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# Treatment of children with amblyopia by perceptual learning

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ABSTRACT

Recent studies have shown that perceptual learning has the potential to treat amblyopia. In this study we tested whether a recent perceptual learning technique that improved visual functions in adults can be applied to improve the vision of children after the conventional treatment of patching has failed. A prospective clinical pilot study was carried out in children who were non-compliant with patching or in whom patching had failed despite good compliance. Each child underwent a complete eye examination before and after treatment. The treatment was based on a perceptual learning technique that was similar to the adult study [Polat, U., Ma-Naim, T., Belkin, M., & Sagi, D. (2004). Improving vision in adult amblyopia by perceptual learning. *Proceedings of the National Academy of Sciences of the United States of America, 101*(17), 6692–6697]. Between blocks, children played a computer game to engage and maintain their attention in order to increase compliance. Each child received two treatment sessions a week, with a total of not more than 40 sessions. Each session lasted for about 1 h and included a total practice time of about 30 min. The age of the children ($n = 5$) was between 7 and 8 years (mean 7.3 years). For the whole group, the average improvement in visual acuity was 1.5 Snellen lines or 2.12 ETDRS lines. The training improved the contrast sensitivity, which reached the normal range after treatment. Thus, the perceptual learning technique can be successfully used to treat children with amblyopia even after the conventional treatment of patching fails.



## 1. Introduction

Amblyopia is the main cause of poor unilateral vision in children, accounting for more than all other causes combined (Attebo et al., 1998; Greenwald & Parks, 1999). It occurs in 2–4% of the North American population (Attebo et al., 1998; Greenwald & Parks, 1999). Amblyopia is characterized by several functional abnormalities in spatial vision (for reviews, see Ciuffreda, Levi, & Selenow, 1991; Hess, Field, & Watt, 1990; Levi, 1991; Levi & Carkeet, 1993), including reduced visual acuity (VA), contrast sensitivity function (CSF), vernier acuity, as well as spatial distortion (Sireteanu, Lagreze, & Constantinescu, 1993), abnormal spatial interactions (Bonneh, Sagi, & Polat, 2004, 2007; Levi, Hariharan, & Klein, 2002; Polat, Bonneh, Ma-Naim, Belkin, & Sagi, 2005; Polat, Ma-Naim, Belkin, & Sagi, 2004; Polat, Sagi, & Norcia, 1997), and impaired contour detection (Hess & Dakin, 1997; Kovacs, Polat, Pennefather, Chandna, & Norcia, 2000). In addition, amblyopic individuals suffer from binocular abnormalities such as impaired stereoacuity and abnormal binocular summation. It was shown that the degree of binocular imbalance strongly influences the depth of amblyopia.

Visual deficiencies are thought to be irreversible after the first decade of life (Greenwald & Parks, 1999; Prieto-Diaz & Souza-Dias, 2000), by which time the critical time for normal development of the visual function has been terminated. The loss of vision is thought to result from abnormal operation of the neuronal network within the primary visual cortex, particularly of orientation-selective neurons and their interactions (Polat, 1999). Traditional amblyopia treatment is based on depriving the "good" eye while optimizing the visual experience of the amblyopic eye. The conventional treatment includes correction of any significant refractive error, elimination of any treatable opacity of the media, and forcing fixation with the amblyopic eye, mainly by occlusion (for a recent review, see Greenwald & Parks, 1999; Prieto-Diaz & Souza-Dias, 2000). Occlusion (patching) of the preferred eye has long been a mainstay of amblyopia therapy, dating back to the 18th century (De Buffon, 1743) and is generally effective. However, it has some disadvantages, including problems of a social or emotional nature, as well as skin irritation and other problems that might affect compliance. Compliance is therefore a major factor in determining the successful outcome of amblyopia treatment (Oliver, Neumann, Chaimovitch, Gotesman, & Shimshoni, 1986; Rahi, Logan, Timms, Russell-Eggitt, & Taylor, 2002). Another method, known as penalization, uses atropine given once a day to eliminate accommodation in the "good" eye. It causes a blurry image in the good eye, thus forcing the amblyopic eye to function. Penalization was found to be an effective method of treatment (Repka & Ray, 1993; Simons, 2005;

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Simons, Stein, Sener, Vitale, & Guyton, 1997). In severe cases of amblyopia, penalization is not practical and is rarely used since it may not be able to degrade the vision in the preferred eye sufficiently to induce the patient to fixate with the amblyopic eye. Both treatment modalities carry the risk of developing iatrogenic occlusion amblyopia.

Perceptual learning is known to improve the performance of a wide range of simple visual tasks acquired by practice (Fahle & Poggio, 2002; Gilbert, 1998; Gilbert, Sigman, & Crist, 2001; Sagi & Tanne, 1994). Research on perceptual learning indicates that practice can result in improvement of many visual tasks in adults, including visual detection or discrimination of orientation, Vernier offset, stereo information, and contrast sensitivity function (Gilbert, 1998; Gilbert et al., 2001; Sagi & Tanne, 1994; Sowden, Rose, & Davies, 2002). Improvements are often specific to stimulus properties such as orientation, location in the visual field, spatial frequency, and eye of origin. These findings have been taken as strong evidence that learning is based on the plasticity of mechanisms early in the visual processing stream, and that the modification takes place at early cortical stages, such as V1 (Crist, Li, & Gilbert, 2001).

Perceptual learning can indeed modify visual functions in amblyopia. This was first shown by improvement of vernier acuity in adults with amblyopia (Levi & Polat, 1996; Levi, Polat, & Hu, 1997). The training was followed by improvement of visual acuity in some observers (two out of the six novice observers). In our previous study (Polat, 2006, 2008; Polat et al., 2004), a technique based on perceptual learning was used to treat amblyopia in 77 adults (treatment group). The ages of the patients ranged from 9 to 55 years. The training induced improvement in a few visual functions. The mean improvement (±SE) in best corrected visual acuity (BCVA) was 2.5 ± 0.2 ETDRS lines in the treatment group; no improvement was noted in the control placebo group ($n = 10$). A significant improvement was found in the contrast sensitivity function as well. The improvement was found to be not related to the age of the patients. Improvement of visual functions was also demonstrated in anisometropic adults after they had undergone training on contrast detection tasks (Huang, Zhou, & Lu, 2008; Zhou et al., 2006).

Since the conventional treatment was given to children up to the age of 6–9 (Greenwald & Parks, 1999; Levi & Li, 2009), the above studies of Polat and colleagues did not train patients younger than 9 years old. A recent study used perceptual learning in younger amblyopes (Li, Provost, & Levi, 2007; Li, Young, Hoenig, & Levi, 2005). Five children (age range: 7–10 years) with amblyopia practiced a positional acuity task. Four of the five observers showed a significant improvement in positional acuity of about 30%. All five observers displayed substantial improvement in Snellen acuity (approximately 26%) after practice. A more recent study (Chen, Chen, Fu, Chien, & Lu, 2008) compared the effects of perceptual learning or patching on improvement of visual acuity and contrast sensitivity only in patients with anisometropic amblyopia (ages up to 18 years old). The mean visual acuities of the amblyopic eyes improved similarly with perceptual learning and with patching (0.25 vs. 0.34 logMAR). In this study, like that of Polat et al. (2004), similar effects of improvement were found among the age groups.

Since our technique of perceptual learning was found to be very effective for adults (Levi & Li, 2009; Polat et al., 2004), the purpose of the present study was to evaluate whether the technique is effective for the treatment of both strabismic and anisometropic amblyopia, in children aged between 6 and 9 years, who had already undergone treatment with patching but were non-compliant with the treatment or in whom patching failed despite good compliance.

## 2. Subjects and methods

The parents of children who had visited the pediatric outpatient clinic, and who met the inclusion criteria, were invited to enroll their children in this IRB-approved prospective clinical pilot study. Inclusion criteria were ages between 6 and 9 years, a diagnosis of unilateral strabismic or anisometropic amblyopia or both, a baseline BCVA (Snellen) between 6/12 and 6/30, no other eye pathologies, and a history of non-compliance with patching or failure to benefit from patching despite good compliance.

Before starting and upon completing treatment, each child underwent an eye examination that included evaluation of BCVA (Snellen), ocular alignment with a prism and cover test, ocular movements, binocular functions (Worth 4-dot, random-dot stereo test), slit lamp biomicroscopy, cycloplegic refraction, and an examination of dilated fundus. Refractive errors were corrected in order to achieve the BCVA with spectacles.

Clinical evaluations were performed by same pediatric ophthalmologist, optometrist, and orthoptist, independently of the treatment. BCVA was tested in the setting of the institute's busy outpatient pediatric ophthalmology clinic by the same optometrist who was not informed that our patients were participating in a study.

CSF was measured at baseline and after the treatment using a wall-mounted chart (Ginsburg, 1984) (S.W.C.T., Stereo Optical Co.) from a distance of 3 m with controlled room lighting ($\sim$140 cd/m$^2$, within the range of 68–240 cd/m$^2$ specified by the manufacturer). These grating stimuli subtended a visual angle of 1.4° at all frequencies.

Each child was treated by a technique based on perceptual learning (Polat et al., 2004). The training task, between training blocks, was interleaved with a video game to engage and maintain the child's attention in order to increase compliance.

The stimuli used for treatment were local gray level gratings, a Gabor patch (GP), with spatial frequencies of 1.5–12 cycles per degree (cpd) modulated from a background luminance of 40 cd m$^{-2}$ (Fig. 1). In all experiments the standard deviation ($\sigma$) of the GP was equal to the wavelength ($\lambda$, $\sigma = \lambda$). Stimuli were presented on a Philips multiscan 107P color monitor, using a PC system. The effective size of the monitor screen was 24 × 32 cm, which at a viewing distance of 1.5 m subtends a visual angle of 9 × 12°. The children were treated in a dark cubicle, where the only ambient light came from the display screen.

Contrast threshold was measured by a procedure in which the child was required to choose between two alternatives (2AFC). The target was presented in one of two images, each lasting 160–320 ms, at an interval of 500 ms. The default duration was 160 ms, but it was increased up to 320 ms when the contrast

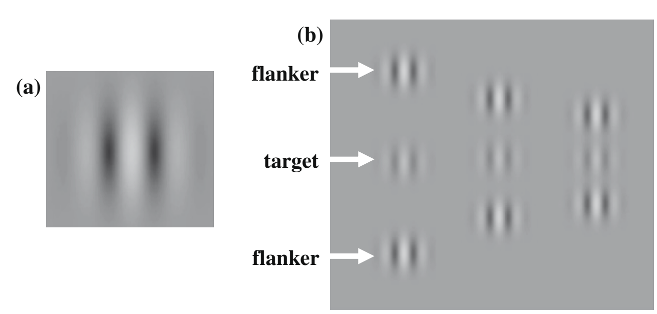


**Fig. 1.** Example of stimuli used in this study: (a) the Gabor patch (GP) – localized gratings with the luminance profile computed as a multiplication of cosine and Gaussian functions. (b) Three configurations of target and flankers used in the lateral interaction experiments with varying target–flanker separations.

threshold was too high. The child, seated 1.5 m from the screen and wearing the best optical correction with the non-amblyopic eye occluded, was required to detect the target, which was shown in only one of the two presentations. A visible fixation circle indicated the location of the target between presentations. Subjects activated the presentation of each pair of images at their own pace. They were informed of a wrong answer by auditory feedback after each pair of presentations.

A standard training session included a contrast detection task of GP (Fig. 1), with and without two similar flanking collinear high-contrast GPs. At each session, the training consisted of one block of contrast detection of the target alone and six blocks when the target was embedded between two collinear flankers, separated at distances between 1 and 9$\lambda$ (Fig. 1). Thresholds for the contrast detection task were measured with a one-up/three-down staircase, with steps of 0.1 log-units, which was used to estimate the stimulus strength at the 79% accuracy level. Over the treatment period, the stimuli were gradually changed from lower to higher spatial frequencies, with four orientations at each size. Patients attended two or three treatment sessions a week, each lasting approximately 1 h including the game, of which half was net practice. The first two sessions were spent measuring basic spatial functions such as contrast sensitivity and performance on spatial interactions, the latter representing degrees of cortical lateral suppression and lateral facilitation. Subsequent sessions were individually designed according to the performance in the previous session. No other treatment was given between the sessions. An assistant helped to ensure that the child understood the tasks and followed the instructions correctly. We used an adaptive procedure (staircase) and therefore the number of trials per block was not constant. In general, the average number of trials was between 40 and 50 per block, multiplied by seven blocks per session, resulting in about 300 trials per session. After 40 sessions, the total number of trials was about 12,000.

## 3. Results

Five children were included in this pilot study. The ages of the included children ranged from 7 to 8 years, with a mean age of 7.3 years. The average number of sessions per patient was 34. The initial VA and clinical details are presented in Table 1.

The CSF of each child was measured using a standard contrast sensitivity chart (Ginsburg, 1984) before and after training (Fig. 2). The CSF showed higher thresholds (lower sensitivity) than those obtained by normal-sighted subjects (gray zone), whereas the low spatial frequencies were within the range of normal and the high spatial frequencies exhibited a strong loss in sensitivity.

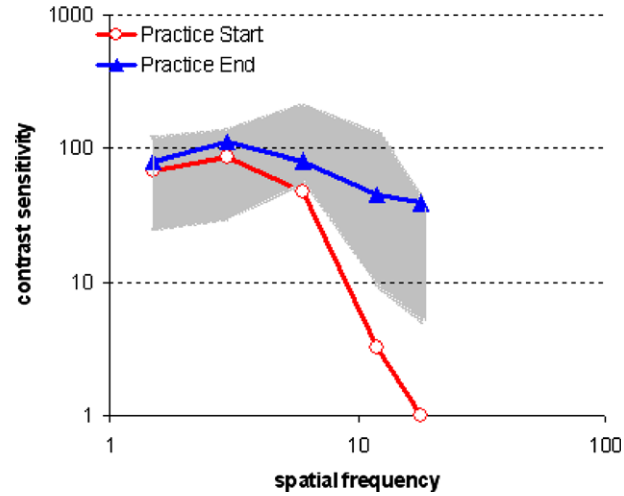


**Fig. 2.** Contrast sensitivity functions (CSF). CSF for the children ($N = 5$), before (open squares) and after training (filled triangles). The gray shaded area indicates the distribution of CSF of normal subjects. Before training, the spatial frequencies of 9, 12, and 18 cpd were reduced. Sensitivity improved remarkably across these frequencies, reaching normal performance (gray shaded area) for all spatial frequencies tested.

Training resulted in remarkable improvement in sensitivity at the high spatial frequencies, which improved to within the normal range (Fig. 2). The improvement of CSF before and after training is significant (*t-test*, $P = 0.0047$).

Fig. 3 presents group VA scores taken at intervals of four training sessions, for two treatment groups of adults ($N = 44$ and 23) from the previous studies and children for comparison ($N = 5$). The VA was measured at the laboratory on one of three ETDRS charts that was changed randomly by a masked optometrist. The performance is documented in terms of the gain in VA relative to the initial VA. The average at each data point is unequal since one child performed only 20 sessions, two performed 32 sessions, and the others performed 40 sessions. The average improvement in all subjects after training was 2.12 ETDRS lines. The training resulted in rapid improvement of about 1.3 lines during the first eight sessions, followed by a slower learning rate, reaching a gain of about 2.5 ETDRS lines after 40 training sessions. (Note that only two children were measured at this data point.) Thus, the overall pace of learning seems to be similar across the three groups.

The visual acuity on the Snellen chart and binocular functions were tested, before and after treatment, by an independent optometrist who was masked and unaware of the treatment at a busy

**Table 1**
Visual acuity (Snellen) before and after treatment, based on a perceptual learning technique.

| Patients | Age | Amblyopia type | Objective refraction amblyopic eye | | | Objective refraction sound eye | | |
|---|---|---|---|---|---|---|---|---|
| | | | Sph | Cyl | Axis | Sph | Cyl | Axis |
| IRO | 8 | Anisometropia | +8.0 | −1.00 | 180 | +1.5 | | |
| LMI | 7 | Anisometropia | +6.0 | −0.75 | 180 | +2.0 | −0.50 | 180 |
| GDE | 7 | Anisometropia + Estropia | −8.00 | −1.00 | 120 | −5.00 | −1.00 | 65 |
| TRO | 8 | Estropia | +3.25 | | | +3.25 | | |
| GNE | 7 | Anisometropia | −5.75 | −2.00 | 175 | −1.75 | −2.00 | 175 |

| | BCVA before treatment | | BCVA after treatment | |
|---|---|---|---|---|
| | Snellen | ETDRS | Snellen | ETDRS |
| IRO | 6/30 | 0.7 | 6/18 | 0.44 |
| LMI | 6/18 | 0.4 | 6/15 | 0.18 |
| GDE | 6/15 − 1 | 0.54 | 6/12 + 2 | 0.46 |
| TRO | 6/12 − 3 | 0.54 | 6/10 − 3 | 0.28 |
| GNE | 6/12 | 0.32 | 6/9 | 0.1 |

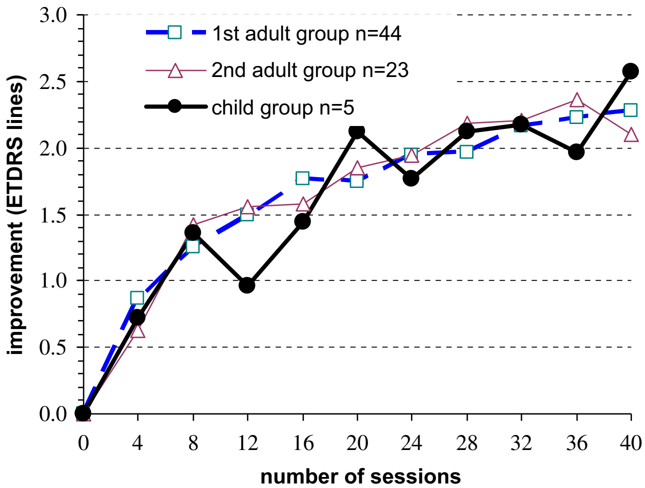


**Fig. 3.** Learning curves. VA learning curves, group data from two adult groups ($N$ = 44 and 23) and child group ($N$ = 5, solid line, filled circles). A relatively rapid improvement in VA during the first eight sessions was followed by a phase of slower learning. Learning seems to occur at the same rate for the adults and children. The last testing session, after 40 sessions: only two children were tested, resulting in a slightly higher average at that point.

outpatient clinic at the hospital. Before treatment, BCVA ranged from 6/30 to 6/12 and it decreased to 6/18 to 6/9 after treatment. Over the whole group, the mean BCVA improved by 1.5 lines (Snellen). The amount of improvement on the Snellen chart was slightly lower than the improvement measured on the ETDRS chart, possibly due to the different amount of crowding in the Snellen Charts compared with equal crowding in the ETDRS chart. Moreover, less time is available for testing the children in the hospital. Thus, the final score may not reflect their full improvement.

One child (TRO) showed improvement in ocular alignment. Before treatment, he had esophoria of 10 prism diopters and after treatment he was orthophoric. Binocular functions improved in two patients. TRO improved in the random-dot test from 400 to 25″ and in the Worth 4-dot test, from a suppressive response at the baseline examination to fusion at the end of treatment. The other patient (GDE), the result of Worth 4-dot test changed from a suppressive response to diplopia. No adverse side effects were noted in any of the treated patients. The improvement in binocular functions is probably due to reduced perceptual differences between the two eyes. Improvement in the visual functions may lead to diminishing the suppression on the amblyopic eye, caused by the good eye. Suppression of the amblyopic eye is considered to be one of the main causes of amblyopia, and reducing the amount of suppression is expected to diminish the likelihood of recurrent amblyopia, thus with the prospect of improved vision.

## 4. Discussion

The five children in this pilot study (mean age 7.3 years) had been diagnosed with strabismic or anisometropic amblyopia or both. Either they had been non-compliant with patching or patching had failed despite good compliance. The results showed that treatment based on perceptual learning was successful in improving visual acuity even more than patching in this group of amblyopic children. It has been suggested that perceptual learning might be an effective tool for treatment of amblyopia (Chen et al., 2008; Levi & Li, 2009; Levi & Polat, 1996; Levi et al., 1997; Li et al., 2005; Polat et al., 2004). The results of this study show that about 40 h of perceptual learning might be even more effective than patching per se that reached saturation, probably due to lack of compliance or lack of an interactive task during the patching. This result is consistent with the comparison made by Levi and Li (2009) between patching and perceptual learning. They showed that about 20 h of perceptual learning in adults (Polat et al., 2004) is equal to about 500 h of patching.

Recent evidence from studies in the cat and the monkey (Kapadia, Ito, Gilbert, & Westheimer, 1995; Levitt & Lund, 1997; Polat, Mizobe, Pettet, Kasamatsu, & Norcia, 1998; Sengpiel, Baddeley, Freeman, Harrad, & Blakemore, 1998; Sillito, Grieve, Jones, Cudeiro, & Davis, 1995) shows that neuronal responses in the primary visual cortex are modulated by remote image parts (neuronal interactions), with both excitatory and inhibitory effects observed, depending on stimulus contrast and configuration. Psychophysical and electrophysiological results show abnormal interactions in amblyopia (Bonneh et al., 2004, 2007; Ellemberg, Hess, & Arsenault, 2002; Levi et al., 2002; Polat et al., 1997, 2004, 2005; Wong, Levi, & McGraw, 2005) and with an absence of facilitation and an extended range of lateral inhibition. It is possible that an abnormal visual input to the amblyopic eye during early development produces distorted patterns of activity in the visual cortex, leading to abnormal development of connectivity and interactions in the amblyopic visual system.

Previous studies (Huang et al., 2008; Polat, 2008; Polat et al., 2004; Zhou et al., 2006) have shown that perceptual learning improves performance in visual acuity (letters), a task that is very different (contrast detection) from the one for which the subjects were trained on stimuli (GPs). This transfer between different visual tasks might result from the practiced stimulus set, which was multi-dimensional. As such, apparently its effect was to improve the early processing of the visual system and consequently all higher levels of processing that depend on the quality of low-level visual representation. In addition, transfer of the improvement to non-practiced tasks (e.g. visual acuity) excludes the possibility of improvement owing to a general "practice" effect of the trained task. Our results are consistent with previous studies in adults (Huang et al., 2008; Polat, 2008; Polat et al., 2004; Zhou et al., 2006), which involved transfer between categories such as training on contrast detection and improvement of visual acuity, or in children, (Li et al., 2005), which involved training on spatial alignment and improvement in visual acuity.

The treatment was monocular while the good eye was patched. Nevertheless, there was some improvement in binocular functions, an effect that was also found in the treatment of adults (Polat, 2008). Thus, apparently improvement in the visual functions of the amblyopic eye might enable cooperative interactions of the normal and amblyopic eyes in binocular functions. Our results are consistent with a previous study (Li et al., 2007) showing that after practicing position discrimination, the two observers that had no stereoacuity demonstrated measurable stereopsis after training.

It should be emphasized that the patients in our study group had either not complied with patching or had not shown any improvement with patching. Nevertheless, they improved remarkably by training, using the perceptual learning technique. It is likely that the advantage of perceptual learning is due to an active task that the subject is required to perform whereas the patching is passive. More importantly, perceptual learning involves specifically training spatial frequencies within a range that can be improved (Polat, 2008; Polat et al., 2004), whereas patching involves equally stimulating all spatial frequencies; thus the spatial frequencies with lower sensitivities have no advantages. It is possible, therefore, that the results of treatment might have been better with a less problematic group of amblyopic children. Also, the duration of treatment in our study was limited to 40 sessions. It is possible that a longer period of treatment might yield better results (Levi & Li, 2009; Polat, 2008).

A disadvantage of this treatment method is that it requires the child's full cooperation and at least a minimal degree of concentration. It is also time consuming for the parents, who are required to bring the child to the clinic for the treatment sessions (usually twice or three times a week). Therefore, future techniques for children should be modified and designed to be entertaining, possibly enriched by video games, without losing the effectiveness of the treatment. Nevertheless, this treatment holds promise for treating children with amblyopia when conventional treatment modalities fail.

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