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Oculomotor behavior of hemianopic chronic stroke patients in a driving simulator is modulated by vision training

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Abstract. *Background*: Visual Restorative function training aims to decrease visual field defect size after acquired brain damage. Some chronic stroke patients regain permission to drive a car after training. This points to a concomitant change in oculomotor behavior, because visual field enlargement is hardly ever large enough for legal driving. This study investigated vRFT-induced changes in oculomotor behavior, using a driving simulator.

Methods: Driving performance and oculomotor behavior were measured before and after training in 6 hemianopia patients who had trained 65 hours with vRFT on a PC at home.

Results: Two patients showed negligible visual field enlargement (VFE) and four showed moderate to substantial VFE. Because less visual cortex is devoted to the processing of peripheral than central visual field the same VFE corresponds to less functional restoration of cortex when the defect is at high eccentricity. When this is taken into account, then precisely the two patients that showed the largest cortical gains made significantly more eye movements in the direction of their visual field defect after training.

Conclusions: vRFT with mandatory eye fixation can result in increased eye movement behavior towards the defect. Our study suggests that a threshold amount of cortical functional restoration is required for this effect.

Keywords: Stroke, homonymous hemianopia, restorative function training, visual field enlargement, driving simulator, attention

Abbreviations

VFD	Visual Field Defect
ADL	Activities of Daily Life
CST	Compensatory Saccade Training
VRT	Vision Restoration Therapy
vRFT	visual Restorative Function Training
SLO	Scanning Laser Ophthalmology
HRP	High Resolution Perimetry
TAP	Tübingen Automated Perimetry
VFE	Visual Field Enlargement
RTR	Risk Taking Ride
CMF	Cortical Magnification Factor
GLM	General Linear Model

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1. Introduction

Roughly 25% of chronic stroke patients have visual field defects (VFDs) (Zihl, 2000a). VFDs, such as

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hemianopia, interfere considerably with Activities of Daily Life (ADL) like reading, exploration and navigation (Zihl, 2000b; Sabel and Kasten, 2000; Raninen et al., 2007). Many studies have explored the human potential for visual field recovery by visual training. Broadly, two strategies have been studied. One strategy is to exploit subjects' voluntary control of eye movements to raise the frequency of exploratory saccades towards their defective field. This method, known as compensatory saccade training (CST) was successful in raising the frequency of saccades towards the defect in 35%–75% of hemianopia patients suffering from a stroke (Kerkhoff et al., 1994; Zihl, 1995; Pambakian et al., 2004). CST does not change the VFD size. Partial restoration of visual function within the field defect, or reducing the extent of the blind field, is the aim of the second approach. For this purpose, Zihl and von Cramon developed a visual training with which the border areas of the visual fields were stimulated using perimetric stimuli (e.g. Zihl and von Cramon, 1979, 1985). A computerized version of this training was developed by Kasten and co-workers (Kasten et al., 1998, 1999), which was termed Vision Restoration Therapy (VRT). In our study, we use a custom training procedure like VRT that we called 'visual restorative function training' (vRFT). Although vRFT follows a very similar training procedure as VRT, the term vRFT was preferred instead of VRT in the present study because our method does not identify areas of residual vision and is not self-adjusting like VRT.

Field enlargement following VRT has been shown in chronic stroke patients using subjective perimetry (Bergsma and Van der Wildt, 2008; Raninen et al., 2007; Mueller et al., 2007; Schmielau and Wong, 2007; Kasten et al., 2006, 2000, 1999, 1998; Sabel et al., 2005, 2000; Julkunen et al., 2003; Poggel et al., 2001; Kerkhoff, 1999; Werth and Moehrenschlager, 1999; Van der Wildt and Bergsma, 1998; Zihl and Von Cramon, 1986, 1985, 1981; Pöppel et al., 1978). Others reported absence of enlargement after VRT (Reinhard et al., 2005; Balliet et al., 1985) or otherwise questioned its beneficial effects (Roth et al., 2009; Horton, 2005 a + b; Plant, 2005). Reinhard et al. compared scanning laser ophthalmology (SLO) with high resolution perimetry (HRP) and Tübingen automated perimetry (TAP) before and after VRT (Reinhard et al., 2005). Within the same patients, visual field enlargement was observed with TAP and HRP but not with SLO (Sabel et al, 2004) and several commentators speculated that eccentric fixation and/or frequent saccades towards the defect explained the positive outcomes of TAP and HRP (Horton, 2005 a + b; Plant, 2005). Dispute also occurred because some fixation control methods are more convincing than others, thereby casting doubt on training effects on visual field size (Bouwmeester et al., 2007; Pelak et al., 2007). Kasten et al. showed that the observed visual field recovery after training is uncorrelated to the patient's eye movements (Kasten et al., 2006). This rather indirect measure for indicating absence of confounding eye movements was recently extended by a direct test: careful measurement of the gaze direction allowed us to exclude trials with fixation drifts or saccades towards the defect during perimetry. Thus the visual field enlargements after vRFT were exclusively based on trials with adequate fixation in our study (Bergsma and Van der Wildt, 2010).

Visual field enlargement by itself does not necessarily imply that behavioral performance improves. This raises the question whether CST and vRFT strategies actually lead to ADL improvement? ADL improvement after VRT has been reported in subjective questionnaires (Roth et al., 2009; Sabel et al., 2004; Mueller et al., 2003), but these may be unreliable (Pambakian, 2004). VRT has also been reported to improve performance in paper-pencil tests of visual exploration and attention (Kasten et al., 1999) and to increase reading speed in trained hemianopia patients with visual field enlargement after stroke (Zihl and Von Cramon, 1985; Bergsma and Van der Wildt, 2010). In a video-presentation of a busy intersection for example, hemianopia patients could detect more peripheral moving traffic objects after vRFT as measured by the onset and amplitude of a saccade towards the object (Bergsma and Van der Wildt, 2009). Because eye movements were not allowed during training, these results may suggest that the enlarged visual field actually 'draws' the eyes towards it and thus is actually used for visual information processing. In an earlier study, we found improvements of peripheral acuity, peripheral color vision and peripheral critical flicker fusion after training. In our opinion, this also suggested information processing capability of regained visual fields after training (Bergsma and Van der Wildt, 2008). CST enlarges the 'scan range' of a patient by instruction to make eye movements towards the affected hemifield (Roth et al., 2009; Pambakian et al., 2005; Nelles et al., 2001) which can lead to ADL improvements (e.g. in hobbies, reading, mobility and orientation) (Sabel et al., 2004; Mueller et al., 2003). Interestingly, VRT has also been reported to cause some hemianopia patients

to scan more in their affected visual field (Pambakian et al., 2004; Kasten et al., 2000, 1998), while in other studies an absence of change in eye movement patterns after VRT is reported (Kasten et al,. 2006). Given the conflicting outcomes on altered oculomotor behavior after VRT, we therefore investigated in this study whether a change in eye movement patterns is a result of vRFT-induced visual field enlargement and not by the fact that vRFT was inadvertently carried out as CST.

Several studies have reported on the important topic of driving abilities of hemianopia patients and on (re-) learning to drive with hemianopia (e.g. Peli et al., 2005; Kooijman et al., 2004; Schulte et al., 1999; Ball et al., 1992). In this study, we therefore compared the pre- and post-training oculomotor behavior of chronic stroke patients with hemianopia while driving in a simulator. Subsequently, the effects of vision training (i.e. vRFT) on driving performance of these patients was investigated by determining the association between 1) visual field enlargement and oculomotor behavior; 2) oculomotor behavior and driving simulator parameters as well as 3) visual field enlargement and driving simulator parameters.

2. Methods

This research followed the tenets of the Declaration of Helsinki and subject's informed consent was obtained. The research was approved by the Medical-ethical Committee of the Utrecht University.

2.1. Experimental protocol

Each patient was subject to the following procedures: 1) pre training perimetry, 2) pre training driving test, 3) vRFT, 4) post training perimetry and 5) post training driving test, whereas healthy control subjects did only follow the pre and post training driving test.

2.2. Experimental subjects

Nine chronic stroke patients with homonymous VFDs volunteered for study participation. In the past, these patients were discharged from a hospital stroke unit after having been diagnosed with stroke. Inclusion criteria were: absence of visuo-spatial neglect (assessed with the line bisection task), stable fixation, (former) licensed driving experience and presence of an absolute field defect. Subject age ranged from 39 to 68 years (mean $\pm$ 1 S.D. = 51.9 $\pm$ 9.7 years). The time between stroke onset and testing ranged from 6 to 100 months (mean $\pm$ 1 S.D. = 33 $\pm$ 35 months). Eye movement data of two patients were lost due to technical reasons (P7 and P8) and are not reported. No data were available of a ninth participant, because this patient dropped out from training and did not participate in the post-training measurements.

2.3. Control subjects

Six actively driving, age-matched healthy persons (C1–C6) volunteered as control subjects in the study. The age of the control subjects ranged from 42 to 70 years (mean $\pm$ 1 S.D. = 57.2 $\pm$ 10.6 years).

2.4. Restorative function training

Custom built software was used to administer vRFT at the patient's home on a computer screen. The program presents, against a dark grey background, the visual stimulus with increasing contrast in the border area between the VFD and the 'seeing' field. vRFT is a custom made program different from Vision Restoration Therapy. However, vRFT follows a very similar training procedure as VRT: it stimulates the defective area. Stimulus diameter ranged from 0.5° near the fovea to 4° at an eccentricity of 40°. Training areas concern the affected hemifield: central 20° for P2–P5, P7, P8; central 30° for P1; 20°–40° for P6. During the training itself, eye movements are not allowed and the patient must exert a covert attention shift towards the affected hemifield. The patient presses a button when the stimulus is detected and, right after detection, chooses the content or the location of the stimulus from a set of possible answers.

If patients made saccades towards the presented stimuli during training, they would have inadvertently changed vRFT into CST. To avoid this pitfall, we

1) Explicitly informed patients that inaccurate fixation could reduce or preclude visual field recovery,
2) had regular patient contact in the early phase of training, during which patients and especially their spouses were asked to judge fixation behavior during training and to correct it if necessary.

In our experience all patients are highly motivated to perform training as requested. As with all therapies which patients carry out at home, one cannot prevent

entirely that the patient occasionally deviates from the required behavior during the training.

2.5. Perimetry

Visual fields were assessed monocularly by measuring the borders of the absolute VFDs with dynamic Goldmann perimetry before and after training. Goldmann perimetry is used as a standard for detecting VFD´s (e.g. Riemann et al., 2000; Wong and Sharpe, 2000). To optimise intra-examiner reliability, we repeated measurements three times at each measured meridian. Also, the instructions of Frisén were closely followed (Frisén, 1990). Visual fields were based on trials with adequate fixation only (a more elaborate description of the perimetry method can be found in Bergsma & vd Wildt, 2008).

2.6. Driving simulator

The 'STISIM Driving' simulator (Systems Technology Inc., Hawthorne, CA, USA) of the psychopharmacology department at the Utrecht University was used. A Dutch driving scenario for the STISIM was developed by 'EyeOctopus BV' in Hoogeveen, The Netherlands. STISIM consists of a car-unit and a projection screen. A video beamer projected images (2.10 m wide and 1.58 m high). The distance of the observer to the screen was 2.30–2.50 m so that the projected image measured approximately $50^\circ - 55^\circ$ horizontally and 40° vertically. Before and after training of patients, participants drove a 20 km Risk Taking Ride (RTR) in the driving simulator, which comprised a ride through busy villages and quiet roads, during which events were added (e.g. pedestrians and cyclists crossing the street, cars or motorcycles overtaking the car that the patient is driving). Before the RTR, participants drove 10 minutes to get accustomed to driving in the simulator. All participants were instructed to follow the current existing driving legislation, follow directions and drive safely. Patients were allowed to look around freely and *no* instructions were given concerning eye movements. Before and after training, patients and control subjects drove the same roads as the patients, with 14 to 17 weeks in between.

2.7. Eye movements

If vRFT has an influence on visual behavior we would expect a significant increase of the number of saccades to the peripheral visual field (i.e. large saccades). Small saccades that keep the line of sight within the central visual field were deemed irrelevant as the central field was intact in all but one patient. Eye movements were recorded on video and transferred to DVDs. The camera was placed behind the driver, simultaneously capturing the projected simulation and a mirror (Ø 15 cm), reflecting the driver's face. From the recordings, the large saccades were later counted in 12 successive RTR epochs that were demarcated by certain objects along the road. This was done three times by one observer (ML). A second observer (DB) –independently- counted the saccades of all patients an additional time. 'STISIM Driving simulator parameters were: average speed, number of collisions with other vehicles or pedestrians, speed limit exceeding and out of-lane-scores (centerline and road edge crossings) were measured.

2.8. VFE eccentricity

It is common knowledge that acuity diminishes with increasing eccentricity (Cowey & Rolls, 1974; Frisén & Glansholm, 1975). This is caused by the fact that with increasing eccentricity, less cortical tissue is devoted to 1 degree of visual angle. Therefore, foveal vision provides for a much higher visual resolution than peripheral vision. This means that a VFE near the fovea is much more striking or conspicuous than a VFE of the same size in the peripheral visual field (Poggel et al., 2007). Expressing VFE in terms of an average border shift (in degrees) does not make a distinction between possible different eccentricities at which VFE occurred. This probably weakens any correlation between training induced improvements and the VFE (in degrees), because a conspicuous foveal VFE is more likely to induce improvements than an *in*conspicuous peripheral enlargement.

Therefore, for each patient we convert the observed VFE into a general cortical measure of enlargement using the Cortical Magnification Factor (Cowey and Rolls, 1974) and compare this to the patients' oculomotor behavior in a driving simulator. We calculated cortical VFE as follows: the trained visual field area is divided in sectors like a pie-chart with angular segments of 2.5°. 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 cortical VFE measure.

In hemianopia, the visual field border is oriented vertically and 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 (see Fig. 1) according to

$$\mathrm{ECSG} = (\mathrm{CMF_B} - \mathrm{CMF_A})^* \sin(\theta) \quad (1)$$

$\mathrm{CMF_A}$ and $\mathrm{CMF_B}$ represent converted eccentricity values at locations 'A' and 'B', denoting the cortical distances from the foveal representation according to the data of Cowey.

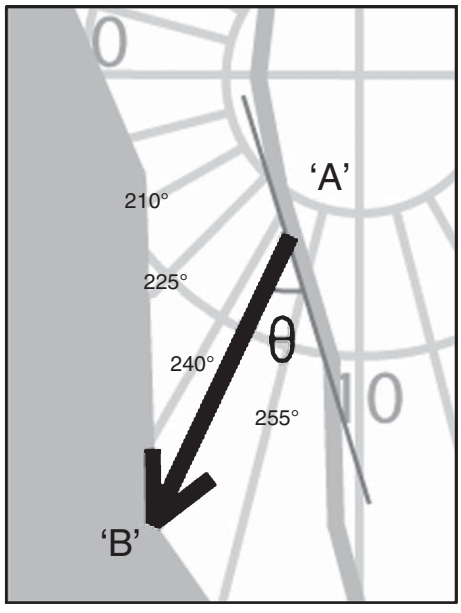

Fig. 1. Example of cortical VFE calculation: The grey line depicts the pre-training visual field defect border. The grey area represents the post-training absolute field defect. The black arrow indicates the border shift in the 2.5° wide sector between angles 242.5° and 245°. Because the border is not 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. VFE is obtained by averaging across all sectors, after application of the sine corrections in each sector. CMF-values are established using the Cortical Magnification Factor of Cowey and Rolls.

2.9. Statistical analyses

Changes in oculomotor behavior (the number of saccades to the left or the right) across epochs were evaluated using Multivariate GLM (MANOVA) in SPSS for all participants.

To study the relationship between visual field enlargement and oculomotor behavior, we calculate the probability that a patient from the experimental group shows a change in saccade pattern *and* a substantial field enlargement by sheer coincidence. This probability is a combinatorial problem:

$$P(n, m; j, k) = \frac{\binom{k}{j}(n-j)!m!}{n!(m-j)!} \quad (2)$$

(m = number of patients with a change in eye movements; j = number of patients that show both change in eye movement and substantial field enlargement; k = number of patients that shows a substantial field enlargement; $\binom{k}{j}$ = number of different sets of 'j' subjects ($j \leq$ k) that can be taken by random selection from a population of 'k' subjects).

We tested three conditions, which were chosen for their increasing specificity of what kind of change in eye movements occurs. The first condition is a pure increase in saccade frequency without a relation to the defected side. The second condition tests for an increase of the saccades to the affected side while the last test defines a specific increase of saccades to the affected side while the saccades to the normal side are not changed after the training or even reduced.

Non-parametric t-tests of pre/post training STISIM measurements were performed *within* the patient group and the control group (paired samples; Wilcoxon signed rank test) and *between* the patient and control groups (independent samples; Mann-Whitney U test). All tests were applied with a two-tailed analysis and 0.05 as the level of significance.

To study the relationships oculomotor behavior - driving simulator parameters and visual field enlargement - driving simulator parameters we used non-parametric t-tests (Wilcoxon signed rank test) with a two-tailed analysis and 0.05 as the level of significance.

3. Results

Hemianopia patients trained for a period of 15 weeks, 5 days a week, 1 hour daily. Personal circum-

stances caused total training time to vary between 70 and 90 hours (mean ± 1 S.D. = 78.1 ± 5.9 hrs). After training, two patients (P3 and P4) showed a significantly increased amount of eye movements towards the affected visual field.

Complete data of six patients were available for analysis (visual field, eye movement scores and STISIM data for P1–P6).

3.1. vRFT effects on visual fields

Figure 2 shows the homonymous pre- and post-training absolute VFDs for the eye in which the blind spot could be measured ($N = 8$). Two hemianopia patients show substantial VFD border shifts of $\geq 5^\circ$ (P3 and P6); four show average shifts between 2° and 5° (P1, P2, P4 and P8) and two hemianopia patients have negligible enlargements ($<2^\circ$, P5 and P7). The average shift was 3.9°.

3.2. VFE eccentricity

As mentioned in the Methods section, VFE can also be expressed in the average amount of cortical tissue that represents the VFE. To do so, we use the Cortical Magnification Factor (CMF) of Cowey and Rolls (1974). The CMF describes the visual field angle in degrees that is processed by 1 mm of visual cortex

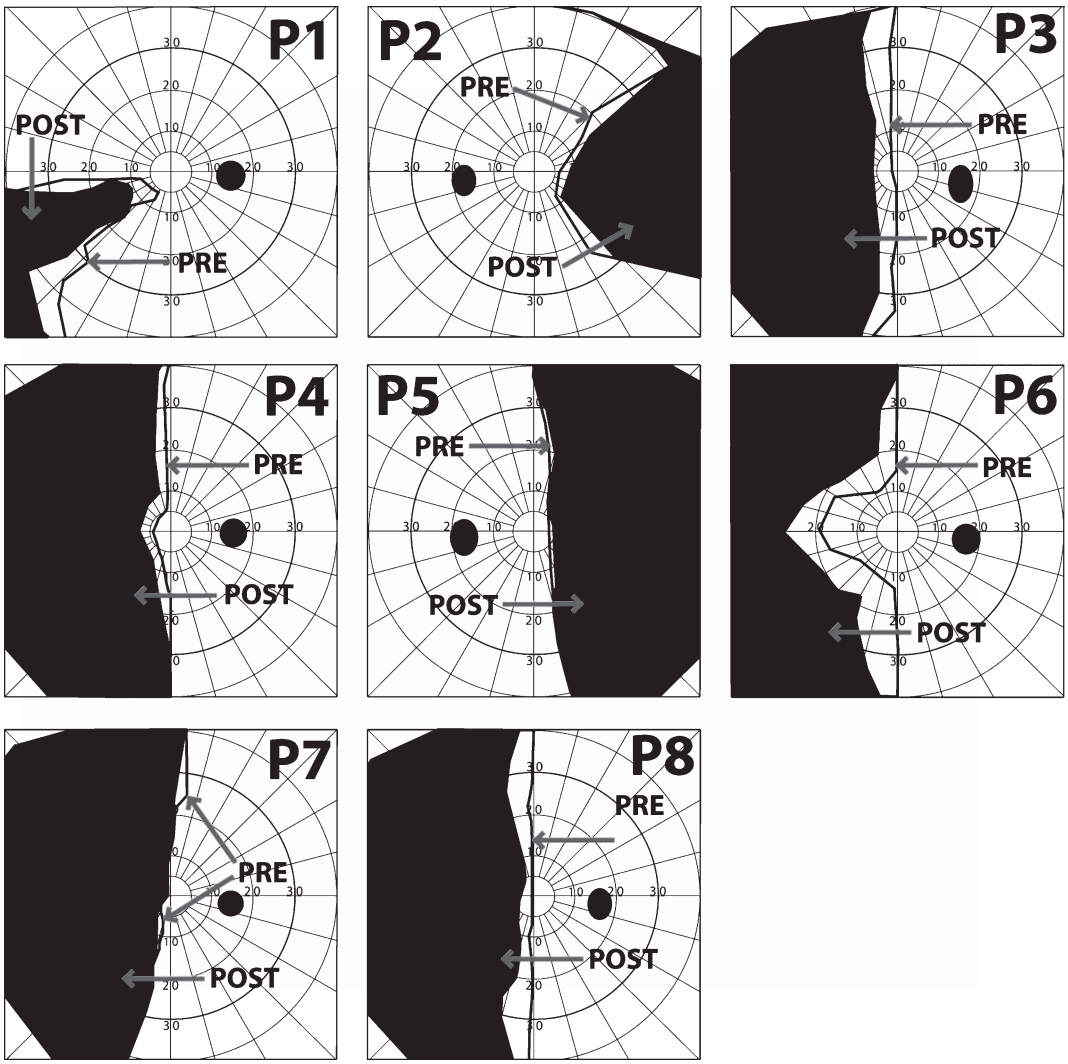

Fig. 2. Pre- and post-training visual fields of trained hemianopia patients.

as a function of the eccentricity (see Table 2). The CMF is known to describe very well the eccentricity dependence of performance on various visual tasks like spatial discrimination, motion detection, and shape recognition. The different VFEs of the 8 patients are shown in table 1. We now see that there are actually 3 patients with negligible VFEs of 0.1 to 1.9 mm (P2, P5, P7), 2 patients with moderate VFEs of 4.2 mm (P1 and P6) and 3 patients with substantial VFEs of 6.7 to 10.2 mm (P3, P4 and P8).

3.3. Oculomotor behavior while driving

The inter-class correlation between the scores of both observers -to define inter-observer reliability- was 0.77 and 0.62 for left and right eye movements, respectively. In Life Sciences, a value ≥ 0.6 is regarded as a sufficient inter-class-correlation (Landis and Koch, 1977), so the observations are considered reliable. The differences between the observer-scores were caused by the fact that some of the smallest saccades were included by one observer, but overseen by the other. However, the somewhat larger and truly large saccades that we were interested in were counted by both observers. The average of the three scores of observer 1 was used for further analysis. Figure 3 shows the average number of saccades to the right and the left for each of the 12 epochs pre- and post-training for the 6 patients with complete data (P1–P6) and 6 control subjects (C1–C6). In 2 out of the 6 patients, a significant increase was found in the amount of saccades in the direction of their (left) visual field defect after training: P3 ($F_{(1,21)} = 5.110$; $p = 0.035$) and P4 ($F_{(1,21)} = 6.931$; $p = 0.016$). Although P1 clearly also made more saccades to his (left) defect visual field after training, this effect was not significant ($F_{(1,21)} = 2.187$; $p = 0.154$).

In patients P3 and P4, the number of saccades is significantly increased in epochs 1–2 and 9–10, during which patients drove in busy villages.

As expected, for the C1–C6, the number of saccades to either right or left did not differ significantly before and after training.

3.4. STISIM parameters (N = 6)

Table 3 sums up the values of the pre- and post-training STISIM parameters (average speed; number of collisions with other vehicles; number of pedestrians hit; number of times speed was exceeded; percentage of total distance driving out of lane). Pre-post STISIM measurements were compared between patient and control *groups*:

(1) Post-training, patient average speed was significantly increased compared to pre-training values (Wilcoxon: $Z = -2.547$, $p = 0.011$). No difference was observed in the control group ($Z = -0.314$, $p = 0.753$). Before training, controls drove significantly faster than patients

Table 1

Description of experimental subjects (hemianopia patients). HH = homonymous hemianopia; HQ = homonymous quadrantanopia. Patients descriptions are ordered from small to large VFEs

Patient	Type of damage	Affected brain area	Visual Field Defect	Gender	Post Onset Time (yrs)	Age (yrs)	Visual Field Sparing (pre)	Visual Field Sparing (post)	VFE (mm cortex)
P7	hemorrhage	Right optic radiation	HH left	F	8.3	40	<1°	<1°	0.1
P5	infarction	Left occipital cortex	HH right	F	1.2	39	4°	4°	1.6
P2	Infarction	Left optic radiation	HH right (incomplete)	F	2.2	47	6°	9°	1.9
P6	Infarction	Right occipital cortex	HH left (incomplete)	M	0.5	57	19°	29°	4.2
P1	hemorrhage	Right optic radiation	HQ lower left	M	1	45	6°	10°	4.2
P4	Infarction	Right optic radiation	HH left	M	0.7	58	4°	8°	6.7
P8	Infarction	Right occipital cortex	HH left	M	0.7	68	<1°	4°	7.8
P3	Infarction	Right optic radiation	HH left	M	6.6	57	2°	6°	10.2

Table 2

Magnification factor (mm cortex per degree of visual angle) at different eccentricities

Eccentricity	2°	5°	10°	15°	20°	25°	30°
Cortical Area for 1°	6 mm	3 mm	1.8 mm	1.1 mm	0.8 mm	0.6 mm	0.5 mm

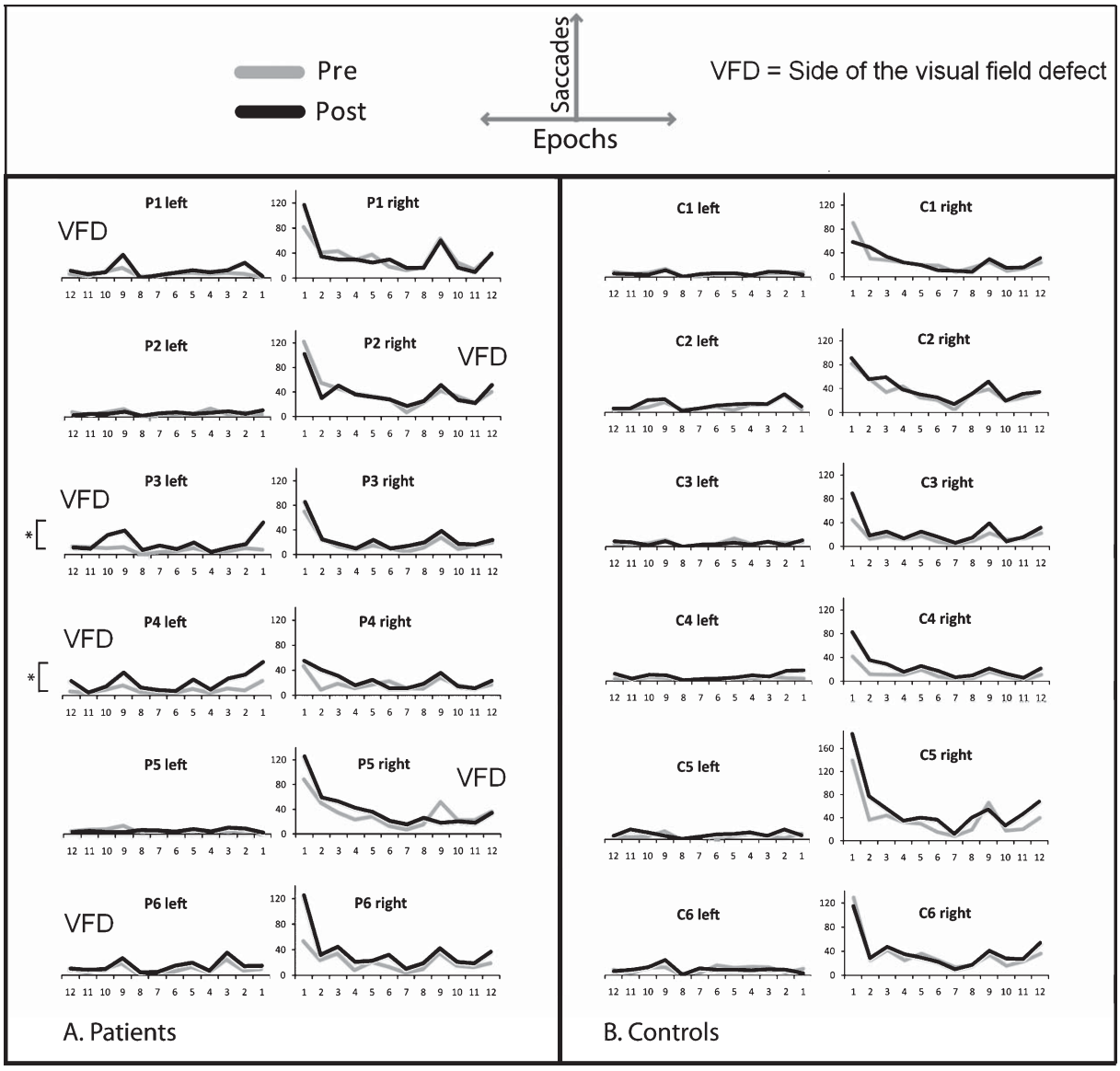

Fig. 3. Average number of left- and rightward saccades (y-axis) of each epoch (x-axis) during pre- and post training RTR in 6 patients (fig 3A) and 6 controls (fig 3B). *: significant increase in the number of saccades to the defect visual field after training ($p \leq 0.05$). No significant differences were found between the pre- and post-training number of saccades to the left or the right of the control subjects. Note the different scale of the y-axis of C5.

(M-W: $Z = -2.236$, $p = 0.025$). After training, the average driving speed of the patient group approached the average of the control group ($Z = -1.061$, $p = 0.289$).

(2) In all patients, except P8, the number of collisions with other vehicles decreased after training. Before training, patients have significantly more collisions than controls ($Z = -2.321$, $p = 0.020$), a difference that disappears after training. Patients do improve on this variable, but not significantly.

(3) In the patient group a slight reduction occurs of the number of collisions with pedestrians after training (mean pre = 1.63, mean post = 1.25;

Table 3
Pre- and post-training values of five different STISIM measurements

STISIM parameters	Average Speed pre	Average Speed post	# Collisions (vehicles) pre	# Collisions (vehicles) post	# Collisions (pedestrians) pre	# Collisions (pedestrians) post	# Speed Exceeding pre	# Speed Exceeding post	% Out of Lane pre	% Out of Lane post
Patients										
P1	34.3	36.3	5	1	1	1	2	1	12.9	11.8
P2	44.7	50.9	4	1	1	2	7	9	15.4	12.7
P3	39.6	42.7	5	2	3	2	5	4	13.9	13.0
P4	46.0	47.6	0	0	2	2	8	7	10.8	9.8
P5	33.0	36.4	1	0	0	1	1	0	15.9	13.9
P6	41.5	44.2	2	0	2	1	2	1	11.6	12.8
Controls										
C1	45.9	48.1	1	0	1	1	10	5	12.8	13.0
C2	50.2	47.8	1	0	1	0	9	6	11.7	11.9
C3	51.5	54.0	0	1	1	1	4	6	12.0	12.0
C4	50.2	50.1	1	2	0	1	7	9	10.7	11.1
C5	44.6	39.5	1	0	0	1	5	3	11.5	1.38
C6	40.4	42.5	1	0	0	1	1	3	12.8	9.5

controls: 0.50 and 0.84 respectively). Before training, the difference between patients and controls just missed significance ($Z = -1.852$; $p = 0.064$), after training the difference is not significant.

(4) All patients, except P2, exceeded the speed limit less often after training (mean pre = 4.25; mean post = 3.25). This change is however not significant ($Z = -1.611$; $p = 0.107$). Controls exceed speed limits more often (mean pre = 6; mean post = 5.34; difference n.s.). Patients and controls do not differ significantly before and after training.

(5) Finally, patients show significantly higher percentages of total distance driving out of lane than the control group before training ($Z = -2.239$, $p = 0.025$), but this difference disappears after training. Again, although 6 patients improve regarding this variable, the improvement is not significant for the patient group as a whole.

3.5. Relation between visual field enlargement and oculomotor behavior (N = 6)

We hypothesize that the change in oculomotor behavior is caused by the visual field enlargement. To study this relation, we calculated the probability that a patient from the experimental group shows a change in saccade pattern *and* field enlargement by sheer coincidence (null hypothesis). Hemianopia patients with large field enlargements (P3, P4) also showed:

(i) significant increase of horizontal saccades (P3, P4)

(ii) significant increase of horizontal saccades to the affected side, irrespective of saccades to the other side (P3, P4), but

(iii) no significant increase of horizontal saccades to the affected side and equal or less saccades to the other side.

Since conditions i and ii both concern P3 and P4, the result of equation [1] is the same: P(6, 2; 2, 2) = 1*24*2/(720*1) = 0.067 ($n = 6$, $m = j = k = 2$).

The null hypothesis that hemianopia patients with significant field recovery make more horizontal eye movements *by sheer coincidence* is close to rejection at the 5% level.

3.6. Relation between visual field enlargement and STISIM parameters (N = 6)

Taking the CMF into account, only P3 and P4 showed a significant field enlargement. P1, P2 and P6 showed medium field enlargement, but they were not significant. We compare pre-post parameter changes between the 2 patient-subgroups (2 hemianopia patients with and 4 hemianopia patients without significant field enlargement). Again, the groups are rather small, so that the tests do not have a high power. This may have caused the fact that we found no significant differences between the two subgroups of patients for the STISIM parameters: Average Speed ($Z = -1.342$; $p = 0.180$); Number of Collisions ($Z = -1.207$; $p = 0.227$); Hit Pedestrians ($Z = -1.238$; $p = 0.216$); Speed Exceeding ($Z = -1.366$; $p = 0.172$) and Out-of-Lane scores ($Z = -0.600$; $p = 0.549$).

3.7. Relation between oculomotor behavior and STISIM parameters (N = 6)

What does a significant increase of horizontal saccades imply for driving behavior? We could not find a significant change in STISIM parameters: Average Speed ($Z = -0.925$; $p = 0.355$); Number of Collisions ($Z = -.705$; $p = 0.481$); Hit Pedestrians ($Z = -0.968$; $p = 0.333$); Speed Exceeding ($Z = -0.787$; $p = 0.480$) and Out-of-Lane scores ($Z = 0$; $p = 1$). This could either be due to the fact that the training does not influence eye movement patterns or to the fact that the patient sample was too small. Therefore, further studies with larger samples are required.

4. Discussion

We trained 8 patients for restoration of the visual field using a strict fixation protocol and collected eye movement data from 6 of these patients in a driving simulator. In the group of 8 patients, we found VFEs ranging from 2–10° in 6 patients with a mean border shift of 3.9°. The two remaining patients showed no enlargement. These results concur with data from Kasten et al. (1998). When VFE is expressed in the amount of cortex (in mm) that is involved, VFEs range from 0.1 mm–10.2 mm. Importantly, in the group of 6 patients with eye movement data, precisely the 2 patients with the largest VFE (10.2 and 6.7 mm; P3 and P4) showed a significant increase in the number of large saccades towards the VFD. In precisely these two patients, the number of saccades was increased in epochs 1–2 and 9–10, during which patients drove in busy villages. Unfortunately, no eye movement data were collected for the third patient with a VFE of 7.8 mm. We conclude that vRFT can show an untrained side-effect: increased frequency of saccades to the defective hemifield *if* a threshold VFE is reached after vRFT. This threshold VFE is about 6 mm cortex. This suggests that above threshold VFE enables patients to attend and direct gaze to the recovered visual field. We could not establish significant improvement in driving behavior as a result of this change in saccadic behavior, probably as a result of lack of statistical power. Before we interpret these results, we address two major questions: (1) was the change in the visual field size reliable and (2) was the change in saccadic behavior caused by that change in field size? The visual field was measured using standard perimetry while strict eye fixation was requested. The field data of Fig. 2 are based only on those trials when the patient maintained fixation, so our estimates of the recovered field are adequate and not affected by breaking fixation during perimetry.

With dynamic perimetry, VFE may be overestimated when patients have increased perception of movement. At the same time, VFE may be *under*estimated by the fact that some patients hesitate to respond when a stimulus reaches the threshold of awareness. Because of this hesitation, the moving stimulus is located somewhat more centrally than should have been, considering the fact that 'coming through' already constitutes 'detection'. We were able to compare a few Goldmann dynamic fields with Octopus static fields within the same patients and noticed that -within patients- some areas are larger in the Goldmann fields while other areas are larger in the Octopus fields, which means that both under- and overestimation are possible within the same patient. Overall, these differences were small (1–4 degrees), so that increased Riddoch perception of motion did not influence perimetry much, if at all, in our patients.

Admittedly, the conversion of the perimetrical field recovery into a cortical measure involves a CMF measure that is derived from normal human subjects (Cowey and Rolls, 1974). Thus, our criterion assumes that for recovery of function the equivalent of the normal amount of human cortex at that eccentricity is required. Interestingly, Korogi et al. confirmed the CMF in patients with cortical damage, suggesting that the CMF remains a valid description of (visual) cortical organization in those patients (Korogi et al., 1997).

Could the observed change in oculomotor behavior be the result of CST? *If* patients made saccades during training, they could convert vRFT into CST. However, we would then expect dissociations between changes in saccadic behavior and field enlargement: first, visual field enlargement as we found, does not occur in CST (Roth et al., 2009). Secondly, we did not find an increase in the number of saccades in the patients without significant field enlargement, which would have been expected after CST. Therefore, we conclude that a threshold visual field enlargement needs to be reached to affect behavioral performance gains. This threshold depends on the CMF (Cowey and Rolls, 1974) and thus the eccentricity of the visual field border. It is possible that directing our patients' *attention* to their blind hemifield during training affected their saccadic behavior. Directed attention to the VFD leads immediately to –temporarily improved residual vision (Poggel

et al., 2006). It is conceivable that repeatedly focusing attention to the VFD leads to an increased expectancy for targets in the blind field, which increases the tendency to make saccades in the direction of the VFD, but that these saccades are (relatively) successfully suppressed during vRFT and 'released' at other moments. This means that successful vRFT may result in both restoration of visual fields *and* substitution by making eye movements. This may explain why some hemianopia patients from patient groups in earlier studies regained permission to drive a car again after training.

Does this also imply better driving in the simulator? As a group, patients did not show significant improvement due to training. However, given the variable training success with respect to field enlargement this may not be too surprising. There are some noteworthy trends in the individual performance. Three patients without significant field enlargement (P2, P5 and P6) showed increases in one or two of the STISIM parameters post training, indicating worse performance. In contrast, the other patients (P1, P3 and P4) only showed equal or improved performance after training according to the STISIM parameters. As mentioned before P3 and P4 showed large field enlargement across the entire vertical meridian. P1 showed near significant field enlargement in a limited range of directions (The lower left, fig. 2). In addition, P1 appears to make more horizontal eye movements (Fig. 3, epochs 2 & 9). Because we measured horizontal movements ignoring the vertical component, an increase in the number of movements to the lower left may have been rendered insignificant because pure horizontal and movements to the upper-left were not increased in patient P1. Thus, the STISIM parameters appear to tally well with the eye movement scores and field-enlargement data.

A final remark must be made concerning the tendency of all subjects to make more saccades to the right than to the left, irrespective of defect or training. We think this is caused by the fact that the speedometer and gear-indicator were displayed in the right visual field. All subjects frequently consulted this display. Also, all road signs and traffic lights were placed on the right side of the road, which subjects looked at regularly.

This study has a number of limitations: first, the small patient sample makes it difficult to significantly relate VFE and STISIM parameters. Second, our study had a pre-experimental design, acknowledging that data from a randomized clinical trial conducted in a larger sample may have produced less biased results with respect to number of saccadic eye movements. Third, the use of an electronic eye tracking device would have made the use of observers redundant and would have provided more precise information about the different aspects of a visual exploration deficit such as saccadic latency, staircase saccades and hypo- or hypermetric saccades. Nevertheless, although the small sample of patients and the eye movement analysis on a nominal scale set limits to the quantitative and statistical power of our findings, we think that our data strongly suggest that vRFT can lead to VFE *and* to an increased number of saccades towards the defect. Further research will provide more insight in the question whether the increased number of saccades has been caused by visual field enlargement or by an increased tendency to make saccades.

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