Comparing explorative saccade and flicker training in hemianopia

A randomized controlled study

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ABSTRACT

Objective: Patients with homonymous hemianopia are disabled on everyday exploratory activities. We examined whether explorative saccade training (EST), compared with flicker-stimulation training (FT), would selectively improve saccadic behavior on the patients' blind side and benefit performance on natural exploratory tasks.

Methods: Twenty-eight hemianopic patients were randomly assigned to distinct groups performing for 6 weeks either EST (a digit-search task) or FT (blind-hemifield stimulation by flickering letters). Outcome variables (response times [RTs] during natural search, number of fixations during natural scene exploration, fixation stability, visual fields, and quality-of-life scores) were collected before, directly after, and 6 weeks after training.

Results: EST yielded a reduced (post/pre, 47%) digit-search RT for the blind side. Natural search RT decreased (post/pre, 23%) on the blind side but not on the seeing side. After FT, both sides' RT remained unchanged. Only with EST did the number of fixations during natural scene exploration increase toward the blind and decrease on the seeing side (follow-up/pre difference, 238%). Even with the target located on the seeing side, after EST more fixations occurred toward the blind side. The EST group showed decreased (post/pre, 43%) fixation stability and increased (post/pre, 482%) asymmetry of fixations toward the blind side. Visual field size remained constant after both treatments. EST patients reported improvements in social domain.

Conclusions: Explorative saccade training selectively improves saccadic behavior, natural search, and scene exploration on the blind side. Flicker-stimulation training does not improve saccadic behavior or visual fields. The findings show substantial benefits of compensatory exploration training, including subjective improvements in mastering daily-life activities, in a randomized controlled trial. ***Neurology*® 2009;72:324–331**

GLOSSARY

ANOVA = analysis of variance; **CI** = confidence interval; **EST** = explorative saccade training; **FT** = flicker-stimulation training; **HH** = homonymous hemianopia; **PC** = personal computer; **RT** = response time; **SLO** = scanning laser ophthalmoscope; **TAP** = Tübingen automated perimetry; **WHOQOL** = World Health Organization Quality of Life assessment.

Homonymous hemianopia impacts quality of life, drastically reducing the patient's spatial orientation, reading ability, and educational and occupational outcome, which represents an important socioeconomic factor. Two distinct rehabilitation approaches have been proposed: 1) compensation with extended saccadic eye-movement exploration toward the blind hemifield to improve the field of gaze and make better use of residual vision, and 2) restitution by stimulating the blind hemifield with the intention to activate potentially unaffected neurons and restore visual function. Despite reports to the contrary,[1,2] there is no evidence that restitution intervention enlarges visual fields. Control studies[3,4] did not confirm reports of visual-field enlargement after restitution training, such that adult visual-cortex revival by training remains unproven.[5] The main problem of restitution-training studies is insufficient fixation control,

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Supported by the Adolf Messer Foundation.

Disclosure: The authors report no disclosures.

missing eye movements during conventional perimetry.[4-6] In contrast, several studies show substantial visual-search improvements after saccade training.[7-11]

However, none of these studies used a control patient group and randomized assignment to ensure that potential confounds were evenly distributed. Another general difficulty in training studies is to reliably exclude spontaneous recovery, which can occur during initial months after brain damage,[12,13] but rarely after 6 months.[14]

The present study aimed to apply compensatory explorative saccade training (EST) in a randomized controlled trial with hemianopic patients beyond spontaneous recovery range, using outcome variables that are relevant for everyday life. In the control group, we used flicker-stimulation training (FT), which is unlikely to affect visual-search behavior. Additionally, we wanted to examine visual-field effects, if FT occurred more peripherally in the blind hemifield instead of stimulating the vertical field border.[1] The study therefore provided a direct comparison of compensation and potential restitution training. We hypothesized that in contrast to FT, EST would improve saccadic behavior and natural exploratory performance on hemianopic patients' blind side.

METHODS

Patients. The study was approved by the University of Tübingen Medical School ethics committee, and informed written consent was obtained from all participants. Thirty patients with postchiasmatic lesions participated, with an equal number of patients assigned randomly to either the EST or the FT group (table). Two FT patients dropped out because of illness and insufficient compliance. Finally, data from 15 EST and 13 FT patients were included. Inclusion criteria were age 18–80 years, isolated homonymous hemianopia or quadrant defect (not crossing the vertical line, no other visual field defects) with duration exceeding 6 months, distance to the midline ≤5°, and visual acuity ≥0.6 (20/33). Exclusion criteria were other diseases of the eye or brain, motor impairments hampering personal computer (PC) use, and other neurologic impairments, particularly epilepsy and hemineglect. Neuropsychological tests were performed to exclude cognitive disorders: dementia (Mini-Mental State Examination[15]) and hemineglect (clock-drawing[16] and line-bisection[17] tests). The groups did not differ regarding age, diagnoses, or duration of disease (table). Twenty-four patients had hemianopia, and 3 of each group had quadrant defects.

Training methods. EST was implemented as an explorative saccadic-search task aimed to improve visual search in the blind hemifield and the use of the total field of gaze. The task was practiced on a laptop placed 30 cm from patients' eyes (total visual field 35° × 47.7°). A custom software program (Borland Delphi 7.0) was used to generate a random array of digits (0–9; 12-point Arial font) distributed with equal probabilities on the blind and seeing sides. Patients had to find and move the mouse pointer over the predefined digit (digit 4). Upon passing over the digit, the program generated a beep and turned it into a red $ symbol, providing positive feedback and preventing double search for the digit. After finding all digits, the screen automatically cleared, and the patient started the next trial by clicking a button centered on the screen; this ensured the initial central fixation. Position and latency for all digits found were stored in a Paradox database for off-line analysis.

FT, potential restitution training, was implemented as a modification of a flickering-letter procedure described recently.[18,19] The training was not supposed to foster exploratory eye movements, but rather stimulate the blind hemifield by suprathreshold stimuli with the intention to improve the sensitivity of this hemifield. Borland Delphi 7.0 was used to generate the flicker stimulus (letters A, H, K, or T; 11.68° × 9.46°, viewed from 30 cm at 21.8° eccentricity; flicker frequency 10 Hz). The eccentric letter presentation reduced the likelihood of eliciting saccades toward the stimulus. As shown previously,[4] stimulation along the vertical field border does not enlarge the visual field, but may induce eye movements toward the blind side. The flicker letters occurred one per trial randomly on both sides with a constant proportion (blind:seeing, 3:1) preventing extended periods without seeing a stimulus. During a session, a panel with all four letters (without flicker), arranged vertically, remained centered on the screen. Patients had to fixate the panel and, within 10 seconds, click the mouse on the panel letter matching the flickering letter. On the seeing side, a green symbol appeared with the correct response as positive feedback; a red symbol along with an annoying beep indicated an error. The presented and clicked letters, along with associated response latency, were recorded in a Paradox databank for off-line analysis.

Training procedure. The patients trained at home, using our laboratory's laptops to ensure standard training conditions (screens, fixed viewing distance, and visual-field area trained), twice for 30 minutes per day, 5 days a week, for 6 weeks. Patients were instructed to avoid head movements during either training. Data were collected three times, before (T1), immediately after (T2), and 6 weeks after training (T3). Log-in file analysis indicated that patients of both groups practiced on average 34 days with 40 blocks per day (no group differences, t test, $p = 0.926$).

Outcome variables. ***Digit-search task.*** The task, identical to EST practiced in one group but administered on a 15-in monitor, provided a more precise response time (RT) assessment than a natural search task described below. It also allowed assessment of EST success as opposed to mere learning effects due to repeated task exposure in both groups. Head stability in this task and during natural scene exploration, fixation task, and perimetry was maintained by a chin rest.

Natural search task (table test). RT (seconds per item) was measured using common objects featured in an uneven but fixed fashion on a table (10 in each quadrant). In a session (one per time point), patients had to find, in each hemifield, 20 distinct objects presented in succession by the investigator. Distinct object-category prototypes (e.g., various toy cars) were used to avoid confounds such as semantic influences or agnosia.

Natural scene exploration and fixation stability. Eye movements during initial fixation and subsequent free explora-

Table Summary data of patients involved in the study

Patient ID	Age, y	Sex	Diagnosis	Affected side	HH duration, mo
Explorative saccade training group					
101	46	M	Ischemic stroke	L	26
102	63	M	Hemorrhage	R	9
103	59	M	Ischemic stroke	L	18
104	65	F	Arteriovenous malformation	R	228
105	54	M	Ischemic stroke	L	48
106	67	M	Ischemic stroke	R	6
107	66	M	Ischemic stroke	L	26
108	69	F	Ischemic stroke	L	17
109	65	M	Ischemic stroke	L	48
110	73	M	Ischemic stroke	L	20
111	58	M	Cerebral abscess	R	28
112	67	M	Stroke*	R	54
113	71	M	Ischemic stroke	L	9
114	31	F	Head injury	R	43
115	53	F	Ischemic stroke	R	8
Mean	60.467				39.200
SD	10.980				54.588
Median	65				26
95% CI	±5.556				±27.625
Flicker-stimulation training group					
201	59	M	Ischemic stroke	R	7
202	76	F	Stroke*	R	7
203	65	F	Hemorrhage	L	292
204	63	F	Ischemic stroke	R	50
205	49	M	Stroke*	R	9
206	69	M	Ischemic stroke	L	104
207	68	F	Ischemic stroke	R	35
208	74	M	Stroke*	L	4
209	61	F	Arachnoidal cyst	R	708
210	65	M	Ischemic stroke	L	22
211	71	M	Stroke*	R	7
212	54	M	Hemorrhage	L	16
213	46	F	Ischemic stroke	L	7
214	50	M	Ischemic stroke	L	36
215	34	F	Hemorrhage	R	14
Mean	60.267				87.867
SD	11.671				186.660
Median	63				16
95% CI	±5.906				±94.461
***p* Value**	0.999				0.589

The groups were compared with two-tailed Mann-Whitney tests; *p* values are shown in the bottom row.

*Not otherwise specified.

HH = homonymous hemianopia; CI = confidence interval.

tion of natural scenes were recorded by a video eye tracker (EyeLink, SensoMotoric Instruments, Teltow, Germany).

During the fixation task, patients had to maintain stable fixation of a cross presented for 20 seconds on a PC monitor (resolution 1,024 × 768). Their fixation stability was measured and computed as the difference between the 90th and 10th percentiles of the gaze positions' distribution along the horizontal coordinate.[20] The distance between the two yields the fixation-stability measure (i.e., the horizontal extent of "eye wandering"); the greater the extent is, the less stable the fixation is. In addition, we assessed the asymmetry of fixational eye movements by computing the difference between the mean and median from the individual distributions of fixations. Although these measures refer to the fixation rather than the exploration task, they could reflect patients' tendency to look toward their blind side. We showed that hemianopic patients spontaneously develop eye movements toward their blind side.[20]

During natural scene exploration, the patients scanned novel scenes (landscapes, street scenes) with a salient object (tower, sculpture) located on either the blind or the seeing side. A total of 30 scenes were selected (10 at T1, T2, and T3) and then mirrored such that the scenes with salient objects on the blind and seeing sides were the same. Twenty single scenes per time point, viewed from 30 cm, were presented randomly for 20 seconds each. Patients had to look at the scene without a specific task or thematic focus.

Perimetry. Standardized threshold-oriented, slightly supraliminal static grid Tübingen automated perimetry (TAP 2000; Oculus, Wetzlar, Germany) was accomplished in the 30° visual field in both eyes with special regard to the vertical field border and the area trained by FT. Fundus-controlled perimetry was performed with a scanning laser ophthalmoscope (SLO 101; Rodenstock, Munich, Germany) using a special triplet stimulus to determine the vertical field border and the 10° visual field with precise fixation control (spatial resolution 0.5°–1.0°).[4,20,21]

Reading speed. Reading speed (words per minute) was assessed during reading black print on a paper. We used standardized texts (International Reading Speed Test, IReST[22]) developed in our collaborative European Union project (www.amd-read.net).

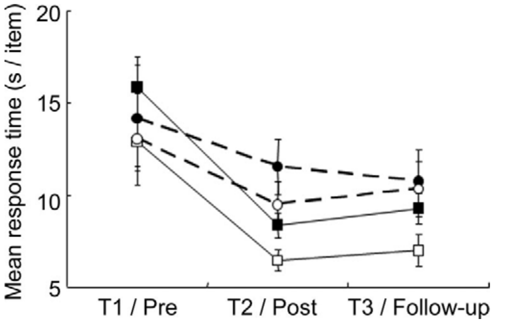
Quality of life. Patients completed a custom vision-related questionnaire and the World Health Organization questionnaire on quality of life, WHOQOL-BREF.[23]

Statistical analysis. Statistical differences were assessed using *t* tests, provided that according to the Shapiro–Wilks test, normality assumptions were met, or otherwise using the Mann–Whitney test. Data were processed (by A.N.S.) using JMP7.0 (SAS Institute, Cary, NC) in a repeated-measures analysis of variance (ANOVA) with side (blind, seeing) and repetition (T1/pre, T2/post, T3/follow-up) entered as within-subject factors, and group (experimental/EST, control/FT) as a between-subjects factor.

RESULTS The means and variability measures are found in table e-1 on the *Neurology*® Web site at www.neurology.org.

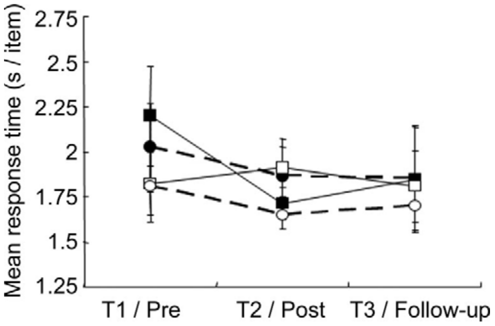
Digit-search task. Figure 1 plots average RT in the task administered to both groups three times, and additionally only in the EST group between T1 and T2 as the training procedure. At T1, longer RT occurred for the blind side, with no group differences

Figure 1 **Digit-search response times**



Mean response time (±1 SEM) for the digit-search task on the screen in the explorative saccade training (EST) group (squares, solid line) and the flicker-stimulation training (FT) group (circles, dashed line), for the blind (filled symbols) and seeing sides (open symbols) before training, after training, and at 6 months follow-up. EST yields greatly reduced response time (post/pre, 47%) for the blind side compared with FT (18%; analysis of variance, group-by-repetition interaction, $p < 0.015$).

Figure 2 **Natural search response times**



Mean response time (±1 SEM) for the natural search task (table test) in the explorative saccade training (EST) group (squares, solid line) and the flicker-stimulation training (FT) group (circles, dashed line), for the blind (filled symbols) and seeing sides (open symbols). Response time selectively decreased (post/pre, 23%) on the blind side after EST, and the improvement persisted at follow-up (paired t test; T2/T1, $p < 0.03$; T3/T2, $p = 0.691$).

for each side [paired t test; blind/seeing, $t(26) = 2.127$, $p < 0.04$; group differences, lowest $p = 0.508$].

After training, the EST group exhibited a substantial uniform RT reduction on both sides, and the improvement persisted until T3. The FT group showed a weaker, uniform RT decrease for both sides [EST: main effects of side, $F(1,28) = 12.989$, $p < 0.001$, repetition, $F(2,28) = 37.26$, $p < 0.0001$; FT: main effect of repetition, $F(2,26) = 6.086$, $p < 0.01$].

Importantly, solely for the blind side, the EST group gained much greater RT reduction after training (47% relative to pretraining throughout) than the FT group. We found main effects of repetition and a striking group-by-repetition interaction for the blind side, but no such interaction for the seeing side. This highlights EST specificity for the improvement of search behavior on the blind side (main effects of repetition, blind: $F(1,26) = 16.451$, $p < 0.0004$, seeing: $F(1,26) = 24.286$, $p < 0.0001$; interactions, blind: $F(1,26) = 7.132$, $p < 0.015$, seeing: $F(1,26) = 1.835$, $p = 0.188$).

Natural search task. At T1, RT showed no group differences for both sides (figure 2; t test; lowest $p = 0.639$).

Solely in the EST group, blind-side RT decreased after training at T2 (23%), and the improvement persisted until T3. In contrast, seeing-side RT remained unchanged (paired t test; blind, T2/T1: $t(14) = 2.278$, $p < 0.03$, T3/T2: $t(14) = 0.406$, $p = 0.691$; seeing: $F < 1$). The FT group showed neither side nor repetition effects.

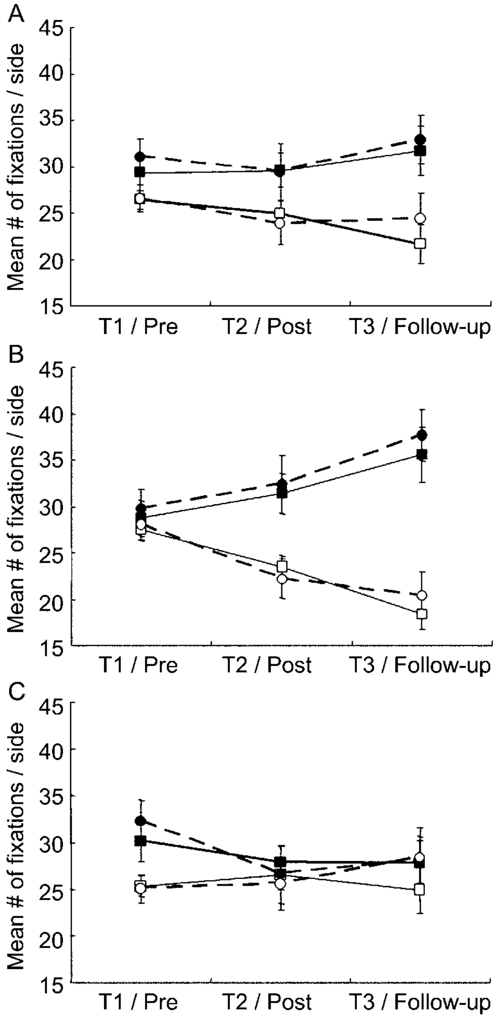
Natural scene exploration. Figure 3A shows the average number of fixations while scanning natural scenes. At T1, more fixations occurred toward the blind side, with no group differences [t test; blind/seeing, $t(26) = 2.536$, $p < 0.02$; group differences, lowest $p = 0.497$].

In the EST group, fixation behavior diverged over time; fixations increased on the blind and decreased on the seeing side (figure e-1). The difference was most pronounced at T3 (238%), suggesting adoption of the learned search strategy in the EST group after training completion. In contrast, the corresponding curves in the FT group remained parallel [main effects of side, EST: $F(1,28) = 51.143$, $p < 0.0001$, FT: $F(1,26) = 16.634$, $p < 0.0002$; side-by-repetition interactions, EST: $F(2,28) = 4.882$, $p < 0.01$, FT: $F < 1$].

The salient object's location markedly affected saccadic exploration. Figure 3B shows the number of fixations with the object located on the blind side. In the EST group, the divergence between the sides became more pronounced. In the FT group, the curves diverged as well [main effects of side, EST: $F(1,28) = 93.184$, $p < 0.0001$, FT: $F(1,26) = 43.97$, $p < 0.0001$; interactions, EST: $F(2,28) = 23.829$, $p < 0.0001$, FT: $F(2,26) = 7.071$, $p < 0.005$].

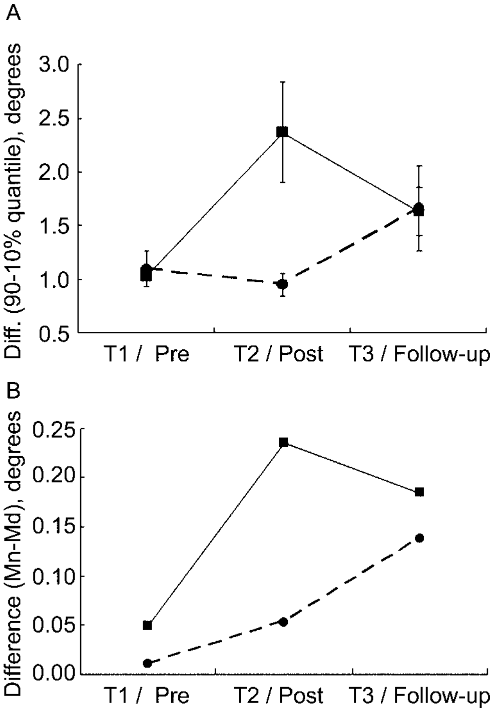
Importantly, with the object location on the seeing side (figure 3C), in both groups at T1, more numerous fixations occurred on the blind side than on the seeing side [paired t test; EST: $t(14) = 2.407$, $p < 0.035$; FT: $t(10) = 2.593$, $p < 0.03$]. However, ANOVA indicated that this prevalence (on average 12%) persisted over time only with EST. In the FT group, neither differences occurred between the sides, nor any changes in this measure [EST: main effect of side, $F(1,28) = 7.46$, $p < 0.01$, interaction, $F(2,28) = 1.462$, $p = 0.243$; FT: lowest $p = 0.122$].

Figure 3 Natural scene exploration: Number of fixations



Mean number of fixations (±1 SEM) during natural scene exploration in the explorative saccade training (EST) group (squares, solid line) and the flicker-stimulation training (FT) group (circles, dashed line), on the blind (filled symbols) and seeing sides (open symbols): independent of the location of the salient object (A), and when the object was found on the blind side (B) or on the seeing side (C). Fixations become overall more numerous on the blind side and decrease on the seeing side after EST (follow-up/pre difference, 238%; analysis of variance, side-by-repetition interaction, $p < 0.01$). Even with the salient object located on the seeing side, fixations in EST group, unlike in FT group, remain more numerous on the blind side than on the seeing side (post/pre, on average 12%; analysis of variance, main effect of side, $p < 0.01$).

Figure 4 Fixational eye movements



Fixational eye movements while fixating a cross in the explorative saccade training (EST) group (squares, solid line) and the flicker-stimulation training (FT) group (circles, dashed line). The distribution of the patient's gaze positions over time is recorded by the eye tracker and represented as an x,y plot. Two spatial locations along the x coordinate are then computed that correspond to the 10th and 90th percentiles of the distribution. The difference between the two (i.e., the horizontal extent of "eye wandering") yields the fixation-stability measure used; the greater the extent is, the less stable the fixation is. (A) Mean fixation stability (±1 SEM), as an averaged difference between the 90th and 10th percentiles of the individual fixation distributions (degrees of visual angle) and (B) asymmetry of fixation distributions toward the blind side, as an averaged difference between the individual means and medians (degrees of visual angle). After EST, fixation stability markedly decreases (post/pre, 43%), and asymmetry of fixations toward the blind side increases (post/pre, 482%). In the FT group, these measures also change, but to a lesser extent. At T3, both groups yield similar fixation stability. This is presumably because by this time, the EST group develops a systematic exploratory strategy, gains a clear distinction between the exploration and the fixation tasks, and better complies with the instruction of stable fixation. In turn, FT may trigger unsystematic eye movements, yielding a gradual decrease in fixation stability.

Fixation stability. Figure 4A plots fixation stability assessed as the average difference between the 90th and 10th percentiles of the gaze positions' horizontal coordinate, and figure 4B plots the asymmetry of the distribution as the difference of its mean and median. The groups did not differ on either measure at T1, but after training (T2) only the EST group exhibited both much reduced (43%) fixation stability and increased (482%) asymmetry of fixations toward the blind side.

Visual fields. Neither the EST group nor the FT group showed any differences in their TAP or SLO outcomes, quantified as the total number of stimuli detected in the blind hemifield (lowest $p = 0.204$).

Quality of life. The EST group reported greater improvements (T2 minus T1 scores) in the WHOQOL social-relationships domain (t test; $t(20) = 2.217$, $p = 0.038$) and, as a trend, physical-status domain

($p = 0.084$) than the FT group. The vision-related questionnaire outcome suggested that the social domain benefited from the patients' reported tendency to better visually spot persons ($p = 0.065$). The EST group tended to judge better their ability to master daily-life activities ($p = 0.064$).

Reading speed. Reading speed stayed unaffected by either training. Although the EST and FT groups differed in their reading speeds at T1, this difference remained unchanged [main effect of group, $F(1,26) = 133.074$, $p < 0.0001$, interaction, $F < 1$].

DISCUSSION

The present study showed a substantial beneficial effect of EST in hemianopic patients. The digit-search task, the training method of the EST group, yielded a markedly improved performance. An FT group enhancement could be explained by mere learning due to the repeated task exposure. The striking superior digit-search performance in the EST group after training, significant only for the blind side, indicates EST specificity for improving the exploratory behavior.

After EST, natural search performance (figure 2) selectively improved on the blind side, and the improvement persisted until follow-up. Furthermore, EST induced an increased exploratory eye-movement activity on the blind side during free scanning of natural scenes (figures 3A and e-1). With the salient object's location on the blind side, both groups showed more numerous fixations on that side (figure 3B). This is especially surprising for the FT group and might be explained by a shift of attention toward the blind side, triggered by negative feedback during training, presumably provoking eye movements toward the object.

In contrast, dissociation between the groups occurred with the objects located on the seeing side (figure 3C). Before training, both groups' fixations were more numerous on the blind side, but only with EST, this prevalence persisted over time. This suggests that EST specifically supports exploratory saccadic activity into the blind hemifield.

All three outcome variables from the search and natural exploration tasks show a strong and specific effect of EST compared with FT. The effects are robust and maintained or even enhanced beyond the training period, i.e., EST patients had learned to consistently apply the search strategy to everyday tasks. Thus, this study substantially extends previous evidence for the benefits of saccade training[7-10,24,25] by using an alternative treatment in a control group and random patient assignment, as has been required by many authors.[26,27]

Interestingly, solely with EST did the fixation stability decrease and asymmetry toward the blind side increase, indicating an enhanced "readiness" (lowered threshold) to perform eye movements toward that side. Indirect triggering of eye movements is seen with FT at follow-up, although less pronounced than with EST (figure 4), yielding similar fixation-behavior values in both groups. Presumably, the EST group developed a systematic explorative strategy, clearly distinguished the exploration and fixation tasks, and better complied with the instruction of stable fixation. This account is supported by an increased difference in explorative eye movements between the sides in the EST group at follow-up (figure 3, A and C). In turn, as in previous flicker-training studies,[18] FT might trigger unsystematic eye movements, yielding a gradual decrease in fixation stability.

The visual fields did not differ over time in either group, either along the field border (SLO) or across the total 30° area (TAP), indicating that neither EST nor FT, as implemented in this study, enlarged the blind field. The result agrees well with previous findings[4,28] that visual stimulation along the vertical field border, introduced as visual restitution training,[1] does not enlarge visual fields but can trigger eye movements. Recent studies[18,19] used a letter flickering at 10° eccentricity, which reduces the risk of eye movements toward the stimulus. Reportedly, two patients normalized their contrast sensitivity in the blind hemifield,[18] and one patient[19] showed ipsilateral (intact) visual-cortex activation by checkerboard stimulation at 10° to 20°. These results could be explained by indirect triggering of eye movements, as observed in our study with even more peripheral stimuli (21.8°) that did not improve visual fields. Therefore, convincing evidence is still lacking that visual stimulation of the blind hemifield leads to restitution of the occipital cortex in a clinically relevant way.[5,6,13,27,29,30]

Because in both groups disease duration exceeded 6 months while dissociations in post-training performance occurred in the EST group compared with the FT group, spontaneous recovery is unlikely to account for the present findings. The groups were uniform and did not differ with respect to essential patient characteristics. It is worth noting that even in patients with longstanding hemianopia who might already have acquired some adaptive strategies, EST shows its effectiveness by specifically activating eye-movement exploration toward the blind side. The lack of dropouts in the EST group indicates good acceptance of the training. Importantly, EST translates into subjective improvement for the patient's functional ability in real-world situations, especially the social domain (likely due to a better person detection) and tendency to better judge physical status, including mastering daily-life activities.

Our study focused on the hemianopic orientation disorder and provides a training method to improve visual search in the midperipheral visual field requiring large saccades. As expected, neither EST nor FT specifically affected reading speed. Rehabilitation of the hemianopic reading disorder requires training with small saccades[8,9,17,31] considering the necessary size of perceptual span.[32-34] Reading training has to take account of the reading direction, field-defect side, its distance to the visual-field center, and adaptive strategies[20,35] such as eccentric fixation[36] and predictive saccades.[37]

The outcome of this randomized controlled study indicates that in patients with hemianopic orientation disorder, compensatory EST selectively improves exploration behavior on the blind side in everyday tasks. FT improves neither exploration nor visual fields.

ACKNOWLEDGMENT

The authors thank Detlef Axmann, PhD, for statistical advice; Egon Weidle, MD, Petra Biermann, and Sonja Maier for support in patient recruiting and examination; Iris Reckert for providing natural scenes; and William F. Hoyt, MD, Manfred MacKeben, PhD, and Nhung Nguyen, MD, for helpful comments.

Received July 9, 2008. Accepted in final form October 15, 2008.

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