms the results from an earlier study: VFE develops gradually during training (Bergsma, 2010). Second, detection thresholds

decrease during training. In an earlier study we observed that, once threshold decrease sets in, it often accelerates quickly within 3-6 training sessions down to a normal or near-normal level (Bergsma, 2010). These observations fit the idea that restoration of original functional circuitry takes place through reconnection of islands of spared local visual networks to the larger perceptual system, instead of a new function being trained and learned. If that is true, it may be expected that other original visual functions that were inaccessible because of the VFD, may also be re-accessed as the VFD subsides. This means that original capacities of the visual system that were absent in the VFD, will return in the regained visual field areas. In this study, we indeed found improvement of non-trained cortical functions (colour and shape perception and reading) after training for detection of elementary white light stimuli. This points to a transfer effect of the training results to higher cognitive functions, in line with findings of other investigators: Zihl & Von Cramon observed that training lowers detection thresholds which leads to improved colour perception (Zihl, 1979) and increased reading speed after training (Zihl, 1985). Kasten et al. showed that computer-based training induced a visual field size increase and an improvement of colour/shape perception (Kasten, 2000).

Methodological Issues

For 3 patients (AM, HBr and RQ) the post-onset time ranged from 6 to 9 months. In these cases residual spontaneous recovery cannot completely be ruled out, but it is not expected (Zhang et al., 2006). We therefore conclude that the visual border shifts are induced by the training in the majority of our patients at least.

Training with simple white stimuli not only improved brightness perception, as expressed by the enlarged visual fields, but also improved performance on other functions such as colour and shape discrimination in 3 out of 7 patients. This was reported before by Zihl & von Cramon (1985) and Kasten et al. (2000), but it does not concur with the results of Pothoff (1995), who argued that these functions must be trained separately. It is not known whether separate training programs with task specific stimuli yields better results, but such an approach is certainly more time consuming than transfer of visual performance improvements to other tasks after a single training program with white stimuli.

The colour- and shape test locations were selected directly around and beyond the visual field border before training started. Because the colours we presented were all filled circles, it might be argued that this caused a shape-bias during this experiment in favour of reporting circles. If this is true, then we would expect patients to make more mistakes than predicted by chance in the shape condition (which means that performance values fall below 0.33, because both conditions contain 3 stimulus variants to choose from) while not so in the colour condition. We observed that the latter is not the case and that no preference exists for choosing circles, so that, although a shape-bias cannot be ruled out, it certainly is not more prominent than a colour-bias.

As can be seen in figure 4, dissociation exists between dynamic perimetry and the recognition of colours and shapes. Already before training, all patients correctly identified a few stimuli just beyond the visual field border (as can be recognized by pre-training scores above chance level). We think this occurs because dynamic perimetry can yield conservative

results within relative field defects. In this area, visual perception is reduced to partial, distorted or otherwise degraded perception and as a consequence, reaction times are increased. However, because the stimulus is being moved towards the fixation point during dynamic perimetry, the increased reaction time will lead to inward displacement of the stimulus detection location, in contrast to the static colour and shape presentation. Thus visual responsiveness to static stimuli may occur just beyond the field border.

Concluding, it is possible to actually improve visual functioning in hemianopic patients by enlarging the visual fields using RFT, which confirms the findings of Kasten et al. (2000) and Zihl & von Cramon (1985), who also found significant correlations between VFE and improved performance. However, the transfer of training effects to other visual functions is not the same for all subjects. In this study we find that VFE does not automatically lead to improved performance on untrained for visual tasks: this depends on a minimum amount of eccentricity-dependant VFE. The estimated cortical surface gain (in mm) as a measure for VFE takes eccentricity of the VFE into account and can quite well distinguish patients that improved significantly from patients that did not. Our data suggest that if training on a simple light detection task causes an ECSG_mm of 6 mm or more one likely will find significant behavioural and perceptual improvements.

After having studied low-level perception processes and a higher cognitive function like reading, it is interesting to find out if the transfer effect will also be noticeable in even higher functions, e.g. driving a car.

Acknowledgements/Funding

The study was approved by the medical ethics committee METC, Utrecht, The Netherlands under protocol number 98/271. We like to thank dr. WR Pestman for his valuable support on statistical analyses and dr. MAHHL Raemaekers for acquisition of the MRI-scans. This study was subsidized by the following Dutch foundations: **Stichting centraal fonds RVVZ** (proj. doss. 795); **Stichting NUTS-OHRA** (proj. SNO-T-08-30); **Stichting Blindenpenning.** The study sponsors had no involvement in study design; in the collection, analysis and interpretation of data; in the writing of the report; in the decision to submit the paper for publication. Informed consent was obtained from all subjects. There are no competing interests.

References

1. Kasten E., Poggel D.A., Sabel B.A. Computer-based training of stimulus detection improves color and simple pattern recognition in the defective field of hemianopic subjects. *Journal of Cognitive Neuroscience.* 2000; 12(6): 1001-1012.
2. Bergsma, D.P., & van der Wildt G.J. Visual training of cerebral blindness patients gradually enlarges the visual field. *British Journal of Ophthalmology*. 2010; 94: 88-96.
3. Zihl, J. *Rehabilitation of Visual Disorders After Brain Injury*. Hove: Psychology Press; 2000.
4. Bergsma, D.P., & van der Wildt G.J. Properties of the regained visual field after visual detection training of cerebral blindness patients. *Restorative Neurology and Neuroscience*. 2008; 26: 365-375.
5. Julkunen L., Tenovuo O., Jaaskelainen S., et al. Rehabilitation of chronic post-stroke visual field defect with computer-assisted training: a clinical and neurophysiological study. *Restorative Neurology and Neuroscience.* 2003; 21(1-2): 19-28.
6. Kasten E., Wust S., Behrens-Baumann W., & Sabel B.A. Computer-based training for the treatment of partial blindness. *Nature Medicine.* 1998; 4(9): 1083-1087.
7. Kasten E., Poggel D.A., Muller-Oehring E. et al. Restoration of vision II: residual functions and training-induced visual field enlargement in brain-damaged patients. *Restorative Neurology and Neuroscience.* 1999; 15(2-3): 273-287.
8. Kasten E., Bunzenthal U., & Sabel B.A. Visual field recovery after vision restoration therapy (VRT) is independent of eye movements: an eye tracker study. *Behavioral Brain Research.* 2006; 25, 175(1): 18-26.
9. Kerkhoff G. Restorative and compensatory therapy approaches in cerebral blindness - a review. *Restorative Neurology and Neuroscience.* 1999; 15(2-3): 255-271.
10. Poggel D.A., Kasten E., Muller-Oehring E.M. et al. Unusual spontaneous and training induced visual field recovery in a patient with a gunshot lesion. *Journal of Neurology, Neurosurgery and Psychiatry.* 2001; 70(2): 236-239.
11. Sabel B.A., & Kasten E. Restoration of vision by training of residual functions. *Current Opinions in Ophthalmology.* 2000; 11(6): 430-436.
12. Sabel B.A., Kenkel S., & Kasten E. Vision restoration therapy. *British Journal of Ophthalmology.* 2005; 89(5): 522-524.
13. Sabel B.A. Vision restoration therapy and raising red flags too early. *British Journal of Ophthalmology.* 2006; 90(5): 659-660.
14. Van der Wildt G.J., & Bergsma D.P. Visual field enlargement by neuropsychological training of a hemianopsia patient. *Documenta Ophthalmologica.* 1998; 93(4): 277-292.
15. Werth R., & Moehrenschlager M. The development of visual functions in cerebrally blind children during a systematic visual field training. *Restorative Neurology and Neuroscience.* 1999; 15(2-3): 229-241.
16. Zihl J., & von Cramon D. Restitution of visual function in patients with cerebral blindness. *Journal of Neurology, Neurosurgery and Psychiatry.* 1979; 42(4): 312-322.
17. Zihl J. Recovery of visual functions in patients with cerebral blindness. Effect of specific practice with saccadic localization. *Experimental Brain Research.* 1981; 44(2): 159-169.
18. Zihl J., & von Cramon D. Visual field recovery from scotoma in patients with postgeniculate damage. A review of 55 cases. *Brain.* 1985; 108(Pt 2): 335-365.

19. Mueller I., Mast H., & Sabel BA. Recovery of visual field defects: a large clinical observational study using vision restoration therapy. *Restorative Neurology and Neuroscience.* 2007; 25: 563-572.
20. Balliet R., Blood K.M., & Rita P. Visual field rehabilitation in the cortically blind? *Journal of Neurology, Neurosurgery and Psychiatry.* 1985; 48(11): 1113-1124.
21. Horton JC. Vision restoration therapy: confounded by eye movements. *British Journal of Ophthalmology.* 2005a; 89(7): 792-794.
22. Horton JC. Disappointing results from Nova Vision's visual restoration therapy. *British Journal of Ophthalmology.* 2005b; 89(1): 1-2.
23. Plant G.T. A work out for hemianopia. *British Journal of Ophthalmology.* 2005; 89(1): 2.
24. Reinhard J., Schreiber A., Schiefer U., et al. Does visual restitution training change absolute homonymous visual field defects? A fundus controlled study. *British Journal of Ophthalmology.* 2005; 89(1): 30-35.
25. Roth T., Sokolov A.N., Messias A., et al. Comparing explorative saccade and flicker training in hemianopia. *Neurology.* 2009; 72: 324-331.
26. Bouwmeester L., Heutink J., & Lucas C. The effect of visual training for patients with visual field defects due to brain damage: a systematic review. *Journal of Neurology, Neurosurgery and Psychiatry.* 2007; 78: 555-564.
27. Pelak V.S., Dubin M., & Whitney E. Homonymous Hemianopia: a critical analysis of optical devices, compensatory training, and NovaVision. *Current Treatment Options in Neurology.* 2007; 9: 41-47.
28. Frisén, L. *Clinical Tests of Vision*. New York: Raven Press; 1990
29. Heijl A., & Krakau C.E.T. An automatic static perimeter, design and pilot study. *Acta Ophthalmologica.* 1975; 53: 293-310.
30. Cowey A., & Rolls E.T. Human cortical magnification factor and its relation to visual acuity. *Experimental Brain Research.* 1974; 21: 447-454.
31. Das A., Huxlin KR. New approaches to visual rehabilitation for cortical blindness: outcomes and putative mechanisms. *The Neuroscientist*. 2010; 16(4): 374-387.
32. Poggel D.A., Kasten E., & Sabel BA. Attentional cueing improves vision restoration therapy in patients with visual field defects. *Neurology.* 2004; 63(11): 2069-2076.
33. Büchel C., & Friston K.J. Modulation of connectivity in visual pathways by attention: cortical interactions evaluated with structural equation modelling and fMRI. *Cerebral Cortex.* 1997; 7: 768-778.
34. Marshall R.S., Ferrera J.J., Barnes A. et al. Brain activity associated with stimulation therapy of the visual border zone in hemianopic stroke patients. *Neurorehabilitation and Neural Repair.* 2008; 22(2): 136-144.
35. Zhang X., Kedar S., Lynn M.J., Newman N.J., Biousse V. Natural history of homonymous hemianopia. *Neurology.*2006; 66: 901-905.
36. Pothoff R.D. Regeneration of specific nerve cells in lesioned visual cortex of the human brain: indirect evidence after constant stimulation with different spots of light. *Journal of Neuroscience Research.* 1995; 15: 787-796.
37. Kasten E., Muller-Oehring E., Sabel B.A. (2001) Stability of visual field enlargements following computer-based restitution training -- results of a follow-up. Journal of Clinical and Experimental Neuropsychology 23: 297-305.
38. Bergsma D.P., Leenders M.J., Verster J.C., van der Wildt G.J., van den Berg A.V. (2011) Oculomotor behavior of hemianopic chronic stroke patients in a driving simulator is modulated by vision training. Restorative Neurology and Neuroscience 29 347–359.