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## Minireview

# Perceptual learning as a potential treatment for amblyopia: A mini-review

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## ARTICLE INFO

### Article history:

Received 23 December 2008

Received in revised form 12 February 2009

### Keywords:

Amblyopia  
 Perceptual learning  
 Sensitive period  
 Critical period  
 Internal noise  
 Template-retuning  
 Occlusion

## ABSTRACT

Amblyopia is a developmental abnormality that results from physiological alterations in the visual cortex and impairs form vision. It is a consequence of abnormal binocular visual experience during the “sensitive period” early in life. While amblyopia can often be reversed when treated early, conventional treatment is generally not undertaken in older children and adults. A number of studies over the last twelve years or so suggest that Perceptual Learning (PL) may provide an important new method for treating amblyopia.

The aim of this mini-review is to provide a critical review and “meta-analysis” of perceptual learning in adults and children with amblyopia, with a view to extracting principles that might make PL more effective and efficient. Specifically we evaluate:

- 1). What factors influence the outcome of perceptual learning?
- 2). Specificity and generalization – two sides of the coin.
- 3). Do the improvements last?
- 4). How does PL improve visual function?
- 5). Should PL be part of the treatment armamentarium?

A review of the extant studies makes it clear that practicing a visual task results in a long-lasting improvement in performance in an amblyopic eye. The improvement is generally strongest for the trained eye, task, stimulus and orientation, but appears to have a broader spatial frequency bandwidth than in normal vision. Importantly, practicing on a variety of different tasks and stimuli seems to transfer to improved visual acuity. Perceptual learning operates via a reduction of internal neural noise and/or through more efficient use of the stimulus information by retuning the weighting of the information. The success of PL raises the question of whether it should become a standard part of the armamentarium for the clinical treatment of amblyopia, and suggests several important principles for effective perceptual learning in amblyopia.

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## 1. Introduction

Amblyopia (from the Greek, amblyos – blunt; opia – vision) is a developmental abnormality that results from physiological alterations in the visual cortex and impairs form vision. It is a consequence of abnormal binocular visual experience during the “sensitive period” early in life.

Amblyopia is clinically important because, aside from refractive error, it is the most frequent cause of vision loss in infants and young children, occurring naturally in about 2–4% of the population; and it is of basic interest because it reflects the neural impairment which can occur when normal visual development is disrupted. The damage produced by amblyopia is generally expressed in the clinical setting as a loss of visual acuity in an apparently healthy eye, despite appropriate optical correction;

however, there is a great deal of evidence showing that amblyopia results in a broad range of neural, perceptual, and clinical abnormalities (see [Kiorpes, 2006](#); [Levi, 2006](#) for recent reviews). Currently there is no positive diagnostic test for amblyopia. Instead, amblyopia is diagnosed by exclusion: in patients with conditions such as strabismus and anisometropia, a diagnosis of amblyopia is made through exclusion of uncorrected refractive error and underlying ocular pathology. Amblyopic patients (especially those with strabismic amblyopia) often exhibit crowding problems ([Levi, 2008](#)), meaning they have better visual acuity when letters are presented in isolation than when they are presented in a line or a full chart. Clinically, crowding is a useful sign to aid in the diagnosis of amblyopia.

Amblyopia is a significant public health problem. However, it can be reversed or eliminated when diagnosed and treated early in life. Thus, there is a premium on early detection of amblyopia and its risk factors. It has been estimated that perhaps as many as three quarters of a million preschoolers are at risk for amblyopia

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in the United States, and roughly half of those may not be detected before school age (Wu & Hunter, 2006). Improved vision screening and access to effective treatment could, in principle, substantially reduce amblyopia as a public health issue.

While amblyopia can often be reversed when treated early, conventional treatment (patching) is generally not undertaken in older children and adults. Moreover, patching itself may lead to a reduction in binocular vision and stereopsis, and to psychosocial problems such as a loss of self-esteem (Webber, Wood, Gole, & Brown, 2008). Thus, it is desirable to minimize the duration and extent of patching. A number of studies over the last twelve years or so suggest that Perceptual Learning (PL) may provide an important new method for treating amblyopia (Table 1).

Eleanor Gibson (1963) defined Perceptual Learning as “Any relatively permanent and consistent change in the perception of a stimulus array following practice or experience with this array...”. Over the last half-century or so, Perceptual Learning has been studied intensively. It has formed the basis of thousands of articles, chapters and books (a Google search results in about 274,000 hits), and for this Special Issue of *Vision Research*. Indeed, advertising for the book *Perceptual Learning* (Fahle & Poggio, 2002; <http://cog-net.mit.edu/library/books/view?isbn=0262062216>) states: “A familiar example is the treatment for a “lazy” or crossed eye. Covering the good eye causes gradual improvement in the weaker eye’s cortical representations. If the good eye is patched too long, however, it learns to see less acutely.” The focus of this review is on a rather narrower definition of perceptual learning – specifically, the notion that practicing visual tasks can lead to dramatic and long-lasting improvements in performing them, i.e., practice makes perfect! Indeed, one strong appeal of the PL approach for treating amblyopia is the widely held notion that perceptual learning can lead to permanent changes in both performance and in neural processing at an early stage of visual coding, perhaps as early as V1 (to be addressed in Sections 3 and 5). The extant evidence suggests that the primary neural damage in the amblyopic visual system takes place in the visual cortex (Kiorpes, 2006; Levi, 2006).

The aim of this mini-review is to provide a critical review of PL in adults and children with amblyopia with a view to extracting principles that might make PL more effective and efficient. Specifically we evaluate:

- (1) What factors influence the outcome of perceptual learning?
- (2) Specificity and generalization – two sides of the coin.
- (3) Do the improvements last?
- (4) How does PL improve visual function?
- (5) Should PL be part of the treatment armamentarium?

Since visual acuity is the sine qua non of amblyopia, we consider not only the effect of perceptual learning on the task that is trained, but wherever possible, on Snellen acuity (see Table 1 and Figs. 1–3).

## 2. What factors influence the outcome of perceptual learning?

Adults are capable of improving performance on sensory tasks through repeated practice or perceptual learning (for recent reviews see Fahle, 2005; Fine & Jacobs, 2002), and this learning is considered to be a form of neural plasticity that also has consequences in the cortex (Buonomano & Merzenich, 1998). Specifically, in adults with normal vision, practice can improve performance on a variety of visual tasks, and this learning can be quite specific (to the trained task, orientation, eye, etc. – see Fahle, 2005). Interestingly, similar neural plasticity exists in the visual system of adults with naturally occurring amblyopia due to high

levels of astigmatism, anisometropia, strabismus and/or form-deprivation, suggesting that perceptual learning may be a very useful approach for amblyopia treatment. Table 1 lists all (14) of the studies of PL in amblyopia published to date. These studies cover a range of tasks including Vernier acuity, contrast detection, letter identification (both first and second-order) and position discrimination. Most of the almost 200 amblyopic observers showed improvement in the trained task (7th column), although the amount of improvement varied substantially both between tasks and between individuals. This section explores the source of the considerable variance.

The effect of PL is often quantified by comparing performance before and after training, and expressed variously as a percent improvement, an improvement factor or as a ratio of threshold performance (PPR – or Post:Pre Ratio). For consistency and to simplify comparisons across studies, the effects of PL are specified as PPR in Table 1, and, where available, the number of observers showing significant learning is also provided (this information is critically important but often not provided). The PPR values for the trained task (Table 1) vary from  $\approx 0.16$  (a whopping factor of 6), to  $\approx 0.8$  (a factor of 1.2). Note that a PPR = 1 indicates no improvement, and the lower the PPR, the greater the improvement. The gray boxes in Table 1 highlight the studies where the improvement on the trained task was, on average, a factor of two or more (PPR equal to or less than 0.5). What factors distinguish studies in which learning is small from those in which learning is substantial?

### 2.1. Age

Because amblyopia only occurs when there is abnormal binocular visual input during the “sensitive period” early in life, it is often assumed that it can only be treated effectively in infants and young children. The studies listed in Table 1 span a broad range of ages – from 7 to 60 years, all outside the conventional sensitive period that is thought to extend to about six. Does age matter?

We suspect that age does not account for the variance across studies. For example, a number of studies with only adults (18 and over) show strong learning (e.g. Levi & Polat, 1996; Li, Klein, & Levi, 2008) while some with only children (e.g. Li, Young, Hoenig, & Levi, 2005) show relatively weak learning. Moreover, neither Polat, Ma-Naim, Belkin, and Sagi (2004) nor Chen, Chen, Fu, Chien, and Lu (2008) found any correlation between age and outcome in their subject populations. Fig. 1 summarizes graphically the effect of age on both the trained task (top panel) and transfer to Snellen acuity (Lower panel). The regression lines (dashed) show a very weak dependence on age in opposite directions in the two panels ( $r = 0.20$  for the trained task and  $-0.25$  for Snellen). Note that we have not included the Fronius data (Fronius, Cirina, Cordey, & Ohrloff, 2005; Fronius, Cirina, Kuhli, Cordey, & Ohrloff, 2006) in the regression, because it is not possible to distinguish between the role of perceptual learning and the loss of the fellow eye, in improving performance. Inspection of Fig. 1 suggests that age, at least within the post sensitive-period years from  $\approx 10$  to 40, has little influence on the outcome of PL.

### 2.2. Task

Fig. 2 compares the effects of PL across tasks (trained task – top; Snellen acuity – bottom). Here it is instructive to compare the tasks that result in the most improvement (lowest PPR values) and those that result in the least (highest PPR values). For the trained task (Fig. 2 top panel), five studies result in PPR values below 0.4 (i.e., a factor of 2.5 or more improvement). Four of the five involve repeated measurements of contrast sensitivity. One (Polat et al., 2004 – green diamond) used high contrast flankers at different separations from the target, to train “lateral interactions”. Both

**Table 1**  
Summary of the extant studies of Perceptual Learning in amblyopia

Study	Task	N observers	Age	Hours/trials	Stopping rule	Trained task (N/N; PPR)	Transfer	Notes
Levi and Polat (1996)	Vernier acuity	6 (5 Highly practiced)	19–53 (Median 26)	6 h 5 K Trials	N Trials (N = 5 K)	6/6 0.46	Ori – partial Eye – partial* Detection – no Snellen – yes (1) PPR ≈ 0.50	Previously unpracticed O's Snellen improved ≈4-fold
Levi et al. (1997)	Vernier acuity	11 (6 Novice; 5 highly practiced – 6 from Levi & Polat, 1996)	19–53 (Median 26)	6 h 5 K Trials	N trials (N = 5 K)	11/11 Practiced ≈ 0.5 Novices ≈ 0.35 (not asymptotic)	Ori – Partial Eye – partial* Detection – no Snellen – yes (5) PPR ≈ 0.57	2 Novices showed full transfer to Snellen; 3 partial transfer
Polat et al. (2004)	Gabor detection (1.5–12 cpd)	77	9–55 (Mean ≈ 35)	≈22 h	Stop after no improvement for 12 consecutive sessions	≈0.38 (averaged over SFs)	Snellen – PPR 0.34 (median)	Varied target SF, orientation, and flank distance during training
Li and Levi (2004)	Position discrimination in noise	7	20–55 (Mean ≈ 37)	≈20 h	N Trials (N ≈ 6 K)	6/7 ≈ 0.77 (averaged over noise levels)	Ori – partial Eye – none Snellen ≈ PPR 0.67 (7/7) Counting – yes Stereo – 1/7 Snellen – PPR ≈ 0.4	3 – Increased efficiency 2 – reduced equivalent noise 1 – Increased efficiency and reduced equivalent noise
Fronius et al. (2005, 2006)	Loss of vision in fellow eye + PL	1	60	2 h/week for 6 months (≈48 h)	N months (N = 6)	Grating acuity ≈ 0.5 Localization ≈ 0.49 Contrast sensitivity ≈ 0.6		Loss of vision in the non-amblyopic eye and training on a variety of tasks
Levi (2005)	Letter identification in noise	4	19–28 (Mean ≈ 23)	6 h 5 K Trials	N Trials (N = 5 K)	4/4 ≈ 0.65 (averaged over noise levels)	Not tested	≈73% reduction in efficiency ≈7% reduction in $N_{eq}$
Li et al. (2005)	Position discrimination in noise	5 All had previous occlusion	7–10 (Mean 8.5)	≈14–20 h	N Trials (N ≈ 2.4–4 K)	4/5 ≈ 0.7 (averaged over noise levels)	Snellen – PPR ≈ 0.74 (5/5)	2 – Increased efficiency 2 – Reduced equivalent noise
Zhou et al. (2006)	Contrast detection Group I – SF near cutoff Group II – full CSF Group III – no training	7 (Aniso) 10 (Aniso) 6 (Aniso)	14–27 (Mean 19.3)	9–19 Sessions (mean 12.7). ≈1000 Trials/session (≈12 h)	3 Consecutive sessions with similar performance	Group 1 PPR ≈ 0.32 Group 2 PPR ≈ 0.56 (1.2–9.7 dB) Group 3 PPR ≈ 0.92 (–0.5–2.4 dB)	Full CSF ≈ 0.52 Snellen ≈ 0.58 Fellow eye ≈ 0.61 Snellen ≈ 0.68 Fellow eye ≈ 0.93 Snellen ≈ 0.99 Fellow eye ≈ 0.85	
Chung et al. (2006)	Identification of contrast defined letters	10	21–58 (Median 27)	8 Sessions ≈ 1000 trials/session (≈8 h)	N Trials (N = 8 K)	8/10 PPR ≈ 0.67	Luminance defined letters – PPR ≈ 0.95 Fellow eye – PPR ≈ 0.90 (1.47–0.64)	

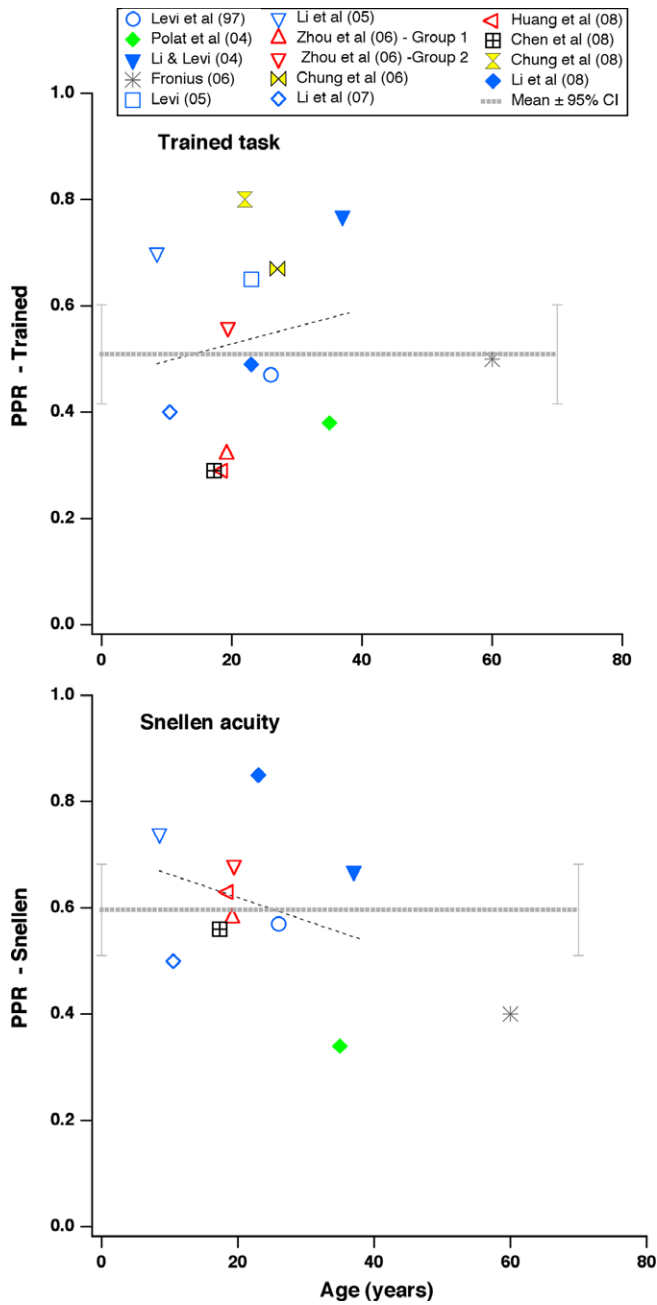
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Table 1 (continued)

Study	Task	N observers	Age	Hours/trials	Stopping rule	Trained task (N/N; PPR)	Transfer	Notes
Li et al. (2007)	Position discrimination in noise	2	9 and 12	≈100 h	Stable plateau	2/2 ≈0.4 (averaged over noise levels) PPR ≈ 0.29	Snellen – PPR ≈ 0.5 (2/2) Stereo – 2/2	2 – Increased efficiency
Huang et al. (2008)	Contrast detection SF near cutoff	10 (7 From Zhou et al., 2006) all aniso	15–22 (Mean 18.6)	8–19 Sessions ≈1000 Trials/session (≈12 h)	3 consecutive sessions with similar performance		Snellen – PPR ≈ 0.63 Untrained SFs	Bandwidth of learning ≈4 octaves Compared to ≈1.4 octaves in normal controls
Chen et al. (2008)	Group 1: Gabor detection (identical to Polat et al., 2004) Group 2: patching	26 (Aniso) 27 (Aniso)	Mean 17.3 (SD 10.9) Mean 13 (SD 10.1)	48 Sessions/29 h (≈48 h) 37.3 Weeks/522 h	Resolution of amblyopia or 3 consecutive sessions with no improvement in acuity	PPR ≈ 0.16–0.48 depending on SF (mean 0.29) PPR ≈ 0.20–0.45 depending on SF (mean 0.33)	Snellen PPR ≈ 0.56 (20/26 – 2 lines or more) Snellen PPR ≈ 0.46 (26/27 – 2 lines or more)	92% retention after 8 months
Chung et al. (2008)	1. Identification of luminance defined letters. 2. Identification of contrast defined letters	11 7/11	15–58 (Median 22)	8 Sessions ≈ 1000 trials/session (≈8 h) 8 Sessions ≈ 1000 trials/session (≈8 h)	N Trials (N = 8 K) N Trials (N = 8 K)	6/11 PPR ≈ 0.80 5/7 PPR ≈ 0.83	Contrast defined letters – PPR ≈ 0.62 Fellow eye – none acuity – none Luminance defined letters – PPR ≈ 1.02 Fellow eye – none acuity – none	Sequential training of two tasks on the same subjects. Note that overall improvement For contrast defined letters after Two rounds of training was 49% PPR = 0.51
Li et al. (2008)	Position discrimination in noise	7	18–39 (Median 23)	30–80 Sessions ≈ 1000 trials/session (≈60 h)	Stable performance for 15–20 sessions	7/7 PPR ≈ 0.49 – depends on size of initial loss. Varies from ≈0.74 to 0.24 (mean 0.49)	Fellow eye (3/4) PPR ≈ 0.79 (direct training leads to further improvement of the fellow eye – PPR ≈ 0.59 Snellen PPR ≈ 0.85	Learning occurs via retuning of the amblyopic decision template and reduced internal spatial distortion

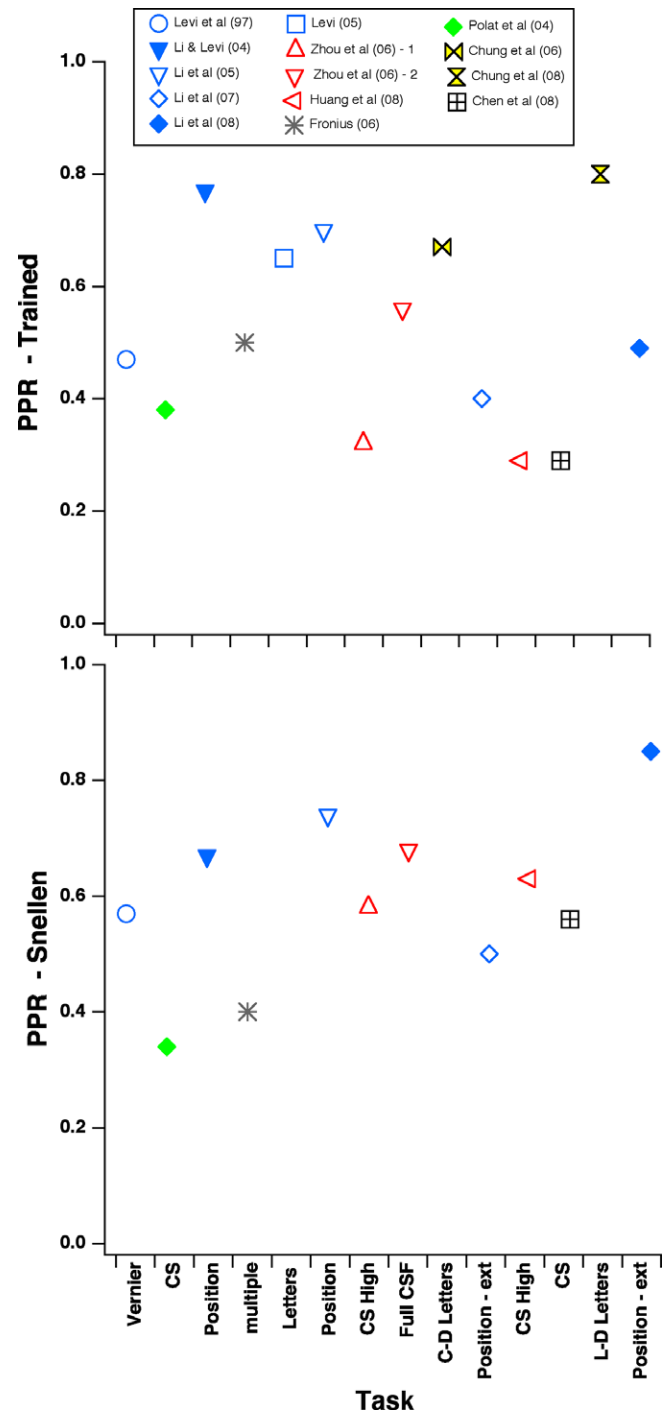
The grey areas highlight studies in which learning was substantial (PPR < 0.5).

\* Mainly trained orientation.



**Fig. 1.** The effect of age on the Pre vs. Post-training threshold ratio (PPR), for the trained task (top panel) and for transfer to Snellen acuity (lower panel). Each symbol shows the mean data for a given study. A gray dotted line shows the mean improvement of previous PL studies. This format is repeated in Figs. 2 and 3.

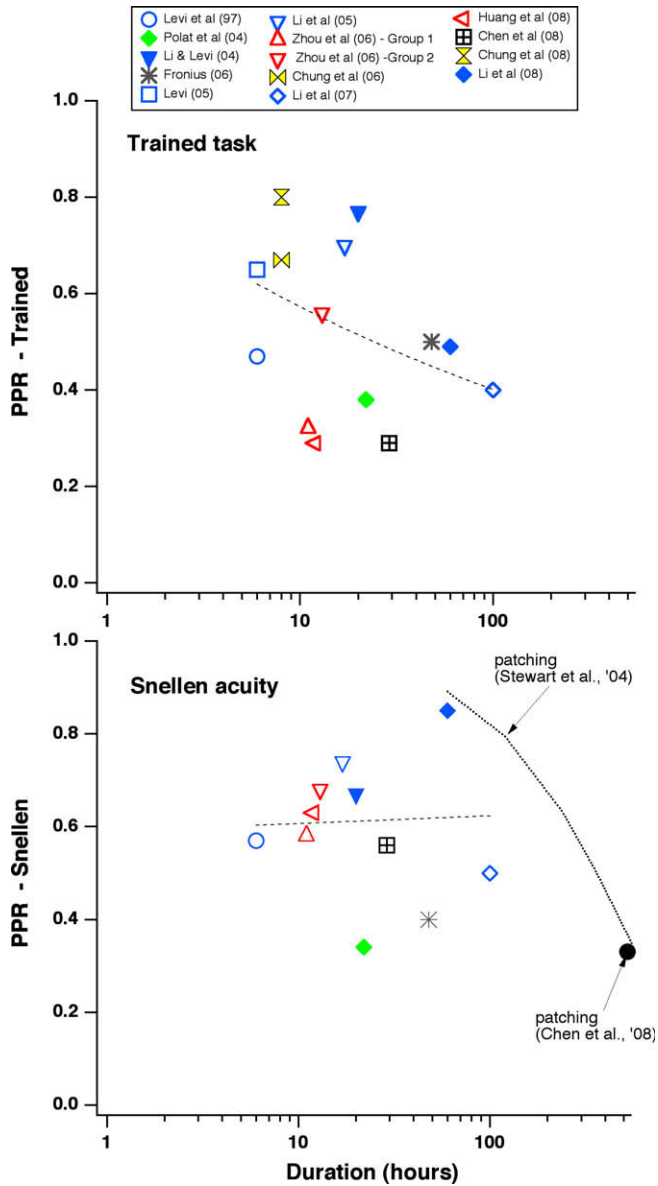
studies trained over a range of spatial frequencies where the amblyopic eye was impaired. Initial training started at the highest spatial frequency at which the amblyopic eye's contrast threshold was impaired (more than twice the normal value) but with a contrast threshold not greater than 15%. During training sessions, the spatial frequency was varied, shifting progressively higher, and four orientations were presented at each spatial frequency. Both studies resulted in substantial improvements in contrast sensitivity and in Snellen acuity. Polat and colleagues attribute the improvement, at least in part, to improved lateral interactions (as evidenced by increased facilitation from nearby flankers). However, the results of Lu and coworkers (Zhou et al., 2006 Group 1; Huang, Zhou, & Lu, 2008 – red triangles) show equivalent improvement on the trained task, after practicing contrast detection near



**Fig. 2.** The effect of task on the PPR (trained task – top; Snellen acuity – bottom). Format as in Fig. 1.

the cut-off spatial frequency, with no flankers. Interestingly, Polat et al.'s subjects showed more improvement in acuity (Fig. 2, bottom) than did any of the other studies. It is unclear whether this should be attributed to the inclusion of flankers in the training, which may have reduced crowding (Chung, 2007), to varying the orientation, or both.

It is interesting to note that Group 1 of Zhou et al. (2006) show considerably more improvement than their Group 2. Group 1 was trained near the cut-off spatial frequency, Group 2 over a broad range of spatial frequencies. This suggests a strategy of focusing training where the impairment is substantial rather than scattering it over a broad range of conditions where performance may be nor-



**Fig. 3.** The effect of duration on the PPR (trained task – top; Snellen acuity – bottom). Format as in Fig. 1. The dashed lines are power functions with exponents of  $-0.15$  (top  $R = 0.34$ ) and  $0.11$  (bottom  $R = 0.59$ ). The dotted line in the lower panel is the dose-response curve for patching from Stewart, Moseley, Fielder, et al. (2004) and Stewart, Moseley, Stephens, et al. (2004). The solid black circle is the patching outcome from Chen et al. (2008).

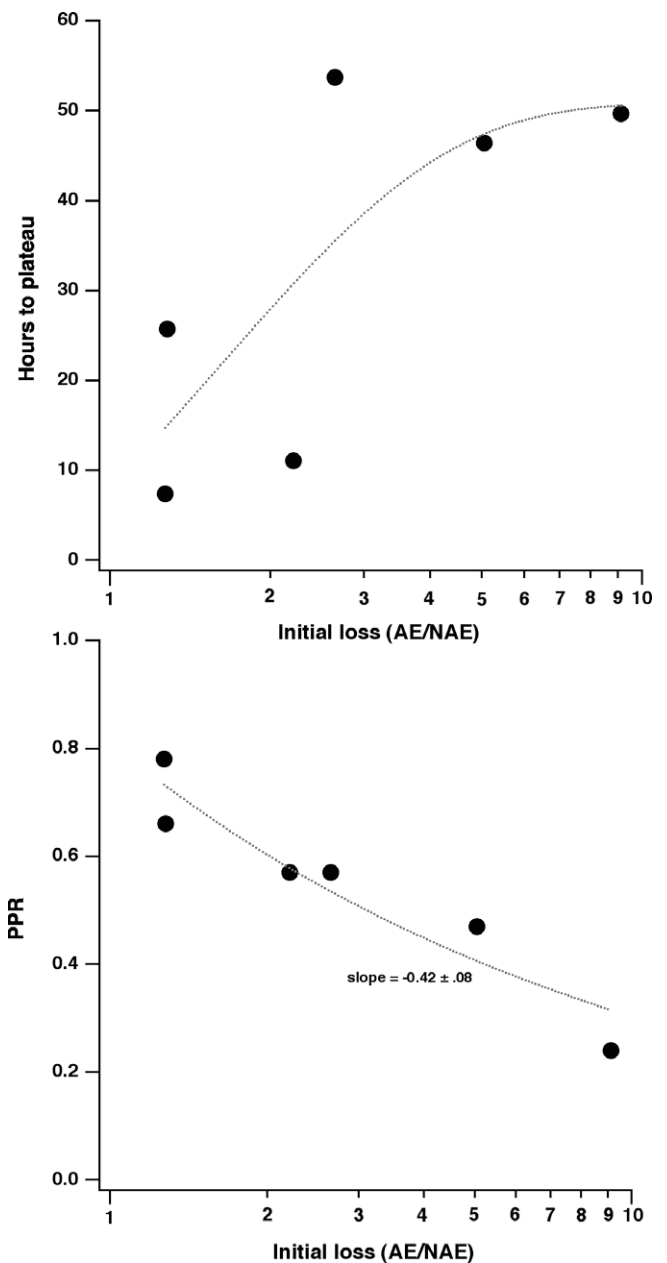
mal or nearly so. It is also somewhat surprising that not all contrast detection experiments lead to large changes in the trained task. Neither identification of near threshold contrast defined letters nor of luminance defined letters (substantially larger than the acuity limit) result in strong learning of the trained task (Chung, Li, & Levi, 2006, 2008; Levi, 2005).

The only task out of the five that resulted in low PPRs ( $<0.4$ ) that did not involve practicing contrast detection was extended positional acuity learning in children (Li, Provost, & Levi, 2007 – Fig. 2 open blue diamond). Li et al. (2007) had two children, aged 9 and 12 years, with previously untreated severe amblyopia practice a position discrimination task repeatedly over three months (100 h,  $>25,000$  trials). After practice both children showed substantial recovery in both positional and letter acuities ( $PPR \approx 0.4$  and 2 to 4 chart-lines) and both also regained significant stereoacuity. We note that two previous studies used the identical 3-spa-

tial alternative forced choice position task and stimulus with much smaller improvements in both adults (mean age 37 – Li & Levi, 2004), and children (mean age 8.5 – Li et al., 2005). Thus, as we will argue below, it is probably not the task but the duration of practice and the severity of the amblyopia that primarily led to the substantial improvement in these children. Indeed, in the first 20 h, the recovery rate was comparable to that of twelve previously treated amblyopes (Li & Levi, 2004; Li et al., 2005). However, extending the treatment dosage for an additional 30 h resulted in substantially greater plateau improvements.

**2.3. Duration of PL**

Duration of training seems to play an important role in determining the effectiveness of PL (Fig. 3 top). As noted above, the two studies in children by Li et al. (2005, 2007) used identical stim-



**Fig. 4.** The effect of severity of amblyopia (initial loss) on the outcome of perceptual learning. Top panel, number of hours required to reach plateau. Bottom panel, PPR following PL. After Li et al. (2008).



uli and tasks, but differed in duration (compare open blue upside-down triangle and open blue diamond in Fig. 3 top). Similarly, the two studies of position acuity in adults by Li and coworkers (Li & Levi, 2004; Li et al., 2008) had very different durations and substantially different outcomes (compare solid blue upside-down triangle and solid blue diamond in Fig. 3 top). The regression line in Fig. 3 (top) has a negative slope; however, the role of duration is clearly not straight-forward. One problem is the question of when one should stop practice. As can be seen in Table 1, the stopping rules vary greatly. The earliest studies (e.g. Levi & Polat, 1996; Levi, Polat, & Hu, 1997) took their lead from PL studies in normal observers, where 3000–6000 trials are generally more than enough to reach stable performance. Other studies used a criterion of three consecutive sessions with similar performance (e.g. Zhou et al., 2006). The two studies by Li et al. (2007, 2008) and the studies of Polat et al. (2004) and Chen et al. (2008) used a more stringent stopping rule. One important factor that interacts with the duration of training (to be discussed below) is the severity of the amblyopia. Duration and severity are inextricably bound up together.

It is interesting to note (Fig. 3 bottom panel), that there seems to be little relationship between the duration of PL and the improvement in Snellen acuity. The dotted line shows the improvement of acuity with patching in children ages 3–8 (Stewart, Moseley, Stephens, & Fielder, 2004), and it is worth noting that all of the PL studies in adults show more improvement than expected from the commensurate duration of patching in children. To date, with the exception of (Chen et al., 2008 – black circle) there are no comparable studies of patching in adults (Chen et al report no effect of age, and they pooled data from children and adults). We will return to this point below.

#### 2.4. Initial performance level

Fahle and Henke-Fahle (1996) suggested that in a large group of observers with normal vision, those with the worst initial performance showed the strongest effects of practice. If this result can be generalized to amblyopia, one might expect that the most severely impaired amblyopes would show the greatest improvement following perceptual learning. Levi et al. (1997) failed to show such an effect in their study of Vernier acuity; however, PL was halted after 5000 trials ( $\approx 6$  h – see Table 1), and inspection of the data suggests that many of the amblyopes had not reached asymptotic performance.

Indeed, most previous learning studies used relatively brief periods of practice (Li & Levi, 2004; Li et al., 2005). For example, Li & Levi asked seven amblyopic patients to practice a positional discrimination task and they seemed to have reached the plateau level and showed a modest improvement (20–30%) in a brief period ( $\approx 20$  h) of training (Li & Levi, 2004; Li et al., 2005). Other studies used a criterion of asymptotic performance on three consecutive sessions, giving a mean length of training of  $\approx 12$  sessions, or 12 h (Huang et al., 2008; Zhou et al., 2006). The most extensive training was provided by Polat et al. (2004). Their subjects practiced a contrast detection task for, on average 45 sessions,  $\approx 22$  h. Interestingly, close inspection of their data, as well as that of the other studies, suggests that observers may still have not reached their ultimate asymptotic performance. This raises the question of whether prolonged perceptual learning would result in more substantial improvement in adults with amblyopia.

A recent study revealed that in two juvenile amblyopes, prolonged perceptual learning yielded an approximately 2.4-fold improvement in performance over 50 h of training (Li et al., 2007). One might argue that the developing brain is more malleable, thus a longer period of training can produce more substantial improvements. However, Fig. 1 argues against this, and it raises the

important question of whether or not similar prolonged perceptual learning would result in more substantial gains in adult amblyopes.

To address this question, Li et al. (2008) adopted a much stricter stopping rule than in previous studies to decide whether training should continue. They found that more practice is required to reach asymptote in severe amblyopia than in mild amblyopia (Fig. 4, top), and that the amount of improvement is roughly proportional to the severity of amblyopia (Fig. 4, bottom). In general, they found that deep amblyopes [VA: 20/50–20/125] required  $\approx 50$  h ( $\approx 35,000$  trials) to reach plateau, and the PPR was as low as 0.24. In contrast, mild amblyopes [VA: 20/25–20/40] required fewer practice trials (7.5–30 h) to obtain stable improvement (with PPR  $\approx 0.6$ –0.8) and normal observers (viewing monocularly) require just 5–7 h. Li et al. concluded that the more severe the visual loss, the longer the time course required to obtain the maximal effect of PL, and the greater the benefit. The exponential time-constants for improvement were  $\approx 19$  h for severe amblyopes;  $\approx 6$  h for mild amblyopes and under 3 h for normal control observers. Consistent with this, Polat (2005), Polat et al. (2004) and Chen et al. (2008) show a significant correlation between the severity of amblyopia (initial visual acuity) and the amount of improvement following PL.

#### 2.5. Type of amblyopia

The prognosis for treating children with amblyopia depends on many factors (some will be discussed later), amongst them, the type of amblyopia has sometimes but not always (e.g. Flynn et al., 1999) been reported to be significant. Does the type of amblyopia influence the outcome of PL? Several studies (Chen et al., 2008; Huang et al., 2008; Zhou et al., 2006) only included anisometropic amblyopes. However, most studies included both strabismic and anisometropic amblyopes, and reported no clear difference in the outcome between strabismic and anisometropic amblyopes (e.g. Polat et al., 2004). In their large-scale study, Mckee, Levi, and Movshon (2003) suggested that the presence or absence of binocularity distinguishes amongst amblyopes, thus it is of interest to consider whether the presence or absence of binocularity plays a role in the outcome of treatment or perceptual learning. To date this question has not been directly addressed, and it would require a large-scale study to answer the question.

### 3. Specificity and generalization – two sides of the coin

The specificity of perceptual learning noted above (Fahle, 2005; Karni & Sagi, 1993; Polat & Sagi, 1994) poses some interesting difficulties. If the improvement following practice were solely limited to the trained stimulus, condition and task, then the type of plasticity documented here would have very limited (if any) therapeutic value for amblyopia, since amblyopia is defined primarily on the basis of reduced Snellen acuity. The question of specificity in normal vision is currently being re-evaluated. For example, recent work (Xiao et al., 2008) shows complete transfer of learning from one location to another, if the second location has been sensitized with an irrelevant stimulus and task. The complete transfer of perceptual learning to new retinal locations revealed by Xiao et al. calls into question both location specificity as a key property of visual perceptual learning, and the well-received belief by many researchers that the retinotopic early visual cortex is the neuronal basis of perceptual learning. Rather it points to a crucial role for non-retinotopic higher brain areas that engage attention and decision making for perceptual learning.

Perceptual learning with the amblyopic eye shows little or no transfer to untrained orientations, (Levi & Polat, 1996; Levi et al., 1997; Li & Levi, 2004), and there is no transfer of learning from a

Vernier acuity task to a detection task (Levi & Polat, 1996; Levi et al., 1997). Interestingly, at least in some amblyopes, there is significant but only partial transfer of learning from the amblyopic to the fellow eye (Levi & Polat, 1996; Levi et al., 1997; Li et al., 2008; Zhou et al., 2006).

Importantly, for amblyopia, perceptual learning of many tasks appears to transfer, at least in part, to improvements in Snellen acuity, as does practicing contrast detection (Table 1 and Fig. 2 bottom). Accompanying the visual acuity improvement, other degraded visual functions such as stereoacuity and visual counting sometimes improve as well (Table 1; Li & Levi, 2004; Li et al., 2007). One surprising exception is learning to identify contrast defined (second-order) letters. Learning to identify near threshold contrast defined letters shows very little transfer to the improved identification of luminance defined (first-order) letters (Chung et al., 2006) nor to improved acuity (Chung et al., 2008). Moreover, learning to identify low contrast large luminance defined letters (letters  $\approx$  8 times larger than the acuity limit) does not transfer to acuity either (Chung et al., 2008). However, it is not clear whether training letter recognition at the acuity limit benefits amblyopic vision. At least, Chung et al.'s studies show that PL can be useful for recovering higher-order contrast processing, which may be useful in seeing under impoverished conditions, or camouflage.

### 3.1. Why does perceptual learning transfer (or not)?

A recent study (Huang et al., 2008) suggests that the spatial frequency bandwidth of learning for contrast sensitivity is very broad in observers with amblyopia ( $\approx$ 4 octaves) compared to that of normal observers ( $\approx$ 1.4 octaves). The broad bandwidth of learning implies broader generalization in the amblyopic visual system. Given this broad bandwidth, why did Chung et al. (2006, 2008) fail to show transfer of improvement to visual acuity after learning to identify large letters? One possible explanation is that the spread of learning may be unidirectional – spreading from near the acuity limit (where Huang et al.'s observers practiced) to lower spatial frequencies, but not the other way around. Indeed, Polat's control group was trained with detecting low spatial frequency, high contrast Gabor targets and showed no significant acuity improvement. This would explain why practicing at a high spatial frequency spreads to a wide range of lower frequencies, but not vice-versa. Whether or not this speculation is correct remains to be tested. However, it is critically important if perceptual learning is to be useful for treating amblyopia.

Perceptual learning is orientation specific, both in normal (Fahle, 2004, 2005) and amblyopic (Li & Levi, 2004) vision, and it is unclear whether the orientation bandwidth for learning in the amblyopic visual system is broader than normal. However, one speculation about why extended perceptual learning for a horizontal position task results in a very substantial improvement on the trained task, but only a very small improvement in Snellen acuity (Li, Klein & Levi, 2008) is that letter identification requires many orientations (not just the trained one). Levi and Polat (1996; Levi et al. 1997) approached this by having observers practice at one orientation for 5000 trials, and then repeated this at other orientations. Polat et al. (2004) trained observers at four orientations for each spatial frequency. As noted earlier Polat et al.'s subjects showed more transfer to acuity (Fig. 2, bottom) than did any of the other studies, but it is unclear whether this should be attributed to varying the orientation, to the inclusion of flankers in the training, or to both.

## 4. Do the improvements last?

In adults with normal vision, the effects of perceptual learning are often reported to be long-lasting (Karni & Sagi, 1993; Polat & Sagi, 1994). The longevity of perceptual learning is clearly of spe-

cial interest when applied to amblyopia. Several studies have examined the longevity of PL. Levi et al. (1997) reported on one anisometric amblyope whose acuity had improved from slightly worse than 20/40 to 20/20 after perceptual learning. He returned to the lab approximately 10 months after the conclusion of the PL. During that hiatus, he had lost his glasses and had been uncorrected for several months. Nonetheless, he retained about 40% of his original improvement. More importantly, on resuming PL, he showed a very rapid improvement in performance to a level equal to or slightly better than that achieved initially. In a later study, we showed that the improvement in visual acuity in the amblyopic eye resulting from position discrimination training was essentially stable for up to at least a year (the longest interval at which we re-tested performance – Li & Levi, 2004).

Several more recent studies have directly addressed the question of retention directly. Polat et al. (2004) examined visual acuity at 3, 6, 9 and 12 months following PL and found only a small decrement in acuity. Similarly, Zhou et al. (2006) report visual acuity was almost fully retained as much as 18 months following cessation of PL, and Chen et al. report that 92% of their subjects retained the improved acuity over an 8 month period. Thus, the improvement in acuity resulting from PL appears to be long-lasting.

## 5. How does PL improve visual function?

Based on the studies reviewed above, perceptual learning appears to be an effective method for improving both task performance and visual acuity in amblyopic vision. We are aware of the well known “positive publication bias”. That is, investigators will publish their results if they find an effect, and not otherwise, so it is possible that there are unpublished negative results. Unfortunately, there is no way of determining anything about these studies, if they exist. With that caveat in mind, it is worth asking why PL is so effective?

There have been many attempts to explain why training or practice results in lower thresholds in normal vision and a full discussion is beyond the scope of this paper. One point of view is that perceptual learning reflects alterations of neural responses rather early in the visual pathway, where neurons are sensitive to local features (Fahle, 2004, 2005; Fiorentini & Berardi, 1981; Schoups, Vogels, & Orban, 1995). An alternative point of view is that improvement in performance is based on high level (or cognitive) processes (e.g., Mollon & Danilova, 1996; Xiao et al., 2008). Recent evidence suggests that learning of orientation discrimination which is retinally local, may be modulated by attention, and thus might involve higher-order visual mechanisms (Ahissar & Hochstein, 1993; Shiu & Pashler, 1992). This result does not necessarily imply that learning occurs at a high level, but might be viewed as attention gating the information flow, possibly at an early level (Fahle, 2004). Moreover, as noted above, there is a complete transfer of learning from one location to another, if the second location has been sensitized with an irrelevant stimulus and task (Xiao et al., 2008), calling into question location specificity, and the notion that the retinotopic early visual cortex is the neuronal basis of perceptual learning.

In order to draw reasonable conclusions about the mechanisms of learning in amblyopic observers, it is important to consider several plausible (but less interesting) possibilities, specifically, fixational eye-movements, accommodation, and learning general strategies for viewing with an amblyopic eye.

Many individuals with amblyopia have inaccurate or unsteady fixation (Schor & Hallmark, 1978), thus improvement after practice could result from observers learning to fixate more accurately. While improved fixation could result from forced use of the amblyopic eye, we believe that this is unlikely to fully explain our results for two reasons. First, Vernier acuity and contrast sen-



sitivity are quite robust to retinal image motion less than about 4 deg/sec (Levi, 1996; Westheimer & McKee, 1975) – considerably faster than the fixational eye-movements of people with amblyopia (Schor & Hallmark, 1978). Second, more accurate fixation would be expected to improve performance at all orientations, while steadier fixation would be likely to improve performance most for vertical stimuli (since the drift is primarily horizontal and would therefore smear vertical contours). However, several studies show that the improvement is selective for orientation (Li & Levi, 2004), being strongest at the trained orientation. Moreover, improvement in fixation would also be expected to improve performance in a detection task; however, there is little evidence of significant transfer of learning from a Vernier acuity task to an untrained detection task (Levi & Polat, 1996; Levi et al., 1997). Finally, Higgins, Daugman, and Mansfield (1982) showed that contrast sensitivity in amblyopia is unaffected by eye-movements.

Another possible explanation of improvement after practice is that our observers learned to better control accommodation with their amblyopic eye. This explanation also seems unlikely to fully account for the results since Vernier acuity and position acuity are relatively robust to the effects of blur (at least for non abutting stimuli, Watt & Hess, 1987). In addition, if the effect of training could be explained by accommodative improvement, then improvement should occur equally for all orientations and tasks, not just in the trained orientation and task. While some of the improvement evident in observers who are performing psychophysics with their amblyopic eye for the first time is undoubtedly the result of learning more accurate fixation or accommodation, or other general strategies for viewing with an amblyopic eye, five of the six subjects in Levi & Polat's original study had previous experience (from a few thousand to millions of trials) in making Vernier judgments with their amblyopic eyes; in these observers fixation and accommodation would be expected to be stable, as would their cognitive strategy, yet each showed a significant improvement in performance at the new orientation. Similarly, several subjects in the study by Li et al. (2008) had a great deal of previous experience in making psychophysical judgments with their amblyopic eyes. Finally, the absence of transfer of learning from a Vernier to a detection task makes it difficult to fully explain the training effects in terms of some generalized cognitive change over time, or by learning to focus and fixate with an unpracticed eye. Thus, we argue that at least some of the improvement in performance must reflect the effects of genuine neural plasticity.

### 5.1. Is the improvement simply an effect of occlusion?

During perceptual learning experiments, the preferred eyes of amblyopic observers are typically patched while they perform the task. Brief periods of occlusion have been shown to result in improvements in young children with amblyopia (Ciuffreda, Levi, & Selenow, 1991; Repka, Beck, Holmes, et al., 2003). Thus, at least some of the improvement may reflect the effects of patching *per se*. The pilot study by Chen et al. (2008) compared perceptual learning to patching (combined with near visual activities). Although their patching group showed a greater improvement in acuity (PPR 0.46) than the PL group (0.56), the duration of patching was, on average more than ten-times the duration of PL (Table 1 and Fig. 3 bottom); thus patching alone cannot explain the effect of PL. Importantly, Polat's (2005; Polat et al., 2004) control group patched for 12 sessions, with no improvement compared to 1.5 lines of visual acuity improvement in the treatment group.

As noted above, patching combined with perceptual learning has a shorter time-constant than patching alone (Li et al., 2007).

### 5.2. Why does PL enhance the effect of patching?

During perceptual learning experiments, observers are engaged in making fine visual discriminations using their amblyopic eyes, under near threshold conditions where their visual system is challenged, thus the learning is intensive and active, and they receive repeated exposure to the same stimuli, and are given feedback. Thus we speculate that perceptual learning in amblyopia reflects the amblyopic brain learning to attend to and use the most salient or reliable information for the task when viewing with the amblyopic eye. This may be akin to strengthening connections that were present in the first place, rather than the development of new connections, perhaps by learning to attend to the information from the (normally suppressed) amblyopic eye. This speculation is consistent with the improvement in efficiency (discussed below). It might also explain why learning transfers to some tasks (such as Snellen acuity and visual counting) but not others.

It should be noted that during normal everyday life, an amblyopic patient wearing a patch may engage in fine visual discriminations and challenges, without undertaking specific perceptual learning, and that may at least in part account for the success of patching alone. Moreover, there is evidence showing that performing near visual activities during patching may be beneficial in treating children with amblyopia (PEDIG, 2005a, 2005b). Our own work shows that playing action video-games with the amblyopic eye results in a range of improved spatial and temporal visual functions including visual acuity (Li et al., 2008b). However, our speculation is that perceptual learning provides intensive, active, supervised visual experience with feedback, and thus may be more efficient than simply relying on everyday experiences.

### 5.3. Psychophysical mechanisms

While we can reasonably safely rule out a number of uninteresting explanations for the improvements in performance, a full discussion of the neural mechanisms underlying the improvement in amblyopic vision following perceptual learning is beyond the scope of this review, but has been extensively discussed elsewhere (Levi & Li, 2008; Li et al. (2008)). Much of the focus of recent work is on the question of whether perceptual learning operates via a reduction of internal neural noise or through more efficient use of the stimulus information by retuning the weighting of the information (referred to as template retuning – see for example Doshier & Lu, 1998, 1999, 2004; Gold, Bennett, & Sekuler, 1999; Li, Levi, & Klein, 2004; Lu & Doshier, 2004). Most amblyopes suffer from abnormally elevated spatial uncertainty, with the neural representation of the visual image being sometimes distorted at the cortical level (Bedell & Flom, 1981; Hess & Field, 1994; Lagreze & Sireteanu, 1991; Levi, Klein, & Sharma, 1999; Wang, Levi, & Klein, 1998).

Using the powerful methods of reverse-correlation (Li, Klein, & Levi, 2006; Neri & Levi, 2006) to measure changes in the perceptual template and “molecular psychophysics” (Green, 1964) to estimate the internal noise, Li et al. (2008) have demonstrated that the perceptual template of the amblyopic visual system can indeed be retuned gradually through repetitive practice, and that the retuned template is less noisy and more effective in interpreting visual information. Thus, practicing position discrimination can reduce spatial distortion (internal positional noise) and enhance sampling efficiency (the ability to extract stimulus information) in amblyopic vision (Li & Levi, 2004, Li et al., 2007, 2008). The improved efficiency is a result of template retuning (Li et al., 2008). In a similar vein, practicing identification of low contrast letters in noise (Levi, 2005) improves the contrast threshold for letter recognition primarily through increased efficiency.

#### 5.4. The locus of learning

Where does perceptual learning take place? The question of whether perceptual learning reflects alterations in neural responses in early visual cortex or alterations in decision processes at a higher level has been much debated (for reviews see Ahissar & Hochstein, 1993; Fahle, 2004), and is beyond the scope of the present review. However, it is crucial for understanding recovery of visual function in amblyopia. The finding that there is partial transfer of learning from the amblyopic to the fellow eye (Levi & Polat, 1996; Levi et al., 1997; Li et al., 2008; Zhou et al., 2006), is consistent with the notion that at least some of the learning takes place at or beyond the level at which the two eyes interact (as early as layers 2 or 3 of V1). Our own work (Li & Levi, 2004; Li et al., 2007, 2008) shows that learning in amblyopia occurs via template retuning and internal noise reduction. Whether this occurs at a higher “decision stage” of visual processing, at a lower level (e.g. cortical area V1) or both [e.g. via feedback, improved lateral interaction (Polat et al., 2004) or at a low level but under top-down control (Ahissar & Hochstein, 1993; Fahle, 2004)] remains a very important open question.

#### 6. Should PL be part of the treatment armamentarium, and if so what PL?

The studies reviewed here make it clear that practicing a visual task improves performance in an amblyopic eye. The improvement is generally strongest for the trained eye, task, stimulus and orientation, but appears to have a broader spatial frequency bandwidth than in normal vision. Importantly, practicing on a variety of different tasks and stimuli seems to transfer to improved visual acuity. The success of PL raises the question of whether it should become a standard part of the armamentarium for the clinical treatment of amblyopia, and if so, whether there are lessons learned from the previous studies that could enhance the effectiveness of PL.

##### 6.1. Clinical treatment of amblyopia in children

For centuries, the standard treatment for amblyopia has consisted of: (1) refractive correction and (2) patching or penalizing the fellow preferred eye, thus “forcing” the brain to use the weaker amblyopic eye.

Interestingly, refractive correction alone can have a substantial effect (a factor of two) on improving acuity in children with amblyopia (even in some with strabismus), with about 25% of the cases resolving completely just with appropriate refractive correction (Moseley et al., 2002; PEDIG, 2006, 2007; Stewart, Moseley, Fielder, & Stephens, 2004). Thus, learning to interpret clear images after prolonged blur may be thought of as a type of perceptual learning.

Penalization of the fellow eye is the most common form of treatment, and is highly effective in young children (see Wu & Hunter, 2006 for a recent review). Typically, patients with mild to moderate amblyopia are prescribed complete occlusion for 2–6 waking hours per day, over several months to more than a year (Pediatric Eye Disease Investigator Group, 2003a, 2003b, 2006; Repka et al., 2003; Stewart, Moseley, Stephens, & Fielder, 2004). Patients with moderate to severe amblyopia are often prescribed 6–10 h or more a day (Pediatric Eye Disease Investigator Group, 2003a, 2003b), and some clinicians recommend more aggressive full-time occlusion for severe amblyopia (Bhola, Keech, Kutschke, Pfeifer, & Scott, 2006; Dorey, Adams, Lee, & Sloper, 2001; Stankovic & Milenkovic, 2007). As reported in a recent large-scale clinical study of children (3–8 years of age), the dose-response rate for occlusion is approximately 0.1 log unit (1 chart line) per 120 h of occlusion, and the treatment efficacy is 3–4 logMAR lines (Stewart,

Moseley, Stephens et al., 2004). The dose-response curve appears to plateau only after 100–400 h (Cleary, 2000; Stewart, Fielder, Stephens, & Moseley, 2005; Stewart, Moseley, Stephens et al., 2004).

The treatment outcome is dependent on a number of factors, including: occlusion dose, the depth of amblyopia, binocular status, fixation pattern, the age at presentation and patient compliance (Loudon, Polling, & Simonsz, 2003; Stewart et al., 2005). A meta-analysis by Flynn et al. (1999) of data pooled from a number of studies (in total almost 2000 children with amblyopia), showed that the two most important factors in the “success” of occlusion (defined as a visual acuity of 20/40 or better) are: the patients’ age and the depth of visual loss before treatment (Fig. 5). Interestingly, for amblyopes of any age with acuity of 20/60 or better (vertical gray line in Fig. 5), the probability of successful treatment is better than 70%. This is important, because the preponderance of acuities in amblyopes is between 20/30 and 20/60 (Ciuffreda et al., 1991; McKee et al., 2003). At these acuity levels, the impact of age is substantially reduced (i.e., the vertical distance between the three data sets is smaller).

Surprisingly, part-time occlusion in young children may also result in a concomitant improvement in stereopsis, in both anisometropic and in strabismic amblyopes (Lee & Isenber, 2003).

##### 6.2. Clinical treatment of older children and adults

It is often stated that humans with amblyopia cannot be treated beyond a certain age (Mintz-Hittner & Fernandez, 2001). In their recent review of randomized controlled clinical trials of patching and penalization, Wu and Hunter (2006) conclude that there is “no compelling evidence that treatment is beneficial for older (over age 10) children with amblyopia.” Since almost all of the perceptual learning studies have been in adults and older children, the success of conventional (and unconventional) treatment in older children and adults is worth examining more closely.

In a randomized trial, 500 amblyopic children ages 7–17 (Pediatric Eye Disease Investigator Group, 2005a, 2005b) were either provided optical correction alone, or optical correction plus patching (supplemented with atropine in 7–12 year olds). Consistent

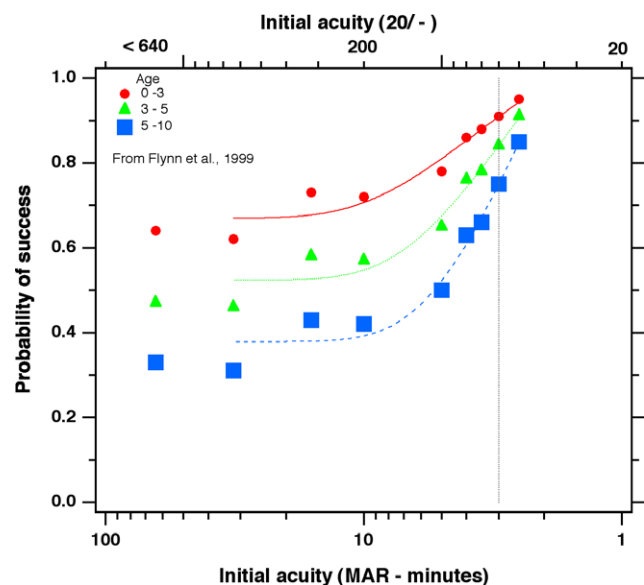


Fig. 5. The probability “success” of occlusion (defined as a visual acuity of 20/40 or better) vs the depth of visual loss before treatment (after Flynn et al., 1999). The three different symbols reflect three different age groups. The vertical gray line is drawn at an initial acuity of 20/60. Most amblyopes have acuities between 20/30 and 20/60.

with the studies described above, almost a quarter of the optical correction alone group improved by at least two lines (0.2 LogMAR) of acuity. Thus, even in older patients, optical correction by itself can improve visual acuity. In the patched group, 53% of the 7–12 year old group responded to treatment (i.e., improved by at least two lines of acuity) compared with 25% of the 13–17 year old group. Note however, that the younger group also received daily atropine, so their fellow eye may have been effectively penalized more hours per day than the older group. Interestingly, treatment was just as effective in the older (13–17 years) patients who had not been previously treated as in the younger (7–12 years) children. This suggests the possibility that some of the plasticity of those who had been previously treated may have already been expended prior to the treatment trial. A very recent report suggests that in 7–12 year olds, weekend atropine alone was about as effective in improving visual acuity and stereoacuity as 2 h of daily patching (PEDIG, 2008).

Although there are no published controlled clinical trials for treatment of amblyopia in adults, there are a number of case series that suggest that amblyopic adults can improve. For example Carl Kupfer (1957) showed marked improvement in acuity, in seven adult strabismic amblyopes, aged 18–22. All seven showed improvements ranging from 71% (20/70–20/20 – PPR 0.29) to a very dramatic improvement from being able to report hand movements only, to an acuity of 20/25 after four weeks (Fig. 6). All of these patients had relatively late onset amblyopia (2 years or later), were highly motivated and Kupfer's treatment was aggressive. The patients were hospitalized for 4 weeks during which time they were continuously patched and given fixation training. However, the very fact that adults with amblyopia can improve, suggests that there is no clear upper age limit for recovery of acuity, at least in strabismic amblyopia with an onset later than 2 years of age or so. Since Kupfer's study, there have been many reports of improvement in acuity of older people with amblyopia (e.g., Birnbaum, Koslowe, & Sanet, 1977; Wick, Wingard, Cotter, & Scheiman, 1992). A case report (Simmers & Gray, 1999) showed that occlusion therapy appeared to improve not only visual acuity, but also position acuity in an adult strabismic amblyope. These reports have in common the fact that treatment, in general, went beyond simply correcting and patching the amblyopic eye.

Plasticity in adults with amblyopia is also dramatically evident in the report of El Mallah, Chakravarthy, and Hart (2000), of amblyopic patients whose visual acuity spontaneously improved in the wake of visual loss due to macular degeneration in the fellow eye (Fig. 7). There are also reports suggesting that some adult

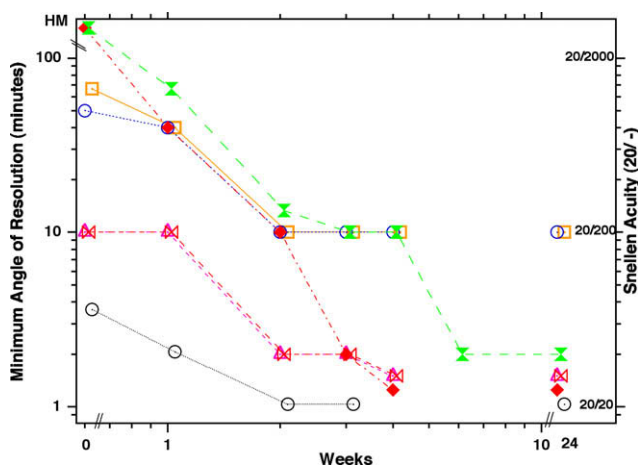


Fig. 6. Acuity (MAR in minutes) vs. weeks of treatment in seven adult strabismic amblyopes (replotted from Kupfer, 1957).

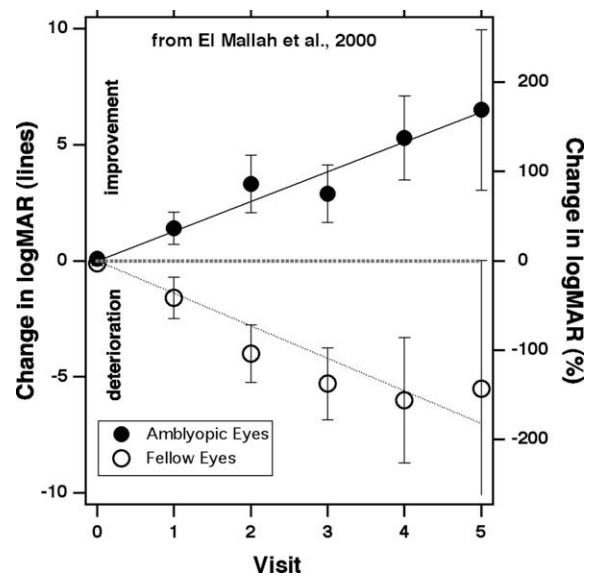


Fig. 7. The change in acuity of the amblyopic (solid) fellow (open) eyes of amblyopic patients whose visual acuity spontaneously improved (positive values) in the wake of visual loss (negative numbers) due to macular degeneration in the fellow eye (replotted from El Mallah et al., 2000).

amblyopes recover vision in their amblyopic eye following loss of vision in their fellow non-amblyopic eye (Rahi et al., 2002; Vereecken & Brabant, 1984). These studies are consistent with the notion that the connections from the amblyopic eye may be suppressed rather than destroyed. Loss of the fellow eye would allow these existing connections to be unmasked, as occurs in adult cats with retinal lesions (Chino, Kaas, Smith, Langston, & Cheng, 1992; Heinen & Skavenski, 1991; but see Smirnakis et al., 2005). Of course removing one eye is not an option for treatment; however these findings strongly implicate suppression by the non-amblyopic eye, which needs to be considered in designing an effective treatment.

### 6.3. Beyond patching/penalization

There have been numerous attempts to increase the effectiveness of treatment for amblyopia, beyond patching and penalization. These attempts range from the sublime to the ridiculous. They include: subcutaneous injection of strychnine, electrical stimulation of the retina and optic nerve, flashing lights, red filters and rotating gratings (reviewed by Revell, 1971), administration of Levodopa (Leguire, Rogers, Bremer, Walson, & McGregor, 1993, and see Levi, 1994) and shocks to the brain via Transcranial Magnetic Stimulation (TMS – Thompson, Mansouri, Koski, & Hess, 2008). A discussion of the many attempts is beyond this review; however, few have been subjected to rigorous scrutiny, and those that were often failed to stand up to it (e.g. Tytla & LaBow-Daily, 1981). A specific example of this is the CAM treatment (Campbell, Hess, Watson, & Banks, 1978), which might be considered to be the first application of “perceptual learning” in amblyopia. The CAM treatment consisted of having amblyopic children passively viewing slowly rotating stripes with their amblyopic eye (while wearing a patch over their preferred eye). Seven different stripe sizes (spatial frequencies) were each shown for 1 min per day (i.e., total time of 7 min per day), in order to provide exposure to a broad range of spatial frequencies and all orientations. To maintain their interest the child played “naughts and crosses” (tic-tac-toe) on a transparent Perspex plate. In their preliminary report, 22 children, median age 8.5 years (4 years, 5 months to 12 years) completed the treatment (i.e., there was no further improvement in visual acuity,



or acuity was equalized in the two eyes). The median PPR was a very impressive  $\approx 0.5$  and the median duration of treatment was 0.35 h (mean 0.75 h). Unfortunately, this promising result was not borne out by the control studies that followed. For example, while Tytla and Labow-Daily (1981) replicated the improvements in both single letter acuity and contrast sensitivity, they found comparable improvements in their control group. This control group, like the experimental group, wore a patch over the non-amblyopic eye and played the same drawing games on a transparent sheet. The only difference between the two groups was that the experimental group was exposed to gratings, while the control group was exposed to a grey disc of the same mean luminance as the gratings. Tytla and Labow-Daily concluded that the improvements could be attributed to the effects of short-term occlusion (with near visual activities) rather than to any effect of the rotating gratings. Similar conclusions were reached by other control studies (Ciuffreda, Goldner, & Connelly, 1980; Nyman, Singh, Rydberg, & Fornander, 1983; Schor & Wick, 1983).

The CAM treatment differs from the perceptual learning studies reviewed above in a number of important ways. First, CAM relies on passive exposure, whereas PL requires active participation and attention. A second important difference is the duration of exposure. As shown above, duration is an important determinant of outcome. However the CAM treatment is very brief. However, one important lesson to be drawn from CAM is that any “promising” new method should be examined critically and there is a clear need for careful controlled studies.

An important aspect of these methods is that many were aimed at “active” stimulation of the amblyopic eye, to supplement patching. Indeed, most of the randomized clinical trials discussed above include an hour a day of near activities during patching, and preliminary evidence suggests that the near activities may enhance the effects of patching (PEDIG, 2005a, 2005b). The studies reviewed above suggest that perceptual learning may be a very effective form of active (we prefer the term “supervised”) treatment.

Finally, since amblyopia always occurs in the context of comprised binocular input, an important consideration in treatment is the ability to “use” the amblyopic when the fellow eye is open, i.e., elimination of suppression and establishment of binocular fusion and stereopsis (Ciuffreda et al., 1991; Mitchell, 2008). Indeed, one of the unwanted side-effects of prolonged patching may be a reduction of binocularity and stereopsis.

#### 6.4. PL when/for who might it be useful?

Based on the clinical studies reviewed above, amblyopia is most often and most successfully treated in infants and young children (less than 6 years old) using a combination of refractive correction, patching and/or penalization and some form of “active” treatment. This treatment is effective and reasonably well tolerated (Wu & Hunter, 2006). However, it can reduce binocularity and stereopsis, and have an impact on the child’s self-esteem (Webber et al., 2008). To date, to our knowledge there are no published accounts of PL in amblyopes in this age group, and because of the high success rate of conventional treatment, it is not clear that PL is a necessary addition to the armamentarium for this age group. It is instructive that in the Chen et al. study, three young children dropped out of the PL group due to boredom. Thus, if PL is to be used as an added arrow in the quiver, we believe it is most likely to succeed in older children and adults with mild and moderate amblyopia. On the other hand, if perceptual learning can be made engaging for young children, along the lines of “Rocketship Psychophysics” (Abramov et al., 1984) it could be very helpful in speeding the treatment, and reducing the unwanted physiological and psycho-social effects of patching.

Although it is now clear that it is possible to improve acuity in older children and adults, treatment via prolonged patching is often less practical because of the visual demands of school and work. In the Chen et al. (2008) study, four adults withdrew from the patching group because they could not tolerate occlusion. Moreover, it is not clear whether patching alone is useful in adults, since there are no randomized patching trials in adults. Thus, if supervised activities such as PL can significantly reduce the duration and increase the effectiveness of patching, PL would be a highly worthwhile clinical option. Two of the published PL papers had control groups. Polat et al. (2004) had 10 subjects who were patched and were given a psychophysical task (but with low spatial frequency, high contrast targets). This placebo group showed no improvement in visual acuity, whereas the PL group showed a substantial improvement in visual acuity (PPR  $\approx 0.34$ ). Zhou et al. (2006) also had a control group whose visual acuity and contrast sensitivity were tested at least 10 days apart, but were given no patching or placebo treatment.

In their pilot study, Chen et al. (2008) had one group of anisometropes perform PL and a second group patch, and they report a better acuity outcome for the patching group (Table 1; PPR 0.46 vs 0.56). However, the two groups differed in age (the patching group had many more children younger than eight and far fewer adults than the PL group), and the duration of patching was more than an order of magnitude longer than the duration of PL. Based on the dose-response rate of patching in their population ( $\approx 0.1$  log units/150 h) they calculate that it would require about 385 h to achieve the improvement that the PL group showed after just 48 h. Li et al. (2007) made a similar argument about the substantial improvement in acuity shown by their juvenile amblyopes. We suspect this may be an underestimate, given that the PL group was older, and may therefore require even longer patching per 0.1 log unit improvement. What is clearly needed is a randomized clinical trial directly comparing patching alone with patching plus PL.

#### 6.5. How much improvement is enough?

Even if PL does indeed reduce the time needed to patch, how much improvement is enough to warrant the time and effort required? Much of the emphasis in the literature has been on the amount of improvement (specified in various ways). Inspection of Table 1 shows that PPR for Snellen acuity may be (on average) as good as  $\approx 0.3$ , i.e., about a factor of three. While this represents a substantial improvement, it is important to consider the initial acuity level. An improvement in acuity from 20/240 (minimum angle of resolution, MAR = 12') to 20/80 (MAR = 4'), while impressive, may provide little or no useful gain in quality of vision in everyday life, because the fellow eye is so much better that binocular vision is precluded. On the other hand, for an initial acuity of 20/40–20/60, a factor of three improvement would effectively eliminate the amblyopia, and may allow the possibility of binocular function (Li & Levi, 2004; Li et al., 2007). Recent work suggests that both anisometropic and strabismic amblyopes may retain binocular function if the signals from the two eyes are appropriately equated (Baker, Meese, & Hess, 2008; Baker, Meese, Mansouri, & Hess, 2007). Importantly, most amblyopes have an initial acuity of 20/60 or better.

#### 6.6. Principles of PL for clinical application

A review of the extant studies suggests several principles for effective perceptual learning in amblyopia. First, although almost all of the published studies demonstrate learning, the most effective methods for transfer to acuity seem to involve practice under conditions where performance is severely impaired (e.g. contrast

detection or position acuity with stimuli near the cut-off spatial frequency), with trial-by-trial feedback. It is less clear whether training should be done at several orientations (although this seems logical) or whether flankers are required to optimize the transfer to acuity. Polat et al. (2004) did both and showed greater transfer to Snellen acuity than Zhou et al. (who did neither). Thus, in future studies, the use of a combination of different visual tasks for amblyopia treatment should also be considered. Second, a stringent stopping rule seems to be important in maximizing learning and transfer (Li et al., 2007, 2008). Third, it seems crucially important to make the stimuli and tasks interesting and engaging. Thus, an ideal paradigm might involve detecting and localizing near threshold Gabor patches with spatial frequency close to the cutoff and varying orientation, in the context of a video-game (e.g. Abramov et al., 1984), with varying degrees of clutter. Randomly interleaved staircases would maintain task difficulty for both tasks and all stimulus conditions, and observers would get feedback. Ideally, both the stimulus details (spatial frequency etc) and the dose would be individualized. However, a large-scale multi-center clinical trial would be necessary to quantify the dose-response relationship for different ages of onset, types and depths of amblyopia and optimize the treatment dose and schedule. Because binocular visual input is crucial in the development of normal binocular vision (Mitchell, 2008), we are currently developing stereoscopic methods to promote recovery of binocular function. Finally, as noted above, since refractive correction alone can have a significant impact on acuity, accurate refractive correction is essential before the commencement of perceptual learning, and the refraction (including the axis and power of astigmatism) should be regularly reviewed and refined during the course of training.

### 6.7. Amblyopia and stroke – compensation or repair

In some respects, the successful treatment of amblyopia in older children and adults has analogies in the recovery of function following stroke. It is now well accepted that stroke patients frequently show improvement in function, but, as in amblyopia, the nature and mechanisms of this recovery are poorly understood. Indeed, specific motor therapies, which include constraining the unimpaired limb combined with extensive training of the impaired limb and behavioral techniques aimed at transfer to the real world can be highly effective (Gauthier et al., 2008). This is, at least on the surface, similar in concept to patching the unimpaired eye and providing extensive supervised experience to the impaired eye. An important question in considering the improvement following stroke is whether it reflects genuine neural recovery (repair) per se, or whether it is due to compensation. Kolb, Cioe, and Williams (2008) discusses this in the context of the “problem of the three-legged cat” – “When cats are struck by automobiles they commonly suffer injury to one of the rear legs. The common veterinary treatment is to remove the injured leg. The cats have severe limitations in movement after the surgery but over a period of months they “recover” and become nearly as agile as before the amputation. The restoration of mobility can be truly impressive to the point that an observer may not even notice that there are only three legs. But the cat has not “recovered” the lost leg. Rather, the cat has compensated for the loss of the leg.”

By analogy, the treatment of amblyopia beyond the sensitive period poses the problem of the “one-eyed amblyope”. Does PL result in the development of new connections, or does it allow compensation by unmasking connections that were suppressed or enabling attention to signals that were present but weak? Understanding how perceptual learning improves performance is crucial, not only for understanding plasticity in amblyopia,

but also following damage to extrastriate cortex in adult animals (Huxlin, 2008).

### Acknowledgements

Supported by a Grant (RO1 EY01728) from the National Eye Institute, NIH, Bethesda, MD. We are grateful to Susana Chung, Zhong-Lin Lu and Uri Polat for their thoughtful comments and input.

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