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Abstract

Background. Cortical visual impairment (CVI) is a severe loss of visual function caused by damage to the visual cortex or its afferents, usually as a consequence of stroke or hypoxic insult. It is one of the leading causes of vision loss in children.

Objective. Several studies have demonstrated limited vision restoration in adult CVI patients who trained on well-controlled psychophysical tasks involving complex motion stimuli. Given the greater potential for plasticity in the young brain, we hypothesized that similar vision training would be more effective in young patients.

Methods. To test this hypothesis, we conducted a proof-of-principle study in one young CVI patient (age 18), to test the training speed, efficacy and generalizability of vision rehabilitation using complex motion stimuli. The patient trained at home and in the laboratory, on a psychophysical task that required discrimination of motion stimuli presented in the blind field. Visual function was assessed before and after training, using perimetric measures, as well as a battery of psychophysical tests.

Results. The patient showed rapid improvements on the training task, with performance going from chance to 80% correct over the span of 11 sessions. With further training, improved vision was found for untrained stimuli and for perimetric measures of visual sensitivity. Some, but not all, of these performance gains were retained upon retesting after one year.

Conclusion. These results suggest that existing vision rehabilitation programs can be highly effective in pediatric patients. Validation with a large sample size is critical, and future work should also focus on improving the usability and accessibility of these programs for young patients.

Rapid recovery from cortical visual impairment in a pediatric patient following vision training: A case study

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1. Introduction

Cortical visual impairment (CVI) is a severe loss of visual function caused by damage to the visual cortex or its afferents, usually as a consequence of stroke or hypoxic insult. It is one of the leading causes of vision loss in children, and its prevalence is higher in communities with limited access to perinatal care. Although spontaneous recovery has been reported (Greenham et al., 2016), many children have impairments that endure throughout their adult lives (Kirton & deVeber, 2013).

Given the substantial plasticity of children's brains, there has been some interest in the development of rehabilitation protocols targeting pediatric CVI. Indeed, there have been reports of improved visual function following training with simple behavioral paradigms that encourage reliance on vision (Lueck et al., 1999; Malkowicz et al., 2006; Tsai et al., 2013). However, these studies have used largely uncontrolled or informal behavioral paradigms, and it is not clear to what extent the improvements were due to restored visual function, rather than altered behavioral strategies (e.g., eye movements). It is also unknown whether the effects of training generalize to visual stimuli that were not part of the training protocol.

In recent years, rigorous programs of vision restoration have been developed and tested for adults with CVI (Bergsma et al., 2017; Das et al., 2014; Huxlin et al., 2009; Jobke et al., 2009; Kasten et al., 1998; Melnick et al., 2016; Poggel et al., 2015; Saionz et al., 2020). The underlying premise of these interventions is that visual plasticity in healthy subjects can be engaged with training protocols that specifically target visual cortical structures with residual function (Awada et al., 2022; Bakhtiari et al., 2020; Das et al., 2014; Liu & Pack, 2017; Sabel et al., 2011). These structures are often found in higher-level cortical areas (Das et al., 2014).

In these rehabilitative paradigms, patients make a simple binary choice about visual stimuli presented to their blind fields. The stimuli are often chosen based on the selectivity for complex motion patterns that is found in some higher-level areas of the visual cortex (Awada et al., 2022; Duffy & Wurtz, 1991; Mineault et al., 2012). For older patients, training with these kinds of stimuli has yielded consistent improvements on objective measures of visual function, with some generalization to untrained stimuli (Awada et al., 2022; Das et al., 2014; Huxlin et al., 2009; Jobke et al., 2009). However, this approach has not to our knowledge been applied in pediatric patients.

We hypothesized that training with complex stimuli would be effective in the younger population, and, importantly, that improvements in visual function would occur more quickly than in older patients. To test this hypothesis, we trained a young CVI patient on the same training protocol that has previously been shown to improve visual function in older adults (Awada et al., 2022). The patient showed rapid gains in visual function that extended to untrained stimulus features and positions. Some of these performance gains persisted for one year after the training, suggesting the possibility of efficient and durable vision rehabilitation in pediatric patients.

2. Methods

2.1. Patient

The patient is an 18-year-old male who suffered damage to the right occipital cortex as a consequence of a hypoxic insult during birth. The clinical neurological examination results showed no evidence of aphasia, cognitive dysfunction or neglect syndrome. Similarly, ocular movements were normal with no evidence of nystagmus, and pupil sizes were regular and reactive with no abnormal findings. The slit lamp examination was carried out for the neuro ophthalmic evaluation. Eye exams pertinent to CVI (including agnosia for motion, akinetopsia, central achromatopsia, prosopagnosia, asterognosis and topographic agnosia) were conducted, and all tests showed no evidence of ocular disease. On the 30-2 Humphrey Visual field (HVF) test, a left homonymous hemifield defect was observed.

The participant was informed about the study and signed a written consent form prior to the participation. The study was approved by the ethics committee of the Nepal Health Research Council.

2.2. Experimental setup

After enrolling in the study, the patient was first retested on Humphrey perimetry, the relevant measure being "recorded threshold sensitivities in numeric scale", averaged across both eyes. This confirmed a large and persistent homonymous deficit in the left visual field (Fig. 1A).

We then tested the patient on various psychophysical tasks in the laboratory, to record baseline performance. During the psychophysical tasks, the patient was seated in a dark room, 57 cm from the monitor, with his head stabilized with a chin rest. During performance of the tasks, the patient was asked to fixate a square point displayed at the center of the screen and to minimize head movements. The psychophysical tasks and associated stimuli were generated using the psychophysics toolbox (http://psychtoolbox.org/) in MATLAB and were presented on a 21-inch Dell monitor, model P2219H (1920 x 1080 pixels, 60 Hz frame rate).

As in previous work (Awada et al., 2022; Cavanaugh & Huxlin, 2017), the initial training location was chosen to be near the vertical meridian but far enough from the seeing field that small fixational eye movements could not improve performance. This initial training location was in the upper left quadrant of the visual field (5 degrees of visual angle (dva) horizontally and 5 dva vertically from the center of gaze, which was the center of the screen).

2.3 Pre-training assessment

Once the initial training location was identified, a battery of psychophysical experiments was conducted to assess visual function. Eye movements in all tasks were monitored using an infrared eye tracker (EyeLink 1000 plus, SR Research) with a sampling rate of 1 kHz and a spatial resolution of 0.1 dva. On each trial, a fixation window of radius 2 dva was established around the fixation point. The patient had to maintain fixation for 500 ms for a stimulus to appear and had to maintain fixation during the entire course of the stimulus presentation. Otherwise, the trial was aborted.

All the tasks made use of a two-alternative forced choice (2AFC) paradigm, in which the patient needed to report the stimulus direction or orientation at the end of each trial with a keyboard button press. The three psychophysical discrimination tasks were:

1. Translating dot motion: The stimulus was a random dot kinematogram (RDK) composed of white and black dots within a 5 dva circular aperture, at a density of 1 dot/deg^2. Dot velocity was 10 deg./second with a lifetime of 100 ms. The direction of motion was either left or right.
2. Drifting grating motion: The stimulus was a drifting grating composed of a Gabor patch with a spatial frequency of 1 cycle/deg. and a temporal frequency of 10 cycles/deg. The size of the Gabor patch was 5 dva. The direction of motion was either left or right.
3. Static orientation: The stimulus was a static grating composed of a Gabor patch with a spatial frequency of 1 cycle/deg. The size of the Gabor patch was 5 dva. The orientation was either vertical or horizontal.

The starting coherence and contrast levels for all stimuli were set to 50%. The coherence/contrast level for each subsequent trial was set using a standard 2-down-1-up adaptive staircase procedure (Leek, 2001).

2.4 Training stimuli and procedure

Once the baseline measures were taken, the participant was made familiar with the training task and started training at home. Training was facilitated by a Web based training platform (Article 19 Group, Montreal) that displayed the stimulus and stored the responses from the participant. The platform allowed for remote monitoring of response data, as well as experimenter-controlled adjustment of the task type, stimulus size, stimulus location, and other parameters.

The training task was an optic flow motion discrimination task (Awada et al., 2022; Elshout et al., 2018). The stimulus was an RDK composed of black dots (0.06 dva) in a 5 dva circular aperture presented against a gray background. Black dots on a gray background were used in order to prevent luminance artifacts that could be specific to the stimulus and detectable in the seeing field. Dot velocity was set to 20 deg./second, and lifetime was 250 ms. Coherence was 100%.

Each trial started with a fixation point on the center of the screen. Following fixation for 500 ms, a stimulus appeared for 500 ms, during which the dots in the RDK underwent either expansion or contraction, both relative to a single point at the center of the stimulus aperture. During the stimulus presentation, dots were added and removed constantly, so that the stimulus density was unchanged through time and between stimulus types. After the stimulus presentation, the participant was asked to indicate the direction of motion (contraction/expansion) using the keyboard or a mouse. Feedback was provided, in the form of a green screen for correct responses and red screen for incorrect responses. The percentage of correct of responses was used as a measure of performance. After performance reached 80% at one location, new locations were selected for further training (Fig. 1A).

Each training session consisted of 500 trials, and a break was provided after every 50 trials. Each session lasted 1-2 hours. The training spanned a total of 4 months with a total of 89 sessions.

2.5 Eye movement control

To ensure compliance with eye fixation, 11 training sessions were done in the laboratory with closed-loop monitoring of eye movement. This was accomplished by a second computer which transmitted eye movement data to the stimulus platform, so that trials could be interrupted if the patient broke fixation. On these trials, a warning message was displayed to the patient, and the data were discarded. This procedure appeared to be effective in enforcing fixation, as performance in the laboratory (11) and at-home sessions (43) did not differ statistically (Wilcoxon rank sum test, Z=0.97, p=0.33).

2.6 Post-training measures

Following completion of the 4-month training, the psychophysical tests mentioned above (*Pre-training assessment*) were repeated. Humphrey perimetry was unavailable because of COVID-19 restrictions in force at that time.

2.7 Follow-up measures

Twelve months after the training ended, the participant was tested in the laboratory, to evaluate the retention of training effects. We repeated the Humphrey perimetry test, as well as the training paradigm and the psychophysical measures obtained before and after training.

Changes in visual sensitivity were computed as the difference between the Humphrey visual fields (HVFs) obtained before and after training. As in previous work (Awada et al., 2022), we normalized these differences relative to differences across the seeing field, the assumption being that changes in the seeing field were primarily due to randomness or due to improved familiarity with the task. Each location's sensitivity difference (z) was therefore quantified as the change in sensitivity at that location (ΔdB) relative to the mean of the sensitivity difference across the seeing field locations (μ), normalized by the corresponding standard deviation (σ):

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

The area of decrease in the blind field was calculated by computing the area represented by individual probe locations and multiplying that by the number of locations where improvement was observed with 99% confidence (z-score > 2.58).

3. Results

3.1 Fast vision rehabilitation in a pediatric patient

The patient was an 18-year-old male with an extensive homonymous visual field deficit, as a consequence of a hypoxic injury suffered during birth. Figure 1A shows the Humphrey perimetry for this patient, which indicates a notable scotoma covering most of the upper-left visual field quadrant, as well as portions of the lower-left visual field. We targeted these regions for rehabilitation with vision training.

As in previous work (Awada et al., 2022; Das et al., 2014; Huxlin et al., 2009), the training protocol began with a motion stimulus placed in a blind field location adjacent to the border of the seeing field (Fig. 1A; colored numbers depict training locations chronologically). The stimulus consisted of a field of dots moving in such a way as to simulate expansion or contraction from a fixed point. This *optic flow* stimulus is known to target high-level visual cortex (Duffy & Wurtz, 1991; Graziano et al., 1994; Mineault et al., 2012; Tanaka & Saito, 1989). The patient had to indicate with a button press which of the two stimuli was presented on each trial. To avoid eye movement compensation effects, the patient was required to fixate near the center of the computer screen, and high-resolution eye tracking was employed on a subset of the sessions to ensure compliance.

As expected, the patient's performance started at chance level (50%) (Fig. 1C, location 1 at (-5, 5) dva, shown in cyan). Over the course of a few days of training, performance rapidly increased, reaching 80% after just 11 days. When the performance stabilized at above 80% performance, the stimulus was displaced by 3 dva rightward and 2 dva downward to location 2 at (-2,3) dva. Performance then dropped to chance level, but after only 7 training sessions at the new location, it again reached the 80% level (Fig. 1C). We then moved the stimulus back to location 1 to check for the retention of the training effect. The performance at location 1 now started at 77%, showing that the perceptual improvement had been sustained. After training for

25 sessions, we moved the stimulus back to location 2 and verified over the course of 5 sessions that performance was sustained between 75-90% at these locations.

3.2 Generalization of training effects across spatial locations

To test the generalization of perceptual improvements across retinotopic space, we moved the location of the training stimulus to three locations that had not previously been trained. One of these was in the lower quadrant, at the border of the blind field (Fig. 1C: location 3 at (-5,-5) dva, shown in gray), and the others were deeper into the upper portion of the blind field (location 4 at (-8,5), maroon and location 5 at (-14,8) dva, red). At all three locations, the patient's performance started at near 80% accuracy and remained stable across multiple sessions (Fig. 1B), indicating that vision rehabilitation had generalized across distant retinotopic locations.

3.3 Generalization of training effects across stimuli features

Following the completion of training, we tested the generalization of performance improvements across stimulus features, using several psychophysical tests at one of the training locations (location 1, cyan). The tests involved three stimulus types for which the patient had not received training: 1) translating dots, in which all dots move in the same direction; 2) drifting gratings, in which a grating pattern moves in a single direction, and 3) static orientation discrimination, in which the subject indicates whether a grating is horizontal or vertical. Discrimination of these stimuli is thought to rely on different brain mechanisms (Das et al., 2014; Liu & Pack, 2017), and so they serve as a measure of the generalization of learning.

The patient's performance was near chance levels for all three stimulus types before optic flow training (translating dots: 62%, drifting gratings: 58% and static orientation discrimination:42%) (Fig 2B top, location 1: light cyan), and the corresponding psychophysical thresholds were high (translating dots: 0.99, drifting gratings: 0.98 and static orientation discrimination: 0.99) (Fig 2 bottom, location 1: light cyan 'pre'). After 4 months of optic flow training, performance increased to 79.5% accuracy for translating dots, 60.5% for drifting gratings and 70.5% for static orientation discrimination (Fig 2B, top ‘post’), with corresponding decreases in thresholds (Fig 2B, bottom). These results indicate that the effects of training on optic flow motion transferred to other motion discrimination tasks and to shape discrimination.

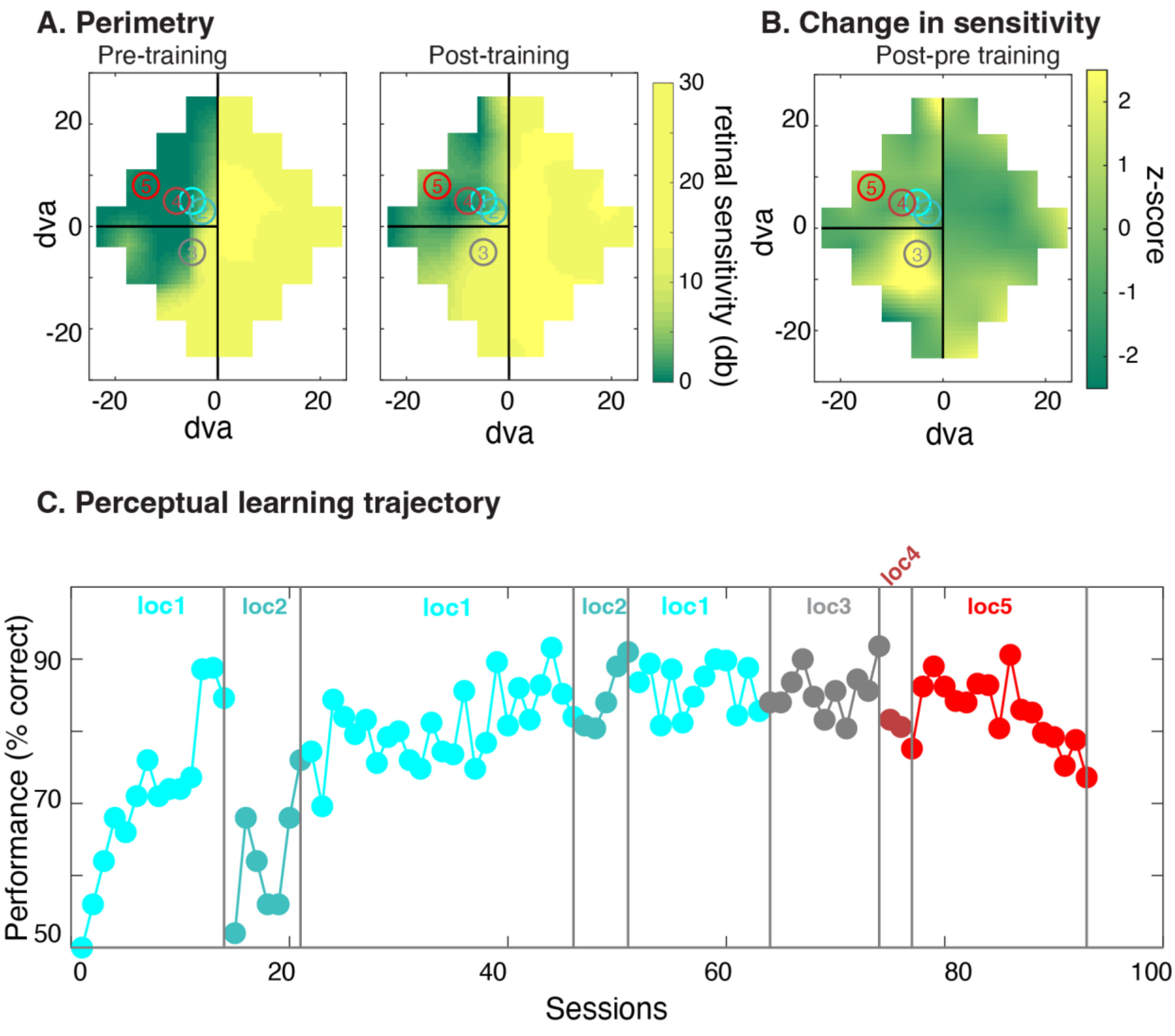

Figure 1 A. HFVs before (left) and after (right) visual training, with circles indicating the size and location of training stimuli. B. Difference in visual sensitivity between pre- and post-training HFV perimetry averaged over both eyes. Colors represent z-score values, with yellow colors indicating significant increases in z-scores (z-score>2.58 or higher than 2 standard deviation from the mean test-retest variability). C. Performance changes for optic flow stimuli located at various positions in the blind field.

3.4 Long-term retention of perceptual learning

To test the retention of training effects in the blind field, the patient was retested on the optic flow discrimination task more than 12 months after the initial training had ended. Fig. 2A shows that high performance was retained at the location where the patient was most extensively trained (location 2 shown in dark cyan). At other locations, (locations 4 and 5 shown in maroon, red), where the patient had initially shown a transfer of learning, the performance dropped to near-chance level: 58% and 47% respectively, 12 months post-training (Fig 2A). One exception was location 3 (Fig2A, gray), located at the border of the seeing field, where transfer was retained 12 months after training, with performance being at 95%. Thus, it appears that long-term retention of rehabilitation effects is possible, with sufficient practice.

3.5 Long-term retention of generalization

To test the durability of stimulus generalization effects, the battery of psychophysical tests was performed 12 months after the training had been completed. These tests were again performed at location 1, where the patient had undergone the most extensive training. The results showed that performance for all three psychophysical tests remained well above chance (Fig 2B, loc1: light cyan, 'post12'): 77% accuracy for translating dots, 63.5% for drifting gratings and 81% for static orientation discrimination. Thus, the general improvements in visual function observed immediately after training were retained after 12 months.

To determine whether the long-lasting improvements generalized across spatial positions, we examined psychophysical performance in the other 4 locations depicted in Figure 2A. Although we collected this dataset in only one session (12 months after training ended), affording only a single data point for each of the 4 locations, the pattern of performance was similar to that for the training stimulus: Performance improvements were retained at the location where the patient was extensively trained (locations 1 and 2 shown in light and dark cyan) and at the border of the seeing field (location 3, gray), but performance fell to near-chance at locations deeper in the blind field (locations 4 and 5 shown in maroon, red).

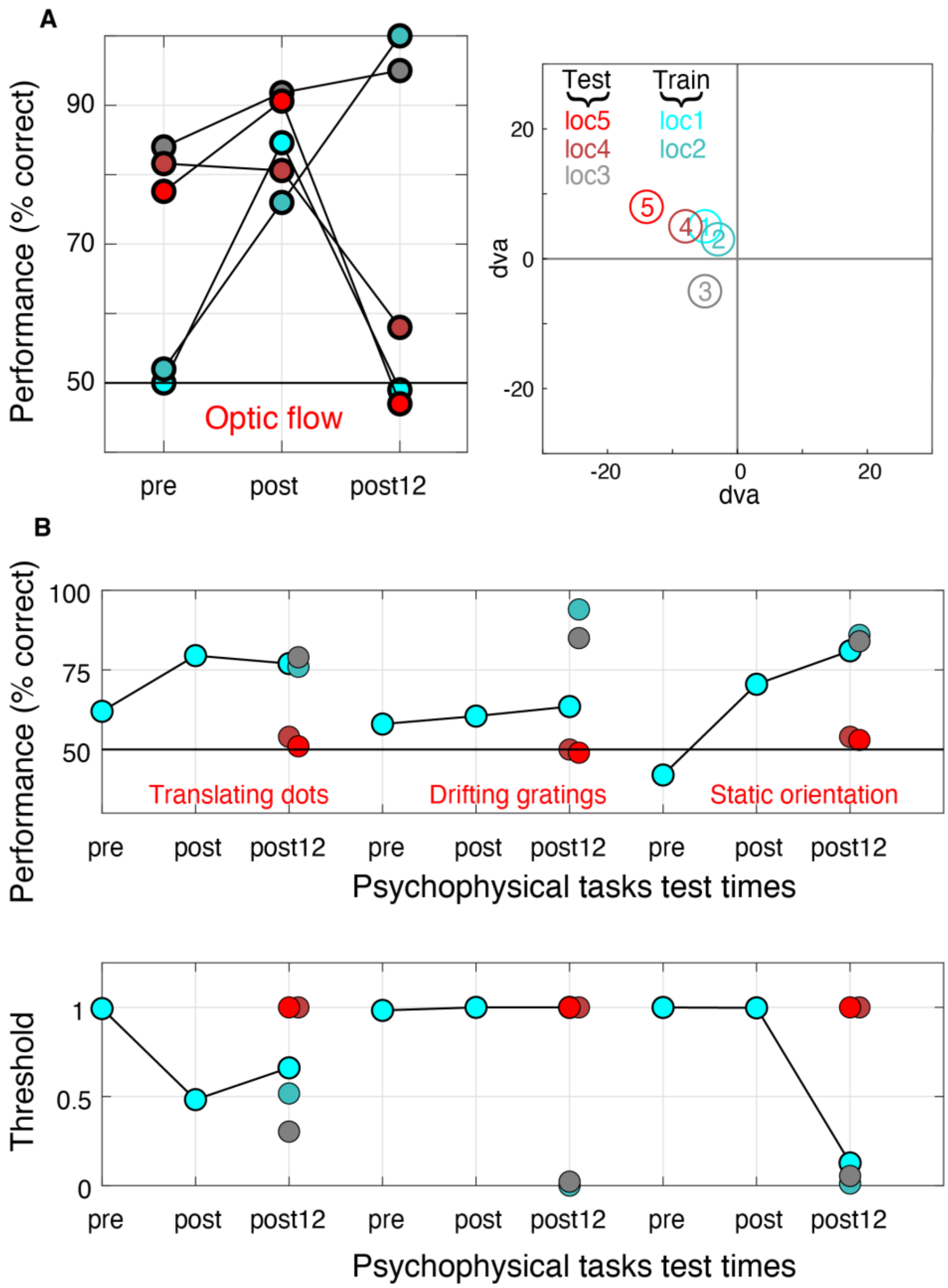

Figure 2 A. Training task performance at three different time points (left) relative to the training protocol for stimuli at different locations depicted in the right panel. Pre: beginning of training, post: end of the training, post12: 12 months after the end of training. B. Performance (top) and detection threshold (bottom) for three separate visual psychophysical tests (translating dots, drifting gratings and static orientation discrimination) measured at the same three time points relative to the training protocol.

3.6 Long-term recovery of visual sensitivity

To test the effects of training on visual sensitivity, we compared the Humphrey Visual Field perimetry obtained before training to that obtained one year after completion of training. Fig 1A (right) shows improved visual sensitivity in the blind field at the one-year follow-up, relative to the pre-training baseline (Fig. 1A, left). We classified probe locations as being in the blind field if the HVF metric of pattern deviation was lower than -6db at that location (Cavanaugh & Huxlin, 2017). Based on this, the pre-training size of the blind field was 1012 deg^2 (34% of the total 3000 deg^2 of probed visual field).

To quantify any improvement in visual sensitivity, we reasoned that some of the changes were likely due to some combination of random variability and improved comprehension of the task, rather than genuine increases in sensitivity. We therefore normalized the changes in sensitivity in the blind field by the variability of the changes across the *seeing* field, to isolate genuine changes in sensitivity in the blind field (Awada et al., 2022; see Methods). Fig 1B shows the distribution of these blind field effects, highlighting increased sensitivity close to and beyond the trained locations.

Based on the number of probe locations that showed significant increases in sensitivity (z-score > 2.58 or alpha < 0.0001), the total area of the blind field shrunk by 112.5 deg^2 with training. The average change in sensitivity in these blind field areas was 12.66+-.75 db, whereas the overall change in sensitivity in the seeing field was 2.55+-2.8 db. The biggest change in sensitivity was near the edge of the training locations and at the border of the blind field. This localized pattern of improvement in visual sensitivity at the border of blind field is similar to the previous reports of improved sensitivity in adult CVI patients trained with motion stimuli (Cavanaugh & Huxlin, 2017).

3.7 Effects of eye movements

Patients with CVI often learn to compensate for visual field deficits by making eye movements that bring the seeing field to the location of relevant stimuli. To ensure that the results reported here were not due to such compensatory strategies, we used high-resolution eye tracking to measure the eye position and its deviation from the fixation point during the tasks.

The average eye position during the pre-training baseline and the post-training test was 0.13+-0.89 and 0.17+-0.90 dva in the x-direction and -1.22+-0.59 and -0.44+-0.96 dva in the y-direction. On average, the participant fixated 0.52 dva closer to the fixation point (away from the stimulus) in the post-training test compared to the pre-training baseline. These results are therefore inconsistent with an explanation in terms of altered eye movement strategies.

4. Discussion

4.1 Summary

This study provides a proof of concept that vision rehabilitation paradigms that have previously been used successfully in adults can also be applied effectively in pediatric patients. The patient in our study had a pronounced homonymous visual field defect that had been stable for many years before training began (Figure 1). In the absence of any intervention, such patients seldom show any improvements in visual sensitivity (Cavanaugh & Huxlin, 2017).

Our results indicate that training with complex motion stimuli produced rapid improvement in visual sensitivity and perceptual performance in the blind field of this patient. The training-induced improvement generalized to untrained locations and to untrained stimulus features, and some of these improvements proved to be durable for at least one year after the completion of training (Figure 2). We therefore suggest that training with complex motion stimuli could be a straightforward and effective treatment for the large population of children suffering from cortical visual impairment.

4.2 Comparison with previous work

Previous studies of visual rehabilitation in pediatric cases have yielded promising results (Lueck et al., 1999; Malkowicz et al., 2006), with one case study reporting fast recovery (5-7 days) (Tsai et al., 2013). However, none of these studies used a rigorous, quantitative metric of visual improvement, and none tracked the patients' eyes with high precision. Eye tracking is important, because changes in eye movement strategies can easily be mistaken for restored visual function.

Another limitation of previous studies is the use of simple stimuli (flashes of light) (Malkowicz et al., 2006) or uncontrolled stimuli (hand-held toys or drawings) (Lueck et al., 1999) for training. A growing literature indicates that plasticity in the visual cortex is highly dependent on the stimuli used during training and that complex stimuli are better for achieving greater generalization and more effective engagement with high-level cortex (Awada et al., 2022; Bakhtiari et al., 2020; Das et al., 2014; Liu & Pack, 2017). While these factors are becoming common in vision restoration paradigms for adult patients, they have not to our knowledge been used in previous studies with pediatric patients.

4.3 Limitations of the present work

Of course, the results presented here are based on a single case study, and it will be important to extend them to larger populations. It will also be important to evaluate whether the same treatment is effective for patients whose CVI results from other causes, such as infection or traumatic brain injury.

For patients who do undergo the training, the requirement for fixation and attentiveness in our paradigm might prove challenging, especially for younger children or for those with physical or cognitive impairments. Thus, an additional goal of future research should be to investigate paradigms that deliver similar visual stimulation without the need for precise behavioral control. Video games might be promising in this regard (Chopin et al., 2019), particularly if they could be distributed in clinics or hospital settings. Our results on the decrease of generalization effects with time suggest that it will be important to make maintenance treatments available for home use as well.

5. Conclusion

In conclusion, there is a high prevalence of cases of children with CVI, particularly in low-income countries (Sahli et al., 2022). This is an important problem for which a satisfactory solution has not been found (Ben Itzhak et al., 2022). Our results suggest that one aspect of rehabilitation could be training with complex motion stimuli, which, for the patient in this study, promoted fast, robust, and durable recovery.

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