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Temporal sensitivity in a hemianopic visual field can be improved by long-term training using flicker stimulation

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Background: Blindness of a visual half-field (hemianopia) is a common symptom after postchiasmatic cerebral lesions. Although hemianopia severely limits activities of daily life, current clinical practice comprises no training of visual functions in the blind hemifield.

Objective: To find out whether flicker sensitivity in the blind hemifield can be improved with intensive training, and whether training with flicker stimulation can evoke changes in cortical responsiveness.

Methods: Two men with homonymous hemianopia participated in the experiments. They trained with flicker stimuli at 30° or with flickering letters at 10° eccentricity twice a week for a year, and continued training with more peripheral stimuli thereafter. Neuromagnetic responses were registered at 1–2-month intervals, and the Goldmann perimetry was recorded before, during and after training.

Results: Flicker sensitivity in the blind hemifield improved to the level of the intact hemifield within 30° eccentricity in one participant and 20° eccentricity in the other. Flickering letters were recognised equally at 10° eccentricity in the blind and intact hemifields. Improvement spread from the stimulated horizontal meridian to the whole hemianopic field within 30°. Before training, neuromagnetic recordings showed no signal above the noise level in the hemianopic side. During training, evoked fields emerged in both participants. No changes were found in the Goldmann perimetry.

Discussion: Results show that sensitivity to flicker could be fully restored in the stimulated region, that improvement in sensitivity spreads to the surrounding neuronal networks, and that, during training, accompanying changes occurred in the neuromagnetic fields.

METHODS

Participants

Two men with homonymous visual field defects, aged 61 (IT) and 64 years (KS), participated in the study. Both participants spontaneously reported that they were aware of movement in the blind half-field, but did not clearly see what was moving. Although termed blind elsewhere in the text for conciseness, the affected visual fields are more truthfully described as functionally depressed. Time from cortical infarction to the beginning of training was 22 months (IT) and 11 months (KS). Both participants had a questionable macular sparing of about 2–3° according to Goldmann perimeter. A local infarction is evident medially in IT’s left occipital lobe, extending anteriorly towards the enlarged left ventral ventricle. KS was not eligible for MRI owing to a permanent metallic bridge in his mouth. Both participants had no other neurological diseases. During psychophysical experiments and neuromagnetic recordings, proper optical corrections were used. The study was approved by the ethics committee of the Hospital District of Helsinki and Uusimaa. Tenets of the Declaration of Helsinki were followed.

Training experiments

Apparatus

Flicker was generated with a PC on a 17” monitor (Eizo Flexscan T575S, Eizo Co, Ishikawa, Japan). The graphics board...
Matrox Graphics, Quebec, Canada) generated 640×480 pixels, with a pixel size of 0.47×0.47 mm². The frame rate was 132 Hz in Dos mode, and the screen luminance was 35 cd/m² (Minolta Luminance Meter LS-110, Minolta Camera, Osaka, Japan). The monitor was used in a white mode (x, y: 0.28, 0.29; Minolta Chroma Meter CL 100, Minolta Camera). A video attenuator was used to increase the amount of grey level information up to 14 bits in Dos mode. A green light emitting diode (LED) on an arch perimeter was used as a fixation point.

**Stimuli**
The luminance of the stimuli, a disc or letters T, L, H and U was sinusoidally modulated. The area of the screen was limited with a black plastic surface to a circle of 10°. Within this aperture, the stimulus diameter or the size of the test letters was chosen to 1–8° depending on the observer’s ability to detect flicker or recognise letters. The screen surrounding the stimulus area served as an equiluminant surround. The viewing distance was 115 cm. The participants had their head movements restrained by a chin rest, and they fixated on the LED while stimuli were presented to their peripheral vision.

**Control of fixation during psychophysical measurements**
Before starting the experiments, both participants were trained not to move fixation towards the hemianopic visual field.
During the training period, the experimenter controlled fixation by looking at the participant’s eyes. After 1 year of training, we were able to monitor eye position online with a video camera (Watek-902H). The frame frequency was 25 Hz (see also blind spot control for IT, below).

**Procedure**

The training stimulus was either a flickering luminance disc or flickering letters. The disk was detected at eccentricities of 10° or 30° along the horizontal meridian, and the flickering letters were recognised at 10°. Detection thresholds (luminance disc) or recognition thresholds (flickering letters) were measured. Thresholds were measured using a three-up one-down two-alternative-forced-choice (2-alternative-forced choice; flicker detection) or 4-alternative-forced choice (letter recognition) procedure in a dark room; the only light sources were the display and fixation point. The program measured six thresholds at each frequency, and the average of these thresholds was the final flicker threshold. This value was first transformed into sensitivity, the inverse of threshold, and then plotted in double logarithmic coordinates. For the disc stimuli, up to seven flicker frequencies between 1 and 35 Hz were used, the frequencies depending on the participant’s ability to detect flicker. For the letter stimuli, up to six different frequencies between 1 and 20 Hz were used. Two stimuli were presented successively. The exposure time of each stimulus was 2 s, with an interval of 600 ms between stimuli in the flicker-detection experiment, but in the letter-recognition experiment, only one letter was shown at a time. A short tone preceded each stimulus, and the response was followed by a sound indicating its correctness. In the flicker-detection experiment, the participant responded by saying after which sound there was flicker. In the letter-recognition task, the participant was required to say which letter was shown. Training was always started at such a combination of stimulus area and eccentricity that the participant could detect all or most of the frequencies shown.

**Figure 2** Development of flicker sensitivity during training at an eccentricity of 30°. Flicker sensitivity in the intact visual field half (IVF) and at three different days in the hemianopic visual field half (HVF) is shown for both participants.

**Figure 3** Recognition sensitivity at 10° eccentricity. Before training in December 2002, both participants IT and KS could recognise flickering letters only at an eccentricity of 5°. HVF, hemianopic visual field half; IVF, intact visual field half.
Both participants trained twice a week for a year, and each session lasted 1–2 h.

The effect of stray light was controlled by directing an additional spotlight to the non-stimulated visual field. The distance of the light was the same as that of the stimulus (115 cm) and luminance of 2500 cd/m², and evoked an illumination of 137 lx (Minolta Chroma Meter CL-200) at the level of the eyes. The average blind hemifield stimulation was 35 cd/m², resulting in an illumination of 0.8 lx. Scattered illumination of 137 lx (Minolta Chroma Meter CL-200) at the surrounding visual field. 26

Follow-up procedure
Before training, Goldmann visual fields were recorded, and neuromagnetic evoked fields were recorded twice. Flicker sensitivity was mapped at 14 meridians at eccentricities of 10°, 20°, and 30°. During training, Goldmann visual fields were recorded once, and evoked fields at 1–2-month intervals. After 1 year of training, Goldmann visual fields and flicker sensitivity were mapped again at 14 meridians. Neuromagnetic recordings continued for a total of 17 (KS) or 24 (IT) months. In the second year, the training was continued, but shifted to larger eccentricities.

Neuromagnetic recordings
Stimuli
The timing of the stimulus was controlled by Presentation software (Neurobehavioin Systems, Albany, CA, USA) running on Windows 98. A data projector with three micromirrors (Vista Pro, Electrohome, Ontario, Canada) projected the stimuli onto a back-projection screen in a dimly lit room. The participants fixated a cross on the back-projection screen at a distance of 51 cm, whereas the contrast of the pattern reversed randomly in the left or right directions at random 900–1100 ms intervals. The black (2 cd/m²) and white (33 cd/m²) checkerboard pattern (5×5° checks) extended from 15° to 25° horizontally. For IT, the pattern extended 35° vertically, and for KS 12° vertically, centred at the horizontal meridian. No net luminance change accompanied the contrast reversal.

Data acquisition
The participants were sitting with head supported under the helmet-shaped coil area. Signals were recorded with a Vectorview neuromagnetometer (Elekta-Neuromag, Stockholm, Sweden), filtered at 0.1–200 Hz, and sampled at 600 Hz. Epochs were time locked to reversal of the pattern, and 100 epochs (100–500 ms) for both hemifields were averaged online for each run. Three runs were recorded for each session. The position of the head was measured from four coils attached to the head. The positions of these coils relative to anatomical landmarks (nasion and left and right crossing point of the tragus and crus helis) were recorded before each session with a three-dimensional digitiser (Polhemus, Colchester, UT, USA).

Control of eye movements during neuromagnetic recordings
Both vertical and horizontal electro-oculograms were recorded, and epochs contaminated by eye movements or blinks (threshold 150 μV) were rejected. To control for stable eccentric fixation during the last recordings for both participants, one experimenter sat inside the shielded room and followed the eye position via a mirror. Before each run of the last recording (KS) or two latest recordings (IT), a view of the stable eye position was calibrated by instructing the participant to look at 0°, 7° and 15° (medial border of the checkerboard) along the horizontal meridian. Eye movements >2° were detectable.

Data processing
The signal space separation method attenuated environmental noise. This method allowed coregistration of the data from separate days to the same virtual channel positions.27 A 100-ms pre-stimulus baseline was applied for the evoked responses, and data were low-pass filtered at 45 Hz. Responses were considered significantly different from 0, when three neighbouring channels showed amplitudes more than two standard deviations above the baseline noise level above simultaneously for >20 ms (12 samples).

RESULTS
Figure 1 shows the Goldmann visual fields of both participants before, during and after training. During training there were small changes in the visual fields but the changes were within the normal variation.

Figure 2 shows the flicker sensitivities at the eccentricity of 30° in the blind and intact visual field halves before training, and after 3 and 5 months of training. Before training, IT could detect flicker at all but the highest frequencies. However, the sensitivities were 1–1.8 log units lower than in the intact visual half field. KS could detect flickers only at 5 and 10 Hz, and his sensitivities were impaired by about 1.8 log units. Three months later, both participants could detect all the frequencies at 30°. However, IT’s sensitivities on the hemianopic side were 0.5–1.0 and those of KS were 0.6–0.9 log units lower than that of the intact visual field half. Two months later (5 months from the start of training), flicker sensitivity was approximately equal in both participants. Thus, both participants reached equal sensitivity between hemifields after about 40 training sessions.

Figure 3 shows changes in letter-recognition sensitivity during training. Before flicker training, both participants could not recognise flickering letters in the blind hemifield only at 5° eccentricity. After 3 months of training (32 training sessions), IT’s recognition sensitivity at 10° became symmetric. KS’s recognition sensitivity at 10° became symmetric after 7 months (56 training sessions).

Figures 4 and 5 show relative flicker sensitivity (flicker sensitivity of the hemianopic visual field halved divided by the corresponding point of the intact hemifield) before and after 1 year of training for IT and KS, respectively. Before training, flicker sensitivity was <0.2 in all locations tested, indicating existing but functionally negligible sensitivity to visual stimulation in the blind hemifield. After 1 year of training, both participants had symmetric flicker sensitivities at 10° and 20° eccentricities. Relative flicker sensitivity had improved from <0.2 to ≥1. In addition, IT’s flicker sensitivity at 30° reached that of the intact visual field half. By contrast, KS’s flicker sensitivity at 30° eccentricity reached that of the intact visual field half only at the horizontal meridian and lower right quadrant.

Figure 6 shows the distribution and changes in the evoked fields during training. For IT, the response to hemianopic field stimulation was located distributed in his right occipital and occipitotemporal channels. For KS, the strongest responses were seen in his left posterior temporal channels. The first significant evoked fields for the blind visual field half stimulation emerged for IT in his fifth measurement session, about 3 months after the start of training. KS’s response emerged for the first time after 5 months of training. After 13 months of training, IT showed a large increase in signal. It was replicated in the two later measurements (16 and
23 months after the start of training). In addition, fMRI mapping of IT showed that both hemifields were represented in the intact hemisphere.\textsuperscript{23}

Two additional experiments studied the contribution of stray light and eccentric fixation to blind field sensitivity. Flicker detection sensitivity was about the same with and without light in the unstimulated hemifield (fig 7).

In IT, flicker-detection sensitivity plummeted at the blind spot compared with the neighbouring eccentricities in the intact hemifield and in the analogous point of the blind hemifield. This finding confirms that IT was not responding to either extraocular or intraocular light scatter, and that his fixation was stable.

**DISCUSSION**

Our results show that long-term training with flicker stimulation improves residual visual function in homonymous hemianopia. The improvement was measurable with flicker sensitivity mapping before and after 1 year of training for IT. (A) Recording sites marked on the Goldmann visual field chart. (B,D) Relative flicker sensitivity before training. The relationship shows flicker sensitivity of the hemianopic visual field half divided by flicker sensitivity of the corresponding point in the intact visual field half. (C,D) Relative flicker sensitivity after 1 year of training. The horizontal line shows the level at which flicker sensitivities in the two field halves are equal.
sensitivity (at least sevenfold at the end of 1 year of training) and MEG measurements, but not with Goldmann perimetry. The difference between perimetric and flicker results could reflect either the different saliency of the two types of stimuli, or that the dynamic and larger area of flicker is qualitatively different from the stimuli in Goldmann perimetry. Given the modularity of the visual cortical system, qualitatively different stimuli may engage different parts of the system. Thus, part of the system could regain functionality whereas other parts remained functionally depressed or blind.

We trained our participants along the horizontal visual meridian. Although improvement spread to the surrounding hemianopic field half, no improvement was detected outside the 30° eccentricity. In addition to improvement in sensitivity, training caused clear changes in the evoked fields. After a few months of training, signals started to emerge and eventually were clearly detectable in both participants. The slow emergence of new activity a long time after the typical period of spontaneous recovery proves that long-term flicker stimulation can cause plastic changes in relatively old people.

The evoked fields in KS resemble the results of MR, who had his strongest response in the posterior superior temporal area contralateral to the stimulated field—that is, at the side of the lesion. By contrast, in IT, the strongest response was ipsilateral to the stimulated hemifield and mainly occipital. This response abruptly increased, almost tripled in amplitude, after 1 year of training, and stayed strong in later measurements. fMRI recordings confirmed that both visual field halves of IT were represented in the intact hemisphere. Representation of both visual half fields in one set of retinotopic areas is a clear anomaly, which could be because of disconnection of the visually responsive areas in the lesioned hemisphere from sensory afferent input. This disconnection may put pressure on plastic changes in other parts of the brain.

Both participants experienced subjective improvement in visual functioning. Their ability to navigate in crowded places without collisions improved, and they could more easily cross the street and walk in a forest without bumping into branches. IT reported a narrow functional field in the morning, which enlarged over a few hours if he actively used it. He also reported a correlation between enlargement and task difficulty, and experienced the biggest enlargements from the flicker training.

Studies contradicting the earlier positive results in hemianopia training have suggested that fixation is unstable and that subjects may learn eccentric fixation. When eye position was carefully controlled, no positive results were evident in perimetry using scanning laser ophthalmoscopy. Our participants had steady fixation during Goldmann perimetry.

Figure 5  Flicker sensitivity mapping before and after 1 year of training for KS.  (A,C) Relative flicker sensitivity before training. (B,D) Relative flicker sensitivity after training.
and no improvement in the size of the visual field during the reported follow-up period. Recently, Sabel et al.\(^1\) showed that perimetry results are dependent on the sensitivity of the method used, and that positive training results close to the blind field border are evident when more sensitive perimetry is measured. Goldmann perimetry may be insensitive to dorsal stream or dynamic perceptual processes.

In contrast with earlier training studies, we stimulated the field much further away from the scotoma border, at 30° eccentricity. Thus, large eye movements would be needed to shift the stimuli into the normally seeing part of the visual field, and it is not possible that the participants could have repeatedly made up to 30° saccades without the experimenter noticing it. During the second year of follow-up, we monitored eye

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**Figure 6** Evolution of neuromagnetic responses for reversing checkerboard pattern. (A) A subset of the 306 channels show the distribution of evoked responses for the first baseline measurement and the three final measurements with maximum training response. The grey mark on the schematic head shows the location of the selected channels. IT’s response was ipsilateral and KS’s was contralateral to the stimulated visual field. (B) The enlarged channels show responses for all follow-up measurements with dates coded in colour. The planar gradiometers in our neuromagnetometer show the strongest response directly on top of the active brain area.

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**Figure 7** Flicker sensitivity with and without additional light in the visual field opposite to the stimulation. HVf, hemianopic visual field half; IVf, intact visual field half.
movements with a video camera. Although the 25-Hz frame rate could miss saccade motion,\textsuperscript{32} fixations last >200 ms\textsuperscript{31} and should have been easily detected if preceding saccades were large enough to reach the stimulus.

Intraocular scatter cannot explain the training results because when the sensitivity of the blind field reached the healthy hemifield, the contrast of the scattered light would be below the detection threshold in the healthy hemifield. In addition, we performed a control experiment with additional glare illumination, but found no fall in flicker sensitivity.

In neuromagnetic measurements, stimulus-driven saccades cannot explain blind hemifield responses, because the pattern reversed abruptly. In the final measurements the experimenter followed the stable eye position, also rendering slow shifts of gaze over 15° a highly unlikely explanation for the results. Light scattering in the eye cannot explain the emergence of neuromagnetic responses, firstly, because there was no net change in luminance and, secondly, because such response should have been already evident in the baseline measurements.

Why does training with flicker improve detection and recognition? This task is demanding and requires shifts of attention to the affected visual field,\textsuperscript{32} thus conforming with the general requirements for cortical plasticity.\textsuperscript{33} Finally, training needs to be repeated often for a long period to result in an improvement.

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