

Training with optic flow stimuli promotes recovery in cortical blindness

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Abstract.

Background: Cortical blindness is a form of severe vision loss that is caused by damage to the primary visual cortex (V1) or its afferents. This condition has devastating effects on quality of life and independence. While there are few treatments currently available, accumulating evidence shows that certain visual functions can be restored with appropriate perceptual training: Stimulus sensitivity can be increased within portions of the blind visual field. However, this increased sensitivity often remains highly specific to the trained stimulus, limiting the overall improvement in visual function.

Objective: Recent advances in the field of perceptual learning show that such specificity can be overcome with training paradigms that leverage the properties of higher-level visual cortical structures, which have greater capacity to generalize across stimulus positions and features. This targeting can be accomplished by using more complex training stimuli that elicit robust responses in these visual structures.

Methods: We trained cortically blind subjects with a complex optic flow motion stimulus that was presented in a location of their blind field. Participants were instructed to train with the stimulus at home for approximately 30 minutes per day. Once performance plateaued, the stimulus was moved deeper into the blind field. A battery of pre- and post-training measures, with careful eye tracking, was performed to quantify the improvements.

Results: We show that 1) optic flow motion discrimination can be relearned in cortically blind fields; 2) training with an optic flow stimulus can lead to improvements that transfer to different tasks and untrained locations; and 3) such training leads to a significant expansion of the visual field. The observed expansion of the visual field was present even when eye movements were carefully controlled. Finally, we show that regular training is critical for improved visual function, as sporadic training reduced the benefits of training, even when the total numbers of training sessions were equated.

Conclusions: These findings are consistent with the hypothesis that complex training stimuli can improve outcomes in cortical blindness, provided that patients adhere to a regular training regimen. Nevertheless, such interventions remain limited in their ability to restore functional vision.

Keywords: Cortical blindness, vision restoration, training-induced brain plasticity, perceptual learning, motion perception

1. Introduction

Cortical blindness is a severe loss of vision that follows damage to the primary visual cortex (V1) or its afferents. It results from damage that often spares

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parts of the visual pathway beyond V1, allowing some visual information to reach the cortex (Holmes, 1918; Smith, 1962; Trobe, Lorber, & Schlezinger, 1973). In fact, some patients are able to respond to stimuli in their blind fields, albeit without consciously perceiving them, a phenomenon known as ‘blindsight’ (Weiskrantz, Warrington, Sanders, & Marshall, 1974). Motivated by the existence of residual visual processing, many groups have attempted to recover visual function by training patients to react to stimuli in their blind fields, using a range of visual tasks, including motion direction discrimination (Das, Tadin, & Huxlin, 2014; Huxlin et al., 2009), orientation discrimination (Das et al., 2014) and detection of flickering stimuli (Chokron et al., 2008; E. Kasten, Wüst, Behrens-Baumann, & Sabel, 1998; Raninen, Vanni, Hyvärinen, & Näsänen, 2007; Sahraie et al., 2006). While perceptual improvements are often observed in these patients, the recovered vision remains highly specific to the trained stimulus positions and features (Das et al., 2014; Huxlin et al., 2009). Thus while the outlook is better for sub-acute patients (Bergsma, Elshout, & van den Berg, 2017; Saionz, Tadin, Melnick, & Huxlin, 2020), vision recovered in chronic patients is generally far from normal (Melnick, Tadin, & Huxlin, 2015; Raninen et al., 2007; Sahraie et al., 2006).

Similar findings have been reported in the domain of visual perceptual learning, which aims to improve performance on specific visual tasks in normally-sighted individuals (Cong, Wang, Yu, & Zhang, 2016; Jehee, Ling, Swisher, van Bergen, & Tong, 2012; Liang, Zhou, Fahle, & Liu, 2015; Wang et al., 2016; Xiong, Zhang, & Yu, 2016; Yehezkel, Sterkin, Lev, & Polat, 2015; Yu, Zhang, Qiu, & Fang, 2016; Zhang et al., 2010). As with cortically blind patients, learning in these participants often fails to generalize, so that improvements are limited to the trained stimulus’s location, orientation and even the eye of training (Batson, Beer, Seitz, & Watanabe, 2011; Hung & Seitz, 2014; Jehee et al., 2012). This specificity has long been suggested to reflect plastic changes in lower-level cortical areas (Furmanski, Schluppeck, & Engel, 2004; Jehee et al., 2012; Shibata, Watanabe, Sasaki, & Kawato, 2011; Yang & Maunsell, 2004), which themselves exhibit a high degree of location, orientation, and ocular specificity. As a result, it has been suggested that one way to overcome such specificity is to use training protocols that encourage participants to use higher-level visual structures in the visual cortex (Doshier, Jeter, Liu, & Lu, 2013; Liu & Pack, 2017). This can be accomplished by altering

the structure of the training task (Doshier et al., 2013; Xiao et al., 2008) or by using more complex training stimuli (Bakhtiari, Awada, & Pack, 2020; Jobke, Kasten, & Sabel, 2008; Liu & Pack, 2017; McGovern, Webb, & Peirce, 2012). The latter approach is preferable for stroke patients, who often struggle with complex behavioral tasks.

One example of a complex stimulus is the random dot kinematogram, a moving stimulus comprised of small dots placed at random positions and often with random velocities. This stimulus specifically activates neurons in higher-level visual cortex, notably the middle temporal (MT) region (Britten, Shadlen, Newsome, & Movshon, 1993). Previous work has shown that patients with cortical blindness can recover some visual function in their blind fields after training with these stimuli, but that the recovered vision still exhibits limited generalization across stimulus positions (Das et al., 2014). Area MT projects to the medial superior temporal (MST) area, which is thought to be the highest-level structure in the primate visual motion processing hierarchy (Van Essen & Maunsell, 1983). Neurons in MST respond to complex motion patterns of the kind that are typically seen during navigation (Duffy & Wurtz, 1991a, 1995; Duffy & Wurtz, 1991b; Graziano, Andersen, & Snowden, 1994; Lappe, Bremmer, Pikel, Thiele, & Hoffmann, 1996; Mineault, Khawaja, Butts, & Pack, 2012; Tanaka & Saito, 1989; Wild & Treue, 2021), and recent work in healthy participants showed that these *optic flow* stimuli yield training effects with greater generalization across stimulus positions and features (Bakhtiari et al., 2020). This suggests that a relatively straightforward way to improve vision rehabilitation protocols is to replace the simple stimuli used in past work with complex motion in the form of optic flow stimuli (Bakhtiari et al., 2020; Joris A. Elshout, van Asten, Hoyng, Bergsma, & van den Berg, 2016).

In this work, we seek to train cortically blind patients with an optic flow stimulus and to examine the resulting transfer across stimulus features and positions. From a conceptual standpoint, this approach has the advantages of leveraging the generalization capacities of high-level cortex and targeting a visual function that is of critical relevance to everyday life. We show that 1) optic flow discrimination can be relearned in cortically blind fields; 2) training with optic flow leads to improvements that can transfer to other stimuli and untrained locations; and 3) such training leads to a significant expansion of the visual field. However, the reduction in the severity of

Table 1

Summary table describing participants demographics and training information. Regular training refers to training that was completed 5 times a week or more. Sporadic training refers to training that was completed less than 5 times a week

Patient ID	Gender	Age	Training interval	Number of training locations	Type of training	Tasks
AAA002	Male	57	13 months	2	Regular	Rotation
AAA005	Female	64	13 months	5	Regular	Rotation
AAA018	Male	65	21 months	2	Regular	Rotation
AAA020	Male	72	24 months	3	Regular	Expansion/Contraction
AAA000	Male	65	19 months	3	Sporadic	Rotation
AAA013	Female	30	12 months	2	Sporadic	Rotation
AAA014	Female	43	6 months	2	Sporadic	Rotation

the deficit remains limited, raising the concern that structural changes in the visual system of cortically blind patients might impose a limit to the recovery that can be attained.

2. Methods

2.1. Participants

We initially screened 37 patients, based on referrals from clinicians in nearby hospitals. Of these, most did not follow up with the training protocol, and many were incapable of maintaining fixation during presentation of peripheral stimuli. These patients were excluded from the study. As a result, only seven participants ultimately participated. All had suffered a stroke causing homonymous visual field defects at least 6 months prior to the onset of training. Participants gave written, informed consent prior to their participation in the study, which was approved by the Ethics Committee of the Montreal Neurological Institute and Hospital. The participants were selected on the basis that their visual deficit was cortical in origin with no associated ocular disease (glaucoma, retinal disease, cataracts), cognitive deficits, or neglect. Patient demographics are shown in Table 1.

2.2. Training and testing

Upon recruitment, participants were required to undergo a battery of baseline measures in our laboratory before beginning the training procedure at home. Improvement in visual function following training, as well as transfer to new locations and tasks, were then assessed with post-training measures in our laboratory. Training periods lasted from 6 to 24 months (Table 1).

2.2.1. Baseline measures

The visual fields of the participants at baseline were mapped out using the Humphrey Perimetry 24-2 FDT Threshold Test (Zeiss MV Matrix 800). This test measured the contrast sensitivity at 55 points within the central 24 degrees eccentricity of the visual field by determining the contrast threshold required to detect counter-phase flickering Gabor patches.

The participants then underwent a series of psychophysical tests to map out the border of the blind field thoroughly, to determine baseline visual function in the seeing and blind fields, and to select a visual field location for training. Participants were placed in a normally lit room 57 cm from the monitor and their heads were stabilized with a chin rest. The psychophysical tests and stimuli were generated through the psychophysics toolbox *Psychtoolbox* on MATLAB (Brainard, 1997) and were presented on a 21-inch *hp* Trinitron CRT monitor (1024 × 768 pixels, 0.37 mm [H], 0.37 mm [V] per pixel, 85 Hz frame rate). Two major tasks were run at different locations in the seeing and blind fields of the participants: a simple motion direction discrimination task and a global motion direction discrimination task.

The stimulus used in the simple motion direction discrimination task was a translating (left vs. right) drifting grating composed of a Gabor patch (Fig. 1a) with a spatial frequency set to 1 cycle/degree and a temporal frequency set to 10 cycles/second. The size of the Gabor patch (2 standard deviation of the Gaussian envelope) was set to 6 degrees. The stimulus used in the global motion direction discrimination task was a translating (left vs. right) random dot kinematogram (RDK; Fig. 1b) composed of small (0.1°) white and black dots within a 6° circular aperture, at a density of 2.6 dots/deg². Dot velocity was set to 10°/sec with a lifetime (whereupon the trajectory of the dot ended and was restarted at a random position)

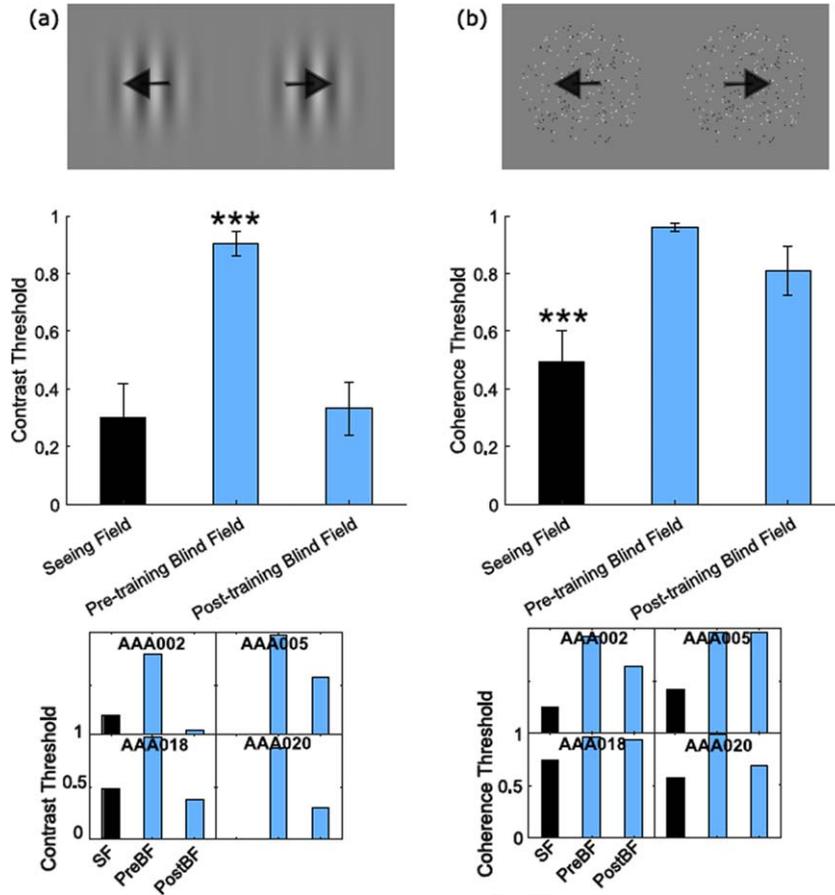


Fig. 1. (a) Simple motion direction discrimination - Gabor patch drifting to the left or to the right (spatial frequency: 1 cycle/degree, temporal frequency: 10Hz). Participants had to report the direction of motion (30–50 trials). Contrast of the Gabor patch for each trial was set through a staircase procedure (initial contrast = 0.5). Contrast thresholds were calculated in the seeing field and in the blind field (blue). On average, the baseline thresholds in the blind field (pre-training blind field) were significantly higher than the threshold in the seeing field ($t(3) = -4.77$, $p = 0.0175$) and the thresholds in the blind field after training (post-training blind field; $t(3) = 8.08$, $p = 0.004$). The threshold in the seeing field (seeing field) and in the blind field after training (post-training blind field) were not significantly different ($t(3) = -0.168$, $p = 0.876$); (b) Global motion direction discrimination – random dot kinematogram translating to the left or to the right (dot size: 0.1° , dot density: $2.6/\text{deg}^2$, dot velocity: $10^\circ/\text{sec}$, dot lifetime: 220 ms). Participants had to report the direction of motion (30–50 trials). The coherence of the stimulus for each trial was set through a staircase procedure (initial coherence = 0.9). Coherence thresholds were calculated in the seeing field (black) and in the blind field (blue). On average, the thresholds in the seeing field (seeing field) were significantly different from the threshold at baseline in the blind field (pre-training blind field; $t(3) = -3.19$, $p = 0.0499$) and the threshold in the blind field after training (post-training blind field; $t(3) = 1.91$, $p = 0.153$). The threshold in the blind field before and after training (pre-training vs. post-training blind field) were not significantly different ($t(3) = 1.91$, $p = 0.153$); Error bars show standard deviation from the mean. *** $p \leq 0.05$. The lower panel shows the seeing field (SF), pre-training blind field (PreBF) and post-training blind field (PostBF) coherence thresholds for each individual subject.

of 220 ms. The dots presented were either “signal dots” or “noise dots”. Signal dots moved coherently in a specific direction, whereas noise dots moved in random directions. The coherence level of the RDK stimulus represented the proportion of signal dots.

Each task followed a two-alternative-forced-choice (2-AFC) paradigm, in which the participant reported the direction of the motion of the stimulus. Each task was composed of 30–50 trials. The starting contrast for the Gabor patches was set to 50%, and

the starting coherence for the RDK was set to 90%. The contrast and coherence level for each subsequent trial was set using a standard 2-down-1-up adaptive staircase procedure (Leek, 2001).

Fixation in each task was controlled with the Eye-Link 1000 eye tracker (SR Research), which has a sampling rate of 1000 Hz and a spatial resolution of 0.1° . Each trial in each task was gaze contingent. The participant was asked to maintain fixation within a $2 \times 2^\circ$ fixation target. If the gaze was not within

1 degree of the fixation target, a tone would sound, aborting the trial and excluding it from analysis. The participant had to maintain fixation during 500 ms for the stimulus to appear, signaled by a tone. As the stimulus was presented, fixation had to remain steady until the stimulus and fixation target disappeared, signaling the end of the trial and cuing the participant to provide a response, using a keyboard button press. Auditory feedback was then given in the form of different tones indicating a correct vs. an incorrect response.

As a measure of visual function, contrast and coherence thresholds were obtained. These were computed using the 2-down 1-up staircase procedure described above, resulting in an 83% convergence level. The last six reversals in each task were averaged to compute the threshold.

At the end of the pre-test session in the laboratory, the experimenter performed one short training session in front of the participant for demonstration followed by a few short trials performed by the participant.

2.2.2. Training procedures

All participants performed their training at home, on personal computers or on computers lent by our laboratory. To ensure that the patients understood and followed the testing procedure, we visited their homes to set up the monitors and to further explain the procedure. Participants were instructed to use one monitor and to leave it in a fixed position for the duration of their training. Screen dimensions were collected, and the participants were instructed to sit at a specific distance from their screen during each training session. Although the hardware available to each patient differed somewhat, all visual displays were at least 61.1×38.2 degrees in size and had a refresh rate of at least 30 Hz. Training was controlled by a browser-based program (Article 19 Group; Montreal) that displayed the stimuli, monitored performance, and stored the data from each trial. The software provided the experimenters with remote access to the data, which allowed us to track performance daily and to identify potential lapses in compliance.

During the first two days of training, patients were trained to perform the task in the seeing field in order to familiarize themselves with the task, after which the stimulus was moved to the blind field, and training began. The initial training location was chosen to be securely in the blind field but close to the vertical meridian, based on pre-testing perimetry. As shown

below, initial performance was near chance, confirming the placement of the stimulus in the blind field. We did not attempt to collect additional measures of baseline performance in the blind field, as such exposure can bias subsequent estimates of learning and transfer (Xiao et al., 2008). Participants were asked to undergo the training regimen regularly, every day if possible, or for a minimum of 5 days a week. Four participants followed this training regimen exactly, while three others performed the training sporadically. Although we were unable to monitor eye position during training, we occasionally reminded the participants of the importance of maintaining fixation.

The training task was an optic flow motion direction discrimination task. The stimulus was composed of an expanding/contracting ($n = 1$) or rotating RDK ($n = 6$) (Fig. 2a), stimuli that are known to target high-level brain regions, like area MST (Duffy & Wurtz, 1991a, 1995; Duffy & Wurtz, 1991b). The RDK was composed of small (0.06 degrees) black dots in a 5-degree radius aperture with a dot density of 2.6 dots/deg². Dot velocity was set to 20°/sec and dot lifetime to 250 ms. The stimulus was presented on a gray background and in a location previously selected through the baseline tests to be fully within the border of the blind field (Fig. 3).

Each training session was composed of 480 trials, interleaved with six short (1 min) breaks; sessions typically lasted approximately 30 minutes per day. Each trial began when a fixation target appeared, accompanied by a tone, for 500 ms. The stimulus then appeared for 500 ms. When the stimulus and fixation target disappeared, two options appeared on the screen and the participant was asked to report the direction of the motion (expansion/contraction or clockwise/counterclockwise) with a mouse or the keyboard. A correct response was signaled by a tone and a green flash while an incorrect response was signaled by a different tone and a red flash (Fig. 2b). The coherence level of the RDK was set to 100% throughout every trial.

The percentage of correct trials was used as a measure of performance. Once the performance reached a plateau, the stimulus was moved 1-2 degrees deeper into or along the border of the blind field.

2.2.3. Post-training measures

To assess performance changes and the transfer of training effects, a battery of post-training tests was undertaken in the laboratory. These included the Humphrey perimetry 24-2 FDT Threshold Test

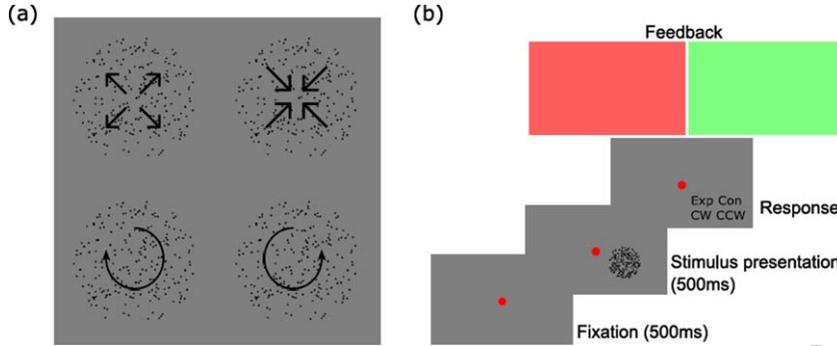


Fig. 2. (a) Optic flow motion direction discrimination stimulus – expanding/contracting or rotating random dot kinematogram (dot size: 0.06° , dot density: $2.6/\text{deg}^2$, dot velocity: $20^\circ/\text{sec}$, dot lifetime: 250 ms, 100% coherence). This stimulus was used in the training paradigm; (b) Training Task – each training session was composed of 480 trials, interleaved with six short breaks. Each trial began when a fixation target appeared, accompanied by a tone, for 500 ms. The stimulus then appeared for 500 ms. When the stimulus and fixation target disappeared, two options appeared on the screen. The participant could report the direction of the motion (clockwise vs. counterclockwise rotation or expansion vs. contraction) with a mouse or the keyboard. A correct response was signaled by a tone and a green flash. An incorrect response was signaled by a different tone and a red flash.

and the same psychophysical tests as baseline, with fixation monitored as described above. Compared to baseline, fixation became more precise during the post-test, as the standard deviation in eye positions decreased on average from 1.48 to 0.54 degrees in the x direction and from 1.70 to 0.76 degrees in the y direction. On average, participants fixated 0.155 ± 0.60 degrees closer to the stimulus compared to baseline. These small changes in fixation indicate that the results we report in the post-test were not due to a change in fixation behavior.

2.3. Statistical analysis

To evaluate the changes in visual function after training, contrast and coherence thresholds were computed in the seeing field, in the blind field at baseline, and in the blind field after training. A standard two-tailed-t-test was performed to compare the threshold values.

To evaluate the changes in the severity of the blind field, the Humphrey perimetry results were compared at baseline and after training. The raw difference between the post-training and baseline thresholds was then computed for each of the 55 points. The distribution of these differences in the *seeing fields* was used as a measure of test-retest variability for each participant. This allowed us to normalize any training-related changes in visual sensitivity according to the variability in each participant's perimetry measurements. This was done for each point in the visual field, as follows:

$$z = \frac{\Delta dB - \mu}{\sigma}$$

Here ΔdB is the raw difference in sensitivity from the post-test to baseline for each point, μ is the mean test-retest variability and σ is the standard deviation of the test-retest variability at different positions in the seeing field.

3. Results

3.1. Improved motion processing in the blind field with training

Before starting the training, we tested participants on a simple motion direction discrimination task with a drifting Gabor patch (Fig. 1a) in their blind and seeing fields. Unsurprisingly, contrast thresholds for discriminating the motion of the Gabor patch were significantly higher in the blind field compared to the seeing field ($t(3) = -4.77$, $p = 0.0175$; Fig. 1a). We also tested participants on a global motion direction discrimination task with a translating random dot kinematogram (Fig. 1b). Coherence thresholds for discriminating the motion of the signal dots were again significantly higher in the blind field compared to a corresponding location in the seeing field ($t(3) = -4.86$, $p = 0.0167$; Fig. 1b).

We then trained the blind field of cortically blind participants on an optic flow motion direction discrimination task, composed of a 100% coherence expanding/contracting or rotating random dot kinematogram (Fig. 2a). At baseline, participants ($n = 7$) were unable to do the task and performed around

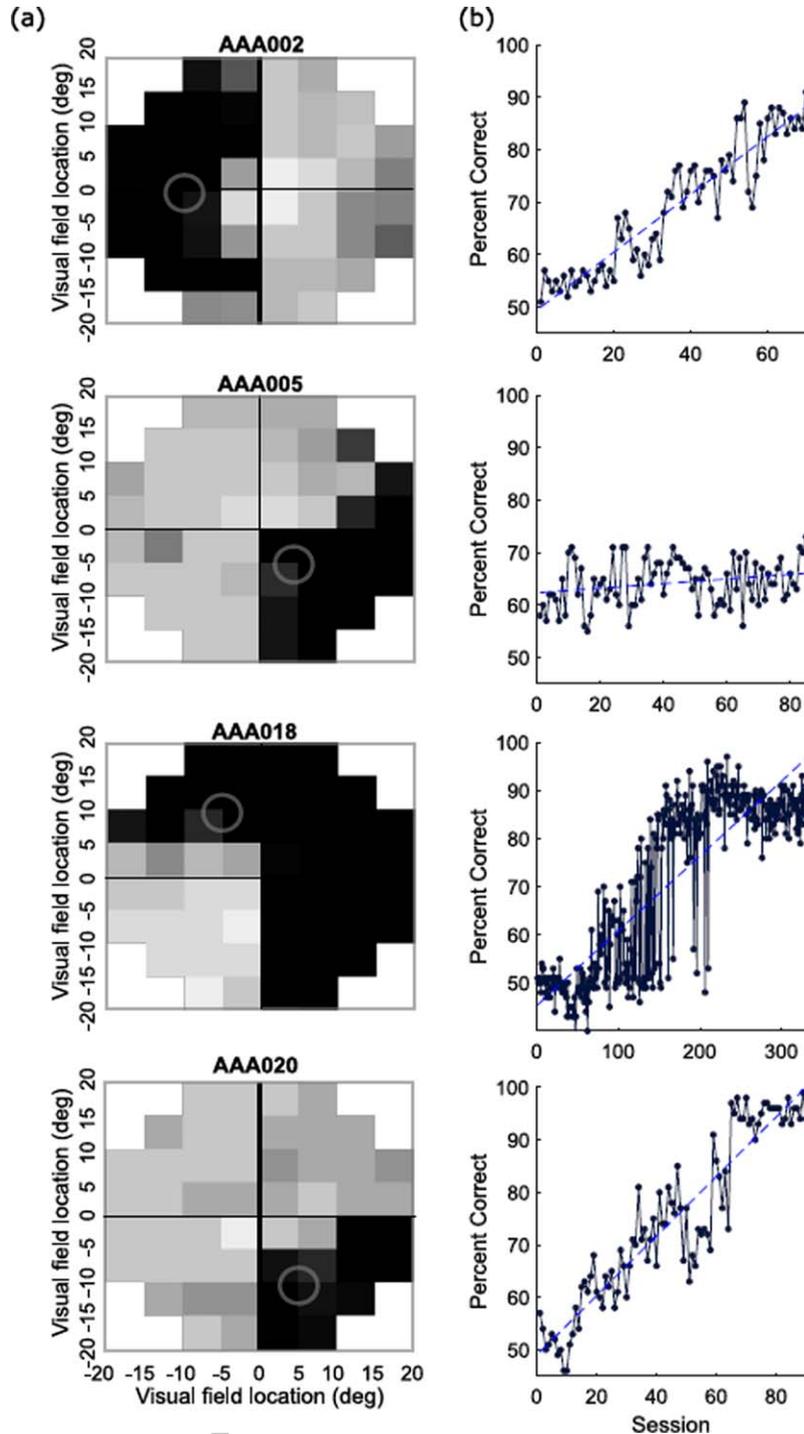


Fig. 3. (a) Baseline visual field, averaged across the two eyes, measured with the 24-2 FDT Threshold Humphrey perimetry test for the 4 participants who followed the regular training regimen (one training session a day, at least 5 times a week). The grayscale represents the average contrast sensitivity for detecting contrast-modulated flickering Gabor patches in dB across the central 20 degrees of visual angle for each participant. Lighter regions correspond to higher sensitivity, and darker regions correspond to a lower sensitivity. For patient AAA020, the baseline visual field is shown only for the right eye; (b) Learning curves at the first training location for the 4 participants shown in (a). Performance started around chance (50% correct) but increased to $\geq 75\%$. The grey circle represents the training location. Learning occurred at different rates for different participants. Blue dashed lines indicate the best fitting regression line. Participants AAA002, AAA005 and AAA018 trained with a rotating stimulus. Participant AAA020 trained with an expanding/contracting stimulus.

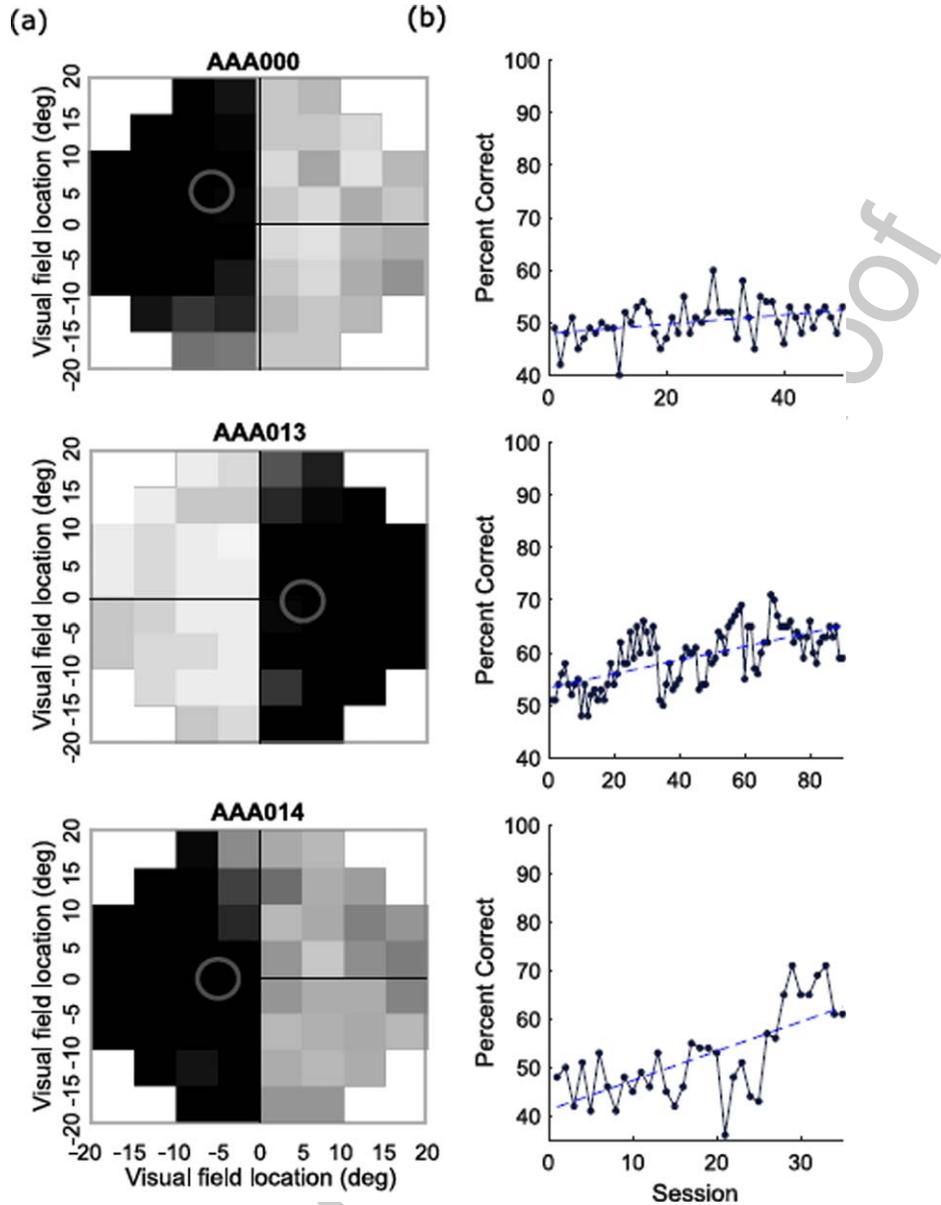


Fig. 4. (a) Baseline visual field, averaged across the two eyes, measured with the 24-2 FDT Threshold Humphrey perimetry test for the 3 participants who trained sporadically. The grayscale represents the average contrast sensitivity for detecting contrast-modulated flickering Gabor patches in dB across the central 20 degrees of visual angle for each participant. Lighter regions correspond to higher sensitivity, and darker regions correspond to a lower sensitivity. (b) Learning curves for the 3 participants shown in (a). Performance started around chance (50% correct) and increased to $\sim 60\%$ at the training location shown in the grey circle. Learning occurred at different rates for different participants. Blue dashed lines indicate the best fitting regression line. All participants trained with the rotating stimulus.

chance level (52 ± 3.93 percent correct; Fig. 3). However, for the four patients who performed regular training, the level of performance increased to $\geq 75\%$, reaching an average of 87.3 ± 9.64 percent correct (Fig. 3). Cortically blind patients can thus be trained to accurately discriminate the direction of optic flow motion in their blind fields. The three

participants who trained on the task more sporadically exhibited smaller improvements (Fig. 4), even when the number of sessions was equated between groups of participants (Fig. 5). After sporadic training, a performance level around 57.7 ± 4.16 percent correct was reached. This shows that regular training is important for improving outcomes.

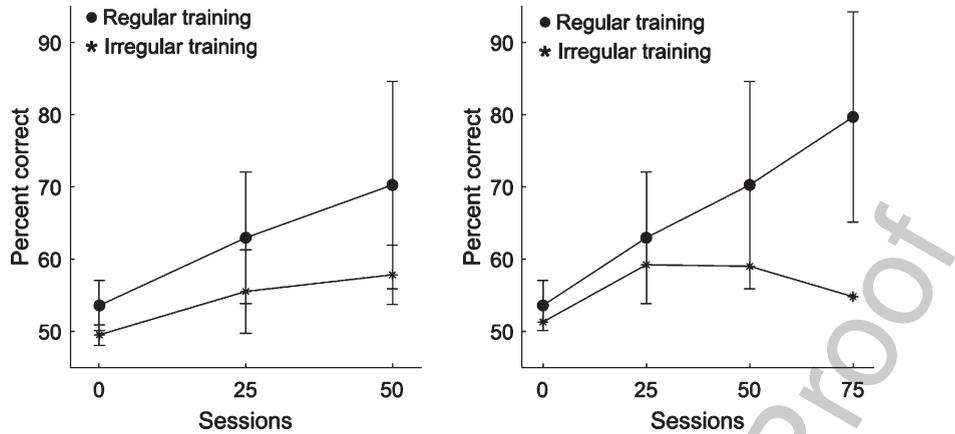


Fig. 5. Performance levels reached after 50 sessions (left) and 75 sessions (right) after regular training (filled circles) and irregular training (asterisks). Red dots represent the average for all 4 participants who completed regular training sessions. Black dots represent the average for 2 participants who completed irregular training sessions (left) and one participant who completed irregular training sessions (right). Error bars represent standard deviation from the mean. Regular training is required for performance to increase significantly and for optic flow motion discrimination to be retrained in the blind-field.

3.2. Transfer to untrained locations

Previous work has shown that training effects in cortically blind patients are highly specific to the trained location (Das et al., 2014; Huxlin et al., 2009; Sahraie et al., 2006): Even small stimulus displacements usually cause performance to drop to chance levels, so that training must begin again at the new location. We examined transfer in 4 participants for whom performance had saturated at one training location. For these participants, we moved the stimulus by 1–2 degrees, either deeper into the blind field or along the border of the blind field (Fig. 6). The new stimulus location was chosen so that the level of pre-training visual sensitivity was identical to that of the trained location.

In all cases, there was some transfer of the training effects, as the level of performance did not drop to chance. Indeed, full transfer occurred for one of the patients (AAA018), while some transfer occurred for two patients (AAA002, AAA020), whose performance dropped to around 65%. In another patient (AAA005), full transfer occurred along the border of the blind field but no transfer occurred as the stimulus was moved deeper into the blind field.

On average, performance dropped from $75.7 \pm 9.35\%$ correct to $68.1 \pm 6.87\%$ correct when the stimulus was moved to a new training location. This is higher than the baseline performance in the first training location ($54.3 \pm 2.05\%$ correct, $n = 4$). Thus, participants were able to retain 64.5% of the performance gained through training when the stimulus was

moved. These results suggest that optic flow motion stimuli could indeed improve transfer, although it is difficult to strictly compare our results with previous ones (Das et al., 2014; Huxlin et al., 2009; Sahraie et al., 2006), due to methodological differences.

3.3. Transfer to untrained types of motion

After completion of their training, participants came back to the laboratory for the post-training measures, which involved performing the same tasks as in the baseline session (Methods). For the participants who completed training regularly ($n = 4$), for motion of a drifting Gabor at the trained location, contrast thresholds were significantly reduced compared to the pre-training test ($t(3) = 8.08, p = 0.004$). In fact, by this measure, sensitivity in the trained blind field location was not different from that found in the seeing field ($t(3) = -0.168, p = 0.876$; Fig. 1a). Training with an optic flow motion stimulus thus fully transfers to a simple motion stimulus that has a different stimulus composition (Gabor vs. dots) and a different direction of motion (rotation or expansion/contraction vs. left/right).

We also tested the four participants on the same global motion direction discrimination task as baseline (Fig. 1b). While there was a slight improvement on this task in the blind field after training compared to baseline (Fig. 1b), it did not reach statistical significance ($t(3) = 1.91, p = 0.153$), and thresholds remained significantly higher than in the seeing field

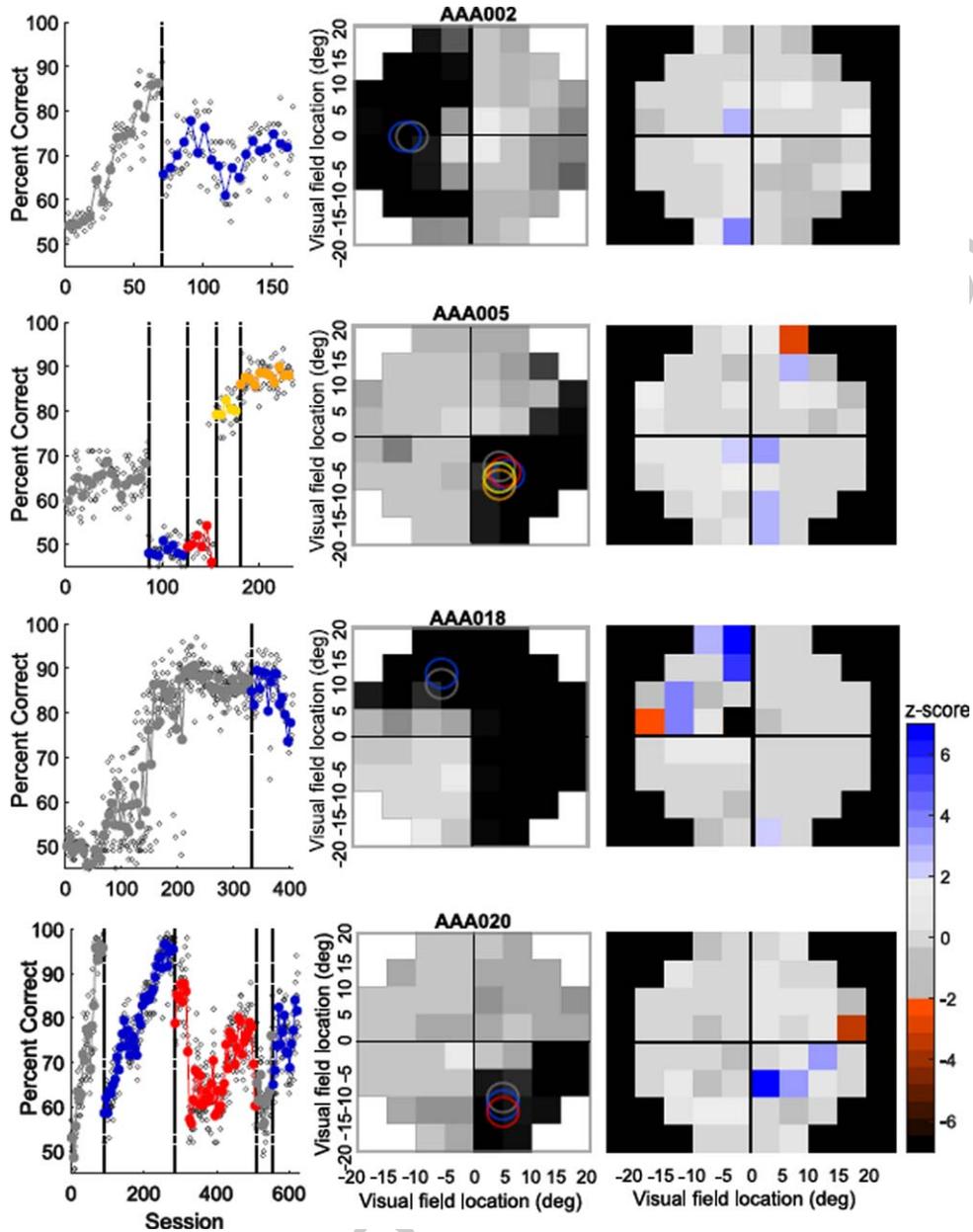


Fig. 6. **Left** Performance at the different training locations shown as circles in the perimetry plots (center). Small black open circles represent individual training sessions. Large colored dots represent the average performance for 5 training sessions at the corresponding training location. Vertical dotted line represents a switch in the training location. **Center** Training locations (colored circles) **Right** Blind field difference in contrast sensitivity between post-training and baseline Humphrey 24-2 FDT Threshold perimetry test, averaged for both eyes. Blue areas represent a significant increase in sensitivity ($z\text{-score} \geq 2$, difference equal to or higher than 2 standard deviations from the mean test-retest variability), red/orange areas represent a significant decrease in sensitivity ($z\text{-score} \leq -2$, difference equal to or lower than 2 standard deviations from the mean test-retest variability). Light gray areas represent a non-significant increase in sensitivity and dark gray areas represent a non-significant decrease in sensitivity.

($t(3) = -3.19$, $p = 0.0499$; Fig. 1b). Training with an optic flow motion stimulus can thus recover simple motion processing but only slightly improves perception of noisy motion stimuli.

3.4. Decrease in severity of deficit

In the post-training phase, we also remeasured visual field perimetry. Contrast sensitivity increased

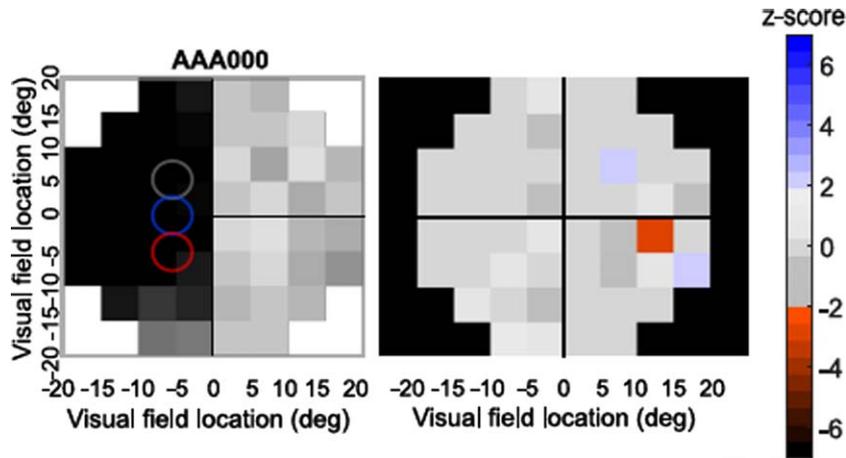


Fig. 7. Blind-field difference in contrast sensitivity between post-training and baseline Humphrey 24-2 FDT Threshold perimetry test, averaged for both eyes for one participant who did not complete regular training. Blue areas represent a significant increase in sensitivity ($z\text{-score} \geq 2$, difference equal to or higher than 2 standard deviations from the mean test-retest variability), red/orange areas represent a significant decrease in sensitivity ($z\text{-score} \leq -2$, difference equal to or lower than 2 standard deviations from the mean test-retest variability). Light gray areas represent a non-significant increase in sensitivity and dark gray areas represent a non-significant decrease in sensitivity. No significant increase in sensitivity is found in the blind field.

by 9.5 ± 5.11 dB on average at the initial training location and 7.17 ± 3.2 dB on average at subsequent training locations. By comparison, the average test-retest variability in sensitivity in the seeing field was 2.00 ± 1.14 dB. To quantify the training-induced improvements in the blind field, we normalized the changes in sensitivity at each position according to each participant's test-retest variability (see Methods). This approach allowed us to account for any secular changes in visual function, as well as non-specific changes due to practice or engagement with the protocol.

Figure 6 shows the normalized visual field perimetry changes for each participant. The locations showing improvements (blue) were mostly centered near the training locations, which were typically near the border of the blind field. As a result, the size of the blind field decreased by a diameter of 10 ± 3.53 deg on average and an area of 78.5 deg^2 on average. We also observed occasional decreases in sensitivity (red), but these were relatively modest, averaging 2.6 ± 0.914 dB, and were often located in the seeing field. These results support previous reports that training in multiple locations can reduce the severity of the deficit in the blind field over an area of $\sim 80 \text{ deg}^2$ while also preventing potential worsening of visual sensitivity (Cavanaugh and Huxlin, 2017).

The increases in sensitivity and the expansion of the seeing field were most likely due to training. All participants in the study were chronic cortically

blind patients (≥ 6 months post-stroke). Spontaneous recovery usually occurs until around 2 months after stroke (X. Zhang, Kedar, Lynn, Newman, & Biousse, 2006), with only rare and modest improvements occurring later. For instance, untrained patients have been reported to recover only an area of 16 deg^2 of the blind field as measured by Humphrey perimetry (Cavanaugh & Huxlin, 2017). Moreover, we found no significant improvements in the blind field for one participant who did not do the training but completed the post-test (Fig. 7). For another participant, whose blind field covered three quadrants of the visual field (AAA018), we only found large significant increases in sensitivity in the upper left quadrant, targeted by training, while the right hemifield remained unchanged.

3.5. Subjective reports of participants and implications for quality of life

Our software provided a mechanism for participants to relay comments to us at any time during their training period. Two participants reported a small opening created in their vision that allowed them to perceive the motion of the stimulus. Two participants also reported the perception of a "ghost" stimulus expanding/contracting or rotating but no perception of fine detail. Overall, participants reported improvements in their ability to read and to drive, as well as relief from other side-effects of cortical blindness,

such as motion sickness. There were no subjective reports of adverse consequences of the training.

4. Discussion

Vision restoration training is an appealing option for cortical blindness patients, as it promises to restore lost visual function without the need for compensatory strategies or optical devices. Previous work has shown that such restoration approaches can have a measurable positive effect on the quality of patients' lives (Elshout et al., 2018). However, at present most patients receive no treatment, and for those who do seek treatment, strategies that rely on eye movement compensation are found to be more effective than vision rehabilitation (Roth et al., 2009). Our results add to the findings of previous studies (Das et al., 2014; Huxlin et al., 2009), which suggest that vision restoration can benefit from a detailed understanding of the selectivity of the primate visual system and from consideration of the properties and limitations of visual perceptual learning.

4.1. Relationship to perceptual learning

Perceptual learning refers to an improvement in visual function after training. The specificity of such training has long been considered a limitation to its practical utility (Awada, Bakhtiari, & Pack, 2021; Batson et al., 2011; B. Doshier & Lu, 2017; Hung & Seitz, 2014; Jehee et al., 2012), but this conclusion has been tempered by evidence showing that specificity can be overcome through specific training paradigms, such as double training (Xiao et al., 2008; Zhang et al., 2010) or reduced task difficulty (Ahissar & Hochstein, 1997). Similar findings were reported for cortical blindness patients (Das et al., 2014). More recent work has shown that specificity can also be overcome by increasing the complexity of the stimulus (Bakhtiari et al., 2020; Liu & Pack, 2017). Specifically, training with a translating random dot stimulus can lead to a higher transfer to untrained stimulus sizes or untrained locations compared to training with a drifting grating. This transfer can be increased even more through training with a more complex optic flow stimulus (Bakhtiari et al., 2020).

In this work, we trained cortically blind patients with an optic flow stimulus and replicated previous findings that complex motion discrimination can be relearned in cortically blind fields and can lead to an improvement that transfers to a simple motion

stimulus (Das et al., 2014; Huxlin et al., 2009). We report long-lasting improvements that were measurable 6 to 24 months after training began and that reached a higher level of transfer to untrained locations than previously reported in the literature (Das et al., 2014; Huxlin et al., 2009). We also report decreases in blind field size and severity.

4.2. Relationship to blindsight

It is worth mentioning that the motion perception improved through training is different from blindsight. Blindsight is usually unconscious and is limited to the detection, but not the discrimination, of motion stimuli (Weiskrantz et al., 1974). But our results, along with much previous work (Das et al., 2014; Huxlin et al., 2009; Melnick et al., 2015) shows that training improves motion direction discrimination, which is severely impaired at baseline, with participants becoming increasingly aware of the stimulus. In fact, perceptual learning studies using motion stimuli detection paradigms tailored for blindsight show no increase in awareness of the stimulus or motion direction discrimination (Melnick et al., 2015; Raniinen et al., 2007; Sahraie et al., 2006), and training in cortically blind patients has effects that extend well beyond the spatiotemporal capacities of blindsight (Das et al., 2014).

4.3. Relationship to visual cortical function

That complex motion processing can be improved in cortically blind fields is not surprising, particularly when the damage is limited to V1 and its immediate afferents (Holmes, 1918; Smith, 1962; Trobe et al., 1973). Complex motion processing usually occurs in higher cortical areas, such as MT and MST (Duffy & Wurtz, 1991a; Graziano et al., 1994; Mineault et al., 2012; Tanaka & Saito, 1989) which are often intact in cortical blindness (Azzopardi, Fallah, Gross, & Rodman, 2003; Holmes, 1918; Mestre, Brouchon, Ceccaldi, & Poncet, 1992; Smith, 1962; Trobe et al., 1973). In fact, the existence of a direct pathway between the lateral geniculate nucleus (LGN) and areas MT and MST has been reported (Berman & Wurtz, 2011; Rodman, Gross, & Albright, 1989; Sincich, Park, Wohlgenuth, & Horton, 2004). This pathway probably underlies some aspects of blindsight (Ajina & Bridge, 2018; Ajina, Pestilli, Rokem, Kennard, & Bridge, 2015; Schmid et al., 2010). Therefore, the improved complex motion processing could be mediated by this pathway.

Consistent with this idea is the finding that the improvements we report are not strictly retinotopic (Fig. 8). This is consistent with recent findings that perceptual learning could reflect changes in the way visual information is read out from higher-level structures in the visual pathway (Bakhtiari et al., 2020; B. Doshier & Lu, 2017; Laamerad, Guitton, & Pack, 2020; Law & Gold, 2008; Liu & Pack, 2017; Wang et al., 2016). We trained our participants with an optic flow stimulus that targets area MST (Durant & Furlan, 2014), where neurons have large receptive fields that can even extend bilaterally (Duffy & Wurtz, 1991a; Mineault et al., 2012; Tanaka & Saito, 1989). Training could have thus retrained the decision structures to rely more efficiently on area MST for perception of the optic flow stimulus, decreasing its retinotopic specificity. Alternatively, or in addition, training could have improved the deployment of attention to relevant visual locations (Byers & Serences, 2012; Halbertsma et al., 2020; Poggel, Kasten, & Sabel, 2004).

Animal studies also report the existence of direct pathways between LGN and cortical areas V2, V3 and V4 (Cowey & Stoerig, 1989; Schmid et al., 2010). These areas contain neurons with selectivity for stimulus features such as orientation (Vanduffel, Tootell, Schoups, & Orban, 2002), motion (Nakhla, Korkian, Krause, & Pack, 2021; Schmid et al., 2010), and color (Conway, 2009). They also exhibit a retinotopic organization (Desimone, Schein, Moran, & Ungerleider, 1985; P. Mineault, Zanos, & Pack, 2013). Thus, these regions could also be targeted with appropriate training protocols, perhaps facilitating a recovery of both motion and form vision.

An alternative possibility is that training recruits and reactivates V1 neurons that have suffered damage but retain some function (Barbot et al., 2020; Erich Kasten, Poggel, & Sabel, 2000). Indeed, areas near the border of the blind field are more likely to contain spared, but abnormal, V1 neurons that do not recover their function spontaneously but can be recovered through training (Huxlin et al., 2009; Erich Kasten et al., 2000; Melnick et al., 2015; Sabel, Henrich-Noack, Fedorov, & Gall, 2011). In that case, the improved performance might be limited by the capacities of these V1 neurons, which does seem to be consistent with our finding that improved training effects transferred most readily to stimuli comprised of Gabor patches. The detection of motion or contrast in such oriented stimuli is a characteristic function of V1 (Chen, Geisler, & Seidemann, 2006; Hubel & Wiesel, 1962). The lack of transfer to noisy random

dot stimuli (Fig. 4b) might also be explained in this way, as V1 neurons are not very sensitive to noisy random dot stimuli (Snowden, Treue, Erickson, & Andersen, 1991). This would suggest that patients in our study were relying on local cues (e.g., individual dots) to perform the task. We chose to use a 100% coherent training stimulus because of the benefits of easy tasks for perceptual learning (Ahissar & Hochstein, 1997; Ahissar & Hochstein, 2004), but future work could combine optic flow stimuli with noise to further encourage the use of high-level areas. Indeed, motion-blind humans with extrastriate lesions are able to perceive motion with 100% coherence but experience difficulties as soon as noise is added to the stimulus (Baker, Hess, & Zihl, 1991), highlighting the importance of extrastriate areas for motion perception of noisy stimuli.

4.4. Limitations

One limitation of our study is that the overall pool of patients was small, as is typical for this field (Melnick et al., 2015). Moreover, we were unable to collect eye tracking data during the training procedure, and as a result there was some uncertainty about the precise position and size of the stimulus from day to day. Again, this is typical of the field, as there is at present little possibility of performing precise eye tracking in a home-based setting. That said, we verified during the post-test that patients did not adapt their fixation behavior in such a way as to bring the stimulus into the seeing field. Finally, we did not collect data from a control group who received no training or a different kind of training. Much previous work (e.g., Cavanaugh & Huxlin, 2017) has shown that there is very little spontaneous recovery in chronic stroke patients, but it would be interesting to perform a direct comparison between training with complex and simpler stimuli, using the same procedures and software (Das et al., 2014; Jobke et al., 2008).

5. Conclusion

In conclusion, this study replicates and extends previous findings that some visual functions can be recovered in cortical blindness (Barbot et al., 2020; Cavanaugh & Huxlin, 2017; Das et al., 2014; Huxlin et al., 2009; Melnick et al., 2015; Saionz et al., 2020), while providing evidence that the specificity in the improvement can be reduced with protocols that target higher-level cortical regions. This approach

thus shows promise for the potential development of effective and rapid rehabilitative strategies to recover vision. Moreover, the ability to perceive optic flow is likely of direct relevance to the patients, since optic flow is fundamental to navigation and other interactions with the environment (Gibson, 1950). Future work should focus on developing protocols that combine lessons from visual perceptual learning (Das et al., 2014) and the stimulus selectivity of the primate visual cortex (Bakhtiari et al., 2020) to further improve outcomes in chronic cortical blindness.

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Conflict of interest

After the submission of this manuscript, author C.C.P. became a stakeholder in Thérapeutiques Blindsight Inc.

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