ARTICLE IN PRESS

Consciousness and Cognition xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Consciousness and Cognition

journal homepage: www.elsevier.com/locate/concog

Transient increase of intact visual field size by high-frequency narrow-band stimulation

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ARTICLE INFO

Article history:
Received 19 September 2013
Revised 11 August 2014
Accepted 3 September 2014
Available online xxxx

Keywords:
Blindsight
High-frequency flicker
Visual field restoration

ABSTRACT

Three patients with visual field defects were stimulated with a square matrix pattern, either static, or flickering at frequencies that had been found to either promote or not promote blindsight performance. Comparison between pre- and post-stimulation perimetric maps revealed an increase in the size of the intact visual field but only for flicker frequencies previously found to promote blindsight. These changes were temporary but dramatic – in two instances the intact field was increased by an area of ~30 deg^2 of visual angle. These results indicate that not only does specific high-frequency stimulus flicker promote blindsight, but that intact visual field size may be increased by stimulation at the same frequencies. Our findings inform speculation on both the brain mechanisms and the potency of temporal modulation for altering the functional visual field.

1. Introduction

Lesions to primary visual cortex (V1) lead to blindness in the contralesional part of the visual hemifield which has been believed to be irreversible for decades. However, detection, discrimination, or the localization of visual stimuli presented in the affected part of the visual field often remain possible (Humphrey, 1974; Pöppel, Held, & Frost, 1973; Sahraie et al., 2006; Stoerig & Cowey, 1997; Weiskrantz, 1980; Weiskrantz, Barbur, & Sahraie, 1995; Weiskrantz, Warrington, Sanders, & Marshall, 1974; Zihl, 1980) and are sometimes accompanied by visual awareness. Based upon dissociation between visual performance and awareness, the term "blindsight" refers to visual capacity in a field defect in the absence of acknowledged awareness (Sanders, Warrington, Marshall, & Weiskrantz, 1974). The dynamic characteristics of visual stimulation of patients with vision loss play an important role for blindsight to occur (Hess & Pointer, 1989). For example, Teuber, Battersby, and Bender (1960) found cortically blind soldiers were able to discriminate light/dark onsets; Weiskrantz (1986) reported better discrimination given rapidly flickering stimuli presented in the blind field of patient DB; and targets have been reported to be better localized in space by blindsight patients when flickered (Perenin, Ruel, & Hécaen, 1980). Interestingly, the specific frequency of dynamic stimulation seems to be crucial for blindsight performance. For example, Barbur, Harlow, and Weiskrantz (1994) studied temporal processing in patient GY and discovered that forced-choice detection scores were significantly better than chance when gratings were presented at frequencies between ~6 and 40 Hz;

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http://dx.doi.org/10.1016/j.concog.2014.09.003
1053-8100/

Trevethan and Sahraie (2003) also found detection of temporally modulated gratings to be enhanced compared to rapid onset/offset but otherwise static presentation (see Sahraie, Weiskrantz, Trevethan, Cruce, & Murray, 2002, also Sahraie, Trevethan, & MacLeod, 2008). Their results indicate the existence of a narrowly tuned temporal channel mediating blindsight performance given presentation within a narrow frequency band between 10 and 33 Hz and with maximum sensitivity at 20 Hz. Similarly, Seifert, Falter, Strasburger, and Elliott (2010) presented data from patient RP, who, in spite of a unilateral right homonymous quadrantanopia, demonstrated better-than-chance discrimination for stimuli flickered on and off in the blind field at temporal frequencies between 33 and 47 Hz.

Findings such as these have led to the conclusion that blindsight performance can be promoted using stimuli either flickered or otherwise temporally modulated indicating that cortical dynamics play an important role in the mediation of blindsight. This conclusion refers to the idea that visual organization (in lesioned as well as in the healthy visual system) is based on patterns of oscillatory neural synchronization (Singer, 1999). Hence, dynamic stimulation at specific frequencies which enhance those oscillation patterns may influence visual capability, possibly enhancing blindsight performance.

This leads to the proposal that, in blindsight, repeating stimulation at rapid frequencies encourages oscillation and consequent synchronization of neurons in surviving areas of cortex with this bringing about the limited visual capability reported in these studies. Some imaging studies have presented results consistent with the idea that stimulus-related neural dynamics can promote blindsight. For example, Vanni, Raninen, Nasanen, Tanskanen, and Hyvarinen (2001) used magnetoencephalography (MEG) to examine cortical activity in response to dynamic visual stimulation in the intact vs. the lesioned hemisphere of a patient with vision loss. The authors found that flickering checkerboard and letter stimuli presented in the affected hemifield failed to generate an early, fast transient response at posterior cortical regions but showed a relatively strong response in the contralateral, superior temporal regions. This later response was interpreted as enhanced processing in higher-order visual areas, with the effect of compensating for lost function in visual areas earlier in the functional hierarchy of the visual system. In another study, Schurger, Cowey, and Tallon-Baudry (2006) presented an orientation-discrimination task including stationary stimuli at a near-threshold level of contrast, to which patient GY responded 'aware' or 'unaware'. Gamma-band oscillations in the range 44–66 Hz, recorded over the left occipito-parietal region, correlated significantly with awareness (but not accuracy), whereas activity at alpha-band frequencies (i.e. 8–12 Hz) did not. Both studies (i.e. Vanni et al., 2001, as well as Schurger et al., 2006) support the idea that the brain is capable of organizing itself in response to stimulation at particular frequencies, and that this response may, for stimulation at certain frequencies, bring about blindsight. With this in mind, it seems reasonable to extend this argument and propose that the stimulus frequencies which promote blindsight may also serve to restore visual function in the field defect. This general expectation has been expressed previously and in the context of studies linking blindsight performance to stimulus presentation at frequencies between 10 and 20 Hz (Sahraie et al., 2008). Several behavioral and neuroimaging studies have confirmed the idea that the visual system is plastic beyond an early, critical period of development, indicating that visual field loss resulting from brain lesions should no longer be considered permanent and irreversible. One line of evidence comes from rehabilitation studies (Bergsma & van der Wildt, 2010; Huxlin, 2008; Julkunen, Tenovuo, Jääskeläinen, & Hämäläinen, 2003; Kasten, Wüst, Behrens-Baumann, & Sabel, 1998; Kasten, Wüst, & Sabel, 1998; Kerkhoff, 1999; Poggel, 2002; Poggel, Kasten, & Sabel, 2004; Raemaekers, Bergsma, van Wezel, van der Wildt, & van den Berg, 2011; Sabel, 1999, 2008; Sahraie, 2007; van der Wildt & Bergsma, 1997; reviewed in Sabel, Henrich-Noack, Fedorov, & Gall, 2011) that have demonstrated training-induced improvement of function, particularly of light-detection performance. There is evidence for the partial restoration of visual function (with about one-third of patients showing either large, small, or no improvement, respectively), and that the training effect, when present, cannot be explained as side effects from behavioral changes like eye movements (Kasten, Bunzenthal, & Sabel, 2006) or observer-criterion shift (Poggel, 2002; Poggel et al., 2004).

Most training methods are specifically designed to improve detection of visual stimuli and are oriented toward measures amenable to perimetric testing, which is still the gold standard for determining the extent of visual field loss. There are some studies suggesting the generalization of training effects to other visual functions, e.g. to the recovery of form or color discrimination (Kasten, Poggel, & Sabel, 2000). More recently, Poggel, Treutwein, and Strasburger (2011) showed that patients with visual field loss after brain lesions also suffer from deficits in temporal resolution as well as in visual reaction times, with topographies for these functions that are partially dissociated from the perimetric maps for light detection. Temporal performance depends in part on the degree of intactness of the respective visual field position – in particular at the border zone of the visual field defect (i.e., areas of residual vision or *transition zones)* – but is not fully determined by these. In an unpublished training study, Poggel, Treutwein, Sabel, and Strasburger (submitted for publication) have shown that a training regime designed for improvement of light detection in brain-lesioned patients also led to improvement in dynamic variables, such as general temporal resolution (i.e., double-pulse resolution, Poggel et al., 2011) and visual reaction times, in areas of residual vision along the visual field border (see Strasburger, Rentschler, & Jüttner, 2011, for review).

The present study aimed to evaluate the potential for modifying the functional visual field using stimuli presented at temporal frequencies found to elicit optimal blindsight performance. The optimal frequencies for blindsight performance were determined empirically, and visual field maps were determined with static perimetry prior to and following a number of treatment sessions. In these sessions, a matrix of illuminated pixels was repeatedly presented in the individually defined area of residual vision (as determined before treatment). Presentation was at frequencies to which patients had previously shown some evidence of blindsight when stimulated in the completely blind field, or, for comparison, at frequencies not associated with blindsight. Treatment outcomes were variable between patients, but in some cases – for frequencies that had previously promoted blindsight but not for those not associated with blindsight – there were large transient shifts of the visual field border.

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2. Methods

2.1. Subjects

Patient RP (f., 55 years) has an upper-right quadrantanopia which overlaps into the lower-right quadrant. This is in accordance with damage, caused by a stroke, in the left occipital cortex. Macular sparing of about 11° to the right and 5° upward is also evident. The experimental stimuli were presented to both eyes in this case. Patient FS (m., 67) had a right homonymous hemianopia without macular sparing, including large areas of relative defects in the upper and lower left part of the visual field, caused as a result of a head injury from a road-traffic accident when he was 42. FS is a well-studied patient in blindsight studies (Kleiser, Wittsack, Niedeggen, Goebel, & Stoerig, 2001; Stoerig & Cowey, 1997; Stoerig, Kleinschmidt, & Frahm, 1998). Patient LE (m., 53) suffered from left optic-nerve lesions due to tumor surgery at the age of 46 and has no evidence of cortical damage. LE was perimetrically blind in the left eye and had diffuse visual field loss in the right eye, with a focus of absolute and relative defects in the upper right and upper left quadrant. In this case, stimuli were only presented to the left eye. (Pre-treatment perimetric maps are shown below in the left-hand panels of Fig. 4.)

Each patient gave his or her written informed consent; the study was approved by the appropriate Departmental Ethics Committee at the Ludwig-Maximilian University, Munich, and was carried out in accordance with the World Medical Association (2000). Prior examinations revealed none of the symptoms characteristic of damage to the parietal lobes, i.e., visuo-spatial neglect (Behavioral Inattention Test [BIT]) or problems maintaining vigilance. All patients were of normal intelligence according to a German test of crystallized intelligence (Mehrfachwahl-Wortschatz-Intelligenz-Test; MWT-B). Patients received reimbursement for time and travel expenses for their participation.

2.2. Testing for frequency-specific blindsight performance

2.2.1. Apparatus

Stimulus image frame generation, event timing, and data collection were controlled by an IBM compatible PC running custom-made software programmed in Assembler and C. These also controlled oscilloscopic image presentation through an Interactive Electronics Systems point-plotter buffer with 4 Mb frame store memory (Finley, 1985). Unlike conventional CRT monitors, point plotters are pixel addressable with timing easily achievable at sub millisecond resolution. Timing was controlled by plotting exactly 999 pixels to ensure image frame control with millisecond resolution. Stimuli were presented on a GBM 2211 FOCUS-oscilloscope monitor screen (15.2 cm × 12.4 cm) with P4, i.e., fast, white phosphor. The use of a P4 phosphor, which has fast phosphor decay, ensured illuminated pixels reduced to 10% of full luminance within 200 microseconds (μs) of image termination. Implicit in the point-plot principle is a trade-off between temporal resolution and the number of illuminated pixels. Given the pixel plot rate of ~1 MHz, we chose each image frame to comprise 799 illuminated pixels, which, with a cascading phosphor decay rate of 200 μs per pixel, gave an overall plot time of 999 μs and a basic plot rate of 1 kHz. Stimuli were presented in a dimly lit room under controlled lighting conditions (mean screen surround luminance: 0.13 cd/m^2, with stimulus luminance maintained at 30.5 cd/m^2).

Patients underwent an orientation-discrimination task in which they were asked to report which of four orientations was presented (left or right diagonal at 45°, horizontal, or vertical) of a grating stimulus of 2.3° × 0.9° size (Fig. 1). The grating

Fig. 1. The appearance of grating stimuli at each of the four orientations used in the experiment.

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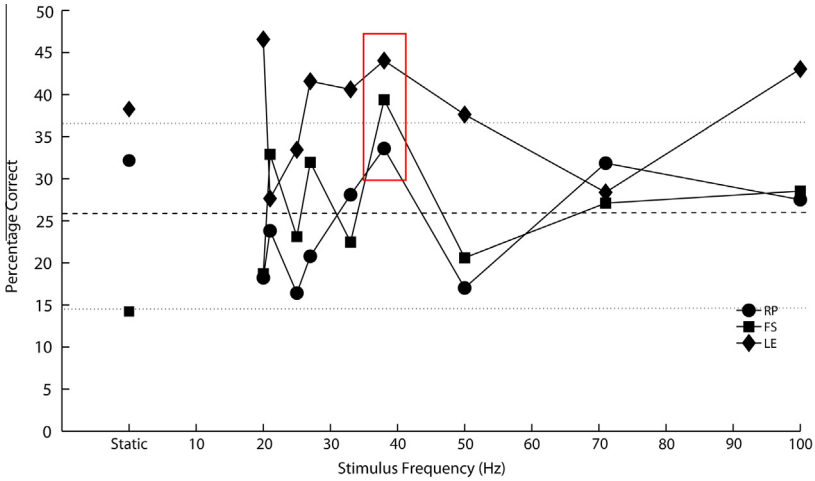

Fig. 2. Percent-correct responses to static and flickering stimuli, the latter presented at various frequencies, graphed against chance performance. The dashed horizontal line centered at around 25% indicates the average response probability for each of four alternative responses. The flanking dotted lines represent the upper and lower (99%) confidence interval thresholds. The trend shows that, for all patients, performance is highest at 38 Hz (indicated by the red outlined box), with exception of patient LE (diamond markers) who performed better following a 20 Hz stimulus. Performance of the two cortically blind patients RP (circles) and FS (square markers) revealed almost the same function with an increase at 21 Hz, 27 Hz, 38 Hz, and 71 Hz, and a decrease at 20 Hz, 25 Hz, 33 Hz, and 50 Hz (with the exception of a discrepant point for RP at 33 Hz). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

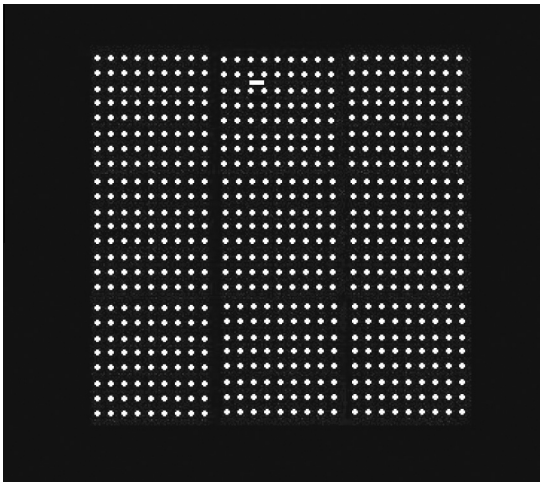

Fig. 3. The 3 × 3 square matrix of nine dots in horizontal and eight dots in vertical line per square. The horizontal bar in the middle square of the first row is an example of a target, which could appear at a random location within the matrix.

consisted of a triad of elongated bars, each with Gaussian-weighted increase and decrease in luminance across the width of the bar. Retinal size was maintained as constant by controlling monitor–eye distance using a chin rest at 57 cm. The positions of the stimulus center (relative to central fixation) were for patient RP at +10.7°/+9.6° of visual angle (at horizontal/vertical eccentricity, respectively), for patient FS at +12.85°/+7.1°, and patient LE at –11.2°/+9.2°; i.e., all stimuli were presented within the central 15° radius of the visual field. Trials upon which an eye movement was made were not analyzed.

2.3. Design and procedure

Stimuli were flickered in square-wave modulation (at 20, 21, 25, 27, 33, 38, 50, 71, and 100 Hz) or were presented as static (i.e., did not flicker but were presented at a background plot rate of 1 kHz). Following a practice block of 40 trials, randomized by frequency and orientation, stimulus presentations by frequency and orientation were varied pseudo-randomly within and between 19 experimental blocks of 40 trials per block. On each trial, following an acoustic cue, a grating was presented on the oscilloscope monitor for 2000 ms. Patients were instructed to fixate a small marker on the screen (position was individ-

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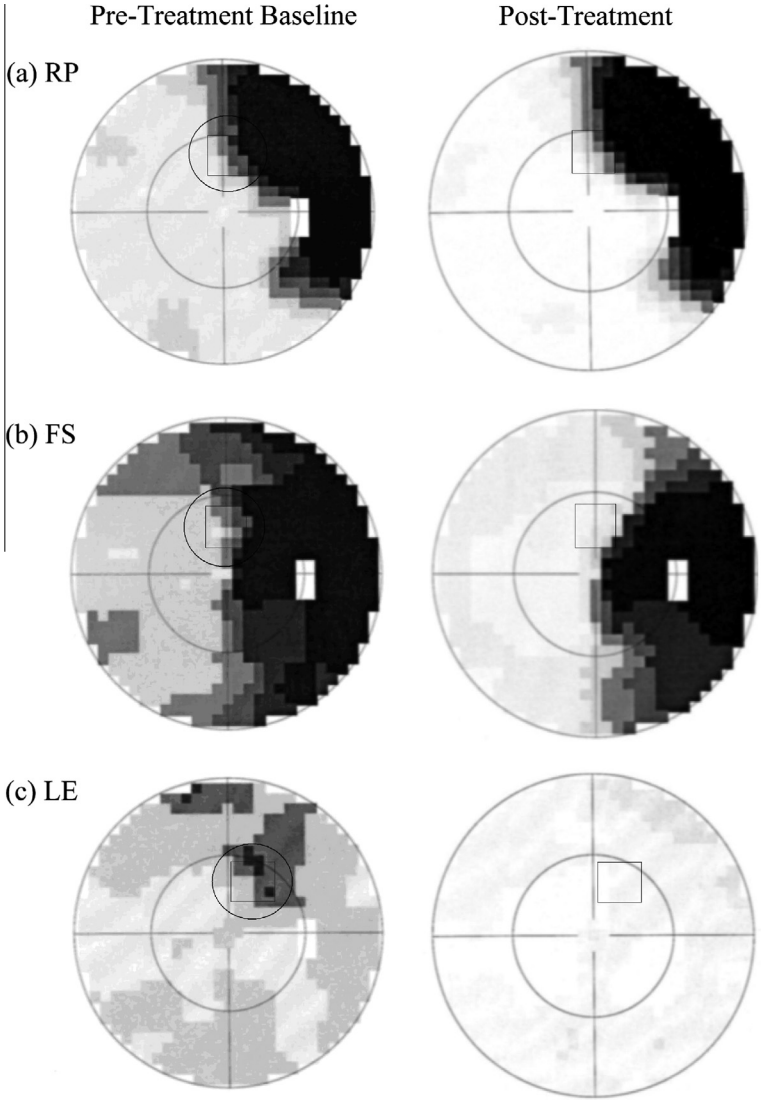

Fig. 4. Perimetries pre- (left) and post-stimulation (right) for patients (a) RP, (b) FS and (c) LE. Each rectangle represents an area of $1^\circ \times 1^\circ$. White regions indicate intact fields where vision is not impaired. Gray regions indicate a relative defect, with the degree of severity (defect depth) increasing with darkness of gray. Black regions indicate absolute defects (blind field regions). The white vertical rectangle marks the blind spot. The critical area of the transition zone selected for stimulation during the intervention period is indicated by the black circle); the size of the stimulus matrix is indicated by a black rectangle within this circle. These images show post-stimulation perimetries following treatment using the most effective stimulus. In (a), Patient RP shows major increase in the intact field compared to relative defects following a 38-Hz stimulus. In Patient FS there was an increase in the intact fields following all stimuli. In (b) are the effects of a 20-Hz stimulus, which reduces the severity of an extensive field of relative defects, as well as reducing the area of the absolute defects. Patient LE shows an increase in the intact fields following all stimuli. In (c) a general reduction in the relative defects as well as increases in the intact field are topographically complex but extensive following a 27-Hz stimulus. Note how the location of the transition zone shifts between the left and right perimetries.

ually determined depending on the visual field topography determined in the perimetric pre-test; see above) and were asked to report the orientation of the presented grating. They were allowed as much time as they required to express their judgments, which were given orally and recorded by the experimenter to avoid the patients shifting fixation from the monitor to the computer keyboard. Eye movements were monitored by the experimenter using a mirror located next to the screen and trials upon which an eye movement was made (in total 3 trials) were excluded from further analyses.

Static perimetry (for all patients) was undertaken using an Interzeag Octopus 101 perimeter and the compatible Octopus Examination Software, and was conducted prior to the study for each eye, separately for each patient, with the results serving as a "pre-treatment" or baseline. Perimetries with the same protocol were also repeated on a number of occasions post treatment, to assess the extent of topographical changes to the visual field. Baselines were determined and the experiment conducted on different days given the length of the procedures involved. Thus, for RP pre-treatment and experimental

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measures were separated by 19 days, for FS by 17 days and for LE by 19 days. With the exception of LE, perimetries were identical to those supplied in advance of the study by consultant ophthalmologists.

As standard in static perimetry, subjects were asked to react to the perception of a white stimulus by pressing a button, while fixating a green cross-hair in the center of the display (eye fixation was monitored and controlled with an infrared-sensitive camera, and in case of eye-movements away from fixation the testing system stopped). Stimulus exposure time was 100 ms, the stimuli were of Goldmann size III (standard), and the dynamic range of stimulus intensity was 0–40 dB. Luminance of the white background illumination was 1.27 cd/m^2. Patients viewed the stimuli with each eye separately or were tested in only one eye (see below). Luminance-increment thresholds are obtained in a conventional 4-2-1 dB adaptive procedure (e.g. Weijland, Fankhauser, Bebie, & Flammer, 2004). Stimulus intensity and location are randomized. The values are corrected for age and their coordinate location on the retina by a comparison with reference values (normative age and location). The Glaucoma test used here (G2 program) examined 59 locations within the central 30° (diameter) region of the visual field. Testing proceeded in four successive steps, with 32 random locations tested in the first two, and the remaining in the last two steps.

2.4. Results

Analysis of responses was based upon the calculation of percent correct for each orientation condition per frequency condition, and compared against chance performance of 25% correct. The variance of this distribution was estimated using a Monte Carlo simulation of 1000 sets of 100 random numbers drawn from a multinomial distribution of four equiprobable alternatives. This permitted calculation of the 99% confidence interval (two-sided) around 25% correct reportage (11.25–36.25%), against which the empirical fraction of correct scores for the three patients were compared.

Results are shown in Fig. 2. For RP, the percentage of correct responses for the different orientations and for static and flickering conditions fell within the 99% confidence interval around chance performance although best performance, which was found at 38 Hz, at 34%-correct just missed significance. Patient FS judged significantly better than chance (39% correct) when the gratings were presented at 38 Hz, and so did LE, who showed better-than-chance performance for the static and almost all temporal conditions, but had further performance peaks at 20 Hz and 38 Hz (47% and 44% correct, respectively). When compared against static presentation, RP performed slightly better at 38 Hz, FS showed a relatively improved performance in all other conditions, while LE was better at 20 Hz, 27 Hz, 33 Hz, 38 Hz, and 100 Hz.

3. Temporal modulation in the blind field

Patients and apparatus were as described for the blindsight test with the following exceptions.

3.1. Apparatus

As illustrated in Fig. 3 the stimuli were a 3 × 3 square matrix of dot arrays, each array comprising nine dots horizontally and eight dots vertically (i.e., 72 dots per square; in total 648 dots per stimulus). The stimuli covered an area of 8° × 8° of visual angle. As an objective control for vigilance and fixation behavior, a target bar was presented within the 3 × 3 matrix, to which patients were asked to respond *present* or *absent*. The target bar had a length of 0.61° and appeared with 25% probability within each 30 s. of stimulus presentation. If presented, the bar remained on screen for 1000 ms at a randomized location in the matrix. Detection performance, which was entirely incidental to treatment, was not analyzed.

The illuminated pixels were presented periodically, and simultaneously, in square-wave modulation at one of three frequencies (20 Hz, 27 Hz, and 38 Hz) or were presented as static (i.e., did not flicker but were presented at the background plot rate of 1 kHz). Stimulation at 20 and 38 Hz had successfully promoted blindsight and were thus the critical conditions for potential improvement of visual function in areas of residual vision. For patients RP and FS, the absence of evidence for blindsight when stimuli flickered at 27 Hz provided a control condition allowing us to ascertain the extent to which any restored visual function could be attributable to stimulation at frequencies related to blindsight. Stimulation with a non-flickering (static) display provided a general control.

Based upon the initial pre-treatment perimetry, the position of a fixation point was calculated for each patient enabling the stimuli to be presented in a particular area within the transition zone. The exact positions of the stimulus center (relative to central fixation) were for patient RP at +1°/+7° visual angle (horizontal/vertical eccentricities), for patient FS at +0°/+5°, and for patient LE at +4.5°/+6.5° of visual angle.

3.2. Design and procedure

Specific areas within the transition zone of each patient were examined with patterns flickering at frequencies to which the patient had shown some evidence of blindsight. To control for any non-specific effects of flicker on visual function, stimuli were also flickered at a frequency at which the patients had *not* shown any evidence of blindsight. A static, non-flickering stimulus was further employed for control purposes. The stimulated areas were individually selected for each patient, based on the depth of the defective positions. Immediately following each round of treatment, patients were asked to undergo a

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further, static visual-field perimetry referred to as the 'post-treatment measure' and taken between 2 and 2.5 h after treatment. A subsequent perimetry was taken one week after treatment. The effectiveness of stimulation in altering the size of the defective fields was assessed by comparing the baseline perimetries obtained before the intervention with the post-treatment measure. Treatment comprised three treatment sessions employing flickering stimulation and one session of static stimulation. Accordingly and in a given intervention, each patient underwent four treatment sessions followed by four separate sessions of post-treatment perimetry. The entire series of treatment and perimetry sessions in each intervention were conducted on the same day and took between 4 and 6 h. Interventions were carried out on one occasion for RP and LE and on two occasions for FS.

The intervention started when patients were sitting in front of the oscilloscope monitor. They were instructed to avoid eye-movements and maintain fixation on a colored fixation point placed on the monitor screen at a location ensuring stimulation of the prescribed region within the transition zone. Each treatment condition (static or flickering at 20-Hz, 27-Hz, and 38-Hz flicker) was presented exclusively and overall for just over 12 min within a series of three treatment epochs each lasting 4 min. There was a break of at least 10 s between treatment epochs and the investigator initiated each new epoch when the patient was ready to resume testing. Treatment in each stimulation epoch was followed within 10–15 min by post-treatment, static visual field perimetry. The global presentation order of treatment in the different stimulation conditions (static as well as flickering at 20, 27, and 38 Hz) was counterbalanced between patients to avoid order effects.

To obtain measures of field areas in the three functional categories, adjacent samples from the graphical outputs in the static visual field perimetry, equivalent to $1^\circ \times 1^\circ$ areas of visual angle, were summed separately for the individually intact, relative defective and absolute blind fields in each eye. This was done first for the baseline condition and then compared against the corresponding measures calculated post-treatment.

4. Results

Fig. 4 shows changes in pre- and post perimetries and Fig. 5 increases in functional visual field area as measured in square degrees of visual angle (deg^2). Table 1 shows shifts in the visual field border for the pre and post perimetries illustrated in

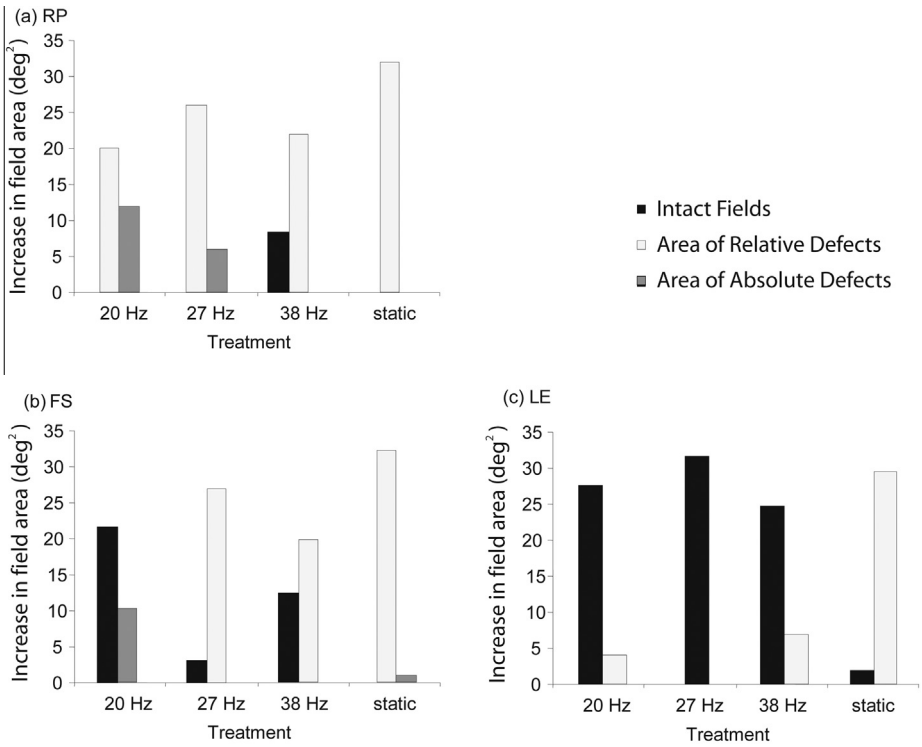

Fig. 5. (a–c) Bars denote the increase in field areas brought about by the stimuli flickering at 20, 27, and 38 Hz, as well as stimuli that did not flicker. The bars are calculated by summing the overall field area in each of the categories: intact, relative defects, and absolute defects (i.e. blind fields), and then subtracting the pre- from the post-treatment areas. The resulting areal differences are expressed in square degrees of visual angle (deg^2). Fig. 4 provides examples of topographic changes, this also shows that, in general, gains in the intact field tend to be at the expense of relative and absolute defects, while gains in the relative defects' area tend to be at the expense of the absolute defects (i.e. blind fields; decreased blind fields are a subtraction of increases and so are not shown). However, differences occasionally include an increase in the blind field as well as in relative defects and intact fields, particularly for frequencies that are not associated with blindsight. This suggests that increases in field sizes represent gains associated with a shift in the location of the field, rather than an increase in area per se.

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Table 1
Horizontal location of visual-field border pre- and post-treatment (2nd and 3rd column) relative to vertical eccentricity (1st column), and horizontal border shift (right-most column, post- minus pre-treatment): patients RP, FS and LE, at 38, 20, and 27 Hz, respectively. Locations refer to the middle of the transition zone. Negative numbers in pre and post borders denote the left meridian. Negative numbers in the last column correspond to a leftward shift.

Patient	V. Eccen.	Pre: hor. VF border	Post: hor. VF border	Pre–post border shift
RP	25	−3.0	−1.7	−1.3
	20	−3.0	−1.7	−1.3
	15	−3.0	−1.7	−1.3
	10	0.9	2.6	−1.7
	5	4.7	11.1	−6.4
	0	12.9	15.0	−2.1
	−5	12.4	15.0	−2.6
	−10	8.6	13.3	−4.7
	−15	8.6	17.6	−9.0
	−20	30.0	30.0	0.0
	−25	30.0	30.0	0.0
FS	25	−30.0	12.0	−42.0
	20	−30.0	12.0	−42.0
	15	−3.0	7.7	−10.7
	10	−1.1	5.6	−6.6
	5	−1.1	1.1	−2.1
	0	1.1	1.1	0.0
	−5	−1.1	−1.1	0.0
	−10	−1.1	1.1	−2.1
	−15	−1.1	5.6	−6.6
	−20	−1.1	1.3	−2.4
	−25	−11.1	1.3	−12.4
LE	25	11.1	30	−18.9
	20	7.3	30	−22.7
	15	−1.1	30	−31.1
	10	5.1	30	−24.9
	5	30.0	30	0.0
	0	30.0	30	0.0
	−5	30.0	30	0.0
	−10	30.0	30	0.0
	−15	30.0	30	0.0
	−20	30.0	30	0.0
	−25	30.0	30	0.0

Fig. 4. The changes in visual field morphologies described below were reversed by the time the follow-up perimetry was taken one week after treatment with follow-up perimetries near identical, with little or no variation relative to those taken pre-treatment.

4.1. Patient RP

As expected, since there had been no sign of blindsight at those frequencies, there were no increases in the intact field for patient RP following stimulation at 20 Hz, and 27 Hz although there were increases in the areas of relative (+20/+26 deg^2) and absolute defects (+12/+6 deg^2), suggesting that, rather than an increase per se, the topography of the visual field had changed at these frequencies. Typically, changes in the relative defects indicated an increased sensitivity to perimetric testing. There was also a large change in the area of the relative blind-field defects following static stimulation (+32 deg^2). Assuming blindsight performance as a prospective index of restorability, an increase in the intact visual and relative-defective fields following stimulation at 38 Hz was expected, in line (although not strictly comparable with) estimates of change in the intact field obtained from measures of VRT (Kasten et al., 1999). Indeed we observed a larger intact visual field resulting from a temporary improvement of sensitivity in transition zones, following the 38-Hz stimulus (+8 deg^2). However, there was no shift of the visual field border and no decreased area of the completely blind visual field.

4.2. Patient FS

Patient FS showed an increase in the size of the intact fields for all frequencies, with no change following static stimulation (20 Hz: +21 deg^2, 27 Hz: +3 deg^2, 38 Hz: +12 deg^2). As with RP, at 20 Hz there was also an increase in the size of the absolute blind field (+10 deg^2), and, at all frequencies except 20 Hz as well as with static stimulus presentation, there were increases in the size of relative blind fields (27 Hz: +27 deg^2, 38 Hz: +20 deg^2, static: +33 deg^2), with small (1 deg^2) increase in the size of the absolute blind field when the stimulus did not flicker.

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Several days after the first intervention, FS was re-examined, this time employing 20 Hz and 27 Hz treatments. This was undertaken to assess the reliability of the results obtained in the first intervention. The procedure used in the second intervention was the same as in the first, except that, prior to this intervention, extra baseline perimetries were taken[1] and, because of small changes in visual field topography, the location of stimulus presentation was slightly changed relative to the first intervention. In the second intervention the matrix stimulus was presented at +1°/+5° of visual angle (relative to fixation). Similar to the first intervention there were no changes in the size of the intact fields for either eye following stimulation at 27 Hz. However, and quite in contrast to the dramatic increase in intact visual field size found in the first intervention in OD, there were no changes in the size in the intact fields in the second intervention.

4.3. Patient LE

Patient LE showed an increase of intact visual field size at all frequencies (20 Hz: +28 deg^2, 27 Hz: +32 deg^2, 38 Hz: +25 deg^2, static: +2 deg^2), alongside much smaller changes in the relative blind field at 20 Hz (+4 deg^2), 38 Hz (+6 deg^2) but with a substantial change following presentation of a static stimulus (+29 deg^2).

5. Discussion

The topography of the functional visual field was examined by static perimetry prior to and after patients underwent an intervention in which they were stimulated with local flicker. Small, flickering stimuli, comprising a matrix of illuminated pixels presented at various, precisely controlled frequencies, were presented at the border between intact and impaired visual field regions (also referred to as "transition zone"). The frequencies chosen were those at which the three patients had shown enhanced blindsight performance in a pilot study. By using a rare technique of dynamic visual stimulation, these frequencies could be narrowly targeted. In the intervention, all patients showed some evidence of a short-term improvement in visual function, indexed by changes in functional visual-field topographies relative to pre-intervention, static perimetry measures. In all cases and in one case uniquely, the intact visual field increased when stimuli were presented at 38 Hz. At this frequency all patients had shown significantly enhanced or better than average blindsight performance in the pilot study. Consistent with expectations, neither patient RP nor FS showed any substantial alterations in the size of their intact visual field when stimulated at 27 Hz, at which frequency no enhanced blindsight was observed. However, and in addition, patients FS and LE showed enlarged visual fields at 20 Hz at which previous detection performance seemed uninfluenced by blindsight. It is possible that the proximity of 20 Hz to a subharmonic of 38 Hz (19 Hz) might account for this effect. There were only small, if any, changes in the size of the intact visual field with static stimulus presentations. When considered in the context of changes to visual field topography in general, this indicates that the propensity for such changes is sensitive to dynamic stimulation at least in the very short term, and for a short period of time thereafter. This finding of substantial area gains, of between 3 and 33 deg^2 of visual angle, is important and requires consideration; especially given that such changes can be obtained even after only one, relatively short intervention session.

Cortically blind patients, whether or not they have blindsight, are able to pick up light scattered into their intact field when a bright stimulus is presented to their field defect during static perimetry. After training with flickering stimuli, which will also scatter light into the intact field, the patients might become better at detecting scattered light, and so their scores in the post-intervention static perimetry tests would improve. At the settings used in the static perimetry, 30.5 cd/m^2 against a background of 0.13 cd/m^2, light scatter into the intact field is almost impossible to eliminate. For example, King, Azzopardi, Cowey, Oxbury, and Oxbury (1996) found that the threshold intensity for detecting a luminous target against similar background intensity by means of light scatter into the intact field alone (using a half-patch to occlude the target) was as low as 1–3 cd/m^2. Furthermore, a yes–no protocol – which is susceptible to response bias – was used in the static perimetry. Consistent with a global response bias, improvements in performance shown in the visual field maps in Fig. 4 occur across the entire visual field, including the intact parts, i.e., are not restricted to the area stimulated by the flickering stimulus in the intervention phase. This would provide a possible alternative explanation for enhanced sensitivity, even influencing the discrimination task (in which there was always a target present and which would not benefit from the presence of scattered light accompanying a target presentation). However, what is not clear in this account is why detection should favor one particular stimulation frequency over others and this indicates stimulation frequency to be the major variable of interest in accounting, not only for restoration, but also blindsight itself (see Poggel et al., submitted for publication; Seifert et al., 2010).

Based upon frequency alone it is difficult to speculate that any particular neural mechanism supports visual field restoration. This is because the brain is likely to adopt a particular frequency of activity based upon the number and the proximity of the to-be synchronized neurons. In addition, in a system with structural damage, function at any given frequency may occur by necessity (because it is the only frequency at which a required number or distribution of neurons can synchronize) and by chance – although the cognitive operation may itself require synchronized activity within a particular bandwidth to be able to function facultatively with other cognitive operations. In this respect, because blindsight performance appears optimal given stimulation at 38 Hz – a frequency within the EEG gamma band that accompanies oscillatory synchronization

[1] FS was tested on two separate occasions over two days due to time constraints and with baseline perimetries taken before each session. Changes noted in the text refer to the immediate baseline perimetry measure.

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during visual binding and awareness (Elliott & Müller, 2004) – one potential explanation for these effects is that alterations in visual field topography come about as a function of stimuli presented at particular frequencies that influence neural binding, and are thus related to mechanisms organizing neural assembly formation in visual cortex (e.g. Singer, 1999). There is some evidence to support this proposal: the MEG studies reviewed above (e.g. Schurger, Cowey, Cohen, Treisman, & Tallon-Baudry, 2008; Schurger et al., 2006) have shown gamma-band activity in occipito-parietal regions during blindsight and have argued that this activity supports an attention-mediated binding of perceptual material, which in turn may bring about blindsight. However, the novel aspect of this study is that the results indicate that this is the case not only for conscious but also for unconscious visual processing. In consequence this indicates that blindsight and normal sight might rely on similar mechanisms (at least as far as the dynamics of vision are concerned), carrying the implication that blindsight could be transformed into a real (or, conscious) experience of visual information.

The increased visual fields observed in this study were not permanent and may be brought about in a similar fashion to alterations in visual receptive-field morphology which can accompany modifications to visual field morphology (e.g. Kapadia, Gilbert, & Westheimer, 1994). These have been argued to require dynamic inter-neuronal binding and, at least in visual cortex, are also not permanent (see e.g. Kapadia et al., 1994; Pettet & Gilbert, 1992; Sober, Stark, Yamasaki, & Lytton, 1997). A large-scale change to the visual field, in terms of several, even tens of degrees-square of visual angle and brought about by brief, dynamic stimulation would be thus quite consistent with the expansion and subsequent contraction of wide-angled receptive fields in later visual mechanisms. In this instance, initial receptive field expansion is brought about as a function of stimulus-induced oscillatory synchronization. The extent and transitory nature of some of the visual restoration reported here is consistent with this idea, although it must be stressed that this model does not fully account for all of the findings, especially the temporary increase in the absolute blind field observed following stimulation at some frequencies. However, a model in which changes to visual ability do not relate to anatomical changes, but are due to changes in the dynamic patterns of connectivity in visual neural networks, might explain why some observers (e.g. in Balliet, Blood, & Bach-y-Rita, 1985) were unable to find an anatomical correlate with improved vision in the defective field.

A possible reason for variations in the efficiency of a given frequency at a given time may reduce to factors such as cortical metabolism that lead to changes in general dynamic structure of the brain and thereby to the frequency to which the system is sensitive at a particular time (see e.g. Hoagland, 1966). Previous studies on visual cortex plasticity after brain lesions have shown that training effects, i.e. an optimal outcome of treatment, depend on various factors so that training regimes specifically tailored to the patient's visual field topography and to the visual function to be improved are more effective than a "one size fits all" regime. This has also been shown for dynamic aspects of vision: while there is some generalization of stimulus detection training to dynamic visual functions and their improvement, very likely training with specific dynamic patterns would result in a higher gain with respect to those functions (Poggel et al., submitted for publication). The results of the present study, albeit rendering only a temporary functional improvement, point into the same direction: an individualized stimulation frequency yields a better outcome.

Acknowledgments

The authors are indebted to the time and patience of the three patients. This research was carried out at the Department of Psychology: General and Experimental Psychology of Ludwig-Maximilians-Universität, Munich, and funded by the DFG (German Research Foundation) Grant EL248/4 to MAE and HS.

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