# "Global" visual training and extent of transfer in amblyopic macaque monkeys

## Lynne Kiorpes

## **Paul Mangal**

Perceptual learning is gaining acceptance as a potential treatment for amblyopia in adults and children beyond the critical period. Many perceptual learning paradigms result in very specific improvement that does not generalize beyond the training stimulus, closely related stimuli, or visual field location. To be of use in amblyopia, a less specific effect is needed. To address this problem, we designed a more general training paradigm intended to effect improvement in visual sensitivity across tasks and domains. We used a "global" visual stimulus, random dot motion direction discrimination with 6 training conditions, and tested for posttraining improvement on a motion detection task and 3 spatial domain tasks (contrast sensitivity, Vernier acuity, Glass pattern detection). Four amblyopic macagues practiced the motion discrimination with their amblyopic eye for at least 20,000 trials. All showed improvement, defined as a change of at least a factor of 2, on the trained task. In addition, all animals showed improvements in sensitivity on at least some of the transfer test conditions, mainly the motion detection task; transfer to the spatial domain was inconsistent but best at fine spatial scales. However, the improvement on the transfer tasks was largely not retained at long-term follow-up. Our generalized training approach is promising for amblyopia treatment, but sustaining improved performance may require additional intervention.

# Introduction

Amblyopia is a developmental disorder of vision that affects 3% to 5% of children worldwide (Simons, 2005; Von Noorden, 1980; Wong, 2012). Although classically defined as a loss of visual acuity in one eye in the absence of any organic ocular disorder, it is now known that individuals with amblyopia have a wide range of

Center for Neural Science, New York University, New York, NY, USA

Center for Neural Science, New York University, New York, NY, USA



 $\searrow$ 

deficits from low-level sensitivity loss to more complex, high-order disorders of visual integration and perception (see recent reviews: Birch, 2013; Grant & Moseley, 2011; Hamm, Black, Dai, & Thompson, 2014; Kanonidou, 2011; Kiorpes, 2006; Levi, 2006, 2013). Cataracts (ocular opacities), anisometropia (unequal refractive errors), and strabismus (misalignment of the visual axes), when they exist in early childhood, are the conditions most commonly associated with the development of amblyopia. There is a critical period for the development of amblyopia that extends over about the first 7 years after birth in humans (Daw, 1998; Levi, 2012; Simons, 2005). Until recently, it was presumed that the critical period for treatment was similar to that for amblyopia development. However, it is now clear that visual plasticity continues to some degree beyond the period of normal development and that the critical period for treatment is likely to be different for different visual functions (Kiorpes, 2015). It remains unclear how long the treatment window actually stays open or if indeed it ever closes (see Bavalier, Levi, Li, Dan, & Hensch, 2010; Daw, 1998; Levi, 2005, 2012; Lewis & Maurer, 2005; Mitchell & MacKinnon, 2002).

A type of intervention known as "perceptual learning" has recently emerged as a promising alternative to patching therapy, the mainstay of amblyopia treatment (see Astle, McGraw, & Webb, 2011; Levi, 2005, 2012; Levi & Li, 2009, Polat, Ma-Naim, Belkin, & Sagi, 2004). Perceptual learning refers to experiencedependent improvement in visual performance demonstrated after repeated exposure to a perceptual task (Gibson, 1963; see Fahle & Poggio, 2002; Lu, Hua, Huang, Zhou, & Dosher, 2011; Sagi, 2011). In the context of amblyopia, the current thinking is that visual perceptual learning may be able to rehabilitate the visual deficits associated with the disorder, particularly in older amblyopes otherwise thought to be beyond the range of treatment. Numerous studies over the past 20

Citation: Kiorpes, L., & Mangal, P. (2015). "Global" visual training and extent of transfer in amblyopic macaque monkeys. *Journal of Vision*, *15*(10):14, 1–15, doi:10.1167/15.10.14.

doi: 10.1167/15.10.14

years have shown that perceptual learning and action video game play may induce beneficial changes in the adult amblyopic visual system (Bavalier et al., 2010; R. W. Li, Ngo, Nguyen, & Levi, 2011; Vedamurthy, Nahum, Bavalier, & Levi, 2015). These changes are thought to be a form of neural plasticity (Bavalier et al., 2010; Buonomano & Merzenich, 1998; Levi, 2005, 2012; Polat et al., 2004) that has the potential for significant, long-lasting visual correction.

Although perceptual learning approaches seem promising, close reading of the literature and a recent meta-analysis of 14 perceptual learning studies showed quite mixed results, with some individuals deriving large benefits from training and others demonstrating little or no benefit (Levi & Li, 2009). One of the primary difficulties in evaluating the literature is a wide range of variation in the metrics used to define posttreatment improvement (Stewart, Moseley, & Fielder, 2003) and the tendency toward reporting of averaged or group data. In some cases, any posttraining change-no matter how small-is reported as "improvement" without consideration of the amount or significance of the change, whereas others apply a particular criterion for what constitutes significant change and report the number or proportion of observers who show significant improvement. Using a post:pre training performance ratio (PPR) to quantify changes in vision across tasks in the reviewed studies. Levi and Li (2009) evaluated the significance of posttraining improvements in vision. They found that most of the observers described individually in the studies (about 200) showed some improvement posttraining. For grouped data, 9 of the 14 studies reported significant visual improvement, defined as PPR values <0.5—a change of at least a factor of 2 (Chen, Chen, Fu, Chien, & Lu, 2008; Fronius, Cirina, Kuhli, Cordey, & Ohrloff, 2006; Huang, Zhou, & Lu, 2008; Levi & Polat, 1996; Levi, Polat, & Hu, 1997; R. W. Li, Klein, & Levi, 2008; R. W. Li, Provost, & Levi, 2007; Polat et al., 2004; Zhou, et al., 2006); the overall range across all reviewed studies was PPR 0.16 to 0.83, with 1.0 reflecting no change and smaller numbers indicating greater benefit. Most recent studies have adopted a statistical criterion for establishing the significance of pretraining-posttraining differences. Levi and Li (2009) found that the degree of visual improvement across individuals hinged on a variety of factors including the severity of initial amblyopia, the duration of training, and the type of training (task and stimulus). A greater number of training trials and longer duration of training in moderate to deep amblyopes produced the greatest benefit. Contrast detection tasks and training close to the acuity limit in spatial domain perceptual learning paradigms produced the best outcomes.

One of the biggest obstacles for the utility of perceptual learning in amblyopia appears to be

specificity of visual enhancements, that is, lack of generalization to other tasks or domains. Extensive perceptual learning protocols often result in beneficial visual changes, but these changes are often specific only to the trained or related perceptual task and may or may not transfer robustly to untrained or dissimilar visual tasks, stimuli, or locations (Astle, Webb, & McGraw, 2010; Chung, Li, & Levi, 2008; Hou et al., 2011; Levi et al., 1997; Levi & Polat, 1996; Li & Levi, 2004; Polat, 2009; Polat et al., 2012; Zhang, Cong, Klein, Levi, & Yu, 2014). Some studies show significant partial transfer to the fellow, untrained eye in the trained tasks and for the trained stimuli (Chung, Li, & Levi, 2006; Levi et al., 1997; Levi & Polat, 1996; R. W. Li, Klein, & Levi, 2008; Zhou et al., 2006). The pattern of transfer is of critical importance when considering rehabilitation strategies targeting the global deficits associated with amblyopia. Some evidence from normal adult observers suggests that specificity may depend on the extent of initial training, such that a greater degree of training results in greater specificity and less transfer (Jeter, Dosher, Liu, & Lu, 2010). In the Jeter et al. (2010) study, the group that trained the least had the greatest transfer, whereas the group trained to asymptotic performance demonstrated limited transfer to tasks with different stimuli and judgments. This presents something of a conundrum for therapeutic intervention in amblyopes because, in this population, more extended training yields greater improvement in performance on the trained task, offering the best hope for a good visual outcome (Astle et al., 2010; Levi & Li, 2009; R. W. Li et al., 2008). In addition, the degree of transfer to untrained stimuli may depend on the difficulty of the task used for the learning (Ahissar & Hochstein, 1997; Z. Liu & Weinshall, 2000; Wang, Zhou, & Liu, 2013) or the precision of the transfer task (Jeter, Dosher, Petrov, & Lu, 2009). It is unclear the extent to which these stimulus-specific constraints affect the benefits of perceptual learning in amblyopic observers; amblyopic observers appear to have broader capacity for generalization than visually normal controls (Huang et al., 2008).

Another important consideration for the case of amblyopia is the duration that improvements are sustained following the training period. The duration of sustained visual enhancement following treatment reflects the real efficacy of that type of treatment. Several studies have examined the long-term effects of perceptual learning episodes by conducting follow-up assessments months after the initial training (Chen et al., 2008; Hussain, Webb, Astle, & McGraw, 2012; Levi et al., 1997; Polat et al., 2004; Zhou et al., 2006). Polat et al. (2004) showed only small losses, on a group level, when visual acuity was examined 3, 6, 9, and 12 months following perceptual learning. It is possible that reexposure to perceptual learning stimuli at regular intervals could have completely sustained the initial improvements derived from training (Hussain et al., 2012). Chen et al. (2008) reported that 92% of their participants retained the improvement in visual acuity that followed perceptual learning of a contrast detection task over the succeeding 8 months. Zhou et al. (2006) tested a few cases 12 to 18 months posttraining and found very good retention in those individuals. These experiments suggest that visual correction induced by perceptual learning can be long lasting.

From the foregoing discussion, it is clear that perceptual learning can provide some benefit to amblyopic observers well beyond the traditional critical period, although the extent of that benefit is quite variable and is influenced by a variety of factors. These studies show that there is often some transfer of visual enhancement across related tasks within the spatial domain and that there is evidence for longevity of the effects. It is unclear what effect this type of training has on vision more generally because, as noted above, amblyopia affects many more visual abilities than just acuity and contrast sensitivity. Understanding the extent of transfer beyond closely related or domainspecific visual functions and retention of benefits is essential for evaluation of a perceptual learning-based treatment for amblyopia. The aims of the present study were to characterize the extent of improvement of visual sensitivity and transfer within and across visual domains following training with a global visual stimulus and establish whether those visual enhancements were retained long term. We conducted the study in an animal model of amblyopia, nonhuman primates with strabismic or anisometropic amblyopia, to evaluate the perceptual learning outcomes in a group of welltrained, well-characterized amblyopes with known visual histories. The aim was to identify consistencies across individuals with similar depths of amblyopia and visual histories. We wished to implement a more generalized training paradigm than is typical to induce broader transfer of learning. To that end, the training stimulus was a global motion display based on randomdot kinematograms, and the task was motion direction discrimination, which included a range of different speeds and discrimination directions, as a function of motion signal strength. Posttraining visual assessments included a within-domain motion detection task, a comparable spatial domain global form discrimination based on Glass patterns, spatial contrast sensitivity, and Vernier acuity. Long-term follow-up assessment was also conducted on a subset of the animals and tasks. To anticipate, despite the similarity of depth of amblyopia across subjects, the outcome was mixed across animals. We found comparable direct effects of perceptual learning to that in the human literature, but mixed transfer of those training benefits with greater transfer within than across domains.

# **Materials and methods**

#### Subjects

Four pig-tailed macaque monkeys (*Macaca nemes-trina*), two males and two females, were subjects in the experiment. Three were adults (>3 years) at the beginning of the study, and one was a juvenile (1.4 years) at the start of testing. One monkey was an anisometropic amblyope, and three were strabismic amblyopes. All animals were born at the Washington National Primate Research Center and were hand-reared in the Visual Neuroscience Laboratory at New York University. Experimental procedures and animal care were in compliance with the NIH Guide for the Care and Use of Laboratory Animals and the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research and were approved by the New York University Animal Care and Use Committee.

#### **Experimental amblyopia**

Amblyopia developed following either early induced strabismus or simulated anisometropia (see Table 1). Each subject was confirmed to be visually normal at the start of rearing, based on preferential looking assessment of grating acuity (Kiorpes, 1992b). Refractive errors and general eye health were evaluated during rearing in all subjects.

Experimental strabismus was induced in three monkeys 25 to 35 days after birth (see Kiorpes, Carlson, & Alfi, 1989; Kiorpes, Kiper, & Movshon, 1993; Kiorpes & Wallman, 1995, for details). Esotropia (inward deviation) of one eye was created by transection of the lateral rectus muscle; the medial rectus muscle was resected and advanced to the limbus, and the conjunctiva was reattached to the globe. Surgery was carried out under ketamine hydrochloride sedation using sterile surgical techniques. The resulting esotropia was moderate, typically ranging from 10 to 25 prism diopters, with a reasonable range of motility of the operated eye. All of the strabismic amblyopic animals used the nondeviated eye preferentially.

Anisometropia was simulated in one monkey by inserting a defocusing extended-wear soft contact lens in one eye and a zero-power lens in the other eye 33 days after birth (see Kiorpes et al., 1993). Defocusing lens power was -8D; the lenses were custom-made, 70% water content with beveled edges (Med Lens Innovations, Front Royal, VA). The lenses were worn Kiorpes & Mangal

Subject	Rearing	Age at training	Total training trials	Number of training days	Initial amblyopia index	Amblyopia index posttraining
MN	Anisometropic	3.75 y	20,500	28	0.44	0.27
KI	Strabismic	4.8 y	29,000	32	0.49	0.49
GA	Strabismic	7 y	26,000	45	0.58	0.61
WU	Strabismic	1.4 y	35,000	48	0.48	0.46

Table 1. Rearing and training data for amblyopic subjects.

continuously for a period of approximately 30 weeks. The status and condition of the lenses were checked at 4-hr intervals throughout each day; missing lenses were infrequent but when noticed were replaced immediately. The lenses were changed and cleaned weekly. Regular ophthalmic examinations were performed to ensure the health of the eyes. Eye alignment was evaluated by inspection daily; no strabismus appeared during the rearing period or thereafter in this animal; however, we would not have detected a small tropia or phoria.

#### Stimuli

The stimuli were presented on a 21-inch monitor (Eizo FlexScan FX-E8, NEC Multisync FP2141SB or Sony CPD-G500) with viewing area subtending 19° at 100 cm, the viewing distance used throughout. The mean luminance of the displays was 30 cd/m<sup>2</sup>. For dot stimuli, dot luminance was 60 cd/m<sup>2</sup> and the back-ground luminance was 0.3 cd/m<sup>2</sup>. For grating stimuli, the space-average luminance across the display was 30 cd/m<sup>2</sup>. Stimulus presentation was controlled by a PC computer running custom software via a VSG2/3 graphics board (Cambridge Research Systems).

#### **Behavioral methods**

Behavioral methods were standard for the lab and similar to those described elsewhere (Kozma & Kiorpes, 2003; Kiorpes, Tang, & Movshon, 1999, 2006). Subjects were tested monocularly in a darkened room with their best optical correction in place (see Kiorpes & Boothe, 1984); the eye not being tested was blocked from viewing the screen. The monkeys were either sitting in a primate chair or freely moving in a testing cage. They viewed the stimuli by placing their face in a face mask with embedded sensors that signaled the presence of the face properly positioned in the mask. The face mask enabled control of viewing distance and viewing eye and enabled positioning of correcting lenses. Trials were animal initiated via activation of the face mask. All psychophysical tasks were two-alternative forced choice. The animals indicated their choice by pulling a right or left grab bar

after viewing each stimulus. Correct responses were rewarded with approximately 0.5 ml of apple juice, and incorrect responses resulted in a short tone for error feedback. Psychometric functions collected for each type of visual assessment were based on three to five stimulus levels and at least 75 trials per stimulus level; the threshold was taken to be the 75% correct level based on probit fits to the log-transformed data sets.

#### **Training task**

The perceptual learning task was a forced-choice directional motion discrimination based on a random dot kinematogram (RDK) stimulus (see Kiorpes et al., 2006; Kiorpes & Movshon, 2004). The stimulus was a single circular patch containing a translational RDK with a density of 48 dots/degree<sup>2</sup>/s (in one case [GA], these parameters were adjusted slightly higher to optimize the animal's performance). The patch subtended 5.7°; the dot size was 4 min arc at 100 cm. The task was to indicate whether the direction of motion was to the right or left of vertical (vertical was implicit; there was no physical indicator; see Figure 1 for



Figure 1. Schematic representation of the training stimuli. The animals practiced random dot motion discriminations with their amblyopic eye at two levels of difficulty (60°, 20° from vertical), each at three speeds, for six total training conditions intermixed across sessions and training days. The task was a single-patch direction discrimination; on each trial, the animal indicated whether the motion was to the left or right of vertical. The arrows indicate the choice directions for the two levels of difficulty; the nonius markers are for illustration only and were not present on the screen during the training.



Figure 2. Schematic representation of the transfer stimuli. The animals were pre- and posttested with the four tasks illustrated. (a) Motion detection required reporting which of two patches presented simultaneously contained coherent motion; the comparison contained random, incoherent motion. (b) Form detection required reporting which of two patches presented simultaneously contained a coherent linear Glass pattern; the comparison contained a random-dipole pattern. (c) Contrast sensitivity was assessed by typical detection of a grating patch on each trial as a function of contrast and spatial frequency. (d) Vernier acuity required reporting which of two square-wave gratings had offset segments. Each eye was tested before and after the training.

schematic illustration). There were six discrimination conditions: two angles, 20° and 60°, and three dot displacements, ranging from 8 min to 32 min (corresponding to a range of speeds of 13.3 to  $53.2^{\circ}/s$ ). The order of the six conditions was randomized at the beginning of the experiment for each animal. The conditions were then interleaved in order throughout the training period. Coherence thresholds were obtained for each condition at the start of training. As the animals improved on the task throughout the training period, new coherence thresholds were established. Training continued until asymptotic performance was reached on all six conditions, meaning that none of the thresholds improved over three consecutive sessions. Only the amblyopic eye was trained. Posttraining performance measures are referenced to the pretraining, initial thresholds.

#### Transfer tasks

Animals were tested on four transfer tasks, one within the motion domain and three from the spatial domain (see Figure 2 for schematic illustrations). The motion domain transfer task was a motion detection, rather than discrimination, task (in one case [GA], the monkey was unable to perform the detection task, so he was tested for transfer with a novel direction on the discrimination task). Like the training task, the stimuli were translational RDKs. However, in this case, the task was to determine which of a pair of stimulus patches contained coherent translational motion; the distractor patch contained random motion with no coherent motion signal (see Kiorpes, Price, Hall-Haro, & Movshon, 2012, for details; Figure 2a). Because different amblyopes are differentially sensitive to the spatial scale of displacement (Kiorpes et al., 2006) we used a range of displacement values for the motion transfer test. Dot displacement ranged from 5.4 to 32 min (corresponding to 4.4 to  $26.6^{\circ}$ /s, with a new stimulus on alternate frames). Performance was indexed by measuring the coherence threshold at each dot displacement, with coherence defined as the proportion of dots that carry the motion direction signal on each frame. The stimulus was displayed for up to 1 s, with a minimum viewing duration of 500 ms.

The three spatial domain transfer tasks were Glass pattern detection, contrast sensitivity, and Vernier acuity. The Glass pattern task was analogous to the motion detection paradigm in that the task was to detect which of a pair of stimulus patches contained a coherent linear Glass pattern (Glass, 1969; Glass & Perez, 1973); the distractor stimulus comprised randomly oriented dipoles (see Kiorpes et al., 2012, for details; Figure 2b). The stimulus display duration was 1 s. This task was used to determine whether a spatial domain stimulus that was similar to the training stimulus-although static-would show greater transfer than would metrics based on grating patterns, such as acuity and contrast sensitivity. As for the motion detection task, performance was indexed by coherence threshold at several displacement scales; displacement here refers to the distance between members of a dot pair and corresponds to a coarseness scale for Glass patterns. Dot displacement ranged from 5.4 to 21 min. Coherence in this case refers to the proportion of dipoles that conform to the linear structure rule. The spatial contrast sensitivity test was a typical sinusoidal grating detection task (see Kiorpes et al., 1999; Kozma & Kiorpes, 2003; Figure 2c). A grating patch vignetted by a two-dimensional spatial Gaussian (spatial frequency range 0.5 to 12 c/°, 4° patch) was presented on one or the other side of the display monitor; it remained visible until the animal made a response. The animal indicated on which side the target appeared. Contrast threshold was measured at each spatial frequency, with order counterbalanced across spatial frequency. The Vernier acuity transfer test was a collinear alignment detection task (Kiorpes, 1992b; Kiorpes et al., 1993; Figure 2d). Two clearly visible, high-contrast square wave grating patterns were presented simultaneously, one on each side of the display monitor. On one side, alternating sections of the grating pattern were offset horizontally, creating a set of Vernier offsets. The underlying grating pattern was either 0.5 or 1.0 c/ $^{\circ}$ . The stimuli were displayed until the animal made a response. The task was to indicate which member of the pair contained the offsets. Detection threshold was measured as a function of Vernier offset strength.

Prior to the perceptual learning training of the amblyopic eye, assessment of performance on the four transfer tests was conducted for each eye. In addition, the best refractive correction for the behavioral testing environment was established for each eye (see Kiorpes & Boothe, 1984). Each eye was trained and tested separately on each task. Thresholds were obtained for each condition on each task, which typically required a similar amount of trials for each eye. The criterion for accepting data as a stable threshold was three runs of 125 trials each showing stable threshold-level performance. Data collection was counterbalanced across eyes for each transfer test. Immediately following the perceptual learning training, the same four transfer tests were repeated to determine if training had affected the subject's amblyopic eye performance beyond the trained task. It was not necessary to retrain the animals postlearning as they remembered the transfer tests. The amblyopic eye was assessed fully, on all transfer tests, before moving on to assess the fellow eye, to maximize

the likelihood of good transfer of the training. These assessments were also meant to reveal any changes in vision accorded to the untrained, fellow eye, which served as a control for any extraneous effects. One to 2 years posttraining, the transfer tests were repeated with the animals that showed the greatest improvements from the perceptual learning training to assess the longterm value of the training.

#### Data analysis

Kiorpes & Mangal

For all threshold measurements, threshold values and standard error estimates were obtained by Probit analysis of log-transformed data sets using a maximum likelihood technique that is standard for the lab (Kiorpes, 1992a). Contrast threshold data were transformed to sensitivity and were fit with a doubleexponential function (Kiorpes et al., 1993, 2006; Kozma & Kiorpes, 2003). Comparisons between the pre- and posttraining data sets were evaluated by computing the log threshold difference between before and after the perceptual learning epoch, at each stimulus value for each transfer test. This approach enabled us to standardize and compare measures across the different tests and between animals so as to see any general effects of the visual training on amblyopia. A change in threshold value of a factor of 2-0.3 log units-was taken as significant, following Levi and Li (2009) and for the purposes of this study represented a significant improvement or decline in visual ability. We also computed an amblyopia index (Kiorpes et al., 1999; Kiorpes, Kiper, O'Keefe, Cavanaugh, & Movshon, 1998; Kozma & Kiorpes, 2003) based on the contrast sensitivity functions for each eye of each amblyope as a measure of depth of amblyopia and compared the amblyopia index before and after training to see if the extent of amblyopia was reduced post-training.

## Results

Four amblyopic monkeys were given extensive experience using their amblyopic eye in a perceptual learning regime. Before beginning the experimental sequence, we characterized each animal's amblyopia by measuring full-contrast sensitivity functions (see Figure 3); we also pretested them on the other transfer tasks. They were then trained on a variable condition, global motion direction discrimination task using only the amblyopic eye. They practiced with the six training conditions interleaved—two discrimination angles, each at three speeds (see the Materials and methods section)—until asymptotic performance was reached on





Figure 3. Amblyopic deficits in contrast sensitivity before training. Contrast sensitivity is plotted as a function of spatial frequency for each eye of each amblyopic monkey. Open symbols are fellow eye data; filled symbols are amblyopic eye data; amblyopia index (ai) is indicated for each data set.

all six conditions. The total number of training trials required to reach asymptote ranged from about 20,000 to 35,000 across the subjects (see Table 1). The change in coherence threshold as a result of the training ranged from -0.03 (essentially no change) to 0.61 log units across all training conditions and subjects.

Two example perceptual learning functions are shown in Figure 4 for anisometropic amblyopic monkey MN. The top panel shows the progression of performance over blocks of 125 trials for the 60° discrimination angle with 16 min dot displacement; the bottom panel shows data from the 20° discrimination angle with 32 min dot displacement. The filled symbols to the left on each plot indicate the initial threshold established prior to the beginning of the perceptual learning epoch; the ones to the right of the data are the averaged threshold from the last three blocks of trials. The change in threshold is taken to be the difference, in log units, between these initial and final thresholds; that value is indicated at the bottom of each panel.

Figure 5 shows the training effect for all six conditions for each animal (different colored bars represent different subjects). We adopted a conservative standard for significant improvement, a change in threshold of a factor of 2 (0.3 log units) or more (Levi & Li, 2009); the fine dashed line at +0.3 indicates significant threshold change from the training by this criterion. There was a great deal of variation across the training conditions and subjects as to the amount of benefit that the training experience afforded. Interestingly, the motion discrimination conditions that are most challenging for amblyopic monkeys (Kiorpes et al., 2006), fine dot displacement-slow speed, showed the least amount of improvement with training. Three of the four amblyopes showed significant training effects on at least one of the conditions; all showed some improvement on most conditions. The deepest amblyope, GA (blue bars), showed the least improvement from the training over all conditions.

Following the training, we retested the animals on the transfer tasks (motion detection, Glass pattern detection, Vernier acuity, contrast sensitivity). An example data set from monkey MN, who showed the largest transfer effects, is shown in Figure 6. Before training (open symbols) and after training (filled symbols) thresholds are plotted for her amblyopic eye on each task (note that contrast detection is plotted as sensitivity - 1/threshold). There was substantial improvement on all four tasks. For motion detection (Figure 6a), MN improved with the larger dot



Figure 4. Learning curves for two example training conditions. Coherence threshold is plotted as a function of blocks of training trials; each block is 125 trials. The filled symbols to the left and right of each curve represent the starting and ending thresholds for that training condition. The change in threshold (in log units) as a result of the training for each example data set is indicated at the bottom of the panel (training effect).

displacements (faster speeds) but not with the smaller displacements, consistent with the trend seen on the trained motion discrimination. For the cross-domain, spatial tasks (Figure 6b through d), she showed improvement on all fine-scale conditions: Vernier acuity (both conditions tested), smallest dot displacement on the Glass pattern detection task, and high spatial frequencies on the contrast detection task.

To characterize the extent of improvement, hence the transfer of perceptual learning effects, we plot the difference, in log units, between the initial and final thresholds for each condition tested. The perceptual learning effects for MN (based on the data shown in Figure 6) are plotted in the top row of Figure 7 (filled symbols). The comparable relationship for the untrained, fellow eye is also plotted for comparison (open symbols) and represents a within-animal control. The dashed lines at  $\pm 0.3 \log$  units indicate a significant change, by our criterion of a factor of 2 difference in threshold. MN showed significant improvement on detection of motion at fast speeds following training as well as on each of the fine spatial scale tasks as illustrated in Figure 6. The fellow eye showed little consistent change over the period of amblyopic eve training and testing, emphasizing that the changes in performance of the amblyopic eye were attributable to the training. Data for each of the other three animals are shown in the rows below MN. All animals showed significant improvement on at least one transfer test; consistent improvement was seen on the motion transfer task. Surprisingly, we did not find better transfer of training benefit to Glass pattern detection than to other grating-based spatial domain tasks.

Unfortunately, no other subject showed the level of transfer benefit that MN did. WU, the youngest of the amblyopes (bottom row), improved on all tasks



Figure 5. The effect of extensive experience on motion direction discrimination thresholds. The monkeys practiced direction discrimination with the amblyopic eye viewing on the six training conditions. Each animal's change in threshold in log units (see Figure 4; Materials and methods section) is plotted for each of the conditions, with the fine discrimination on the left and the coarse discrimination on the right. Individual animals are represented by different colors.



Figure 6. Transfer of perceptual learning for an example subject. Pre- (open symbols) and posttraining (filled symbols) data for the amblyopic eye of anisometropic amblyopic monkey, MN, are shown for each of the four transfer tests. Motion (a) and Glass pattern detection (d), and Vernier acuity (c) are plotted in terms of threshold; contrast detection (b) is plotted in terms of sensitivity. MN showed transfer on at least one of the conditions for each transfer test, even for tasks in the spatial domain.

following training but showed significant improvement only for motion detection and Vernier acuity. His thresholds improved for the fellow eye as well as the amblyopic eye on several conditions (contrast sensitivity and Glass pattern detection), leaving open the possible influence of development or other nontraining-related factors in his case. Both KI and GA showed significant transfer to the related motion detection task but did not improve on other tasks; KI actually showed poorer performance posttraining on Glass pattern detection and contrast sensitivity (she was not tested for Vernier acuity). For GA, no Glass pattern detection data are shown because he was unable to perform the detection task at all with his amblyopic eye at pretest. We evaluated the amblyopia index prior to and following training in each animal to see if the extent of amblyopia, as measured by contrast sensitivity, was reduced by our perceptual learning paradigm. Only MN showed substantial reduction in her amblyopia by this measure (Table 1).

Although the animals showed inconsistent results across the range of transfer tests, all showed perceptual learning effects within the motion domain, and transfer to the spatial domain, at fine spatial scales, was not uncommon. Therefore, we were very interested to see if the gains that resulted from perceptual learning were retained over the longer term. We retested three of the four subjects approximately 18 months posttraining (range = 1.4-3 years). The long-term follow-up data are shown in Figure 8, where we have plotted amblyopic eye perceptual learning effects immediately posttraining (blue symbols and lines, from Figure 7) along with the difference between pretraining thresholds and threshold at long-term follow-up (red symbols and lines). It is clear that the improvement was in most cases not maintained. Some notable exceptions are a subset of the conditions on which significant improvement was seen following perceptual learning: motion detection (KI, WU), Vernier acuity (WU), and high spatial frequency contrast sensitivity (MN). To see whether the original training effects were maintained, we compared



Figure 7. Transfer of perceptual learning for all subjects. The difference between initial and final threshold, in log units, is plotted for each animal (by row) for each task and condition tested (by column). The perceptual learning effects for MN's amblyopic eye (plotted in Figure 6) are represented in the top row of Figure 7 (filled symbols). The comparable relationship for the untrained, fellow eye is also plotted for comparison (open symbols). The dashed lines at  $\pm 0.3$  log units indicate a significant change, a factor of 2 difference in pre- versus posttraining threshold.

the thresholds reached on the six training conditions at the end of the perceptual learning training and those at follow-up in two animals. The training effects were retained in the youngest subject (WU) but not in the older one (MN) (data not shown).

# Discussion

Our goals for this study were to characterize the extent of perceptual learning effects following training with a global visual stimulus, assess transfer within and across visual domains, and establish whether resulting visual enhancements were retained long-term. Despite selecting amblyopes with a similar depth of amblyopia, the outcome was mixed across animals. We found comparable direct effects of perceptual learning to that in the human literature but mixed transfer of those training benefits with greater transfer within the training domain—motion—than across domains to spatial vision. Long-term retention results showed little lasting benefit of the training or transfer in the adult subjects, although there was retention of the training effect in the youngest subject.



Figure 8. Retention of transfer effects. Three subjects were retested posttraining: MN, +1.5 years, KI, +3 years, WU, +1.4 years. Amblyopic eye perceptual learning effects immediately posttraining (blue symbols and lines from Figure 7) are plotted along with the difference, in log units, between pretraining threshold and threshold at long-term follow-up (red symbols and lines). Axes and dashed lines are as in Figure 7.

We conducted this perceptual learning study in an animal model of amblyopia, nonhuman primates with strabismic or anisometropic amblyopia, to evaluate perceptual learning outcomes in a well-trained, wellcharacterized population of essentially psychophysically experienced amblyopes with completely documented visual histories. The hope was to identify consistencies across individuals with similar depths of amblyopia and visual histories. The pattern of the training effects was indeed quite similar across subjects; however, the pattern of the transfer effects was more variable. Given that these animals were well-experienced psychophysical subjects, unlike most perceptual learning studies in humans, we were not sure we would find substantial changes in threshold with training. Some reported perceptual learning effects may represent a combination of task learning and psychophysical practice effects when conducted with inexperienced observers. However, we found similar direct effects of the perceptual learning experience on thresholds (0–0.6 log units) for the trained task to those reported in many human amblyopia studies (0-0.8 log units; see Levi & Li, 2009). So, in fact, the perceptual learning regime was effective despite the

experienced status of the participants, which confirms findings in humans that even well-practiced or previously treated amblyopic subjects can benefit from PL intervention (Levi & Polat, 1996; Levi et al., 1997; X.-Y. Liu, Zhang, Jia, Wang, & Yu, 2011; Polat, Ma-Naim, & Spierer, 2009; see also Levi & Li, 2009). This outcome reinforces the idea that perceptual learning training can improve performance regardless of whether the participants are highly experienced or not.

We wished to implement a more generalized training paradigm than is typical in order to induce broader transfer of learning. To that end, the training stimulus was a global motion display based on random-dot kinematograms, and the task was motion direction discrimination. Global motion stimuli have only occasionally been used before as a perceptual learning training stimulus, but they have previously been demonstrated to be effective in visually normal human adults (Ball & Sekuler, 1982, 1987; Z. Liu, 1999; Shibata et al., 2012; Wang et al., 2013; Zhang & Yang, 2014). Such training has in some cases been shown to generalize to nontrained directions (Z. Liu, 1999; Wang et al., 2013; Zhang & Yang, 2014). No prior study has used a general training paradigm like ours, including multiple directions, speeds, and difficulty levels. Our expectation, that this general training would effect broad transfer across tasks, within the motion domain as well as across domains to spatial vision, was partially borne out. We found improvement on a motion detection task in every animal and examples of cross-domain transfer especially at fine spatial scales. We did not find better transfer of training benefit to Glass pattern detection than to other grating-based spatial domain tasks, despite the similarity in the stimuli across domains. Cross-domain transfer in amblyopia has been reported in one previous study. Hou et al. (2011) trained amblyopic adults on a contrast detection task using sinewave gratings and tested for improved sensitivity on grating motion detection and discrimination as well as improvement in spatial domain tasks such as visual acuity. They found modest improvement on motion contrast sensitivity along with substantial improvement on contrast sensitivity across untrained spatial frequencies.

Because posttraining visual assessments showed within- and across-domain transfer to untrained tasks, we were interested to assess retention of the training and transfer effects. Long-term follow-up assessment was conducted on a subset of the animals and tasks. Here the results were quite disappointing. In a few cases, posttraining improvements were retained, but this was not the rule. Even the direct effect of the training, on the global motion direction discrimination, was not retained in the adult that showed the greatest training benefit overall. This outcome contrasts with reports in the human literature that training effects are often long lasting in amblyopes, at least up to 1 year or 18 months, although there is a fair range of individual variability (Li & Levi, 2004; Polat et al., 2004; Zhou et al., 2006), which in most cases is masked due to the presentation of group data. The nearly complete lack of retention in the monkeys may be the result of their experience with multiple different visual discrimination tasks posttraining and posttesting. At various times following posttesting, these animals were trained and tested on one or more different psychophysical tasks; it is possible that such experience interfered with long-term retention of the perceptual learning effects. The human studies that assessed longterm retention involved training and testing on closely related tasks, with no intervening psychophysical experience between initial assessment of the effects of the training and follow-up assessment. In addition, human subjects likely engage in more diverse visual tasks posttraining, as part of normal daily experience, which may serve to maintain gains made through perceptual learning.

Two prior studies have employed a form of perceptual learning in visually abnormal animals. Nakatsuka et al. (2007) provided prism-reared (but nonamblyopic) monkeys with training on a stereoscopic depth discrimination, improving stereoacuity approximately sevenfold. Murphy, Roumeliotis, Williams, Beston, and Jones (2015) trained monocularly deprived cats on an orientation-in-noise discrimination. Their cats showed improvement on the order of a factor of 2 on the discrimination task over the period of the training. In each case, the training was binocular, and despite the fact that the animals did not achieve "normal" thresholds, the studies showed clear evidence of perceptual learning in the animals and further suggest that binocular training can help to ameliorate the effects of abnormal binocular visual experience established during the critical period. Also, these studies lend support to new efforts to treat amblyopia in human adults using various types of binocular training (Birch, 2013; Hess, Mansouri, & Thompson, 2010; Knox, Simmers, Gray, & Cleary, 2012; J. Li et al., 2015; Ooi, Su, Natale, & He, 2013; Vedamurthy et al., 2015).

## Conclusions

This study, in amblyopic nonhuman primates, showed that even well-experienced, mature amblyopes can benefit from extensive visual training. We used a global stimulus and training paradigm to try to effect general improvement in vision of amblyopes; the results were mixed, but generalization was apparent in some cases. Although the improvements in sensitivity were for the most part not long lasting, it is not hard to imagine creating paradigms to continue interventions periodically so that long-term, generalized improvement may be maintained.

Keywords: perceptual learning, amblyopia, global motion, Glass pattern, Vernier acuity, contrast sensitivity

## Acknowledgments

This research was supported by National Institutes of Health Grant EY05864 to L. Kiorpes and National Center for Research Resources Grant RR00166 to the Washington National Primate Center. The authors acknowledge the contributions of Amelie Pham, Solmaz Shariat Torbaghan, Michael Gorman, and Chao Tang to this work.

Commercial relationships: none. Corresponding author: Lynne Kiorpes. Email: lynne@cns.nyu.edu. Address: Center for Neural Science, New York University, New York, NY, USA.

### References

- Ahissar, M., & Hochstein, S. (1997). Task difficulty and the specificity of perceptual learning. *Nature*, *387*, 401–406.
- Astle, A. T., McGraw, P. V., & Webb, B. S. (2011). Can human amblyopia be treated in adulthood? *Strabismus*, *19*, 99–109.
- Astle, A. T., Webb, B. S., & McGraw, P. V. (2010). Spatial frequency discrimination learning in normal and developmentally impaired human vision. *Vi*sion Research, 50, 2445–2454.
- Ball, K., & Sekuler, R. (1982). A specific and enduring improvement in visual motion discrimination. *Science*, 218, 697–698.
- Ball, K., & Sekuler, R. (1987). Direction-specific improvement in motion discrimination. *Vision Research*, 27, 953–965.
- Bavalier, D., Levi, D. M., Li, R. W., Dan, Y., & Hensch, T. K. (2010). Removing brakes on adult brain plasticity: From molecular to behavioral interventions. *Journal of Neuroscience*, 30, 14964– 14971.
- Birch, E. E. (2013). Amblyopia and binocular vision. Progress in Retinal and Eye Research, 33, 67–84.
- Buonomano, D. V., & Merzenich, M. M. (1998). Cortical plasticity: From synapses to maps. *Annual Review of Neuroscience*, 21, 149–186.
- Chen, P. L., Chen, J. T., Fu, J. J., Chien, K. H., & Lu, D. W. (2008). A pilot study of anisometropic amblyopia improved in adults and children by perceptual learning: An alternative treatment to patching. *Ophthalmic and Physiological Optics*, 28, 422–428.
- Chung, S. T. L., Li, R. W., & Levi, D. M. (2006). Identification of contrast-defined letters benefits from perceptual learning in adults with amblyopia. *Vision Research*, 46, 3853–3861.
- Chung, S. T. L., Li, R. W., & Levi, D. M. (2008). Learning to identify near-threshold luminancedefined and contrast-defined letters in observers with amblyopia. *Vision Research*, 48, 2739–2750.
- Daw, N. W. (1998). Critical periods and amblyopia. Archives of Ophthalmology, 116, 502–505.
- Fahle, M., & Poggio, T. (2002). *Perceptual learning*. Cambridge, MA: MIT Press.
- Fronius, M., Cirina, L., Kuhli, C., Cordey, A., & Ohrloff, C. (2006). Training the adult amblyopic eye with "perceptual learning" after vision loss in the non-amblyopic eye. *Strabismus*, 14, 75–79.

Grant, S., & Moseley, M. J. (2011). Amblyopia and

real-world visuomotor tasks. *Strabismus*, 19, 119–128.

- Gibson, E. J. (1963). Perceptual learning. Annual Review of Psychology, 14, 29-56.
- Glass, L. (1969). Moire effect from random dots. *Nature*, 223, 578–580.
- Glass, L., & Perez, R. (1973). Perception of random dot interference patterns. *Nature*, 246, 360–362.
- Hamm, L., Black, J., Dai, S., & Thompson, B. (2014). Global processing in amblyopia: A review. Frontiers in Psychology, 5, 583.
- Hess, R. F., Mansouri, B., & Thompson, B. (2010). A binocular approach to treating amblyopia: Antisuppression therapy. *Optometry and Vision Science*, *87*, 697–704.
- Hou, F., Huang, C.-B., Tao, L., Feng, L., Zhou, Y., & Lu, Z.-L. (2011). Training in contrast detection improves motion perception of sinewave gratings in amblyopia. *Investigative Ophthalmology and Visual Science*, 52, 6501–6510. [PubMed] [Article]
- Huang, C.-B., Zhou, Y., & Lu, Z.-L. (2008). Broad bandwidth of perceptual learning in the visual system of adults with anisometropic amblyopia. *Proceedings of the National Academy of Sciences*, USA, 105, 4068–4073.
- Hussain, Z., Webb, B. S., Astle, A. T., & McGraw, P. V. (2012). Perceptual learning reduces crowding in amblyopia and in the normal periphery. *Journal of Neuroscience*, 32, 474–480.
- Jeter, P. E., Dosher, B. A., Petrov, A., & Lu, Z.-L. (2009). Task precision at transfer determines specificity of perceptual learning. *Journal of Vision*, 9(3):1, 1–13, doi:10.1167/9.3.1. [PubMed] [Article]
- Jeter, P. E., Dosher, B. A., Liu, S. H., & Lu, Z.-L. (2010). Specificity of perceptual learning increases with increased training. *Vision Research*, 50, 1928– 1940.
- Kanonidou, E. (2011). Amblyopia: A mini review of the literature. *International Ophthalmology*, *31*, 249–256.
- Kiorpes, L. (1992a). Development of Vernier acuity and grating acuity in normally reared monkeys. *Visual Neuroscience*, 9, 243–251.
- Kiorpes, L. (1992b). The effect of strabismus on the development of Vernier acuity and grating acuity in monkeys. *Visual Neuroscience*, *9*, 253–259.
- Kiorpes, L. (2006). Visual processing in amblyopia: Animal studies. *Strabismus*, 14, 3–10.
- Kiorpes, L. (2015). Visual development in primates: Neural mechanisms and critical periods. *Developmental Neurobiology*, 75, 1080–1090.

- Kiorpes, L., & Boothe, R. G. (1984). Accommodative range in amblyopic monkeys. *Vision Research*, 24, 1829–1834.
- Kiorpes, L., & Movshon, J. A. (2004). Development of sensitivity to visual motion in macaque monkeys. *Visual Neuroscience*, 21, 851–859.
- Kiorpes, L., & Wallman, J. (1995). Does experimentally-induced amblyopia cause hyperopia in monkeys? Vision Research, 35, 1289–1297.
- Kiorpes, L., Carlson, M. R., & Alfi, D. (1989). Development of visual acuity in experimentally strabismic monkeys. *Clinical Vision Sciences*, 4, 95– 106.
- Kiorpes, L., Kiper, D. C., & Movshon, J. A. (1993). Contrast sensitivity and vernier acuity in amblyopic monkeys. *Vision Research*, 33, 2301–2311.
- Kiorpes, L., Kiper, D. C., O'Keefe, L. P., Cavanaugh, J. R., & Movshon, J. A. (1998). Neuronal correlates of amblyopia in the visual cortex of macaque monkeys with experimental strabismus and anisometropia. *Journal of Neuroscience*, 18, 6411–6424.
- Kiorpes, L., Tang, C., & Movshon, J. A. (1999). Factors limiting contrast sensitivity in experimentally amblyopic monkeys. *Vision Research*, 39, 4152–4160.
- Kiorpes, L., Tang, C., & Movshon, J. A. (2006). Sensitivity to visual motion in amblyopic macaque monkeys. *Visual Neuroscience*, 23, 247–256.
- Kiorpes, L., Price, T., Hall-Haro, C., & Movshon, J. A. (2012). Development of sensitivity to global form and motion in macaque monkeys (*Macaca nemestrina*). *Vision Research*, 63, 34–42.
- Knox, P. J., Simmers, A. J., Gray, L. S., & Cleary, M. (2012). An exploratory study: Prolonged periods of binocular stimulation can provide an effective treatment for childhood amblyopia. *Investigative Ophthalmology and Visual Science*, 53, 817–824. [PubMed] [Article]
- Kozma, P., & Kiorpes, L. (2003). Contour integration in amblyopic monkeys. *Visual Neuroscience*, 20, 577–588.
- Levi, D. M. (2005). Perceptual learning in adults with amblyopia: A reevaluation of critical periods in human vision. *Developmental Psychobiology*, 46, 222–232.
- Levi, D. M. (2006). Visual processing in amblyopia: Human studies. *Strabismus*, 14, 11–19.
- Levi, D. M. (2012). Prentice Award Lecture: Removing the brakes on plasticity in the amblyopic brain. *Optometry and Vision Science*, 89, 827–838.

- Levi, D. M. (2013). Linking assumptions in amblyopia. *Visual Neuroscience*, *30*, 277–287.
- Levi, D. M., & Li, R. W. (2009). Perceptual learning as a potential treatment for amblyopia: A minireview. *Vision Research*, 49, 2535–2549.
- Levi, D. M., & Polat, U. (1996). Neural plasticity in adults with Amblyopia. *Proceedings of the National Academy of Sciences, USA, 93,* 6830–6834.
- Levi, D. M., Polat, U., & Hu, Y. S. (1997).
  Improvement in vernier acuity in adults with amblyopia. Practice makes better. *Investigative Ophthalmology and Visual Science*, 38, 1493–1510.
  [PubMed] [Article]
- Lewis, T. L., & Maurer, D. (2005). Multiple sensitive periods in human visual development: Evidence from visually deprived children. *Developmental Psychobiology*, 46, 163–183.
- Li, J., Spiegel, D. P., Hess, R. F., Chen, Z., Chan, L. Y. L., Deng, D., ... Thompson, B. (2015). Dichoptic training improves contrast sensitivity in adults with amblyopia. *Vision Research*, 114, 161–172.
- Li, R. W., Klein, S. A., & Levi, D. M. (2008). Prolonged perceptual learning of positional acuity in adult amblyopia: Perceptual template retuning dynamics. *Journal of Neuroscience*, 28, 14223– 14229.
- Li, R. W., & Levi, D. M. (2004). Characterizing the mechanisms of improvement for position discrimination in adult amblyopia. *Journal of Vision*, 4(6): 7, 476–487, doi:10.1167/4.6.7. [PubMed] [Article]
- Li, R. W., Ngo, C., Nguyen, J., & Levi, D. M. (2011). Video-game play induces plasticity in the visual system of adults with amblyopia. *PLoS Biology*, 9, e1001135.
- Li, R. W., Provost, A., & Levi, D. M. (2007). Extended perceptual learning results in substantial recovery of both positional acuity and visual acuity in juvenile amblyopia. *Investigative Ophthalmology and Visual Science*, 48, 5046–5051. [PubMed] [Article]
- Liu, X.-Y., Zhang, T., Jia, Y.-L., Wang, N.-L., & Yu, C. (2011). The therapeutic impact of perceptual learning on juvenile amblyopia with or without previous patching treatment. *Investigative Oph-thalmology and Visual Science*, *52*, 1531–1538. [PubMed] [Article]
- Liu, Z. (1999). Perceptual learning in motion discrimination that generalizes across motion directions. *Proceedings of the National Academy of Sciences*, USA, 96, 14085–14087.
- Liu, Z., & Weinshall, D. (2000). Mechanisms of

generalization in perceptual learning. Vision Research, 40, 97–109.

- Lu, Z.-L., Hua, T., Huang, C.-B., Zhou, Y., & Dosher, B. A. (2011). Visual perceptual learning. *Neurobiology of Learning and Memory*, 95, 145–151.
- Mitchell, D. E., & MacKinnon, S. (2002). The present and potential impact of research on animal models for clinical treatment of stimulus deprivation amblyopia. *Clinical and Experimental Optometry*, *85*, 5–18.
- Murphy, K. M., Roumeliotis, G., Williams, K., Beston, B. R., & Jones, D. G. (2015). Binocular visual training to promote recovery from monocular deprivation. *Journal of Vision*, 15(1):2, 1-17, doi:10. 1167/15.1.2. [PubMed] [Article]
- Nakatsuka, C., Zhang, B., Watanabe, I., Zheng, J., Bi, H., Ganz, L., ... Chino, Y. M. (2007). Effects of perceptual learning on local stereopsis and neuronal responses of V1 and V2 in prism-reared monkeys. *Journal of Neurophysiology*, 97, 2612– 2626.
- Ooi, T. L., Su, Y. R., Natale, D. M., & He, Z. J. (2013). A push-pull treatment for strengthening 'lazy eye' in amblyopia. *Current Biology*, 23, 309–310.
- Polat, U. (2009). Making perceptual learning practical to improve visual functions. *Vision Research*, 49, 2566–2573.
- 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, USA, 101,* 6692–6697.
- Polat, U., Ma-Naim, T., & Spierer, A. (2009). Treatment of children with amblyopia by perceptual learning. *Vision Research*, 49, 2599–2603.
- Sagi, D. (2011). Perceptual learning in Vision Research. Vision Research, 51, 1552–1566.
- Shibata, K., Chang, L.-H., Kim, D., Náñez, J. E., Kamitani, Y., Watanabe, T., & Sasaki, Y. (2012).

Decoding reveals plasticity in V3A as a result of motion perceptual learning. *PLoS ONE*, 7, e44003.

- Simons, K. (2005). Amblyopia characterization, treatment, and prophylaxis. *Survey of Ophthalmology*, *50*, 123–166.
- Stewart, C. E., Moseley, M. J., & Fielder, A. R. (2003). Defining and measuring treatment outcome in unilateral amblyopia. *British Journal of Ophthalmology*, 87, 1229–1231.
- Vedamurthy, I., Nahum, M., Bavalier, D., & Levi, D. M. (2015). Mechanisms of recovery of visual function in adult amblyopia through a tailored action video game. *Scientific Reports*, 5, 8482.
- Von Noorden, G. K. (1980). *Binocular vision and ocular motility*. St. Louis, MO: C.V. Mosby Co.
- Wang, X., Zhou, Y., & Liu, Z. (2013). Transfer in motion perceptual learning depends on the difficulty of the training task. *Journal of Vision*, 13(7):5, 1–9, doi:10.1167/13.7.5. [PubMed] [Article]
- Wong, A. F. (2012). New concepts concerning the neural mechanisms of amblyopia and their clinical implications. *Canadian Journal of Ophthalmology*, 47, 399–409.
- Zhang, J.-Y., Cong, L.-J., Klein, S. A., Levi, D. M., & Yu, C. (2014). Perceptual learning improves adult amblyopic vision through rule-based cognitive compensation. *Investigative Ophthalmology and Visual Science*, 55, 2020–2030. [PubMed] [Article]
- Zhang, J.-Y., & Yang, Y.-X. (2014). Perceptual learning of motion discrimination transfers to an opposite direction with TPE training. *Vision Research*, 99, 93–98.
- Zhou, Y., Huang, C., Xu, P., Tao, L., Qiu, Z., Li, X., Lu, Z. L. (2006). Perceptual learning improves contrast sensitivity and visual acuity in adults with anisometropic amblyopia. *Vision Research*, 46, 739–750.