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Restoration of vision II: Residual functions and training-induced visual field enlargement in brain-damaged patients

Erich Kasten*, Dorothe A. Poggel, Eva Müller-Oehring, Janna Gothe, Tilman Schulte and Bernhard A. Sabel

Institute of Medical Psychology, Otto-von-Guericke University of Magdeburg, Germany

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Abstract

Purpose: Brain damage is often accompanied by visual field defects which have been considered to be non-treatable. In recent years, however, new diagnostic methods have revealed hitherto unknown residual vision, which was found, for instance, in transition zones near the blind visual field sectors and in spared islands of vision within the blind regions ("blindsight"). Furthermore, animal studies revealed a high degree of plasticity in the visual system suggesting the possibility that recovery of vision may be induced by systematic visual training.

Methods: Here we summarize a series of studies with patients suffering from visual field defects after brain lesion using some most recently developed computer-based programs for the diagnosis and treatment of visual field defects. Specifically, high-resolution perimetry (HRP) was applied to first diagnose residual function in or near the "blind" sector of the visual field. Thereafter, visual restitution training (VRT, see Kasten et al., Nature med. 4, 1998, p. 1083) was used daily for 6 months to provide systematic stimulation of these areas of residual vision.

Results: In a number of studies, we have observed not only residual visual functions within or near the field defect, but we were also able to follow the course of spontaneous recovery of visual functions within weeks or months after visual system damage. Furthermore, even long after spontaneous recovery is complete, computer-based visual restitution training (VRT) in or near the areas of residual vision results in a significant enlargement of intact areas, both after optic nerve damage and postchiasmatic lesions. Using VRT, we found a border shift of about 5 degrees of visual angle which cannot be explained by eye movements or eccentric fixation. We observed a transfer of this training effects to other tasks such as form and color detection, as well as to tests of visual exploration which were not specifically trained. Moreover, 72 % of the patients reported subjective improvements of vision. Training-induced visual field enlargement persisted for at least one year, even in the absence of training beyond 6 months of treatment.

Conclusions: The visual system possesses a remarkable plasticity which becomes apparent in visual field enlargement during spontaneous recovery and specific visual training. Animal studies indicate that a minimum number of residual neurons surviving the lesion, in the order of 10 %, provides a sufficient substrate for recovery of vision. Though the precise mechanisms of training-induced visual field enlargement need to be further explored, VRT can be introduced for routine clinical treatment of patients with visual field defects.

Keywords: Plasticity, functional restitution, visual field defects, residual neuronal structures, training, rehabilitation

* Correspondence to: Dr. Erich Kasten, Institut of Medical Psychology, Otto-von-Guericke-Universität, Leipziger Str. 44, 39120 Magdeburg, Germany. Tel.: +49 391 6117100; Fax: +49 391 6117103; E-mail: Erich.Kasten@Medizin.Uni-Magdeburg.DE

1. Introduction

Patients suffering from visual deficits commonly experience many limitations in their activities of daily living. Visual orientation may be severely impaired as shown in the following self-report:

"As I am driven to Calgary, I am continually surprised by automobiles and buildings suddenly appearing in my good field, when I look to the left. I have no idea that they are there (...) I was determined to return to my previous lifestyle as quickly as possible and attended the Winter Conference on Brain Research. I had real difficulty in reading slides at talks, however, and had to sit well back in the audience in order to follow them. Presumably, this allowed me to get most of the information into my right visual field.(...) I also decided to try skiing that week. I was able to ski without difficulty, although I tended to overcompensate for my field defect and actually ran into a tree in my good field whilst trying to avoid a bush several meters away on the left!. (...) I still miss capital letters when reading a text (...) and I am puzzled by the odd spellings or messages. For example a sign stating 'Women' can be misread as 'Men' or one saying 'telephone' may be misread as 'lephone'." [37].

Since partially blind patients have problems with the (complete) exploration of visually complex environments, they often miss people or objects in their blind field. Therefore, the risk of accidents and injuries is increased and in most countries patients are not allowed to drive motor vehicles [28,58,60]. For many patients, especially those without macular sparing, reading difficulties are the most prominent cause of suffering. Understandably, visual field impairments are often the cause of unemployment, loss of self-confidence and of independence, frequently resulting in reactive depression.

To understand the consequences of lesions in the visual system, let us first consider the neuroanatomical situation in the human brain.

On their way from the retina to the occipital lobe, visual pathways traverse the entire brain. Moreover, there are several other cerebral regions, located in parietal, frontal and temporal lobes, as well as subcortical structures, involved in visual information processing. Consequently, any lesion of the brain bears an evident risk of inducing visual deficits. After stroke, trauma or brain surgery, for instance, the probability of acquiring a visual field defect is very high, sometimes in the order of 20–30 % [e.g. 13,20,39,79].

Presumably, the high incidence rate of visual field defects after brain lesions as well as the almost ubiquitous problems caused by those impairments in patients' everyday life should have led to a vigorous effort of designing diagnostic and treatment strategies. Yet, this was not the case. One of the reasons may be that after the early discovery of Hubel and Wiesel's feature detectors [15–19], research has focused on characterizing with increasing detail the fine structure of the visual system, leading to the concept that the visual cortex is strictly organized (e.g. in topographical units) and possesses a high degree of specificity. As a consequence, visual field loss has long been considered unchangeable so that no need was felt to attempt visual rehabilitation in patients with "permanent" visual field loss.

Nevertheless, in recent years, we have witnessed a new development in neuroscience, a paradigm shift, namely that the brain possesses a remarkable plasticity, being able to compensate for lost functions during a period of recovery following injury [9]. Meanwhile, even the visual system, previously considered to be hard-wired, proved to possess a remarkable flexibility in adapting to short-term as well as long-term changes in the brain, and numerous animal studies attest to this fact [1,6,8,10,14,35,44,47,55,69, 87].

With regard to the clear-cut evidence of visual system plasticity in animals, the question arises to what extent the human visual system also possesses the potential to adapt to loss of functions. We have therefore conducted a series of studies, including two well-controlled clinical trials with the goal to restore lost visual function, the essence of which will now be summarized.

2. Measurement of visual field defects and characteristics of residual vision

The clear documentation of plasticity in the human visual system requires a methodologically sound demonstration of (sometimes small) changes of visual functions over time. Therefore, the issue of proper diagnosis of residual visual functions is not a trivial one [88]. Though much of the details can be found in the original publications, knowledge of some methodological detail is needed here to appreciate the clinical studies which were conducted in our laboratory with patients suffering from visual field defects.

2.1. Diagnosis of vision

In our clinical studies, we used two approaches to quantify the loss of visual functions and any residual capacities: (a) the Tübinger Automated Perimeter ("TAP-2000") and (b) high-resolution perimetry ("HRP", which – strictly speaking – is actually a campimetric procedure).

TAP-2000 is a standard tool for the diagnosis of visual system dysfunction [40] routinely used by German ophthalmologists. We used TAP to determine the total size of each eye's blind area by presenting static (non-moving) stimuli adapted to the central threshold of visual perception at eccentricities up to 30° or 90° of visual angle, respectively. Fixation of the eyes was controlled with a video camera.

HRP is a diagnostic computer program developed in our laboratory [29] designed to perform high-resolution qualitative perimetry of the central visual field. Moreover, color and form recognition can be examined by special subroutines. HRP consists of three programs: "PeriMa" measures the responses to 500 small, stationary white (i.e. suprathreshold) dots on a dark background in a 25×20 grid (stimulus size: 0.15°). A second program, "PeriForm", tests the

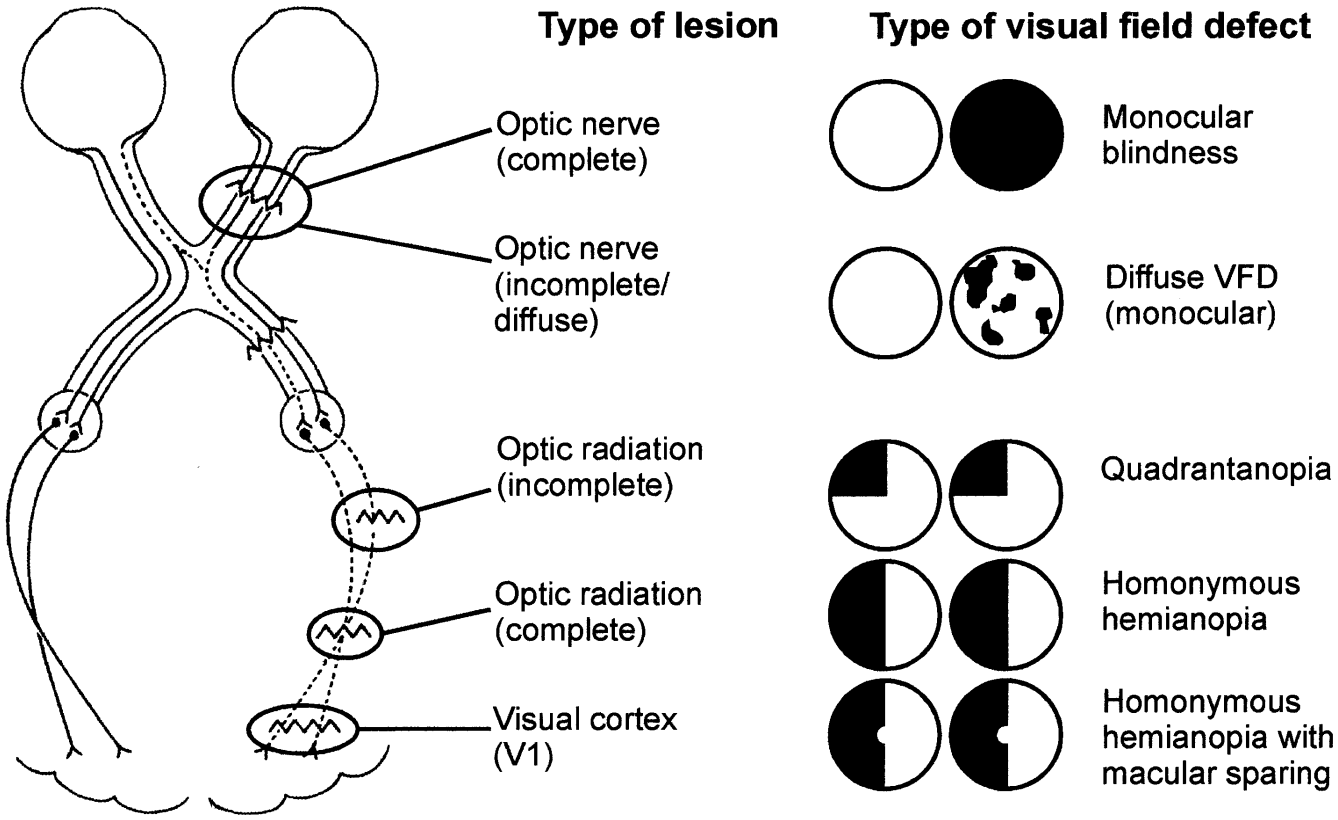

Fig. 1. Schematic overview of visual field defects (white = intact, black = blind areas) which result from lesions at different locations of the visual system.

ability to recognize forms, e.g. lines of different orientation or letters ("A", "B", "C" and "D", stimulus size: 2°). "PeriColor" is a program testing color recognition in the visual field. Colored squares (red, green, blue) and a gray square of matched luminance (stimulus size: 2.5°) are presented in random order. For a detailed description see [29].

Our initial studies were done using a 14"-monitor with a viewing distance of 30 cm that allows visual field measurements up to 44° horizontal and 34° vertical eccentricity. In later studies we used a 17"-screen providing an area of 54° × 43° for detailed examination. By shifting the position of the fixation point from the center to an eccentric location, a special region of interest (e.g. a blind quadrant or hemisphere etc.) within the visual field can be assessed, but the fixation point has always to be positioned at eye level, horizontally as well as vertically.

HRP is conducted in a darkened room, and the head of the subject is stabilized with a chin-rest. In a standard trial of PeriMa, stimuli are presented in random order at 500 positions on the screen. The patient hits a button whenever he or she detects a stimulus. Feedback on correct or incorrect detection, respectively, is provided by high vs. low tones. Correct fixation is ascertained with a small fixation point that changes its color, e.g. a change from bright green to yellow that cannot be detected with eccentric fixation. The subject is instructed to keep his or her eyes on the fixation point during the test and to press a key upon the color change. Our computer-based programs allow the use of different levels of stimulus and background luminance and of different stimulus sizes; additionally, different levels of stimulus duration and flexible time intervals between stimuli can be selected so that the test situation can be adapted to the individual abilities and needs of a subject (e.g. long intervals between stimuli for patients with slowed reaction time).

This set of programs allows the assessment of visual field size with a much higher spatial resolution and flexibility than commercially available devices. The major advantage of this procedure is the possibility to concentrate measurements to a certain, patient-specific part of the visual field and to provide very detailed and objective information about the functional status of different parts of the visual field.

Any observation of change, e.g. spontaneous or training-induced increase of intact visual field size, must be based on reliable diagnostic methods. In order to assess the reliability of measuring visual field size with our computer-based HRP, we repeatedly examined 27 patients (mean age 53.2 years ± 17.7) with postchiasmatic damage of the visual system [30]. Each subject was tested at five different sessions with the three HRP sub-programs (see above). Retest reliability for each test was determined by correlating five consecutive measurements for each patient.

Average correlations of the number of detected/ correctly recognized stimuli calculated for all patients amounted to $r = 0.86$ (PeriColor), $r = 0.91$ (PeriForm), and $r = 0.94$ (Peri-

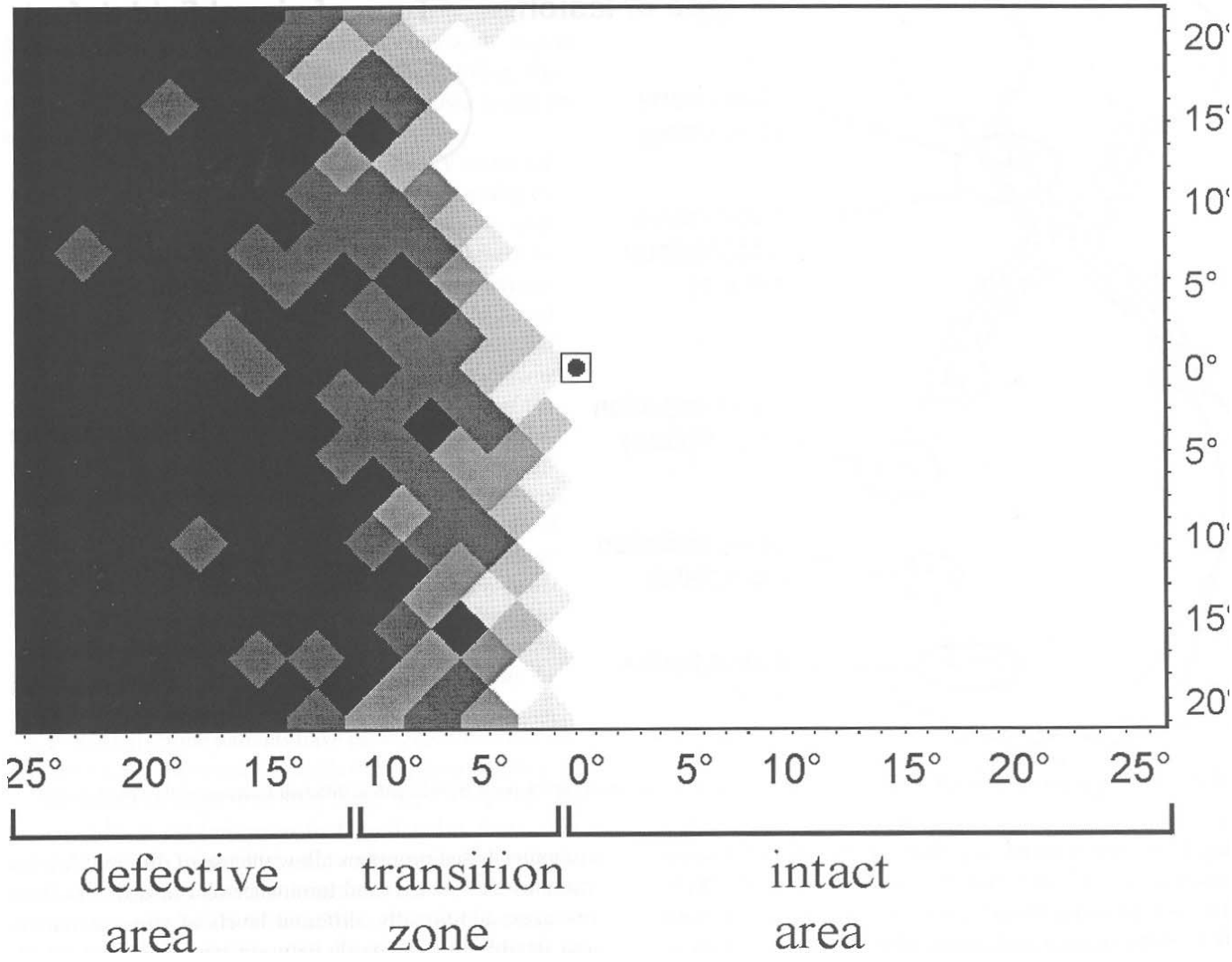

Fig. 2. Diagnosis of residual vision. Superimposed evaluations of the central visual field (program PeriMa, ±25° eccentricity) using HRP; Black = blind areas, white = intact areas, gray = areas of relative defects, i.e. transition zones with residual vision.

Ma), respectively, showing a high degree of reliability of each test. Variability of visual field size, indicated by the individual standard deviation over five measurements, was found to be very low: ±4.2 % for stimulus detection, ±6.2 % for form recognition, and ±6.4 % for color recognition, respectively [30]. These results indicated that computer-based HRP is a very reliable method that can be used for the observation of even small changes in the visual field of a patient in order to evaluate effects of spontaneous or training-induced recovery from visual field loss.

2.2. Residual vision

Standard text books of neurology/neuropsychology [e.g. 36] teach that after visual system injury, the visual field has either intact (white) or deficient (black) sectors (Fig. 1). Occasionally reference is made to "relative defects", but the nature of these is rarely considered to be meaningful. Generally speaking, visual field measurement aims at determining the position and size of the visual field defect (e.g. as an indicator of the localization and size of the lesion), but most methods are not designed to allow evaluation of any residual visual capacities. However, a precise description of the functional status of areas in the visual field becomes essential once an attempt is made to improve these functions.

In order to gain a better understanding of residual visual functions in patients with cerebral blindness, we carried out a study [31] addressing the following questions:

(1) Are there areas of partial (or residual) performance in light detection ("transition zones") in patients with cerebral blindness?

(2) Can patients discriminate colors and forms in these transition zones of their visual field?

(3) Do any patients possess stable "islands" of residual vision in blind areas of the visual field?

(4) Can colors and forms be discriminated in such islands?

As described above, with computer-based HRP we found only minor variations of visual field borders in repeated

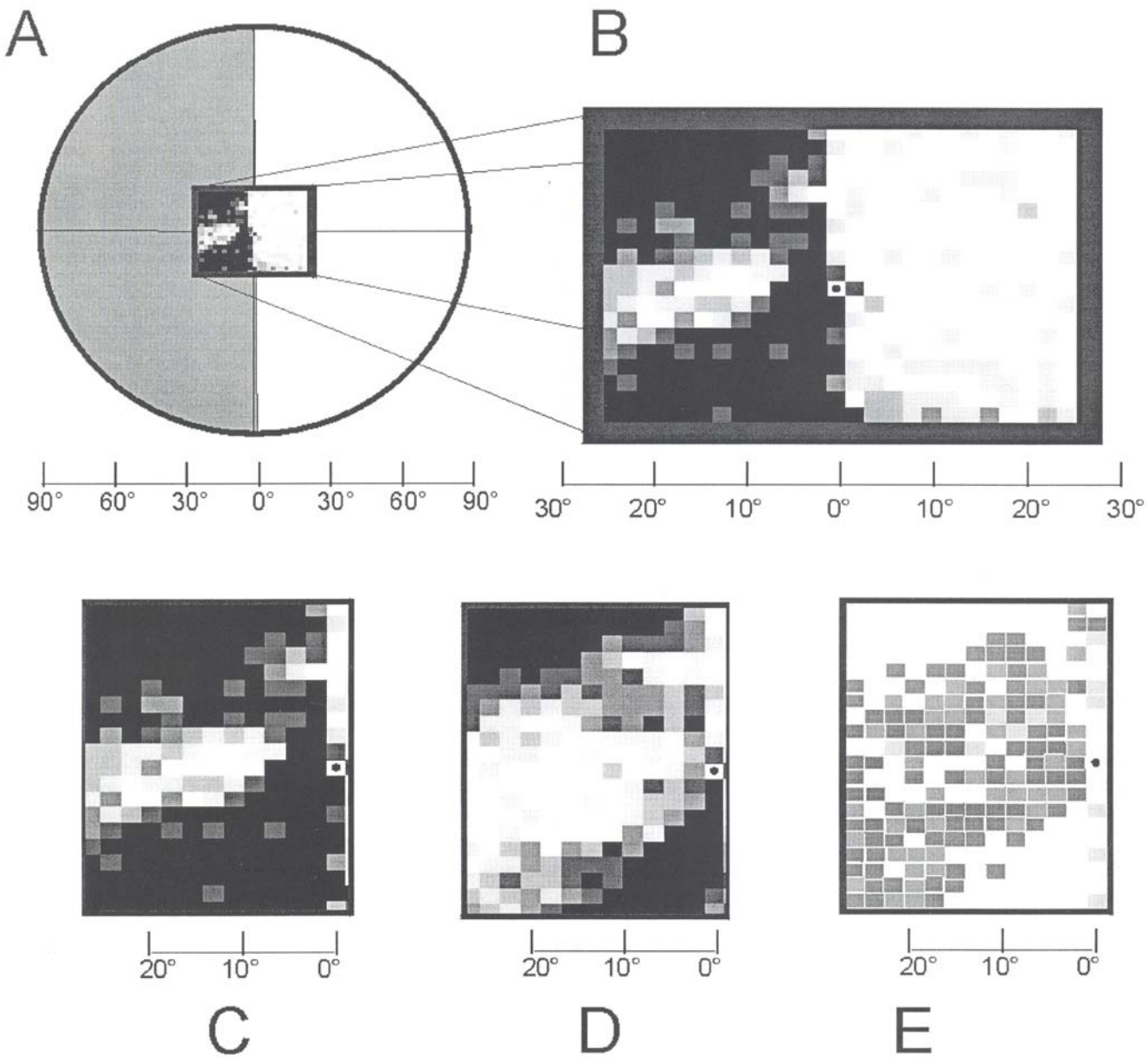

Fig. 3. Results of training of a female patient after an accident with lesion of the right occipital lobe as shown by HRP. Within the blind hemifield a "visual island" was found. Black = blind; white = intact; gray = relative defect. A: Total visual field; B: Enlargement of the center; C: Trained area, baseline before therapy; D: Final outcome; E: Difference to show increase of visual field size, gray = area of improvement (from [32]).

measurements when patients were tested well after spontaneous recovery had reached a plateau. Although the absolute number of detected stimuli remained almost constant over five measurements, the positions of detected stimuli changed considerably along the border of the intact and the deficient sector of the visual field. When five visual field tests are superimposed, the probability of light detection at each stimulus position can be computed. Between the intact areas (stimulus always detected in five consecutive tests; white squares in Fig. 2) and blind fields (never detected, black squares), most patients show a transition zone where stimulus detection was achieved only in some trials out of a total of five presentations (gray area in Fig. 2). These variations are not due to eye movements because fixation is controlled throughout the test by equiluminant changes of the fixation point's color. Furthermore, "transition zones" induced by eye movements should be predominantly located in the central area around the fixation point since saccades to that part of the visual field are more probable than larger eye movements to the peripheral parts. However, none of our patients showed such a pattern of an artificial transition zone.

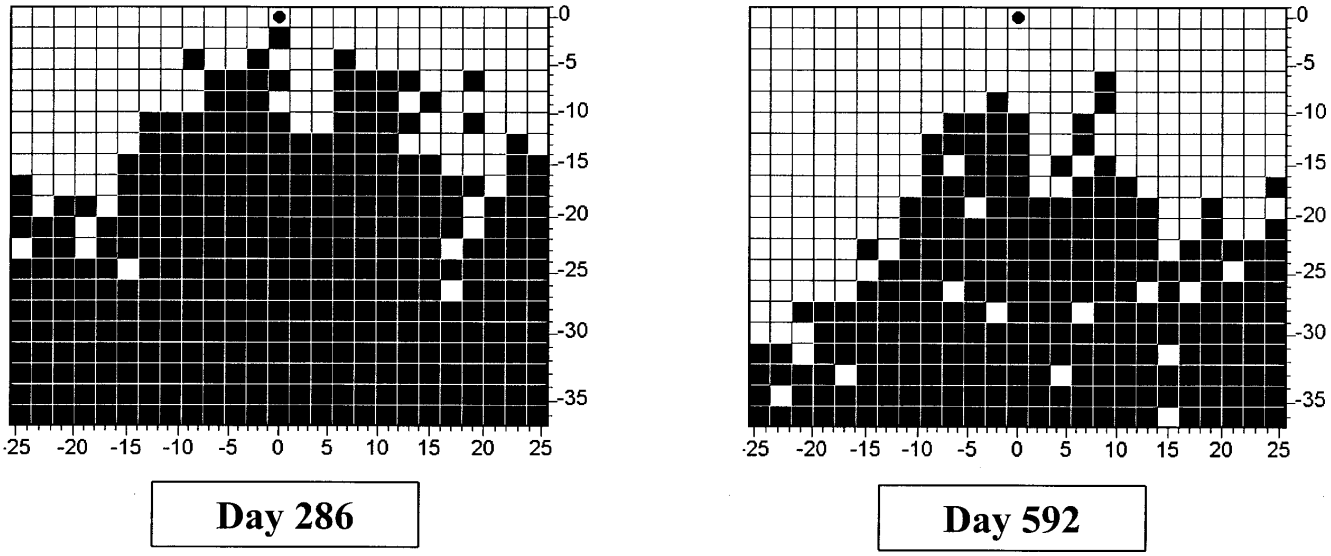

Fig. 5. Spontaneous recovery. Single case study of a male patient. Black indicates undetected stimuli positions and white intact areas. In this patient a surprising enlargement of the intact visual field was found due to spontaneous recovery even without training.

However, as early as 1917 Poppelreuter [53] observed spontaneous recovery from visual dysfunctions in soldiers with gunshot wounds. Since then, several investigators have studied spontaneous enlargement of visual field defects with rather heterogeneous results: e.g. different authors mentioned rates of recovery between 7 % and 85 % improvement [5,12,38,39,43,67,68,78,79]. These divergent findings may be explained by the different methods of perimetric measurement as well as by varying criteria of what exactly comprises an improvement. Furthermore, patients with different demographic and neuropsychological characteristics were studied. Thus, the few studies on the subject of recovery of vision yielded very heterogeneous results with regard to the percentage of patients showing recovery and the duration and extent of visual field enlargement. As a consequence, it is currently not possible to predict to what extent and in which time course a given patient may recover. However, one common finding was that patients having visual field borders with broad zones of "relative" defect (i.e. relatively large transition zones) usually showed a larger amount of spontaneous recovery [67].

In order to gain more information on quantitative and qualitative aspects of spontaneous visual field enlargement, we observed in great detail the course of recovery in one patient suffering from homonymous hemianopia of the lower visual field caused by an occipital gun shot wound [48,49]. The following case report from our laboratory is an impressive example of spontaneous recovery and post-lesion dynamics:

Patient R.V. had suffered an occipital gunshot wound at the age of 29 years. Initially, R.V. had been completely blind but only a few days after the lesion, he reported a first diffuse perception of light. Within two weeks, vision recovered in the upper right quadrant. Almost three months after the incident, the upper half of the visual field was completely intact, but still progress in the lower visual hemisphere continued. At six months, a perimetric examination revealed an intact visual field in the left and right periphery of the lower visual field. Although the average duration of spontaneous recovery usually ranges between three weeks [78] and six months [43], R.V. still continued to improve. The first measurement with our HRP programs (light detection, color discrimination, form recognition) was performed exactly six months after the incident. Due to the high resolution of our method, we were able to observe the progress of spontaneous recovery over almost one year after initial examination with HRP (see Fig. 5). We found that visual field enlargement gradually proceeded from the visual field border into the blind area. Finger-like, intact regions extended into the defect field, similar to those observed previously [43]. The greatest recovery was found in partially defective areas, i.e. in transition zones between intact and blind parts of the visual field. Over a period of one year, i.e. up to 18 months after lesion, we observed a gain of 20 % in the visual field area covered by the computer screen during campimetric tests. Peripheral parts of the visual field showed a larger extent of recovery than foveal areas. In parallel with the improvement in light detection, performance in color and form discrimination increased, showing the same pattern as the gain in stimulus detection, i.e. recovery started in partially defective zones along the visual field border. In areas regained during spontaneous recovery, R.V. could at first only detect the presence of a stimulus, but some weeks later, perception of forms and colors was fully intact at those stimulus positions.

Our single case observation thus indicates that the visual system possesses a high degree of plasticity even when large cortical areas are damaged. This capacity is retained even months after the lesion, at least in some patients. Par-

tially defective areas seem to play an important role in functional recovery [31,55]. Although the mechanisms of recovery of vision are as yet unknown and can best be studied in animals [87], observation of spontaneous recovery as an indicator of visual system plasticity raises the question if plasticity may be actively manipulated, e.g. by applying training-procedures to induce restitution of visual functions.

3.2. Training-induced enlargement of visual field defects

In parallel with an increase of knowledge on brain anatomy and the development of neuropsychological theories, treatment methods aiming at the restitution of different psychological domains (e.g. memory, attention, speech/language etc.) have been constantly improved [26]. The visual system, however, is generally considered to be very strictly organized, possessing almost "hard-wired" neuronal connections that seem to be necessary for efficient visual information processing. Therefore, the increase of physiological and anatomical knowledge actually impeded progress in research on visual rehabilitation. However, since the 1940s, animal studies provided first hints of visual system plasticity, showing that visual deficits induced by lesions or deprivation can either recover spontaneously or that they can be reinstated by systematic training (see e.g. [1,6,7,8,9,10,14,34,44,47,56, 69,87]). Note that even the very investigators who so elegantly documented the specificity of the visual system reported that the visual system can also recover from damage, even beyond the critical period [15–19].

Only in the 1980s, first attempts were made to study recovery from visual field defects in man. In their pioneering experiment, Zihl [77,78] and his colleagues found a significant increase of visual field size in patients with postchiasmatic brain lesions, when luminance thresholds were systematically measured at the same position of visual field border. However, their results were criticized because alternative explanations of the effect, such as methodological artifacts, could not be ruled out, e.g. spontaneous recovery or a change in the patients' fixation [2,3]. Meanwhile, other authors have presented single-case studies showing visual field enlargement using various devices [54,59,66,71], but the absence of any prospective, randomized, placebo-controlled clinical trial rendered these findings conspicuous in the eyes of many neuroscientists.

In 1990, we started developing computer programs with the goal to achieve restitution of visual functions in brain-damaged patients (VRT-programs). Here, a training program was developed (and subsequently refined) which permits systematic stimulation of partially defective areas, i.e. transition zones [29].

In one of the training programs, "Visure", a large flickering stimulus that moves from the intact area into the blind field, crossing the transition zone on its way, is presented on a dark computer screen. The patient has to press a key on the computer keyboard whenever he or she sees the stimulus appearing on the monitor. When the subject stops responding because he/she cannot see the stimulus any longer, it starts to move into the opposite direction, i.e. back into the intact area. When the patient indicates that he or she can see the stimulus again by pressing the key, the stimulus turns around and again moves into the defective area. During a treatment session, this process is repeated, line by line, so that the entire visual field border is stimulated.

Once the patient can detect 90 % of the stimuli presented in the program "Visure", the more difficult program "Seetrain" is applied in a second stage of training. In this program, stimuli increasing in brightness are presented at random locations in a previously defined area of the visual field. Stimulus detection is indicated by pressing a key on the computer keyboard, and reaction times designate at which level of brightness the stimulus can be perceived by the patient. Both training procedures require stable fixation which is controlled in the same manner as in the diagnostic programs described above.

Our programs run on commercially available personal computers so that visual field training can be done at home. Since partially blind patients are able to use the program independent of staff or highly specialized technical equipment, a large number of training sessions can be achieved. Over a period of six months, each patient performs two training sessions of half an hour each every day. Treatment results are stored on a disk so that compliance and changes in visual field size can be recorded minutely from session to session.

In a first pilot study [27], eleven patients took part in a training program lasting approximately one year. During this period, subjects performed between 80 and 300 hours of computer-based training. Three untreated patients were found to suffer a slight decrease of visual field size, while the treatment group ($n = 8$) showed a reliable enlargement. They experienced not only a significant improvement in detection of white light stimuli but also an increase in color and – to a lesser but notable degree – shape discrimination. An additional training of form recognition also proved to be beneficial.

Treatment outcome depended on the age of the patients and on the size of the brain lesion, but, much to our surprise, we did not find a significant correlation of time since lesion or cause of lesion, respectively. Only two patients in the training group did not show a significant improvement of vision.

These pilot results encouraged our view that systematic stimulation of partially defective areas can lead to a restitution of visual functions. However, because of many methodological limitations, the conclusions of the first trial were only preliminary and any final statement on whether visual restitution is possible could only be made on the basis of a more strictly controlled clinical trial.

We therefore initiated a randomized, double-blind, placebo-controlled trial with post-chiasmatic patients [32] who were screened for defined inclusion and exclusion criteria during baseline assessment. Basic diagnostic procedures included, among others, perimetric measurements (TAP-

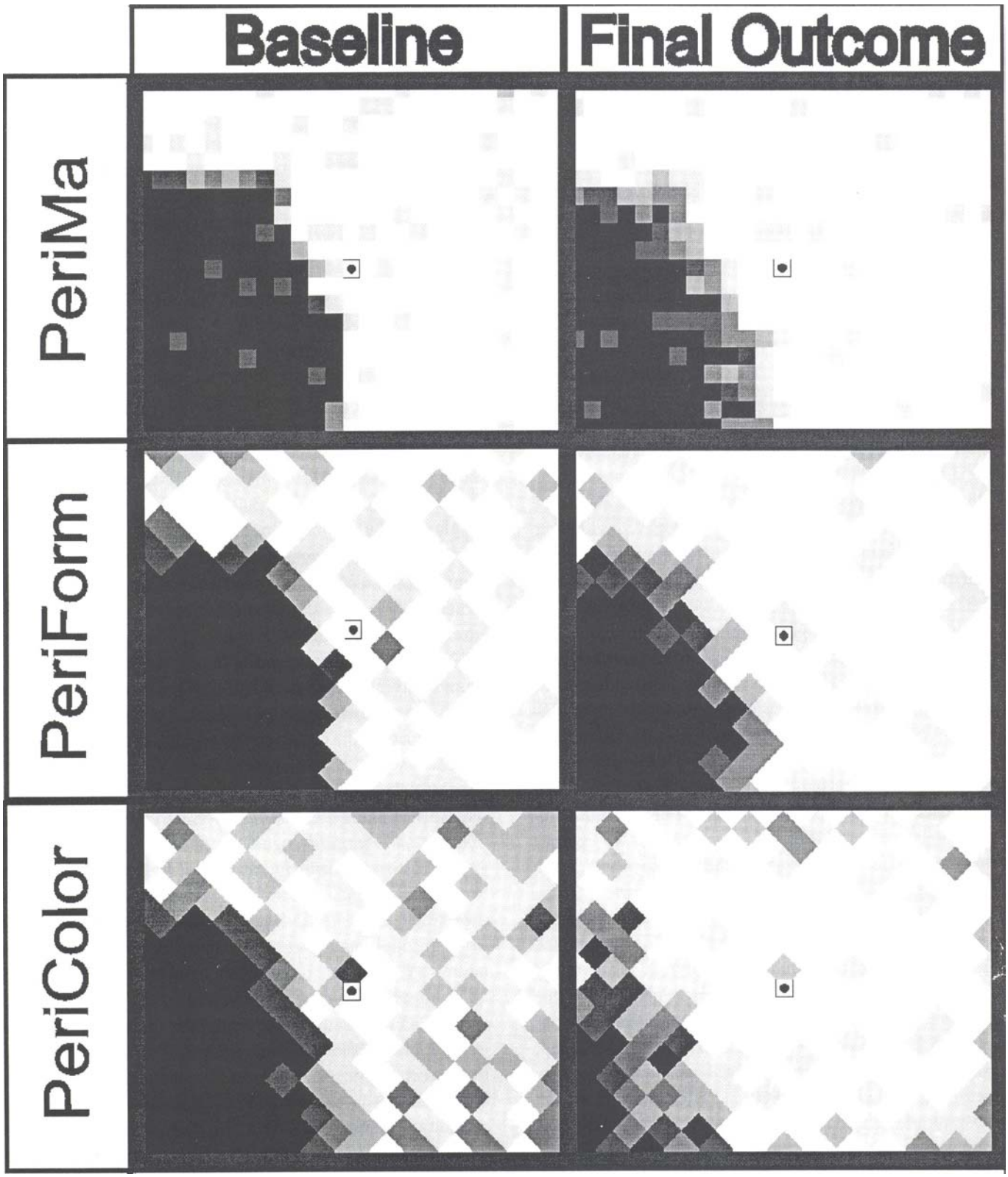

Fig. 6. Results of the training of a female patient after stroke of the posterior cerebral artery. Left column: Baseline investigations before therapy. Right column: final outcome after restitution training. Black = blind; white = intact; gray = relative defect. Upper panel: light detection task (high resolution perimetry, HRP; with PeriMa), middle panel: form recognition task (PeriForm), lower panel: color recognition task (PeriColor).

TABLE 1. Our results are in agreement with the opinion of most other authors. This table summarizes the results of all previous studies during the last 20 years in which visual field stimulation was performed with the goal to increase visual field size.

Study (Author, Year)	*Number of patients*	*Control group*	*Blind or double-blind*	*Prae-post design*	*Katamnest. examin.*	*Effect (significance)*
Zihl, 1980 [77]	n =16	no	no	yes	no	yes
Zihl & Cramon, 1985 [78]	n = 44	no	no	yes	no	yes
Balliet et al., 1985 [3]	n = 12	no	no	partial	no	no
Schmielau, 1989 [59]	n = 2	no	no	partial	partial	yes
Kerkhoff et al., 1994 [34]	n = 22	no	no	yes	yes	yes ($p < 0.05$)
Potthoff, 1995 [54]	n = 2	no	no	partial	no	yes
Kasten & Sabel, 1995 [27]	n = 14	partial	no	yes	yes	yes ($p < 0.05$)
Werth et al., 1997 [71]	n = 20	no	no	yes	partial	yes
Wüst, 1997 [74]	n = 19	yes	B	yes	yes	yes ($p < 0.05$)
Tegenthoff et al., 1998 [66]	n = 1	no	no	partial	no	yes
Kasten et al., 1998 [32]	n = 19	yes	DB	yes	yes	yes ($p < 0.05$)

2000), five repeated HRP-measurements, and several tests yielding information on different neuropsychological functions.

Nineteen patients with postchiasmatic brain lesions and homonymous visual field defects took part in the prospective trial. The age of each patient's lesion had to be greater than one year (note that our original publication of this trial [32], contains a printing error in Table 1: age of lesion was years, not months). Subjects were randomly assigned to either the experimental or control group under double-blind conditions. While the experimental group received visual field training with the VRT-programs described above, the placebo group performed a fixation training ("Fixtrain"). Here, e.g., patients had to respond to a change of the form of stimuli presented in the periphery of the visual field. In contrast to the training programs used in the experimental group which require stable fixation, adequate performance in the program "Fixtrain" can only be achieved by making eye movements towards the stimulus.

Patients in both groups were trained over a period of six months (about 175 hours of training). Every month, the training data were analyzed and, depending on the progress, the training level was adjusted. After six months of training, the initial diagnostic procedures were repeated. On the basis of measurements with TAP-2000 and HRP, we determined the position of the visual field border before and after training, i.e. we measured the distance of the blind area from the vertical zero meridian at 0°, ±10° and ±20° eccentricity. A change in visual field size within a group was defined as the difference of the average positions of visual field borders before vs. after training.

The experimental group showed a significant increase of intact visual field size in the trained area amounting to 7.8 % ± 2.5 % (mean ± S.E.). Taking the individual baseline value as 100 %, this final outcome was 29.4 % above each patient's pre-training value. The average shift of the visual field border was about 5° (4.9° ± 1.7°) of visual angle. In contrast, visual field size in control group patients decreased by an average of 3.1 % ± 3.4 % or by 0.9° ± 0.8° of visual angle over the training period, respectively.

The training procedure was performed only with white or gray stimuli. We were therefore interested to determine whether there was any generalization of training effects on the discrimination of colors and forms. We analyzed the data of 20 patients (9 female and 11 male, postchiasmatic lesions) with an average age of 51.2 ± 12.5 years (mean ± SD). Patients who showed a significant visual field enlargement with respect to the detection of white light stimuli (n = 9; average increase of 9.1 % ± 2.2 % S.E. stimuli detected in PeriMa) also improved in color discrimination (average increase of 9.3 % ± 2.0 % stimuli correctly recognized in PeriColor) and form recognition (average increase: 8.3 % ± 2.0 % stimuli correctly recognized in PeriForm). In contrast, four patients who did not get better in the light detection test (–0.8 % ± 0.5 %) showed small or no changes in form recognition and color discrimination (–1.8 % ± 1.1 % and 2.1 % ± 5.3 %, respectively). Subjects performing the placebo training (n = 7) exhibited a decrease of 6.5 % ± 4.6 % in light detection performance and accordingly a deterioration in color discrimination (2.0 % ± 4.4 %) and in form recognition (4.2 % ± 3.8 %). From these results we conclude that in patients with postchiasmatic injury, visual restitution training not only improved the function that had been trained specifically, but the effect generalized to other visual modalities, i.e. color and form discrimination [33]. Thus, VRT clearly induces a functional plasticity in patients with postchiasmatic brain lesions.

Since we have regularly observed that rats can recover rather well from optic nerve injury, a lesion where no visual pathway is left uninjured which could be held responsible for functional recovery, this type of lesion is of particular theoretical interest [87]. Therefore, in a second, independent trial, patients with optic nerve injury were treated with VRT [32,74]. Specifically, nineteen subjects were assigned to ei-

ther the experimental or the control group under blind conditions (age matched). Baseline investigations and training procedures were essentially the same as in the trial with patients suffering from postchiasmatic lesions described above.

The training effect of VRT was even more pronounced in patients with optic nerve injury than in the group with postchiasmatic lesions. Visual field size in the experimental group increased by 21.9 % ± 3.1 % (mean ± S.E.). In the control group, we also found an increase of 6.0 % (±2.5 %). Taking the individual baseline value as 100 %, this final outcome was 73.6 % over each patient's pre-treatment value. The average shift of visual field border in the experimental group amounted to about 6° of visual angle (5.8°, ± 1.2°). Unlike the postchiasmatic group, patients with prechiasmatic lesions showed improvements occurring primarily in the early stage (within weeks) after the training had started. It is interesting to note that optic nerve patients also showed an improvement of visual acuity, but in contrast to postchiasmatic patients, there were no generalized effects of light detection training on form or color perception, i.e. we found no transfer to other visual functions.

The increase of the number of correctly detected light stimuli over the period of training could have been induced either by a shift of sensitivity (i.e. a true training effect) or by a shift of the patients' criterion to press a key on the computer keyboard, thereby mimicking a training effect. Therefore, we tested whether the number of false positives (i.e. patient pressed a key although no stimulus was presented) increased systematically with the number of detected stimuli in the PeriMa-test which would indicate a shift in response criterion. Before training, all patients ($n = 38$, postchiasmatic and optic nerve patients) showed an average of 8.6 ± 1.6 (mean ± S.E.) false positive reactions in a HRP-test of 500 stimulus presentations. After six months of training, the average number of false positives had decreased to 7.4 ± 1.4, i.e. there was no significant increase in this variable which would explain the patients' improved performance in PeriMa. Additionally, we did not find a significant correlation between the amount of improvement in HRP-tests and the change in the number of false positive reactions ($r = 0.05$).

For a clinical setting, it is important to determine if training effects are transferred to other (neuropsychological) functions and to everyday life. Therefore we examined whether VRT influenced independent visual tasks testing other functions than HRP but presumably being also important for everyday life. We found some transfer of VRT to performance in paper-pencil-tests of visual exploration and attention (ZVT; d2-test). In patients with optic nerve lesions, we observed a positive transfer with regard to the time to complete the ZVT, i.e. visual exploration became more efficient in the experimental group. There was also a trend of improved performance in a task of selective visual attention involving visual scanning of stimulus details (d2-test) that just missed significance. Patients with postchiasmatic defects improved significantly in the d2-test, but in the ZVT, the decrease in reaction time also did not reach significance. These results indicate that benefits of visual field restitution even generalize (at least in part) to measures very different from campimetric or perimetric tests, suggesting that patients may be better able to cope with demands of the visual environment after training.

Because the increase of correctly detected numbers of stimuli on a computer monitor may only be of academic interest without practical consequences in everyday life, we also assessed subjective changes in visual functions using a questionnaire. Many patients reported a positive influence of the training on activities of daily living: 72 % of the patients of the experimental group but only 17 % of control group patients reported subjective improvements of vision in everyday life.

Most recently, we tested if our patients had maintained their regained vision after training had been discontinued for more than 6 months. The results showed a stable visual field size compared to HRP-measurement immediately after training, suggesting that they may have used (i.e. regularly activated) their partially surviving brain regions in everyday life and thus sustained the training effects (unpublished observations).

4. Discussion

Over the past two decades, numerous studies were conducted indicating that, despite its strict neuronal organization and specificity, the visual system can adapt to lesion-induced changes. These phenomena of neuronal plasticity within the visual system can be observed on the behavioral level in terms of recovery from visual field defects or other dysfunctions caused by brain-injury. Patients suffering from visual field loss can either recover spontaneously, or restitution can be induced by special training procedures [54,59,66,71,77,78] (see Table 1).

While there is clear evidence for a training-induced enlargement of intact visual field size in patients with cerebral lesions, the neuronal mechanisms underlying this process are still unknown. However, animal studies (on a molecular or neuro-anatomical level) and some interesting findings in our clinical research (i.e. on the behavioral level) may help us to gain some insight into these neurobiological mechanisms.

The capacity of the visual system to adapt to lesion-induced changes of the demands on information processing has been vastly underestimated for a long time. This was mainly due to the widespread concept that the visual system is hard-wired, maintaining its strict topographical order and receptive field properties under any circumstances. However, in various animal studies it has been confirmed that there is a considerable overlap of receptive fields in the visual system and an astonishing degree of plasticity [52]. There are short-term as well as long-term changes in receptive field size and localization, i.e. the brain is perpetually undergoing processes of "rewiring" in an attempt to

adapt to temporary alterations (special demands of the environment, shifts of attention, changes in the synchronicity of neuronal activation) or more permanent situations (e.g. brain lesions) [7,11,15–19,24,25,75,86].

So far, receptive field changes have been observed exclusively in animals, but whether, in fact, they form the basis of recovery of vision has not been determined [87].

Since phenomena of functional recovery cannot be studied at a neuro-anatomical or molecular level of analysis in humans, the only possibility to gain some insight into the mechanisms underlying this process is to look for parallels between findings on the behavioral level (in patients) and neurobiological results of animal studies. Some evidence for possible changes in receptive field properties induced by our training-procedures comes from the comparison of training success of patients with prechiasmatic vs. postchiasmatic lesions.

As described above, visual field enlargement was larger in the group of patients suffering from optic nerve lesions than in subjects with postchiasmatic brain injury. In the case of damage to the optic nerve, receptive fields in the thalamus and visual cortex are still intact, ready to receive new visual information. The training-procedure might contribute to improve the processing of even very small amounts of information being transmitted via the lesioned optic nerve, i.e. making stimulus detection more reliable by using partially damaged nerve fibers within the optic nerve and re-establishing a continuous flow of information from the periphery to the visual cortex. The basis of recovery from prechiasmatic lesions could be the taking over of function for (partially) blind areas by neighboring receptive fields within the primary visual cortex.

In contrast, lesions to the visual cortex itself induce a loss of receptive fields on a very high level of information processing. Compensation for lost neurons is therefore much more difficult than in prechiasmatic lesions where cortical areas, i.e. the sites of plasticity [11], remain intact since a greater number of neurons with more complex functional connections within cortical networks are affected and the few remaining cells in partially damaged neuronal tissue have to deal with more visual information in order to ensure a normal (or almost normal) level of function as far as behavior is concerned.

Another hint at the role of receptive field changes in processes of spontaneous or training-induced recovery from visual field defects comes from the observation of the amount of visual field enlargement at different positions within the visual field according to the cortical magnification factor [61]. While there are rather fast and also comparatively large shifts of the visual field border in peripheral parts of the visual field, an improvement in foveal areas is more difficult to achieve [76,78]. In the central visual field, training usually induces small changes, progressing very slowly. Since receptive fields in this region are small and vast areas of V1 are responsible for small portions of the visual field, visual field enlargement can be induced only by very intensive stimulation. Albeit, even very small shifts of the visual field border in the central sector are noticed by the patient, as this region is essential for reading and other tasks of everyday life. In contrast, on the basis of the larger receptive fields in the periphery of the visual field, improvement is achieved more easily, but here even large shifts of the visual field border are subjectively less relevant for the patient.

Other mechanisms on the neuronal level that might be involved in the recovery from visual field deficits are axonal sprouting/formation of new synaptic connections and the disinhibition of silent synapses. In numerous animal studies these processes have been observed, although the concepts of neuronal growth and synaptic changes at least in the visual system still seem to be more closely connected with development than with functional recovery after lesion in adulthood.

From our clinical studies, we could draw some parallels to findings on neuronal/ synaptic changes in animal research. It seems very likely that within V1, new lateral connections between neighboring neurons occur or that existing connections that are inhibited under normal conditions, are activated following the lesion. This would explain the phenomenology of visual field enlargement we found in spontaneous and training-induced recovery of patients with cerebral lesions: i.e. there is a systematic increase of intact visual field size, showing a gradual progress from the visual field border into the blind area.

Moreover, there is some evidence that new neuronal connections are formed even between different subregions of the visual cortex. We found that there was some generalization in functional recovery induced by systematic stimulation with white light. This kind of training did not only improve the perception of white light, but it was also beneficial for the discrimination of colors and forms, i.e. it exerted an influence on other visual modalities. Information concerning the color, motion and shape of an object is believed to be processed separately in the parvo- and magnocellular system [41,42,45,64]. However, the findings of many investigations, e.g. using event-related brain potentials, suggest that colors and shapes that can be easily discriminated are identified and selected in parallel [46,62,63,70]. The striate area V1 transmits information to higher-order visual areas such as V2, V3, V4 and V5 which are involved in color and form recognition [4,22,23]. A lesion of the optic nerve or the primary visual cortex produces a “bottleneck” for visual information that should normally proceed to higher cortical areas. Of course, each stimulus has not only a luminance but also a form and a color. It may therefore be argued that any training of stimulus detection must have some influence on form and color perception [65]. Presumably, connections between V1 and other regions of the visual cortex that have been interrupted by a lesion of the optic nerve or primary visual cortex are re-established even with an unspecific training procedure.

Another mechanism that might be an important basis for functional recovery within the visual system could be an in-

crease of synaptic efficiency. Successful functional recovery can only occur if the few neurons surviving the lesion can somehow increase their performance and take over functions of those cells lost during brain injury. Partially surviving neurons located at the visual field border seem to provide the essence for a successful restitution of visual functions in most patients. Transition zones may be the functional representation of these partially damaged regions in the visual system [32,56]. According to the hypothesis of "minimal residual structures" [55], very few neurons surviving in a lesioned area of the brain could be sufficient to induce functional recovery either spontaneously or by systematic stimulation, i.e. visual field training. The brain can compensate for the lesion with just a few fibers remaining in the damaged system itself. This requires that the fibers are diffusely injured, and often even 10% intact cells are sufficient for recovery of function to occur [50,51,57]. We speculate that by repetitive visual stimulation of these surviving neurons in a long-term training schedule, these cells may be reactivated, perhaps by reducing the threshold of firing. Based on this argument, a training-induced enlargement of the visual field border would enhance information transfer to the intact, higher visual areas V2–V5, where an appropriate performance of this information is possible. However, it is still unclear, whether re-current feedback (top-down activation) is necessary for the identification process [21]. Clearly, this should be the focus of future research.

In conclusion, our studies extend the notion of functional plasticity within the visual system gathered in animal studies to visual rehabilitation in man (see [80–92]. Restitution of visual functions can be achieved by a very intensive, systematic long-term stimulation of partially defective areas. Although complete restitution seems unlikely in the light of the results presented above, visual field enlargement is beneficial for the majority of patients. In our opinion, neuropsychological rehabilitation of patients suffering from visual field defects should therefore focus preferentially on restitution training before any compensatory programs are applied.

Based on animal studies we propose that a minimum number of residual neurons surviving the lesion, in the order of 10 %, provides a sufficient substrate for recovery of vision in man [87]. Though the precise mechanisms of training-induced visual field enlargements need to be further explored, visual restitution training (VRT) is ready to be used in routine clinical treatment of patients with visual field defect.

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