Computer-based training for the treatment of partial blindness

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Partial blindness after brain injury has been considered non-treatable. To evaluate whether patients with visual-field defects can profit from computer-based visual restitution training (VRT), two independent clinical trials were conducted using patients with optic nerve (n = 19) or post-chiasmatic brain injury (n = 19). In post-chiasma patients, VRT led to a significant improvement (29.4%) over baseline in the ability to detect visual stimuli; in optic nerve patients, the effects were even more pronounced (73.6% improvement). Visual-field enlargements were confirmed by the observation of a visual-field expansion of 4.9°–5.8° of visual angle and improved acuity in optic nerve patients. Ninety five percent of the VRT-treated patients showed improvements, 72.2% confirmed visual improvements subjectively. Patients receiving a placebo training did not show comparable improvements. In conclusion, VRT with a computer program improves vision in patients with visual-field defects and offers a new, cost-effective therapy for partial blindness.

In recent years, computer technology has been utilized to train mental functions of the human brain. For example, some encouraging findings have been reported whereby children with language learning deficits can benefit from computer-based training[1], but the claim that computer-based training can facilitate brain functions as well in other functional domains has not yet been convincingly substantiated. Using the visual system as a paradigm, we now show that computer-based training may be used as an effective treatment for partial blindness of adult brain-injured patients.

Loss of visual functions is a frequent consequence of brain injury due to stroke or trauma. Patients typically lose sight in one-half of the visual field while the other side often remains unimpaired. This partial blindness, termed hemianopia, is generally considered untreatable because it is believed that proper vision requires a highly specific neuronal organization, which is laid down during early development[2]. Despite this specificity in neuronal organization, there is, however, a considerable degree of plasticity in the injured visual system[3–5] and lost visual functions can recover spontaneously to some extent in animals[6,7] and humans[8]. For example, following eye closure in kittens, which disturbs neuronal connectivity in visual cortex, opening the eye is followed by partial reversal of the deficits[9], even after the critical period of 3–4 months of age[10]. Spontaneous post-lesion neuroplasticity also occurs in the adult visual system as documented by extensive receptive field reorganization following lesions in the retina or cortex[3,4].

Because training of visual functions can improve visual performance in kittens[11] and monkeys[12,13] in which spontaneous recovery is complete, the question arises whether visual training is able to restore lost vision also in humans. Evidence in favor of this possibility derives from studies in which measurements of incremental thresholds were made repeatedly in the same retinal location, resulting in small expansions of visual-field borders in patients with visual-field defects. This observation suggests that visual training may be effective in humans[12].

To evaluate whether true restitution is possible in the visual system of patients with visual-field defects, we developed a computer program using algorithms with which the visual system can be trained systematically. Using this technology, we conducted two independent, placebo-controlled clinical trials in patients suffering from damage to the visual cortex or optic nerve and show here for the first time a substantial reduction of blindness by repetitive stimulation of the visual field.

Training software for visual deficits

Training was carried out with a personal computer for use at home where patients practiced daily for 1 h in a darkened room for a 6-month period (Sundays off, see ref. 13). A special algorithm was developed that produced on a monitor repetitive visual stimulation of the transition zone[14], which is usually located in the border region between the intact and damaged visual-field sector (see Fig. 1 legend for description). Daily performance data were stored on disc, which permitted monitoring of compliance and continuous adaptation to the patient´s progress.

During VRT, the patients were required to fixate continuously on a fixation point, the location of which was determined by strictly defined criteria prior to group assignment. Every day, hundreds of visual stimuli were then presented in succession in the transition zone, and the patients responded to each stimulus by pressing an appropriate key. We used an individually adapted training protocol, which was determined by the characteristics of the transition zone to increase the probability of therapeutic benefit, and to reduce the testing and training time and thus increase compliance. The placebo condition was a fixation training program, requiring eye movements to stimuli near the foveal region for a comparable amount of time. Note that fixation training is expected to result in activation of the foveal region. Compliance checks and adjustments of training level difficulty were done monthly.

The patients participating in the trials were selected from a larger pool of 130 cases with either optic nerve injury or damage to the primary visual cortex. They were screened on the basis of predetermined inclusion and exclusion criteria and repeated baseline assessments were carried out. The data reported here are from two independent clinical trials each with an experimental and a control group. In the first trial, two groups of optic nerve injury patients, restitution (treatment) and placebo

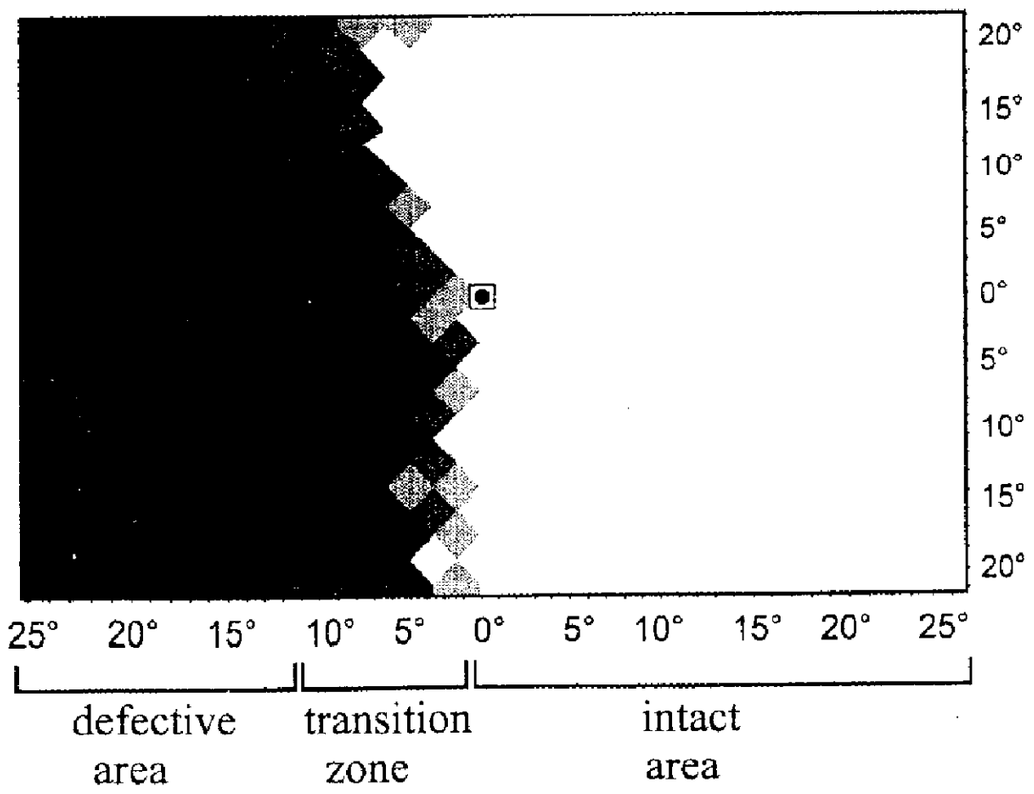

Fig. 1 In the visual restitution training [NovaVision VRT (Medinova Medical Cons GmbH, Magdeburg, Germany)], visual stimuli are presented on the screen in such a manner that the majority of stimuli appear in the transition zone (gray area), as well as near the border of the transition zone and the defective field. If the patient reaches criterion (90% accuracy), the more difficult training level is chosen. We used stationary stimuli of varying luminance in unpredictable, randomly chosen locations in ascending levels of difficulty.

(control), were matched according to age of the patient (blind conditions, $n = 19$). In the second trial, patients with post-chiasmatic injury were randomly assigned (double-blind, $n = 19$). Thereafter, the patients were instructed to train with visual tasks on the monitor at home. Only one patient from the placebo group failed to meet the requirement to train for a total of 150 h. This patient dropped out from the study.

Trial design

Patient selection. The trial was approved by the local medical ethics committee. The 38 patients included in the study had to have both a visual-field defect and post-chiasmatic or optic nerve damage as shown by CT, MRI, surgical records or ophthalmoscopic documentation of optic nerve atrophy. Patients were not entered if any one of the following exclusion criteria applied (number of excluded cases are given in parentheses): Insufficient fixation ability ($n = 11$), neglect ($n = 1$), non-optic nerve heteronymous visual-field defect ($n = 7$), disorders of the eye ($n = 9$), no residual vision ($n = 2$), no visual deficit ($n = 1$), age >75 yrs ($n = 4$), age <18 yrs ($n = 1$), died ($n = 2$), lesion age <12 months ($n = 3$), epilepsy or photosensitivity ($n = 2$), cognitive deficits ($n = 12$), not willing to participate in trial ($n = 27$), and no-shows after initial screening ($n = 10$).

Baseline assessment. There were no differences in the baseline characteristics between the groups with respect to age, sex, classification of the injury or injury size (Table 1). After the initial screening, we obtained informed consent and patients attended one practice session to familiarize themselves with the diagnostic procedure of high-resolution perimetry (HRP, Fig. 2) and the monocular Tübinger automatic perimeter 2000 (TAP) under standardized environmental luminance conditions. This was followed by 2–4 separate sessions of baseline evaluation with HRP. The accumulated values of these repeated measures served as the baseline value. Thereafter, the patients were assigned either to the treatment or placebo group.

In "HRP" (which is an advanced version of the program described in ref. 15), 500 stimuli with luminance clearly above detection threshold are presented on a 17-inch computer monitor (see Fig. 2). The patient was required to fixate constantly on a fixation point (center star) and press a key within 750 ms. White, bright stimuli were presented in succession for 150 ms duration, each at 500 different positions (25 × 20 grid; dark monitor screen; stimulus size (SS) 0.15°; stimulus luminance (SL) 95 cd/m²; background luminance (BL) <1 cd/m²). To ensure proper fixation during home training, the fixation point (a star of 4-mm diameter) randomly changes its color from bright green (95 cd/m²) to bright yellow (100 cd/m²), whereupon the patient is required to press any key within 500 ms. Perimetry tasks and training are performed with a chin support to ensure a stable head position at a 30-cm distance from the monitor. The overall resolution of HRP is about four-times greater than that of TAP (ref. 15).

TAP is a static perimeter used in routine clinical practice where the visual field up to 30° eccentricity is determined using 191 stimuli with near-threshold luminance[16]. Proper fixation of the eye is monitored using a video camera. TAP has methodological limitations, however, because the patient's subjective criteria may change over time when responding to stimuli near threshold, and the resolution is relatively low. Therefore, TAP performance was chosen as a secondary outcome measure. The analysis of all perimetry procedures included only values obtained in the area in which training took place (treatment group) or an equivalent area in the placebo group. Visual acuity was measured with Landoldt ring values from which the minimal angle of resolution was calculated. In addition, standardized patient history interviews were conducted to determine whether treatment led to subjective improvements of vision in everyday life.

Table 1 Baseline characteristics of the study participants according to treatment

Characteristics		Restitution group ($n = 19$)	Placebo group ($n = 19$)
Age of patient (yrs)		47.7 ± 12.9	55.3 ± 16.2
Sex:	male	11	13
	female	8	6
Classification of injury			
Age of lesion (months)		6.8 ± 11.4	7.2 ± 6.3
Post-chiasmatic injury		9	10
	- due to trauma	4	0
	- due to stroke	2	8
	- due to other	3	2
Optic nerve atrophy		10	9
	- due to trauma	4	3
	- due to neuropathy	3	3
	- due to other	3	3
*Size of visual-field defect in percent**			
	- ≤ 25	4	4
	- ≤ 50	9	8
	- ≤ 75	3	4
	- > 75	3	3

The patients were either randomly assigned to the treatment group (post-chiasma trial) or they were matched according to age (optic nerve trial). The groups did not differ with respect to age, sex, lesion size or lesion age.
*Percent within the area of the visual field covered by the computer monitor.

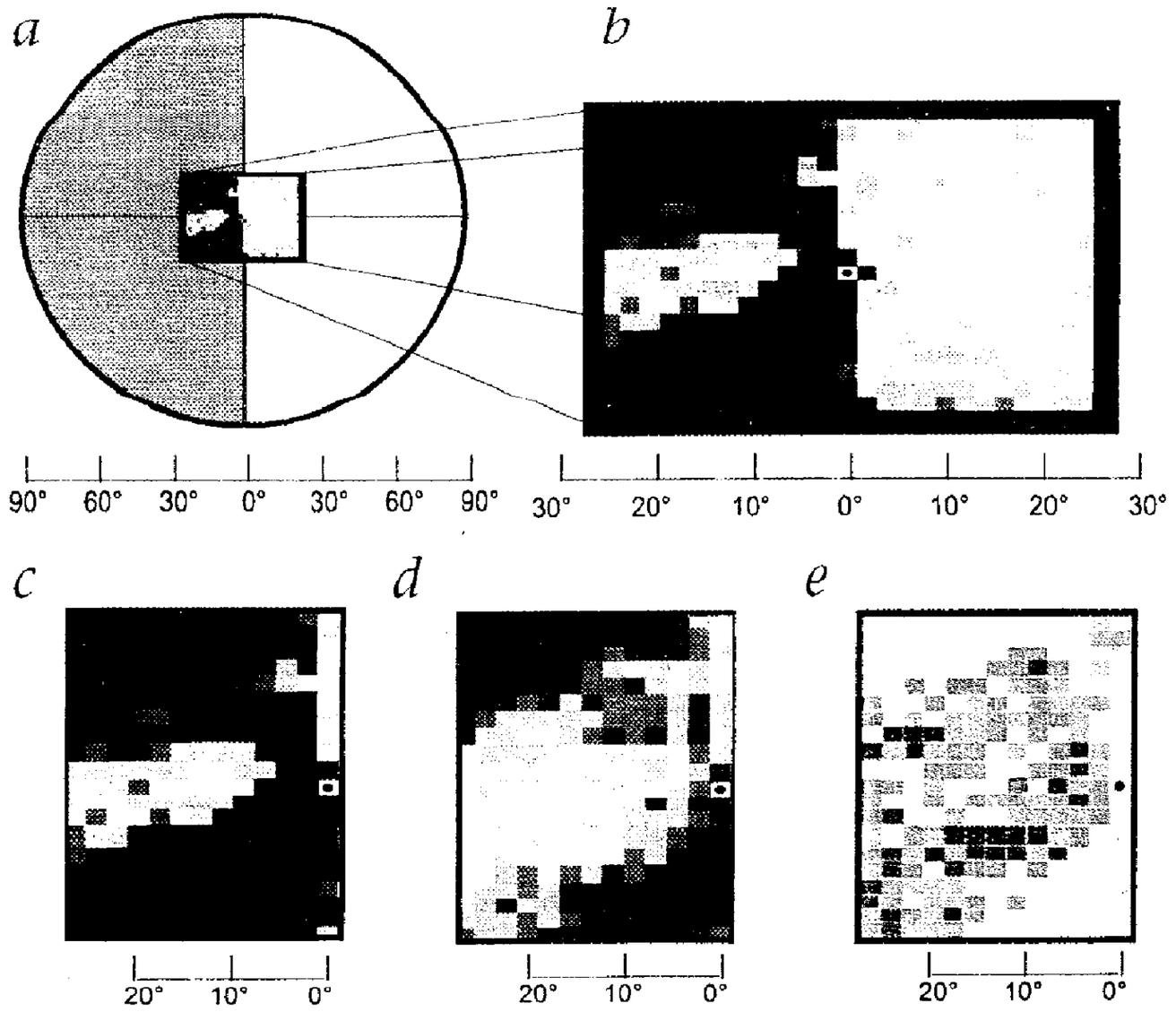

Fig. 2 High resolution perimetry (HRP). ***a***, Visual field of patient showing the defect (shaded half of the circle) on the left side. The central square represents the area assessed by HRP. ***b***, Enlargement of the center square in (*a*); black, no visual function; white, intact vision; gray shades, area of inconsistent responses (lighter gray indicates greater number of hits). ***c***, Zoom of (*b*), showing island of residual vision. ***d***, Same area as in (*c*) but after VRT, and ***e***, C/D difference to show increase (green) or decrease (red) of performance at follow-up.

Final outcome measures and statistics. After 150 h (about 6 months) of training, final outcome evaluation was carried out using the same procedures as those used for baseline assessment. For statistical analysis of parametric data, a two-way ANOVA with subsequent post-hoc comparisons was calculated for each study. Students *t*-test was used for individual group comparisons.

Methodological considerations. There are several reasons why visual-field enlargements can not be explained by methodological artifacts, such as improved perception of scattered light or experimenter/patient expectation: (1) Patients who benefited from the training did not show any improvements in non-trained visual-field sectors (data not shown); (2) the placebo groups did not show comparable improvements; and (3) HRP and TAP were objective, automated and independent procedures.

We can also rule out the possibility that the apparent visual-field enlargements are due to eye movements: (1) We directly observed the eye movements and implemented a fixation control procedure; (2) the 150 h of training time clearly exceeds the number of hours required to learn compensatory eye movements (about 8 h); and (3) visual-field enlargements occur after both optic nerve and post-chiasmatic brain injury. Thus, the only reasonable conclusion is that any improvements in visual functions are, in fact, due to true restitution.

Visual-field enlargements

Primary outcome measure. Both restitution groups, but not the control groups, showed significant improvements in their ability to perceive small visual stimuli well above detection threshold (HRP) after the training (Table 2). In that part of the visual field which was trained, patients receiving VRT responded to stimuli more frequently (hits) than the control group (post-chiasma patients: 29.4% over baseline, optic nerve patients: 73.6%, $P < 0.05$) and control patients showed either no improvement (post-chiasma patients: 7.7%) or significantly smaller improvements (optic nerve patients: 14.4%, see Table 2; percentages are calculated for each individual patient using the baseline value as 100%). Optic nerve patients thus profited most from the training (Fig. 3).

The position of the visual-field border was assessed before and after treatment as well (Fig 4). Because in some optic nerve patients the lesion was located on both sides of the visual field, here the border was determined on both sides of the zero vertical meridian. A border shift was noted in both

Table 2 Diagnostic values of visual functions before and after training according to treatment groups

Characteristics	Baseline		Final outcome		Change over baseline at final outcome		F-value
	Restitution	Placebo	Restitution#	Placebo	Restitution	Placebo§	
Post-chiasmiatic injury							
No. hits in HRP	97.3 ± 19.2	92.3 ± 12.0	116.9 ± 19.8*	83.4 ± 11.7§***	19.6 ± 6.2	-7.8 ± 8.5**	6.77**
Border position in°	5.4 ± 1.5	5.1 ± 2.3	10.3 ± 1.8***	4.2 ± 1.8§***	4.9 ± 1.7	-0.9 ± 0.8**	9.68***
No. of misses in TAP	53.0 ± 9.1^{+}	69.2 ± 11.2	50.1 ± 9.2^{+}	71.9 ± 12.0	-2.9 ± 3.0	2.7 ± 3.0	1.89
TAP border position in°	3.51 ± 1.0	3.43 ± 0.99	3.94 ± 1.0	2.92 ± 0.7§***	0.43 ± 0.3	-0.51 ± 0.34*	3.86$^{(*)}$
Optic nerve injury							
No. hits in HRP	203.2 ± 27.8	197.7 ± 37.0	312.8 ± 24.4***	227.8 ± 45.7	109.6 ± 15.5	30.1 ± 12.7***	15.31***
Border position in°	8.5 ± 1.8	5.8 ± 1.0	14.4 ± 2.4***	10.1 ± 1.5$^{(*)}$	5.8 ± 1.2	4.3 ± 0.7	0.43
No. of misses in TAP	87.9 ± 13.9	94.6 ± 17.6	63.9 ± 10.6***	89.8 ± 15.8	-24.1 ± 3.8	-4.8 ± 3.85***	3.76$^{(*)}$
TAP border position in°	3.6 ± 0.9	3.8 ± 1.2	5.7 ± 1.0***	5.1 ± 1.7#**	2.1 ± 0.5	1.4 ± 0.5	0.91
Acuity	21.0 ± 5.6	11.8 ± 3.0	12.6 ± 2.3***	11.9 ± 3.1	-8.4 ± 4.4	0.1 ± 1.52*	5.51*

Study results in mean ± s.e.m.; data were analyzed by a two-way ANOVA with post-hoc planned comparisons using the LSD-test. F-values are taken from the two-way ANOVA with type of training as independent factor A and time (before or after training) as dependent factor B. Significant differences are shown as comparison to baseline # or between groups at the respective time points (§); $^{*}P < 0.05$; $^{**}P < 0.025$; $^{***}P < 0.01$; (*) trend of $P < 0.10$. Note that both groups differed significantly in the number of hits in TAP at both time points ($^{+}$: $P < 0.01$). °Degrees of visual angle from zero vertical meridian. The change over baseline data was analyzed by Students *t*-test.

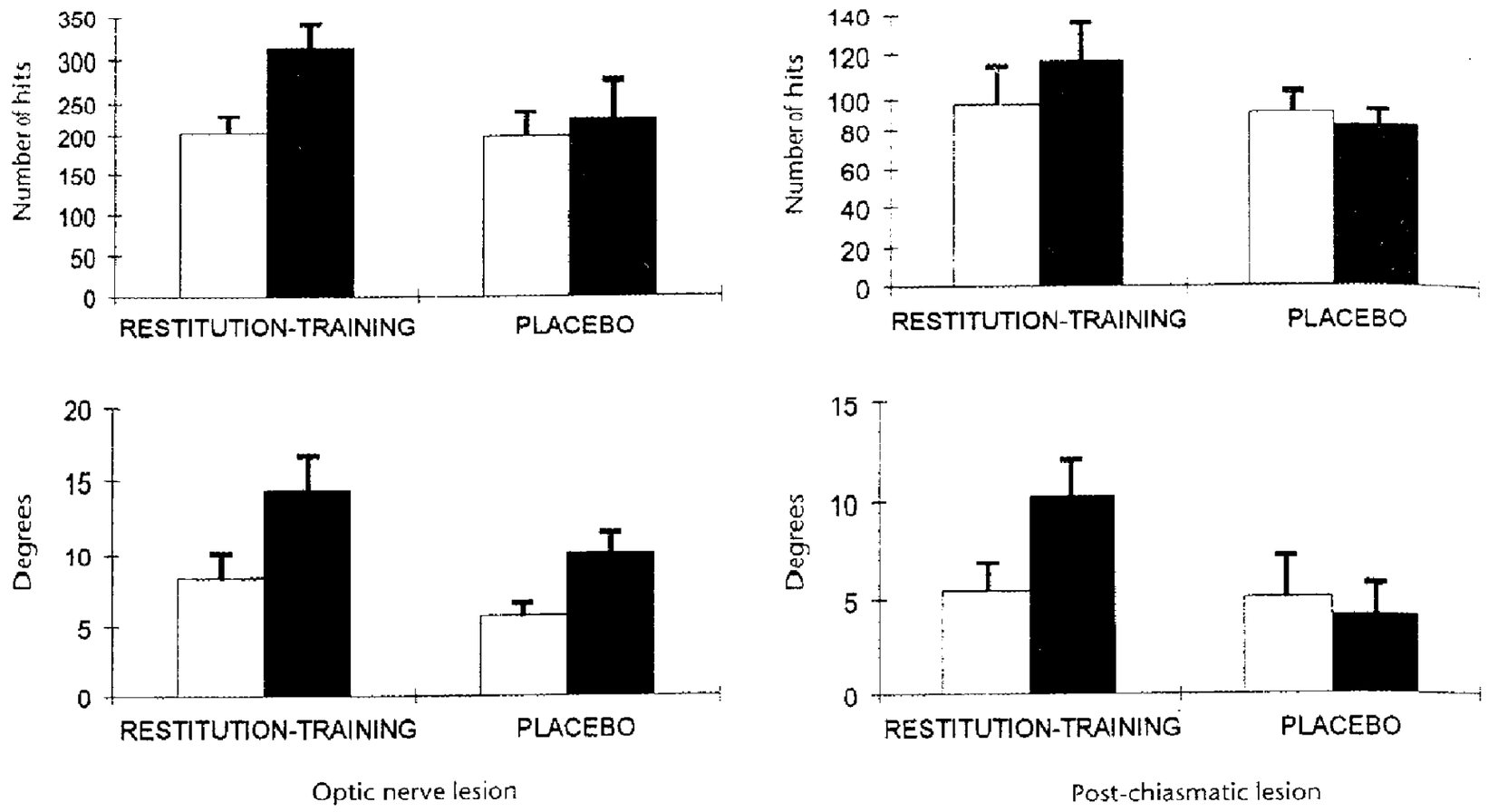

Fig. 3 Visual functions before (white bars) and after (black bars) restitution training or placebo (fixation training) of patients that sustained either optic nerve or post-chiasmatic damage (mean ± s.e.m.). HRP data are displayed as number of detected stimuli, that is, hits (upper panel). The lower panel shows the position of visual-field border from zero vertical meridian in degrees of visual angle.

optic nerve (5.8° ± 1.2) and post-chiasmatic patients (4.9° ± 1.7), with smaller changes (optic nerve: 4.3° ± 0.69, not significant) or no changes (post-chiasma: -0.9° ± 0.8) in the placebo groups. Most patients (18 out of 19) benefited from the VRT as documented by the primary outcome measure: For HRP, the percent improvement above baseline was either smaller than 20% (n = 5), up to 50% (n = 5), up to 100% (n = 4), or in four patients, above 100% (maximum in one patient: 200%; definition of percentage see above).

Secondary outcome measures. In optic nerve patients the area of absolute defect as measured by TAP decreased significantly in the restitution group but not in the control group. In post-chiasmatic patients there was no such difference in TAP performance. Calculating the visual-field size by determining the visual-field border using TAP data in degrees of visual angle, restitution training led to a border shift, that is, visual-field size increase, of only 0.43° ± 0.34 in the restitution and -0.51° ± 0.34 decrease in the placebo group of the post-chiasmatic patients. In optic nerve control patients the border shift was 2.1° ± 0.5 and 1.4° ± 0.5, respectively.

Of the 38 patients participating in the trial, 30 responded to a post-trial questionnaire with which subjective improvements were checked. 72.2% of the patients receiving VRT (n = 18) but only 16.6% of the control group (n = 12) reported subjective improvements of vision (Chi-square = 8.89, $P < 0.003$). No noteworthy differences between the groups were noticed due to age or sex of the patients, the size or side (right/left) of the visual-field defect and the age of the injury.

Functional significance of computer-controlled training

We have shown for the first time that VRT on a computer monitor leads to significant visual-field enlargement both after optic nerve and visual cortex injury. Fixation training (placebo) did not increase the size of the visual field in post-chiasmatic patients, although a small improvement was noticeable in optic nerve patients. About 95% of all the restitution group subjects experienced a visual-field enlargement with a mean increase in light detection of 56.4 percent ± 12.3 above baseline and an average increase of 4.9° or 5.8° of visual angle in post-chiasmatic or optic nerve patients, respectively. This magnitude of change is functionally meaningful. First, a 5° increase in visual field corresponds roughly to one-half of this journal page at arm's length distance and as little as 2–3° of foveal vision are generally sufficient for reading[16]. Second, the large ma-

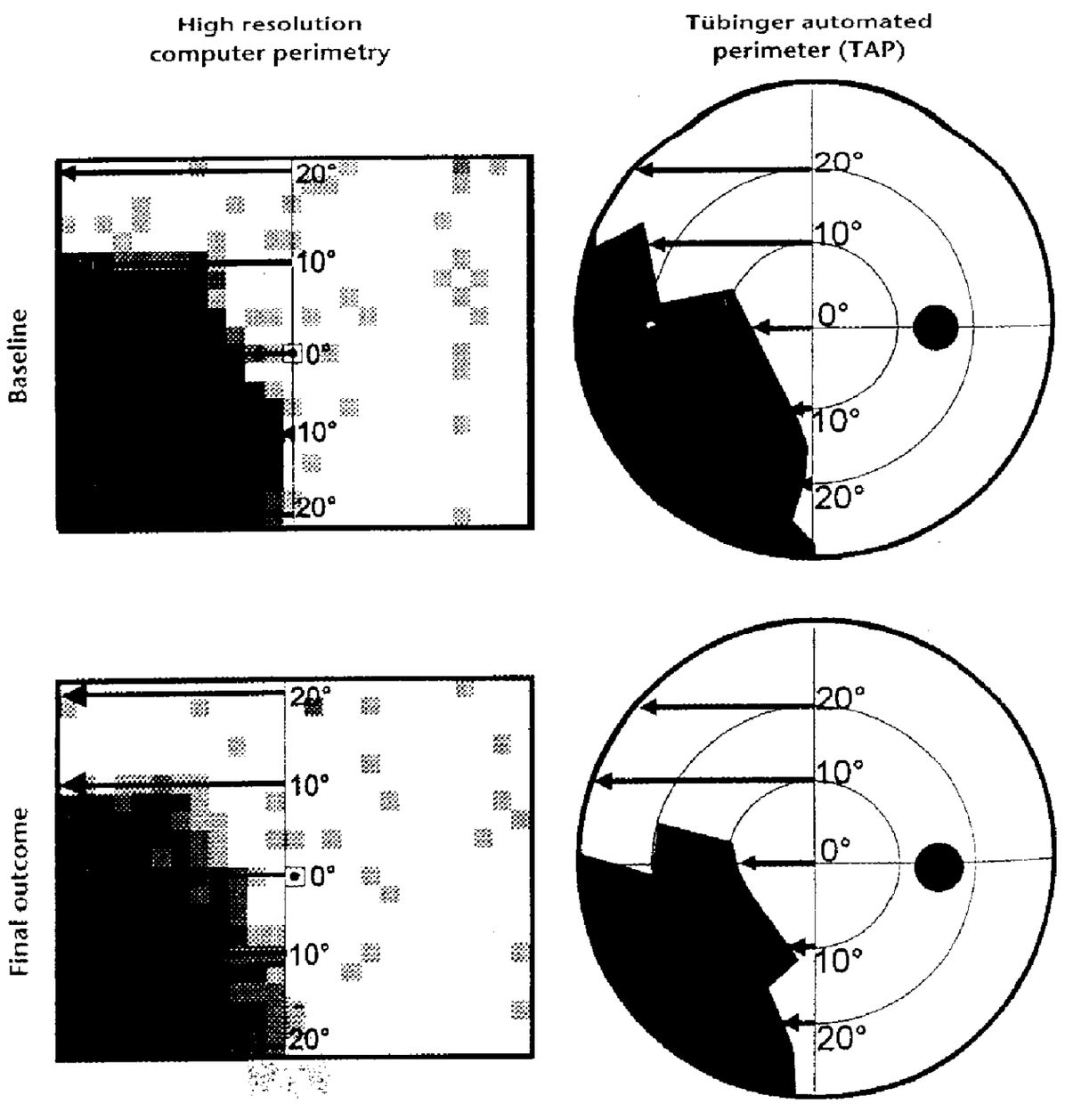

Fig. 4 The border in HRP or TAP was determined by measuring the distance of the black squares (that is, location without hits, see legend to Fig. 1) from the zero vertical meridian at the vertical position of +20°, +10°, 0°, -10° and -20° of visual angle. The extent of visual-field enlargement was determined by averaging these measurements and calculating the pre-post difference. Note that the border in HRP differs from that obtained with TAP perimetry.

jority (about 72.2%) of our patients receiving restitution training reported subjective improvements.

The neurobiological mechanisms involved in visual restitution are still unclear, but converging findings in animals and humans provide some initial clues. We propose that training reactivates surviving neurons of the partially damaged structure itself, that is, the border region ("transition zone") or islands of residual vision that exist in some patients with visual cortex injury[17,18]. Transition zones, usually located between the intact and damaged area of the visual field (see gray areas in Figs. 1, 2 and 4) are proposed to be a functional representation of surviving neurons in partially injured tissue[7,14]. According to the hypothesis of "minimum residual structure"[19], survival of as little as 10–15% of neurons is sufficient for recovery of basic visual functions to occur, that is, very few residual neurons in these partially injured areas may be sufficient to reactivate visual functions[6]. This may also explain why patients with optic nerve injury profited more from restitution training in our trial because their transition zones are particularly large (that is, areas of diffuse injury, data not shown). We therefore propose that residual neurons in the partially damaged visual system which activate visual targets only insufficiently, perhaps because of "disuse", become activated by repetitive visual stimulation during restitution training. This repetitive activation, in turn, strengthens synaptic connections, thus improving visual functions in previously blind or impaired areas of the visual field.

It is conceivable that training leads to receptive field enlargements similar to those shown by Kaas and coworkers[4]. They found spontaneous cortical map enlargements of 5° over the course of several months in (non-trained) monkeys after retinal lesions, a value that is almost identical to the average 4.9°–5.8° visual-field enlargement seen in our patients.

As regular visual stimulation of the damaged border region by VRT can significantly enlarge the visual field, the plasticity potential of the adult visual system can be utilized for therapeutic purposes in humans. The use of an in-home computerized training program is both cost-effective and convenient with no apparent side effects, though the training is not recommended for patients with photosensitivity or epilepsy.

In conclusion, our study extends the results of previous animal studies to humans and illustrates that patients who suffer from partial blindness due to trauma or stroke can benefit from VRT, regaining some of their lost vision. The general implication of our findings is that computer-based training programs can significantly increase human brain function, thus providing new strategies for the therapy of ophthalmological and neurological disorders.

Acknowledgments

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ON THE MARKET

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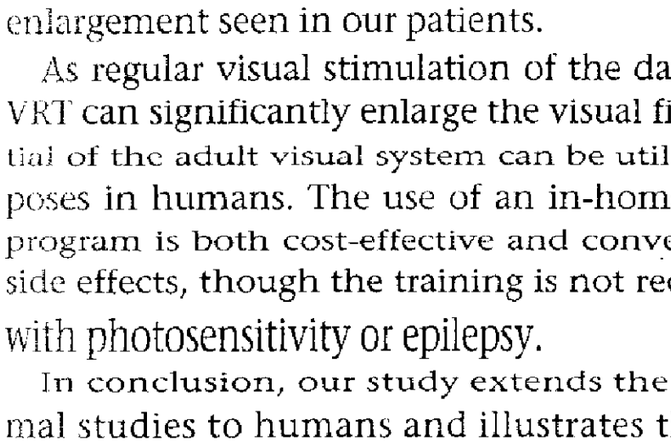

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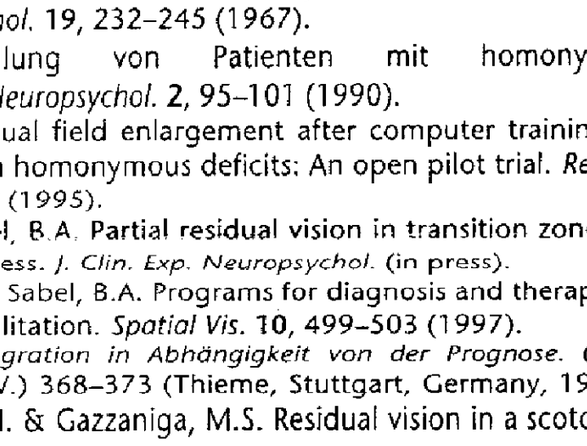

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