

Visual hallucinations during spontaneous and training-induced visual field recovery

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Abstract

Visual hallucinations after post-geniculate visual system lesions were shown to be associated with spontaneous recovery of visual functions. We investigated the occurrence of hallucinations during spontaneous recovery and additionally tested whether hallucinations were re-instated in a phase of vision restoration therapy (VRT). Nineteen patients with post-geniculate lesions and homonymous visual loss participated in a prospective study, and 121 patients with various lesions were included in a retrospective study using a questionnaire including verbal descriptions as well as drawings of hallucinations experienced by the patients. In both samples, visual-field size was determined before and after 6 months of VRT. Many patients in both groups experienced post-lesion hallucinations (mostly colors, objects, motion) which subsided after spontaneous recovery of visual functions (increase of visual field size, recovery of more complex visual function) was ended. Hallucinations re-emerged during training. However, the majority of patients reported simple, unformed visual hallucinations (uncolored phosphenes, spots, flashes), especially when visual field recovery was most intense. Hallucinations were mainly found in patients with large shifts of the visual field border. They occurred in blind areas, particularly in areas of residual vision where recovery was predominantly observed. Hallucinations may reflect functional recovery in partially lesioned brain areas. While the colored/formed hallucinations during spontaneous recovery may represent non-specific activation of higher visual areas, the simple, unformed training-related hallucinations may indicate recovery in the primary visual cortex during treatment. Hallucinations should not generally be discarded as pathological or unimportant symptoms, but they may be functional indicators of visual system plasticity. © 2007 Elsevier Ltd. All rights reserved.

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1. Introduction

In addition to loss of visual function, patients with lesions of the visual pathway often experience “positive symptoms”, such as hallucinations. Patients suffering from cortical lesions report striking, realistic visual percepts in the absence of stim-

ulation by objects in the external world (Anderson & Rizzo, 1994; Beniczky et al., 2002; Kölmel, 1985, 1988; Lance, 1976; Merabet, Kobayashi, Barton, & Pascual-Leone, 2003; Ramachandran, 1999; Vaphiades, Ceesia, & Brigell, 1996; Vogeley & Curio, 1998).

Remarkably similar hallucinatory experiences are associated with very varied neuropathological syndromes, encompassing structural damage and disturbed neural function in several cortical and subcortical brain regions, such as migraine, intoxication with drugs, epilepsy, Parkinson’s disease, dementia and certain forms of psychosis (Manford & Andermann, 1998). Most fre-

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quently, visual hallucinations are observed in Charles Bonnet syndrome, commonly associated with retinal diseases, e.g., age-related macular degeneration, or other conditions affecting the peripheral visual pathway. Patients with that syndrome typically experience hallucinations during low arousal in the total or local absence of visual input (Ffytche & Howard, 1999; Manford & Andermann, 1998; Menon, Rahman, Menon, & Dutton, 2003; Santhouse, Howard, & Ffytche, 2000; Teunisse, Cruysberg, Hoefnagels, Verbeek, & Zitman, 1996).

Whereas hallucinations in Charles Bonnet patients are mostly chronic and not related to changes in visual function, hallucinations after post-geniculate visual system lesions seem to follow the time course of visual recovery: Hallucinations typically start several days after the lesion and gradually subside within days or weeks, their cessation often coinciding with the end of spontaneous increase of intact visual field size (Kölmel, 1985, 1988). One of our patients with infarction of the left middle artery experienced spectacular hallucinations in the completely blind upper right quadrant of the visual field and in a partially defective zone bordering the blind region for about 1 year, which disappeared when spontaneous recovery ceased (Kasten, Müller-Oehring, Poggel, & Sabel, 1998). Thus, visual hallucinations may represent an epiphenomenon of spontaneous recovery and processes of cortical reorganization (Kölmel, 1988; Wunderlich et al., 2000; Tan, Sabel, & Goh, 2006).

The neural mechanisms underlying hallucinatory experiences in patients with post-geniculate lesions of the visual system are still unclear, and at present it is unknown whether they rely on similar mechanisms as Charles Bonnet syndrome. Anderson and Rizzo (1994) and Vaphiades et al. (1996) suggested that hallucinations after post-geniculate lesions are caused by either pathological activation or loss of inhibitory input in neural ensembles bordering the damaged area. In both, normally-sighted and visually impaired subjects, increasing the activation of visual cortex by electrical stimulation with electrodes (Foerster, 1976; Penfield & Rasmussen, 1950) or with transcranial magnetic stimulation (TMS) (Cowey & Walsh, 2000; Gothe et al., 2002) elicits percepts ranging from unformed white phosphenes to colors and geometrical objects, to faces, landscapes and scenes. Conversely, visual hallucinations may be inhibited by blocking visual cortex activation by appropriate electrical stimulation, e.g., with TMS (Merabet et al., 2003), or pharmacological agents (Kornreich, Dan, Verbanck, & Pelc, 2000; Manford & Andermann, 1998).

After deafferentation, hyperexcitability of visual system neurons is found in peri-lesional regions in cat visual cortex (Eysel et al., 1999). This increased activation may be a cause of visual hallucinations and provide a link to cortical reorganization. Evidence that cortical regions at the border of damaged or deafferented areas represent the substrate for the recovery of visual functions comes from numerous animal experiments (Chino, 1999; Eysel et al., 1999; Sabel, 1999). In patients with visual field loss, spontaneous and training-induced increase of intact visual-field size was observed primarily in areas of residual vision, which are typically located between intact and blind regions (Kasten, Müller-Oehring, et al., 1998; Kasten, Wüst, et al., 1998; Poggel, Kasten, Müller-Oehring, Sabel, & Brandt,

2001; Poggel, Kasten, & Sabel, 2004) and presumably correlate with partially defective neural tissue at the border of the lesion (Kasten et al., 1999; Sabel, 1999).

The question arises whether visual hallucinations in patients with post-geniculate brain damage are causally related to functional improvement and neuronal plasticity. The high inter-individual variability of spontaneous improvement in visually impaired patients (Poggel et al., 2001) makes a causal relationship between hallucinations and recovery difficult to establish: Conclusions have to be based on the observation of temporally coincident processes. In the current study, we followed a two-pronged approach: first a retrospective analysis of hallucinations occurring in the phase of spontaneous recovery following visual-system lesions; and, second, a combined prospective and retrospective study with the same patients that involved inducing neuronal plasticity and visual-field enlargement through Vision Restoration Therapy (VRT).

2. Methods

Data on functional recovery and visual hallucinations was collected in two independent studies. First, a sample of 19 patients with lesions in the post-geniculate visual system participated in a prospective clinical trial designed to study the role of attention in the restoration of vision (Poggel et al., 2004). This group was closely monitored on a monthly basis with respect to visual-field size and the occurrence of hallucinations. In the second, retrospective study, 121 patients with various types of visual-field loss who had undergone Vision Restoration Therapy (VRT) answered a questionnaire.

All subjects gave their written informed consent before taking part in the study. The design of the trial was approved by the local ethics committee of the University of Magdeburg and was in accordance with the ethical standards in the Declaration of Helsinki.

2.1. Prospective clinical trial

2.1.1. Patient sample

The 19 patients (mean age: 42.6 ± 12.8 years; 7 female) with homonymous visual-field defects after post-geniculate lesions (visual cortex or optic radiation) were recruited for a clinical trial evaluating the outcome of Vision Restoration Therapy (Poggel, 2002; Poggel et al., 2004). Fifteen of them had suffered cerebral infarction, mostly involving the posterior cerebral artery, three had had vascular malformations (aneurysm bleeding and/or surgery) and one had experienced brain trauma. Average time since lesion at the beginning of the first pre-training visual-field examination was 35.9 months (range: 6.7–189.9 months).

Patients with the following characteristics were excluded from the study: age below 18 or above 75 years, damage to the retina or optic nerve or other ophthalmic disorders, cognitive deficits, impairment of attentional functions (including neglect), psychiatric disorders, photosensitive epilepsy and diseases with an obvious risk of progressive visual and/or cognitive impairment. In addition, visual-field size, assessed by high-resolution campimetry (see below), had to be stable, i.e., an increase or decrease in visual-field size of <2% over at least 4 weeks before the study started (pre-training baseline).

The purpose of the training study was to assess the influence of visuo-spatial attention on training-induced recovery of visual functions (Poggel et al., 2004). Patients were randomly assigned to an experimental group who received training with a visuo-spatial attention cue, and a control group who received conventional training without cueing. There were no differences between these groups with respect to the hallucinations observed. Therefore, all 19 patients were grouped together and results below are presented for the complete sample.

2.1.2. Visual-field testing

A high-resolution, computer-based campimetric test (HRP, Nova Vision, Magdeburg) was used to assess visual-field size and to determine areas of

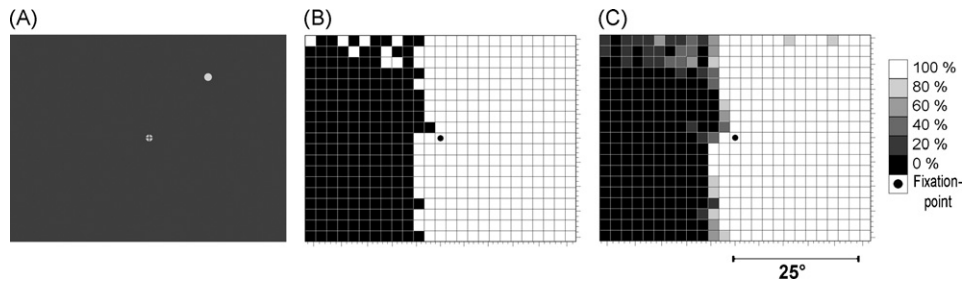


Fig. 1. Visual field testing with high-resolution perimetry (HRP). (A) Computer screen during testing (see Section 2 for description). (B) Result of a single HRP-test in a patient with left-sided hemianopia (black = blind areas, white = intact areas). (C) Results from five consecutive HRP-tests superimposed to show areas of residual vision (grey) where the probability of stimulus detection is reduced. Shades of grey indicate the severity of the lesion.

residual vision (ARVs). Testing was carried out under standardized conditions in a darkened room. On a dark CRT screen (luminance = 26 cd/m²), white light stimuli (luminance = 96 cd/m²; size = 0.76°; presentation time = 150 ms) were presented in random order at 474 positions in the visual field (Fig. 1). Subjects pressed the space bar on the computer keyboard upon detection of a stimulus and also in response to the program's fixation control, an isoluminant change in the color of the fixation point. Fixation was also controlled by the experimenter observing the subject's eye position in a mirror. For a detailed discussion of monitoring fixation see Poggel et al. (2004). Total duration of the visual-field test was approximately 20 min. Visual-field size was additionally determined using standard Tübingen Automated Perimetry (TAP 2000; TEC), employing a detailed threshold test for stimulus locations within 30° eccentricity and an overview of the complete visual field (intact positions, relative and absolute defects within 90° (TAP 2000) or 60° (TEC), respectively).

2.1.3. Pre-training baseline measurements

Before visual-field assessment, all patients went through a structured interview in which they provided some background information on the lesion and development of symptoms, activities of daily living, and treatment history. They were questioned on whether they had experienced hallucinations during or after the lesion and if so, they were asked to describe the phenomenology, time course, and their emotional reaction. Although we encouraged patients to talk about their experiences, we took great care not to suggest that they may have perceived hallucinations.

Campimetric measurements were repeated five times over a baseline period of at least 4 weeks, the results were superimposed and the detection probability calculated for each stimulus position. For each patient, the area of residual vision was defined as the region at the visual-field border enclosing stimulus positions with a detection probability between 20% and 80% (see Poggel et al., 2004, and Fig. 1).

2.1.4. Vision restoration therapy

Each VRT session comprised 500 stimuli presented at random locations mostly at the visual field border within an individually determined training area (see Poggel, 2002; Poggel et al., 2004, for a detailed description of VRT). Training stimuli appeared on a dark computer screen, each target increasing in brightness from dark grey to bright white over 2000 ms. Stimulus size, fixation control, mode of response, and viewing distance were identical to high-resolution campimetry (see above). The duration of one training session was approximately 30–35 min. Patients performed the training at home over a period of 6 months with approximately two sessions per day. After each session, data were saved on a disk and patients received feedback on the number of detected stimuli.

2.1.5. Control examinations during training and post-training baseline measurements

At the end of each training month, each patient received a control examination during which visual-field size was assessed by high-resolution computer-based perimetry (HRP), training results were analyzed and the training area was re-adjusted to the visual-field border according to the progress the

patient had made. Patients also underwent a short interview including a subjective evaluation of the progress during the previous month or potential problems. To avoid biasing patients toward perceiving and/or reporting visual hallucinations, we used a very general question (“Has there been anything unusual happening during the last month?”) to prompt patients' reports. Only when patients spontaneously mentioned visual hallucinations, they were questioned with respect to details (e.g., description of the phenomena, time and frequency when they occurred, location in the visual field, etc.). After the 6th training month, post-training baseline measurements identical to the pre-training examination were performed and the patients underwent a detailed interview, including questions on hallucinations during the training period.

At the 6-month interview, patients were also assessed by questionnaire on the hallucinations they had experienced during their spontaneous recovery and the training phase.

2.1.6. Questionnaire on visual hallucinations and categorization of hallucination types

The questionnaire was applied in the patients' native language, German (Poggel, 2002). In summary, patients were asked to describe the general appearance, geometry, colors, temporal characteristics, as well as any correlation with external events, e.g., emotional stress. We also questioned patients about their medical history to identify the presence of diseases that may be associated with hallucinations or similar phenomena, such as migraine, epilepsy, psychosis, and drug intoxication/alcoholism. Patients were encouraged to draw the images they had perceived with a pencil or colored pens on a blank page in the questionnaire form, so that their descriptions did not entirely depend on their ability to verbally describe the hallucinations.

The questionnaire was structured in such a way that the initial question was as general and open as possible (e.g., “Have you ever perceived things that were not real at any time before, during or after the visual field loss occurred?”) to avoid biasing the patients' reports. Only after a positive reply, patients were subsequently guided through a set of more specific questions. Information about the location of the hallucinations within the visual field were extracted from answers of the patients to initial open questions (“Please try to describe these experiences as precisely as possible in your own words!”), their drawings of the hallucinations, or from remarks handwritten under the question on the location of hallucinations. Patients in the prospective study also described the location during the interviews in the monthly control examinations.

For further analysis and quantification of data, we categorized the hallucinations described by the patients following a classification originally proposed by Wilbrand and Sanger (cited after Fahlke, 2003) which has been used in clinical settings as well as for numerous experiments on visual hallucinations. We categorized the patient's hallucination as “simple” or “unformed” if the phenomena were described as unformed/diffuse, small or extended light flashes, either completely uncolored or color tinges, and did not involve complex patterns of motion (beyond very slow billowing or wafting), repetition of patterns (e.g., palinopsia), or complex temporal characteristics. A hallucination was labeled as “complex” or “formed” when the patient described geometrically formed and/or colored percepts and/or complex patterns of motion, repetition, and/or realistic objects and scenes. This classification was maintained throughout the study and was applied to both study samples.

2.2. Retrospective questionnaire study

2.2.1. Patient sample

One hundred and twenty one patients (mean age: 53.1 ± 15.7 years; 44 female) filled out mailed questionnaires. Most ($n=65$) had suffered cerebral infarction, others had traumatic brain injury (17), inflammation (3), tumor (18), aneurysm (10) and surgery (4); 4 had visual-system lesions of unknown cause.

This retrospective study included patients with visual-field loss after optic nerve lesion, subcortical damage or cortical lesions. In 6 patients with post-chiasmatic lesions, extensive lesions of the visual pathway (e.g., during traumatic injury) resulted in bilateral partial blindness, 41 patients had a right and 54 a left unilateral defect (hemianopia or quadrantanopia in most cases). For most patients, blind areas had clear boundaries with varying amounts of residual vision at the visual field border. In some patients, especially those with pre-chiasmatic lesions, visual field defects were diffuse, i.e., distributed across large parts of the visual field and/or without clearly defined boundaries of blind regions. As this sample was recruited from a clinical unit and confidentiality had to be assured, none of the exclusion criteria of the prospective clinical trial (see above) were applied.

2.2.2. Study protocol

All 121 participants had completed or were still undergoing Vision Restoration Therapy at the clinical centre in Magdeburg, Germany. All 204 patients registered at the centre received a personal letter from Nova Vision staff explaining the goal of the study. Participation in the questionnaire study was voluntary and anonymous. Patients who consented were given the option of disclosing their identity to the researchers and granting permission for their visual-field measurement to be included in the analysis. They were then asked to fill out a questionnaire on hallucinations identical to that used in the prospective clinical trial (see above).

Of the 121 patients who returned the questionnaire, only two did not disclose their identity, so that visual-field measurements were related to information from the questionnaires for the remaining 119 patients. Visual-field testing and the course of training were essentially the same as that described above, except that patients performed only pre- and post-training baseline measurements and were not monitored monthly during the training phase. Some patients (14%) who were suffering from physical or cognitive impairment (mostly deficits of vigilance) following brain lesions received only three or four instead of five visual-field tests before and after training.

Since there were no monthly control examinations in this sample, the data recorded during the training sessions were used to estimate visual field size during the course of training. The increase of visual field size in a given training month was estimated by subtracting the average number of detected stimuli of the first ten training sessions from the average of the last ten sessions. Information about the occurrence of hallucinations was extracted from the initial general question whether hallucinations had been experienced at all (in the phase of spontaneous recovery or during VRT), and from answers to subsequent more detailed questions, e.g., in which training month the hallucinations occurred.

2.3. Data analysis

Data were analyzed using the SPSS program (SPSS Inc., Chicago, IL). χ^2 procedures and Mann–Whitney tests were used to compare data, and non-

parametric correlations were calculated (Spearman's Rho). An alpha of 0.05 (two-tailed) was applied for all tests.

3. Results

3.1. Hallucinations during spontaneous recovery after the lesion

3.1.1. Prospective clinical trial

In structured interviews with the sample of 19 patients with post-geniculate visual system lesions and homonymous visual-field defects more than half of the patients reported that they had hallucinations in the early phase after the brain lesion (see Table 1). These hallucinations were mostly of the complex, formed type (Table 1; Fig. 2). Based on CT and MRI results and doctors' reports in patient files, there was no relationship of the location of lesion (e.g., sparing of primary visual cortex, involvement of subcortical areas/optic radiation, etc.) with the type of hallucination experienced by the patient (e.g., frequency of simple vs. complex hallucinations in patients with cortical versus optic radiation versus combined lesions: $\chi^2 = 6.709$; $p = 0.15$). All but one patient were able to indicate the location of the hallucinations, five "seeing" them in blind areas and four more precisely in partially defective border zones. The hallucinations typically persisted for several days or weeks after the lesion before gradually subsiding.

Quantitative information on the changes in visual-field size in the early phase after the lesion was incomplete, either because perimetric examinations had not been performed repeatedly or because patient records were unavailable. Within this limited data set, patients who experienced hallucinations ($n = 10$) did not differ from those that did not report hallucinations ($N = 9$) with respect to the degree of spontaneous recovery (Mann–Whitney U -test: $Z = -0.192$, $p = 0.848$). The spontaneous recovery was estimated by calculating the difference of visual field size early after the lesion (data obtained from patient files, provided they were available) and immediately before the start of VRT (data collected by us). The patients with vs. without hallucinations soon after lesion also did not differ with respect to their subjectively estimated spontaneous increase in visual field size in the pre-training visual analogue scales (Mann–Whitney test: $Z = 0.00$, $p = 1.00$).

3.1.2. Retrospective trial

In the retrospective questionnaire used to investigate hallucinations in 121 patients who had sustained various types

Table 1
Frequency of hallucinations during spontaneous and training-induced recovery

| | Prospective trial ($n = 19$) | Retrospective trial all ($n = 121$) | Retrospective trial homonymous ($n = 101$) |
|--|--------------------------------|---------------------------------------|--|
| Percentage patients with hallucinations | | | |
| Spontaneous recovery phase | 52.6 | 34.7 | 29.7 |
| Training phase | 84.2 | 16.5 | 9.9 |
| Percentage patients with simple hallucinations (of all patients) | | | |
| Spontaneous recovery phase | 50.0 | 38.1 | 33.3 |
| Training phase | 87.5 | 85.0 | 80.0 |

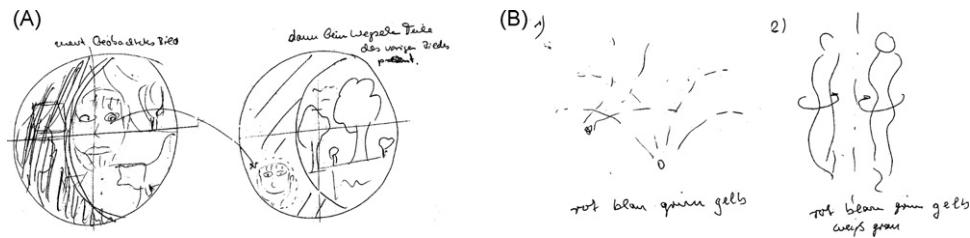


Fig. 2. Drawings of formed visual hallucinations during spontaneous recovery. (A) A female patient (age 35, infarction of the right hemisphere) explained: “When I looked at a person or at an object for some time and then looked away, in the lower left, in the part of my visual field that no longer existed, little segments of those objects or persons appeared.” The patient’s drawing shows the time-lagged repetition of visual scenes from the intact area in the blind field (palinopsia). (B) Drawings made by a 63-year-old male patient with a left-sided infarction, who described: “(I see) colored fireworks, explosions, turning, rotating colored figures and humanoid shapes (heads and serpentine bodies).” He indicated the colors of the hallucinations under the drawings (“red, blue, green, yellow” for the fireworks and “red, blue, green, yellow, white, grey” for the humanoid shapes).

of pre- and post-geniculate lesions, approximately one third (see Table 1) described hallucinations in the early post-lesion phase, again mostly those of the formed type (Table 1; Fig. 2). There were no significant differences between male and female subjects ($\text{Chi}^2 = 2.355$; $p = 0.162$), between patients with left or right hemispheric lesions ($\text{Chi}^2 = 3.443$; $p = 0.073$), or between patients with different aetiologies of visual-field loss ($\text{Chi}^2 = 6.547$; $p = 0.478$). However, hallucinations were more frequently reported by patients with diffuse visual-field loss (large areas of residual vision and/or lack of clearly defined visual field borders, e.g., in some patients with damage to the optic nerve) than in subjects with circumscribed, mostly homonymous visual-field defects ($\text{Chi}^2 = 6.762$; $p = 0.019$).

Patients retrospectively reporting unformed hallucinations indicated greater *subjective* spontaneous recovery after the lesion than patients with formed hallucinations (patient records with more objective data on spontaneous recovery in the immediate post-lesion phase could not be obtained for this study) but the difference is just below significance (spontaneous recovery (mean % visual field \pm S.E.M.): unformed hallucinations: $25.2 \pm 10.6\%$, formed hallucinations: $9.6 \pm 2.0\%$; Mann–Whitney *U*-test: $Z = -1.885$, $p = 0.059$). The median duration of hallucinations in the period after the lesion was 28 days, with significantly more patients experiencing hallucinations within 90 days after the lesion than after this period ($\text{Chi}^2 = 5.538$; $p = 0.019$). The first 90 days is when spontaneous recovery is typically most pronounced.

For a better comparison with the prospective trial, we analyzed the data of those patients in the retrospective group who suffered from unilateral, homonymous visual-field defects, like the patients from the former study. Of the 101 patients with homonymous visual loss one third (Table 1) had hallucinations of some type, the majority being formed hallucinations (Table 1). Because data from the questionnaires did not allow the identification of specific lesion sites for each patient, differences between patients with cortical versus subcortical damage to the visual pathway could not be determined. Also, for this sample there were no perimetric data available that would have allowed calculating the amount of spontaneous visual field recovery before the start of VRT. Patients without visual hallucinations in the early phase after the lesion indicated less subjective increase of visual field size during spontaneous recovery (mean without hallucinations: $4.09 \pm 1.60\%$) than patients with hallucinations

(mean with hallucinations: $12.75 \pm 3.95\%$; Mann–Whitney *U*-Test: $Z = -2.077$, $p = 0.038$).

3.2. Hallucinations during vision restoration therapy

3.2.1. Prospective clinical trial

The 19 patients with post-geniculate lesions had their visual-field size and occurrence of hallucinations closely monitored before, during, and after 6 months of Vision Restoration Therapy (VRT). Significantly more patients experienced hallucinations in that period (Table 1) than in the spontaneous recovery phase ($\text{Chi}^2 = 3.958$; $p = 0.047$), but interestingly those were mostly of the unformed, simple type, i.e., mainly either phosphenes similar to the training stimuli or bright fog, diffuse light, or flashes. Even patients who had initially reported complex, formed hallucinations had mostly simple, unformed hallucinations during VRT. The hallucinations were experienced exclusively during the training sessions. Especially when the hallucinations were similar in appearance to the training stimuli, we questioned patients how they could be sure that the phenomena they reported were not simply residual percepts of real training stimuli. In fact, many patients initially confused the hallucinations with real training stimuli, but received a “false positive” feedback tone upon pressing the response button. In some cases, patients made eye movements to the site of the perceived “stimulus”, but could not see any stimulus at that location. Moreover, the hallucinated “training stimuli” did not follow the time course of the real stimuli which increased in brightness and then disappeared, but they persisted with constant brightness over long periods of time in a training session or quickly flashed and immediately disappeared.

All the patients who experienced hallucinations after their lesion reported recurrence of the phenomena when they started VRT. The mean interval between the lesion and the start of VRT was 35.9 months (S.E.M. = ± 9.6 ; range: 6.7–189.9 months). There was no significant difference in the lesion age between patients with vs. without hallucinations, respectively (Mann–Whitney *U*-Test: $Z = -0.671$, $p = 0.502$). Seven patients indicated that the hallucinations were located in blind areas and nine reported them to be located in the border regions of the defect.

The training-related hallucinations predominantly occurred in the first few months of treatment when visual-field

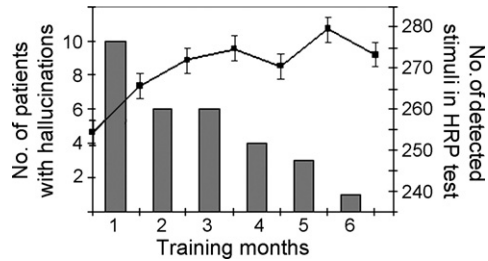


Fig. 3. Occurrence of visual hallucinations correlates inversely with training progress: more patients experience hallucinations in early stages of training where visual field increase is most pronounced. The time course of increase in visual-field size detected by campimetry (high-resolution perimetry, HRP; line graph) and number of patients reporting visual hallucinations (bar graph) during 6 months of Vision Restoration Therapy.

recovery was most pronounced (see Fig. 3). The correlation of the percentage of patients reporting training-related hallucinations during a given training unit with the recovery of stimulus detection performance in the visual field test in the same training unit just missed significance (Spearman's $Rho = 0.638$; $p = 0.087$).

Patients who experienced hallucinations during training showed a somewhat larger increase of the visual field (mean increase: 19.7 stimuli in high-resolution perimetric testing; S.E.M. = ± 5.4) than those not reporting hallucinations (11.9 stimuli ± 5.9) but this is not significant. Patients with simple hallucinations improved more (mean increase = 20.6 stimuli ± 6.1) than those with complex hallucinations (13.2 stimuli ± 5.3) during training; again this difference was not significant, presumably because the sample was small and the variation in training outcome high. Except in the 3rd month of training, the increase in intact visual field during the respective training month did not significantly differ between patients with vs. without hallucinations (training month 3: Mann–Whitney U -Test: $Z = -2.072$, $p = 0.038$).

3.2.2. Retrospective trial

The retrospective questionnaire was answered by 121 patients with various pre- and post-geniculate lesions, after they had received 6 months of VRT. Visual-field size was determined before and after the training period. During the treatment phase, progress was monitored based on the data from the training sessions (see Section 2). In contrast to the findings for the prospective study, considerably fewer of the patients in this group reported hallucinations during VRT than in the period following the lesion (Table 1), however, the majority of these patients reported the simple type, similar to proportion in the prospective study (Table 1; Fig. 4).

Training-related hallucinations were more frequent in patients who reported hallucinations after the lesion than in those who did not experience such phenomena after lesion ($\chi^2 = 14.079$; $p = 0.001$). There was no difference with respect to time since lesion between patients reporting hallucinations and those who did not experience such phenomena (Mann–Whitney U -Test: $Z = -0.170$, $p = 0.865$). Hallucinations were usually reported during the first month of the training period, the phase of most intense recovery, and attenuated as training progressed and the rate of visual-field enlargement decreased as estimated based on the training results of each training unit (Fig. 5). In training months with a larger percentage of patients reporting hallucinations, the visual field increase (based on data from training sessions) was greater (Spearman's $Rho = 0.825$; $p = 0.043$).

Patients experiencing hallucinations during training showed a greater improvement in the high-resolution perimetric test (HRP) after the training period (mean increase = 10.0 stimuli, S.E.M. = ± 3.3) than in those who did not (6.6 stimuli ± 1.1) but the difference was not significant (Mann–Whitney U -Test: $Z = -0.867$, $p = 0.386$). They also had a larger average maximum shift of the border of the visual field towards the blind area (mean = 8.1° visual angle, S.E.M. = $\pm 2.1^\circ$) than patients without such experiences (4.6° visual angle $\pm 0.6^\circ$), but the

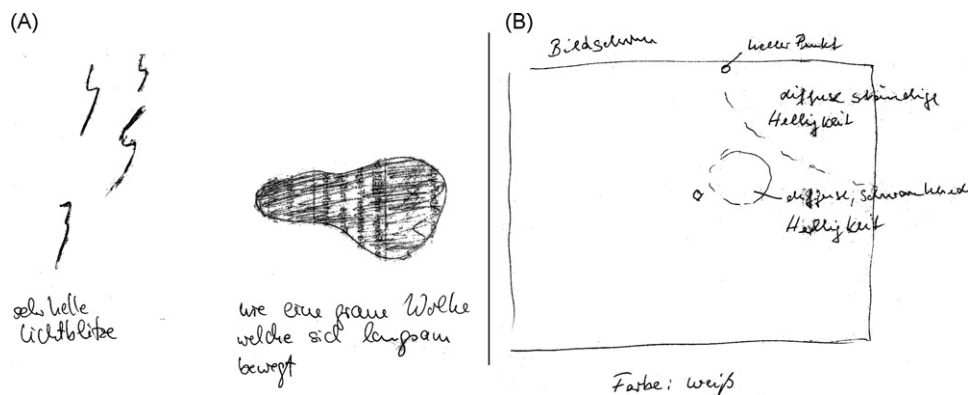


Fig. 4. Drawings of simple visual hallucinations during VRT-induced recovery. (A) A 38-year-old female patient with a visual-field defect after bleeding of an angioma in the left hemisphere stated: "I see shadows coming from the right, like a cat stealing into my visual field. Like a grey cloud that moves slowly. Very bright flashes of light." The patient drew bright flashes of light (left) and a grey cloud (right) in the questionnaire. (B) A male patient, 42 years old, suffering from an infarction of the left hemisphere, reported: "During training sessions, I constantly see a bright, clearly demarcated dot of light on the screen. Moreover I see several areas of diffuse light, varying in brightness." In his drawing, he depicted the screen with the locations of hallucinations: bright dot of light (upper middle), constant diffuse bright field (upper right) and diffuse field of variable brightness (centre). They are all located to the right of the fixation point which is marked by the small circle in the centre.

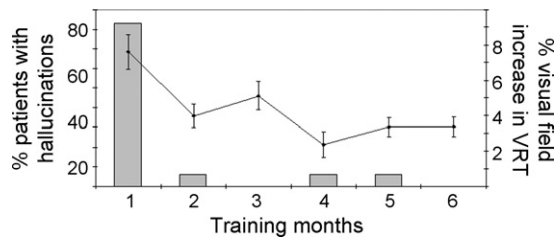


Fig. 5. Relationship between reduction in hallucinations and increase of intact visual field size (retrospective study). The time course of monthly visual-field increase with respect to the previous month during Vision Restoration Therapy (VRT; line graph) and percentage of patients reporting hallucinations (bar graph) over 6 months of training.

difference did not reach significance (Mann–Whitney *U*-Test: $Z = -1.619$, $p = 0.105$). Since we hypothesized that unformed hallucinations are caused by activation of primary visual cortical areas and could thus be more indicative of cortical plasticity in those areas, we tested whether patients with unformed hallucinations showed a more intense shift of the visual field border than those with formed hallucinations. In fact, the maximal shift of the visual-field border was significantly larger in patients with unformed hallucinations (mean = 9.0° visual angle, S.E.M. = $\pm 2.1^\circ$) than in those without hallucinations or with formed hallucinations (4.6° visual angle $\pm 0.6^\circ$; ANOVA: $F = 4.150$; d.f. = 2, $p = 0.020$). We also hypothesized that long-range horizontal connections in the visual cortex might be activated in patients with a large shift of the visual field border toward the blind field, i.e., shifts of more than 7° visual angle cannot be explained by changes in receptive field size (Gilbert, 1998). Visual hallucinations might result from such an activation of long-range horizontal connections. We found that more patients who regained large portions of intact visual field through VRT, i.e., maximum shift of visual-field border towards the blind area greater than 7° visual angle, experienced hallucinations than those with a smaller amount of recovery or no improvement ($\chi^2 = 7.298$; $p = 0.026$). Patients who reported hallucinations also tended to indicate a greater subjective area of visual field recovered by VRT than patients with no hallucinations (mean increase with hallucinations = 28.7% , S.E.M. = $\pm 9.3\%$; without hallucinations: $14.0 \pm 2.5\%$; Mann–Whitney *U*-Test: $Z = -1.732$, $p = 0.083$).

For a better comparison of the prospective and retrospective study, data from patients with unilateral, homonymous visual-field loss (and hence most likely post-geniculate visual field loss) were analyzed separately. Only a small percentage of these (Table 1) experienced hallucinations, but most of these phenomena were categorized as simple. The time since lesion was not significantly different in patients with vs. without training-related hallucinations (Mann–Whitney *U*-Test: $Z = -0.183$, $p = 0.855$). Patients who experienced hallucinations during training exhibited a larger increase in the number of detected stimuli in the HRP visual field test and a larger shift of the visual field border into the blind area, but in that small subgroup the differences did not reach significance. Since there were insufficient post-training visual field data available for the two patients with complex training-related hallucinations, we could

not compare differences of training outcome between patients with simple and complex hallucinations, respectively.

4. Discussion

4.1. Hallucinations and neuronal plasticity

The hypothesis that visual hallucinations in partially blind patients are a positive sign of neural plasticity and recovery of function was proposed in the 1980s (Kölmel, 1985, 1988), but the link between hallucinations and recovery of visual functions has not previously been quantitatively investigated. As we now show, hallucinations are experienced not just during spontaneous recovery in the early weeks after the onset of lesion but can be reinstated by VRT. This process can be triggered even many years after injury.

Although VRT, together with other visual restorative approaches, is still criticized on both technical and rehabilitation grounds (Horton, 2005; Plant, 2005; Reinhard et al., 2005), the purpose of this study was to show a connection between functional recovery and hallucinations, not to evaluate VRT as a method which has been done elsewhere (Kasten, Müller-Oehring, et al., 1998; Kasten, Wüst, et al., 1998; Poggel et al., 2004).

The results of our prospective and retrospective studies suggest that hallucinations are causally linked to plasticity in the visual system. This is supported by the temporal and topographical association of hallucinations with the increase in visual field size. We found that a substantial number of patients experienced hallucinations during VRT (i.e., temporal association with recovery), which was being used to induce recovery of visual function, and that hallucinations were associated with the extent of recovery, i.e., the extent to which the border of the visual field shifted into the blind area (topographical association with recovery).

Topographically, hallucinations occurred more frequently in those patients who benefited most from VRT, i.e., those who experienced a shift of the visual border of more than 7° visual angle. Such a large shift, especially in more central areas of the visual field, cannot be explained by increased receptive-field size of neurons in V1. We speculate that long-range horizontal connections within the primary visual cortex are activated during VRT (Gilbert, 1998; Poggel, 2002; Poggel et al., 2004), and hallucinations may be an epiphenomenon of this process. The hallucinations were typically located in the defective part of the visual field, particularly in areas of residual vision, which are the regions in which restoration of vision is most pronounced.

With respect to the temporal association between the occurrence of hallucinations and visual field recovery, the period when hallucinations were reported coincided with the period when expansion of the visual field was greatest, i.e., observations of hallucinations during spontaneous recovery are paralleled by the time course of training-induced hallucinations: both types of hallucinations diminish when visual field recovery slows down and disappear when recovery is complete (Fig. 3). However, due to missing data in patient files and inconsistent methods of visual field testing in the period immediately after the lesion,

a quantitative connection between the amount of spontaneous recovery (before the start of VRT) and the occurrence of visual hallucinations could not be established in our study. A systematic longitudinal study starting at the onset of vision loss with repeated visual field testing using the same perimetric method and patient reports on hallucinations would be desirable to test this hypothesis.

4.2. Mechanisms producing hallucinations

Two main hypotheses have been proposed to account for hallucinations. Based on studies with patients suffering from lesions of the occipital lobe and/or optic radiation and homonymous quadrantanopic or hemianopic visual field loss, Kölmel (1985) suggested that the hallucinations are elicited by, first, an occipital lesion that cuts off the bottom-up input to higher visual areas and, second, a rostral subcortical lesion that leads to a release of mental images by disinhibiting higher visual areas. In contrast, Ramachandran (1999) considers the deafferentation of visual cortical areas sufficient to explain the type of hallucinations observed in patients with Charles Bonnet syndrome: the visual cortex receives top-down activation but fails to receive the normal bottom-up veto from the blind areas, so the mental images appear like perceptual impressions from the real world, although patients can discriminate between real percepts and hallucinations.

Although both hypotheses may be correct for different subsets of patients, they do not adequately predict the occurrence of hallucinations in all patients with lesions of the visual system. Kölmel's hypothesis cannot explain why visual hallucinations are observed in patients who suffer from retinal or optic-nerve lesions without cortical or subcortical damage, whereas Ramachandran's deafferentation hypothesis fits patients with peripheral lesions but cannot explain why hallucinations are not experienced by all patients with (partial) blindness and sometimes only for a limited time after the onset of blindness. In particular, both fail to account for hallucinations that emerge in areas of residual vision, which is the most frequent location of hallucinations in our patients.

The surviving neuronal substrate in the partially defective regions (Sabel, 1997, 1999) may still be able to transfer visual information to cortical regions, albeit not very reliably and with low signal quality. Such areas are typically largest in patients with diffuse visual-field loss, e.g., resulting from damage to the optic nerve, but are also found in regions bordering the lesion in patients with homonymous hemianopia or quadrantanopia. In our study, subjects with diffuse visual-field defects and large areas of residual vision reported a significantly higher frequency of hallucinations than patients with homonymous visual-field defects and smaller areas of residual vision. This would be expected if the underlying partially defective cortical areas are hyperactive. Furthermore, patients who were able to locate the appearance of hallucinations typically reported them at the visual-field border, where regions of residual vision are typically located.

These observations indicate that the hallucinations described by our patients may result from hyperexcitability of the visual

cortex in regions bordering the lesion. Support for this conclusion comes both from VRT studies and from animal experiments. During VRT, V1 is systematically activated, principally in the partially defective border zones of the lesion or its cortical representation (Kasten et al., 1999; Sabel, 1999). Daily repetitive activation of areas of residual vision during training may cause hyperactivity of V1, reflecting or exaggerating its normal function which may be one of the prerequisites for functional recovery. In animal experiments, hyperexcitability was observed after retinal and cortical lesions, where metabolic rates and electrophysiological activation were considerably increased in a ring-shaped cortical zone around the region affected by a lesion resulting from either direct damage or loss of input from retina, optic nerve or thalamus (Eysel et al., 1999).

Cortical hyperexcitability in partially blind patients may amplify even sparse inputs from the periphery, so that incomplete or low-quality information may elicit greater activation than normal and thus trigger hallucinations. In patients with pre-geniculate lesions, the cortical hyperexcitability might also be induced trans-synaptically (Eysel et al., 1999). Our observations indicate that hyperexcitability precedes an improvement of the signal-to-noise ratio in areas receiving inputs from partially damaged regions because as patients spent more time on VRT, many found it easier to discriminate the real training stimuli from the hallucinations. As reliable perception was regained at a particular position in the visual field, the hallucinations gradually disappeared, presumably because neuronal activation normalized and the signal-to-noise ratio improved.

The hyperexcitability of visual areas discussed above may also be a result of an imbalance between excitatory and inhibitory neural connections in the brain after lesion. Such lesion-induced hyperexcitability is not found in the healthy visual system so that we would not expect visual hallucinations to be induced in normal subjects. Indeed, visual hallucinations were not noted at any time in healthy subjects ($n = 3$) who used VRT for testing purposes as intensely as the patients in this study (unpublished data). Thus, for example a release of inhibition during recovery may be responsible for re-establishing the balance and the abatement and eventually disappearance of hallucinations. Such inhibitory sources may be neighboring regions of the visual cortex or even intact brain areas of the contralesional hemisphere (via callosal connections) or sub-cortical connections.

Top-down inputs to areas of heightened neural activation in the border regions around the lesion, or around the representation of the lesion in the visual cortex, may also contribute to the generation of hallucinations (Ramachandran, 1999), particularly as neurons in hyperexcitable regions are more likely to discharge spontaneously than in intact areas. Thus, hallucinations could arise either from bottom-up processes, through incomplete inputs to partially defective areas, or they may be triggered top-down without external input, or they may result from a combination of both.

Kölmel (1993) suggested that the phenomenology of hallucinations may serve as an indicator for the localization of brain activity during spontaneous recovery. Visual recovery in the early phase after brain lesions typically encompasses

many different functions (perception of simple light stimuli, discrimination of colors, motion perception, perception of shapes and patterns) and hence multiple regions of the visual brain. Therefore, the variety of hallucinations and the high percentage of complex hallucinations observed during spontaneous recovery presumably reflect recovery in these widespread brain regions. In contrast, during treatment with VRT, the systematic stimulation selectively activates primary visual cortex (V1) so that hallucinations reflect or exaggerate normal V1-function. Patients with simple, unformed hallucinations during VRT indeed showed a more pronounced increase of intact visual field size than those with complex hallucinations, presumably because the hyperactivity underlying hallucinations was concentrated in early visual cortex regions relevant for recovery of white light detection. Thus, the change in type of hallucinations, from predominantly formed, complex hallucinations during spontaneous recovery to mainly unformed, simple hallucinations during VRT-induced recovery, may indicate a shift in the visual areas of the brain in which the processes of plasticity and functional recovery occur.

We therefore propose that the occurrence of visual hallucinations should be closely monitored in patients with lesions of the visual system. Instead of being discarded as symptoms of psychiatric disorder or curious yet unimportant transient phenomena, hallucinations may be the hallmarks of the self-healing processes of the visual system: a functional expression of changes in the excitability of the visual cortex that precede or parallel the return of lost visual functions.

Disclosure

E. Kasten is a consultant to Nova Vision Inc. and B.A. Sabel is a shareholder of the company. S. Kenkel is now an employee of Nova Vision Inc.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuropsychologia.2007.03.005.

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