

# STABILITY OF VISUAL FIELD ENLARGEMENTS FOLLOWING COMPUTER-BASED RESTITUTION TRAINING -RESULTS OF A FOLLOW-UP-

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## **ABSTRACT**

In a previous randomized placebo-controlled clinical trial, we observed significant visual field enlargements induced by computer-based restitution training in patients with cerebral lesions (Kasten et al., *Nature med.*, 4, 1998, 1083-87). Now we asked the question whether this effect is stable after training was discontinued? Here we report data of a follow-up study after a training-free interval (mean 23.5 ± 2.3 months after end of therapy). 16 patients of the original restitution group and 6 patients of the placebo group were re-examined. On average, in high resolution computer campimetry (stimulus detection: PeriMa, form recognition: PeriForm, color perception: PeriColor) as well as in conventional automatic perimetry (TAP-2000) both groups showed no significant decline in the number of correctly detected stimuli after training was discontinued. However, cluster analysis revealed three different types of patients, who showed either increase (Type-I), decrease (Type-II) or stability (Type-III) in performance. We propose that many patients learn to use the regained visual capacities not only in the setting of a computer training but also in every day life, while other patients do not use the areas of restored vision and show a decrease of visual functions after the end of training. The Type-I group does not need continuous training, while the Type-II group may benefit from phases of refreshment exercises.

**Key words:** visual-restitution-training, neuropsychology, visual-field-defects, recovery, brain plasticity, cerebral blindness, follow-up

## **INTRODUCTION**

About 20-30% of brain damaged patients suffer from visual disabilities (Kerkhoff et al., 1994), but only few therapeutic approaches exist to treat these deficits. Several attempts were made with special mirror glasses and fresnel prisms, but most patients were confused by the double pictures of the left and the right visual half in the same part of the retina (e.g.: Bell, 1949; Kölmel, 1988; Rossi et al., 1990; Lachenmayr und Vivell, 1992). A simple way to compensate for a hemianopic visual defect

is the training of eye movements into the direction of the blind field. An automated training method for saccadic eye movements was developed by Zihl (1988, 1990), named the „Electronic Reading and Exploration Device“ (EREX). A considerable number of studies show the effectivity of the EREX-apparatus (e.g.: Zihl, Krischer & Meissen, 1984; Zihl, 1988; Pommerenke & Markowitsch, 1989; Lütgehetmann & Pommerenke, 1990; Brainin & Palmberger; 1990; Kerkhoff et al., 1992; Zihl, 2000). Zihl (1981) and Zihl and von-Cramon (1985) found a significant increase of visual field

size in patients with postchiasmatic damage of the visual system, when luminance thresholds were systematically measured at the same position of visual field border. Other authors have presented single-case studies showing visual field enlargement using various devices (Schmielau, 1989; Potthoff, 1995; Werth & Möhrenschräger, 1997; Tegenthoff et al., 1998).

Since 1990 we developed computer-based training procedures for patients with visual field defects. Initially, we conducted a pilot study with 11 patients (Kasten & Sabel, 1995) followed by two prospective, randomized, placebo-controlled clinical trials with 38 patients which sustained visual field defects (Kasten, Wuest, Behrens-Baumann & Sabel, 1998c). Visual restitution therapy consisted of a computer-based training program, which the patient performed at home for one hour daily over a period of six months. During that time several thousands of visual stimuli were presented systematically on the computer monitor to stimulate areas of residual vision located between the intact and the blind visual field sector („transition zone“, see: Kasten, Wuest & Sabel, 1998a). While most patients of the placebo-group experienced no change in the visual field size, the restitution-group displayed a reliable visual field enlargement as revealed by a significant shift of the visual field border and by improvements in the detection of small visual stimuli (Kasten et al., 1998c).

From these findings the question arose, how stable these visual field enlargements are after treatment is discontinued. Namely, if there is a considerable decrease of performance after the end of the therapy, the patients may need lifelong training or refreshment sessions. On the other hand it is conceivable that the patients learned to better use the restored areas not only in the setting of a computer training but also in activities of daily life, such that they are continuously stimulated and maintain the restored functions.

The aim of the present study was to determine if or to what extent restored areas of vision are maintained after training is discontinued.

## **METHODS**

We investigated 22 patients, i.e. 8 female and 14 male, average age  $55.4 \pm 3.2$  years (mean  $\pm$  S.E.). The

cause of the visual deficits were: 1. vascular diseases (e.g. stroke, cerebral hemorrhage, insufficient blood circulation,  $n=6$ ), 2. trauma or brain surgery ( $n=8$ ) or 3. cerebral inflammation and other lesions ( $n=8$ ). All patients had either a postchiasmatic damage causing a homonymous visual field defect ( $n=11$ ) or a lesion of the optic nerve resulting in heteronymous field defects ( $n=11$ ). The time interval after end of therapy was  $23.5 \pm 2.3$  months (minimum 6, maximum 47 months).

All patients had been screened for a number of exclusion criteria: age below 18 or above 75 years, other visual diseases (e.g. lesions of the eye, reduced foveal visual acuity, color blindness), nystagmus, visual neglect, motor deficits (e.g. hemiplegia), cognitive deficits (e.g. serious sustained attention or impaired memory) or mental diseases (e.g. psychotic depression). Because spontaneous recovery is known to occur within the first year after the brain damage, only patients whose lesions were older than one year were selected for the study. There were no significant differences between the restitution and the placebo groups with respect to age, year since lesion and kind of lesion.

Data for the main studies (Kasten et al., 1998c) were acquired in two independent clinical trials with (1.) patients suffering from post-chiasmatic lesions or (2.) damage of the optic nerve. In both trials identical training methods were used, and subjects were assigned randomly to either the restitution or the placebo groups. Originally, 38 patients were included in the two studies. However, since not all participated in the follow-up study, we could only obtain data of 22 of the 38 subjects. We were able to recruit 17 out of the 19 restitution patients of the original studies. One patient of this group showed a total decrease of visual functions because he had suffered from another stroke of the posterior cerebral artery with further reduction of visual field size; his data were excluded. Therefore, the number of re-examined patients of the restitution group was only 16.

From the placebo groups we could only examine 6 patients (out of 19) in this follow-up. For ethical reasons, all placebo patients had been offered the restitution program after completion of our previous trial. Therefore, the data of these patients can not be used. As a consequence, the number of re-

examined placebo patients was rather small.

### Diagnostic and training procedures

The diagnostic and treatment procedures were described in detail previously (e.g.: Kasten, 1994; Kasten, Wiegmann & Sabel, 1994; Kasten & Sabel, 1995; Kasten, Strasburger & Sabel, 1997a; Kasten, Schmielau, Behrens-Baumann et al., 1997b; Sabel, 1997; Sabel, 1999; Kasten, Wuest & Sabel, 1998 a, b; Kasten et al., 1998c; Kasten, Gothe, Bunzenthal & Sabel, 1999a; Kasten, 1999b; Kasten, Poggel, Mueller-Oehring et al., 1999c; Sabel & Kasten, 2000). Briefly, all diagnostic examinations were carried out under constant luminance conditions. Moreover, standardized instructions for each patient were presented on the monitor at the beginning of each program. Perimetry and all computer-based campimetric programs were carried out with a head chin support to provide for a stable head position. The total size of each eye's blind area was determined by static monocular perimetry using a Tübinger Automatic Perimeter 'TAP-2000' (30° visual field). Fixation was controlled with a video camera and catch trials were given. Additional visual diagnosis was done with a set of computer-based programs presented on a 17" cathode ray tube. These computer-based programs allow the assessment of visual field size with much higher spatial resolution than commercially available perimeters and were thus termed "high resolution campimetry" (HRP). Vision was investigated by tests for detection of stimuli („*PeriMa*"), shape recognition („*PeriForm*") and color discrimination („*PeriColor*"). Correct fixation is ascertained with a small fixation point that changes its color, e.g. from bright green to yellow and instructing the patient to press a key upon change. For a detailed description of these programs and normative data see Kasten et al. (1997a, 1999a, b).

After multiple baseline measurements of the visual field defect, each patient assigned to the restitution group received a disk with the training software adapted to her/his specific deficit (*Visure*, *Seetrain*), while each subject in the placebo-group received a simple foveal fixation training (*Fixtra*). In the *Visure* program, a large flickering stimulus moving from the intact area into the blind field is presented on a dark computer screen. In the

more difficult program "Seetrain" stimuli increasing in brightness are presented at random locations in a previously defined area of the defective visual field. Stimulus detection is indicated by pressing a key on the computer keyboard. Both training procedures require stable fixation which is controlled in the same manner as in the diagnostic programs (described above).

The "Fixtra" program was used in the placebo group. This is a simple fixation training, which requires the detection of movements or changes of the shape of the stimulus. In contrast to the treatment programs Fixtra has no fixation point and eye movements towards the stimulus are allowed.

Patients were instructed to train for one hour each day in a darkened room at home for a minimum of 150 hrs. within six months. The results of every session were saved on disk for subsequent analysis.

Whenever the patient has reached a pre-determined level of performance, the difficulty of the program was adjusted to the next level (e.g. smaller size of stimuli, decreased contrast of stimuli). Compliance checks and adaptations of training difficulty as well as control examinations with high resolution perimetry were carried out monthly. The rationale for using an individually adapted procedure was to increase the therapeutic benefit and compliance by avoiding non-challenging or over-challenging training levels. For a detailed description of the training programs see our previous articles (e.g.: Kasten et al., 1998c; Kasten et al. 1999a; Kasten, 1999b; Kasten et al., 1999c; Sabel & Kasten, 2000).

We analyzed not only the number of detected stimuli, but in addition the position of the visual field border between the deficient and the intact region was examined by measuring the horizontal distance from the vertical meridian at the positions of upper 20°, upper 10°, 0° (center), lower 10° and lower 20° of visual angle, respectively. In patients suffering from unilateral visual field defects the data only refer to the defective half-field. In patients with visual field defects in both hemispheres (i.e. most patients with lesions of the optic nerve), we calculated the mean distance between the vertical meridian and the left and right visual field border. Many patients had no clear border between the

intact and the defective visual field but rather displayed a large transition zone and scattered defects. Therefore, the visual field border was defined by the distance between the vertical meridian and the first stimulus location in which a minimum of two undetected stimulus events occurred. In the follow-up only two computer-based campimetric examinations

with the PeriMa-program were carried out. Therefore, these results were referred to as average of the first two examinations of (a) baseline, (b) final outcome and (c) follow-up examinations in computer based campimetry.

Statistical analyses were performed with the STATISTICA program (StatSoft Inc., Tul-

Restitution group	Baseline	Final- Outcome	t-test 1.	Follow-up	t-test 2.
PeriMa (light detection task)	51.9 ±5.5%	59.2 ±4.8%	p=0.004	58.4 ±5.4%	n.s.
PeriForm (form recognition)	52.8 ±5.6%	55.2 ±5.0%	n.s.	55.2 ±5.5%	n.s.
PeriColor (color perception)	54.6 ±4.6%	61.0 ±4.2%	p=0.003	55.8 ±4.6%	n.s.
Conventional Perimetry (TAP-2000), right eye	63.6 ±7.4%	67.0 ±6.1%	n.s.	66.2 ±6.6%	n.s.
Placebo group	Baseline	Final- Outcome	t-test 1.	Follow-up	t-test 2.
PeriMa (light detection task)	41.0 ±9.8%	39.7±11.%	n.s.	39.9±11.%	n.s.
PeriForm (form recognition)	42.2 ±9.4%	37.5±10.%	n.s.	41.9±12.%	n.s.
PeriColor (color perception)	42.7 ±8.1%	39.9 ±8.8%	n.s.	45.5 ±8.7%	n.s.
Conventional Perimetry (TAP-2000), right eye	72.9±11.%	73.8±14.%	n.s.	67.7±18.%	n.s.

Tab.1: Results of the three examinations (baseline, final outcome and follow up) as number of detected/recognized stimuli in percent (mean ± S.E) for the restitution group (upper table) and the placebo group (lower table). The results of t-test 1. compares the baseline and the final outcome data and the t-test 2. the final outcome and the follow-up results (t-test for dependent samples).

sa, USA,1995). The level of significance was set at  $p < 0.05$ . Unless specified otherwise, the following results are displayed as mean ± standard error.

## RESULTS:

Due to the reduced number of patients (22 out of 38) in which the follow-up examinations could be carried out, the training results presented here, show some differences when compared to our earlier published data (Kasten et al., 1998c).

Table 1 and the graph in Figure 1 show the detailed results of all investigations. On average, the perimetric and campimetric examinations of the patients of the restitution group had shown an increase of performance during the training and now a small, but insignificant decrease after the interval without therapy. In the PeriMa results this decrease in follow-up was only  $-0.8 \pm 2.4\%$ , in TAP-2000 data between  $-0.8 \pm 1.1\%$  (right eye) and  $-3.1 \pm 2.7\%$  (left eye). However, despite this loss, in both measure-

ments the stimulus detection was still considerable better than before the beginning of the training.

In the restitution group, enlargement of the visual field borders due to the training was  $2.7^\circ \pm 0.6^\circ$  between baseline and final outcome. Now, in the follow up we found a small increase of an additional  $0.4^\circ \pm 0.9^\circ$  (n.s.). In contrast, the placebo group experienced a decrease of  $-0.53^\circ \pm 0.37^\circ$  between baseline and the end of training and a small insignificant increase of  $0.13^\circ \pm 0.6^\circ$  at follow-up.

Results of form and color campimetry were as follows: While the follow-up examination with the PeriForm-program led to an absolutely stable enlargement ( $0.0 \pm 1.8\%$  increase), the results of the PeriColor test showed a decrease ( $-5.2 \pm 5.4\%$ ), which, however, was also still above baseline values.

In contrast, in the follow-up of the placebo patients we found inconsistent data, which may be the result of the small number of subjects within this group. After the training-free interval the result of the PeriMa stimulus detection task was sta-

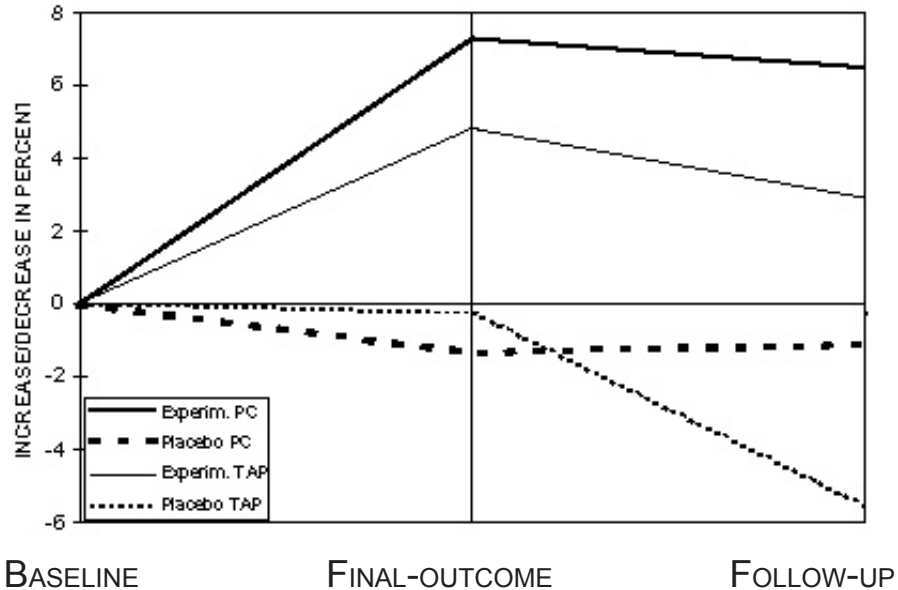


Fig. 1: Change in percent performance of standard perimetry (TAP-2000, thin lines) and high resolution campimetry (PeriMa-program, fat lines) for the restitution group (straight lines) and the placebo group (interrupted lines). The graph shows an increase of the restitution group during the therapy and only a small decrease in the follow-up after 6 months without therapy. On the other hand, the patients of the placebo group showed a decrease of visual functions as revealed by both methods.

ble ( $0.2 \pm 1.2\%$ ), in PeriForm ( $4.4 \pm 3.0\%$ ) and PeriColor ( $5.6 \pm 3.7\%$ ) an increase occurred. However, in conventional TAP perimetry the patients experienced a decrease ( $-6.1 \pm 4.1\%$  right and  $-4.4 \pm 4.0\%$  left eye).

In our two clinical double-blind studies (Kasten et al., 1998c), visual field enlargement of patients with lesion of the optic nerve was much higher than in the group with postchiasmatic damage. We now addressed the question whether there are any differences in the stability of the restored visual areas between these groups. In perimetry and computer campimetry the postchiasmatic damaged group was somewhat more stable (PeriMa:  $0.1 \pm 1.3\%$ , PeriForm:  $0.2 \pm 1.0\%$ , PeriColor:  $-2.1 \pm 2.7\%$ , TAP right eye:  $1.3 \pm 0.7\%$ , TAP left eye:  $0.9 \pm 0.7\%$ ) than the optic-nerve group (PeriMa:  $-1.6 \pm 4.9\%$ , PeriForm:  $-0.3 \pm 3.9\%$ , PeriColor:  $-3.6 \pm 3.7\%$ , TAP right eye:  $-4.5 \pm 1.5\%$ , TAP left eye:  $-8.6 \pm 6.7\%$ ). But a t-test between (a) the post-chiasmatic damaged patients and (b) the group with lesion of the optic nerve showed no significant differences in the three com-

puter-based diagnostic procedures (PeriMa, PeriForm and PeriColor); in TAP perimetry we found a significant difference only for the right eye, which may very well be by chance.

Also, age seems to have no effect on stability of regained vision after the end of therapy. In the patients of the restitution group we only found non-significant Pearson's correlation coefficients between age and the change of visual functions in the follow-up results (between  $r = -0.40$  and  $r = 0.35$ ).

In addition we checked whether the lesion type (hemianopia, quadrantanopia, scotoma) may have had an effect on the follow-up results. Spearman Rank Order correlation coefficients between the lesion type and stability of regained vision in the restitution group were small and insignificant (between  $R = 0.16$  and  $R = -0.49$ ). Similarly, there was no influence of the sex of the patient (between  $R = 0.09$  and  $R = 0.27$ , all non-significant).

To determine if there are any differences between patients as to how they respond to the non-training interval, we calculated a cluster-analy-

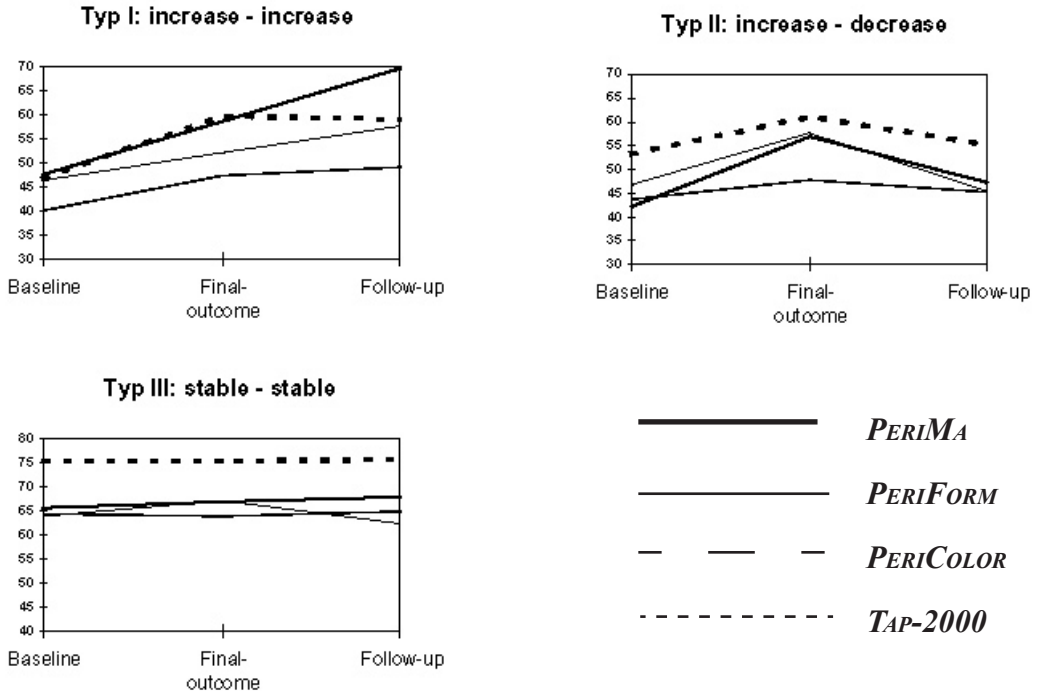


Fig. 2: In the restitution group cluster analyses revealed three different types of patients. The first group (Type-I) showed an increase during the therapy and a further increase in the time interval after training was discontinued. These patients may have learned to use the regained area of vision in daily life. The second group (Type-II) achieved an increase due to training, but suffered a reduction of visual field size thereafter. Interestingly, we found a third group (Type-III) which was absolutely stable. These patients showed neither increase nor decrease in the training and also no change during the training free interval. Explanations: bolt lines = PeriMa stimulus detection; middle fat lines = PeriForm form recognition; thin lines = PeriColor colour perception, interrupted lines = conventional perimetry (TAP-2000). All results are given in percent detected/recognized stimuli.

sis (k-mean clustering) with the increase/decrease of the results of computer campimetry and conventional perimetry.

We were able to identify three different main clusters (see table 2). These three cluster could be interpreted as I. patients who achieved further increases after the end of the training, II. patients showing a decrease and III. a third group with an absolutely stable performance after the training free interval. Figure 2 shows the development of visual performance in these three groups.

## DISCUSSION

Catamnestic assessments in neuropsychological therapy are rare, and especially in the field of training of visual field defects follow-up has never been performed before. Yet, they are very important to investigate the efficiency of a training procedure and the stability of such effects. For instance, in the field of therapy of aphasia, neglect or cognitive planning most authors found a sufficient stability of the effects and no or only small insignificant decreases in catamnestic studies after the end of therapy (see e.g.: Alderman & Ward, 1991; Alderman, Fry & Youngson, 1995; Aten, Caligiuri, & Holland,

1982; Avent, Edwards, Franco et al., 1995; Brindley, Copeland, Demain & Martyn, 1989; Burke, Zencius, Wesolowski & Doubleday, 1991; Cramon & Matthes-Cramon, 1994; Diller & Riley, 1993; Dordain & Normand, 1981; Hartman & Landau, 1987; Poeck, Huber & Willmes, 1989; Schwartz, 1995; Weinberg, Diller, Gordon et al., 1977). Negative results are rare (see e.g.: Fanthome, Lincoln, Drummond & Walker, 1995).

The results presented here of a follow-up of visual functions in brain damaged patients after a training free interval of above six months leads to the same conclusion. Training effects were basically maintained over time, showing sufficient stability. A small decrease must be taken in account, but the level of visual functions in the restitution group was still above the pre-training baseline.

An explanation of the decrease of several visual functions in the placebo group is difficulty. Firstly the group is too small for any reliable conclusions. When our project was finished, all patients of the placebo group was offered to train with the restitution program. Only some of the placebo patients had no interest in this clinical training, but only these could be re-examined as a true placebo-group in the follow-up. Since we have not investigated the reasons for the rejection of the restitution training, this group may be self-selected and not representative for the total placebo-group. However, this does not reduce the aim of this study, i.e. the examination of the stability of visual field enlargement in the restitution group.

Is an increase of about 3° only of academically interest or does it have practical consequences in every day life? Our computer-based training procedure allows only the stimulation of a central area representing a large amount of brain tissue in the striate cortex. Therefore, in central parts of the visual field, any training success will be more difficult to achieve than in the periphery. Consequently, an enlargement of a few degrees of visual angle in the central area implies a restitution of a considerably greater area of neuronal tissue in the striate area than a comparable shift in the peripheral parts. From this point of view a presumably „small“ increase of only 2.7° average visual field enlargement can be a great success for the patient and may lead to considerable improvements in everyday life. In

the main study we had developed a questionnaire for the assessment of subjective changes in visual functions. In this 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. Therefore, even if the increase is small, we believe that the enlargement can be helpful for many patients.

Interestingly, in the group which received the restitution program, we were able to identify three different types of patients. The first type (Type-I) showed an increase during the therapy and a further increase during the training free interval. These patients may have learned to use the regained area of vision in daily life. The second type (Type-II) achieved an increase due to training, but had a reduction of their visual field size thereafter. Additionally, we found a third group (Type-III), which was absolutely stable; these patients showed neither increase nor decrease during the training and also no change during the training free interval.

These results have many implications for a planning of the therapy. If we can find predictive factors in future studies, the Type-I patients do not need further training, while the Type-II group needs phases of refreshing training to hold a stable visual field enlargement. Patients with Type-III visual field seem to have no benefit from the procedure. Until now, the number of patients in these three groups are small and larger patient groups need to be trained to identify the predictors to decide which patient belongs to which group. This is an important task for further studies in the field of visual rehabilitation training.

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