Extended Perceptual Learning Results in Substantial Recovery of Positional Acuity and Visual Acuity in Juvenile Amblyopia

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Purpose. Children with amblyopia demonstrate modest improvements in both positional and visual acuities (~30%) after a short period (15 hours, 4000 trials) of perceptual learning. The present study was conducted to determine whether extended training is necessary for optimal treatment of amblyopia.

Methods. Two children, aged 9 and 12 years, with previously untreated severe amblyopia (Snellen acuity, 20/100–20/125) practiced a position-discrimination task repeatedly over 3 months (100 hours, >25,000 trials by each observer). The task was to judge which of three pairings of two groups of eight Gabor patches was misaligned. Positional noise was used to investigate the neural mechanisms involved in learning position discrimination.

Results. After practice both observers showed substantial recovery in both positional and letter acuities (~60% and 2–4 chart lines) and both also regained significant stereoacuity. In the first 20 hours, the recovery rate was comparable to that of 12 previously treated amblyopes. However, extending the treatment dosage for an additional 30 hours resulted in substantially greater plateau improvements. These improvements were primarily the results of a marked increase in sampling and processing ability and, to a lesser degree, to a decrease in spatial distortion.

Conclusions. The results show that in two juvenile amblyopes, perceptual learning extended over an accumulated dosage of ~50 hours may be an efficient and effective adjunct to occlusion for reversing amblyopia. When combined with occlusion, perceptual learning may significantly speed up the time to recovery in children with amblyopia. (*Invest Ophthalmol Vis Sci.* 2007;48:5046–5051) DOI:10.1167/iovs.07-0324

Amblyopia is a developmental disorder of spatial vision.[1,2] The key clinical feature is reduced corrected visual acuity, without any manifest eye disease. For several centuries, the main method of treatment of amblyopia has consisted of patching or penalizing the fellow preferred eye, thus "forcing" the brain to use the weaker amblyopic eye. Typically, patients with mild to moderate amblyopia are prescribed complete occlusion for 2 to 6 waking hours per day, over several months to more than a year.[3–7] Patients with moderate to severe amblyopia are often prescribed 6 to 10 hours or more a day,[8] and some clinicians recommend more aggressive full-time occlusion for severe amblyopia.[9–11] 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 hours of occlusion, and the treatment efficacy is 3 to 4 logMAR lines.[5] The dose–response appears to plateau only after 100 to 400 hours.[5,12,13] The treatment outcome is dependent on occlusion dose, the depth of amblyopia, binocular status, fixation pattern, the age at presentation and patient compliance.[12,14]

One recently proposed method for improving the effectiveness and efficiency of treatment that has received considerable attention is "perceptual learning," (i.e., repeated practice of a visual task). For example, practicing Vernier acuity,[15,16] position discrimination,[17] contrast detection,[18–20] grating resolution[20] and letter recognition[21,22] all induce some degree of recovery of vision in adults with amblyopia, often (though not always) with transfer to visual acuity. It is important to note that during the training sessions, the nonamblyopic eye is occluded, and so the improvements most likely result from the combined effects of occlusion and perceptual learning.

One might expect that young children, whose developing brain should be more plastic, would show greater improvement than adults after perceptual learning. However, we found a similar degree of improvement in children as in adults after perceptual learning.[23] It is worth noting that those children had already undergone occlusion therapy before the start of the experiments. It is possible that prior treatment may have already resulted in improvement in vision, leaving limited room for further improvement.

In the present study, we sought to explore the limits and time course of perceptual learning as an adjunct to occlusion in two previously untreated childhood amblyopes (9- and 12-year-old) and to investigate the neural mechanisms underlying the visual improvement using positional noise. In our previous studies,[23] observers underwent a 10-session training course (~15 hours). Given the fact that the effects of occlusion only plateau after 100 to 400 hours,[5,12,13] in this present study we extended the period of training to 50 to 60 sessions (~90–100 hours) and compared the dose–response relationship of occlusion combined with perceptual learning with that of occlusion therapy reported from previous studies.

Methods

Observers

Both children received a diagnosis of previously untreated severe amblyopia. Observer AL, 8.8 years old, had unilateral strabismus, and observer SG, 12 years old, was anisometropic. Both had reduced vision of 20/100 to 20/125 (Snellen line letter acuity) in their amblyopic eyes, with normal vision (~20/16) in the fellow sound eyes. They also presented mild crowding deficits (about 1 letter line), meaning they had better visual acuity when isolated letters were presented.[24] Both of them failed stereo tests, indicating that they had no gross stereopsis (or >400 arcsec). Their clinical data are summarized in Table 1. In this study, visual acuity was measured using Bailey-Lovie logMAR letter charts (National Vision Research Institute of Australia, 1978). Ste-

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TABLE 1. Clinical Data of the Two Children

Observer	Age (y)	Gender	Type	Cover Test	Eye	Refractive Error (Subjective)	Line Letter Acuity (Single-Letter Acuity)	Stereo Tests
AL	8.8	M	Strab.	R 4^{Δ} XT	R	$+3.50/-0.50\times50$	$20/100^{-2}$ ($20/80^{-1}$)	Failed
					L	$+3.50$	20/16	
SG	12	M	Aniso.	NMD	R	$+0.75/-0.25\times55$	$20/16^{-2}$	Failed
					L	$+4.00/-0.50\times95$	$20/125^{+2}$ ($20/80^{-2}$)	

Strab., strabismus; Aniso., anisometropia; NMD, no eye movement detected.

reotests (Randot [Stereo Optical Co., Inc., Chicago, IL] and Frisby [Clement-Clarke Ltd., Harlow, UK]) were used to measure stereoacuity for observers AL and SG, respectively. Neither of the observers had prior experience in psychophysical experiments.

The participants practiced the position-discrimination task repeatedly over 3 months, 4 to 5 days a week. Each training session was approximately 1.5 to 2 hours including breaks (~15–30 min). Testing and training were performed with the observer wearing best optical correction, and the visual acuity values reported throughout the paper are for best corrected acuity. All testing was performed in the Amblyopia Research Laboratory at the University of California-Berkeley. The research adhered to the tenets of the Declaration of Helsinki. The experimental procedures were approved via the University Committee for Protection of Human Subjects. Assent was obtained from child observers, and informed consent was obtained from their parents before the children began the study.

Position Discrimination

The stimuli and methods are essentially identical to those used in a previous study of perceptual learning in childhood amblyopia[23] and are described briefly as follows. A three-alternative, forced-choice (3AFC) procedure was used to determine the position-discrimination threshold. As illustrated in Figure 1, the observer's task was to select the one misaligned pair of Gabor patch groupings out of three choices (top, middle, or bottom). Each grouping consisted of eight discrete Gabor patches (carrier spatial frequency = 5 cyc/deg; λ = 12 arcmin) arranged in a horizontal row.

FIGURE 1. Visual stimuli with positional noise. The observers' task was to indicate which of three pairs of Gabor patch groupings was misaligned (top, middle, or bottom). Positional noise was introduced by jittering the position of the Gabor patches according to a Gaussian distribution in vertical direction. In this example, the top stimulus is not aligned; the average patch position of the *right* Gabor patch grouping is higher than that of the *left* Gabor patch grouping. Trial-by-trial feedback was provided audiovisually to observers (e.g., the angel adjacent to the top grouping).

To understand the underlying mechanisms of perceptual learning, we introduced positional noise to the Gabor patches by varying their vertical positions according to a Gaussian distribution function. The use of positional noise with a linear noise averaging model allows us to measure the sampling efficiency (ability to extract and use stimulus information) and internal positional noise (perceptual distortion of spatial vision). The average offset of each jittered Gabor patch grouping was constrained to be 0 by uniformly shifting the eight patches. An offset cue was produced by randomly shifting the right Gabor patch grouping up or down.

A modified interleaved staircase method was adopted to control the offset magnitude between the two Gabor patch groupings and track the individual thresholds.[23] The response data were fit with a Weibull psychometric function, and positional threshold was defined as the offset at which 66% correct responses were obtained.

Observers were trained at three (AL) or four (SG) positional noise levels (including zero); 132 responses were required for each noise level. Each session consisted of 396 and 528 trials for observers AL and SG, respectively. Fewer positional noise levels and trials were required from observer AL because of his younger age. Viewing was monocular at 2 m, and the eye not being tested was covered with a standard black eye patch. The experiment was self-paced, and a break was given whenever the subject requested one. More than 25,000 trials were performed by each observer over a 3-month period (~90–100 hours in total).

The visual stimuli remained on the screen until the observer gave a response, so that observers were able to analyze each pair of Gabor patch groupings carefully before responding. The adaptive staircase adjusts the visual task difficulty automatically according to the observer's individual performance, so that most of the time the observers are challenged by stimuli that are close to their visual limit. Our experimental design involves the element of direct feedback and a computer game situation of competing for better scores. Trial-by-trial feedback was provided audiovisually following each trial to keep the child engaged.

Noise Averaging Modeling

A positional averaging model was used to quantify the effects of external noise (σ_e) on the threshold (σ_{th}):

$$\sigma_{th}^2 = 2d'^2\left(\frac{1}{k} - \frac{1}{n}\right)(\sigma_e^2 + \sigma_i^2),$$

where σ_i is the equivalent input noise (or uncalibrated internal spatial distortion), k is the number of samples extracted, and n is the total number of samples. The term $1/n$ is present in equation 1 because of the 0 mean adjustment of each Gabor patch grouping. In this study, each grouping consisted of eight Gabor patches; hence $n = 8$. For 66% correct response probability, the detectability (d') was 1.1.[25] By measuring the thresholds at different external noise settings, σ_i and k can be estimated with a least-squares algorithm. To quantify the ability to extract stimulus information for positional averaging, sampling efficiency (E) was defined as

$$E = \frac{k}{n} \cdot 100\%.$$

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Results

Learning Position Discrimination

Practicing the task repeatedly substantially improved positional acuity in both observers. Figures 2A and 2B show the positional thresholds as a function of training sessions for both observers (AL and SG). On average, performance improved approximately 27% after the first 10 sessions, only slightly more than occurred after 7 to 10 sessions in five previously treated children with amblyopia (19.2% ± 5.5%).[23] The important new finding is that performance continued to improve, reaching a stable plateau only after 25 training sessions for all noise levels (as shown by the bilinear regression fit in Fig. 2). At plateau, across all noise levels position thresholds of both observers improved ~60% (AL: 65.2%; SG: 55.6%).

In Figures 2C and 2D, the threshold data are replotted as a function of external positional noise, and the curves represent the fitted threshold-vs.-noise (TvN) functions. These TvN curves show that when the external noise is relatively small compared with the observer's internal positional noise, thresholds are more or less constant; however, once the external noise exceeds the observer's equivalent internal noise (at the "knee point" in the curve), thresholds increase with the external noise. For clarity, we divided the training sessions into six groups and calculated the average thresholds for each curve fitting. The TvN curves shift systematically downward from session to session as thresholds decrease. The pretraining positional thresholds of the amblyopic eye (sessions 1 to 2: blue circles), especially for 0 and intermediate noise levels, were substantially elevated when compared with those of the fellow nonamblyopic eye (gray squares) as shown in Figures 2C (observer AL) and 2D (observer SG). On average, the positional thresholds measured in the amblyopic eyes were elevated by 311%, 163%, and 31% for 0, 0.67, and 1.33 arcmin noise levels, respectively, in comparison to the fellow eye for the two observers. Of interest, the posttraining performance of the amblyopic eyes (red curve) for medium and high noise levels was significantly *better* than the pretraining performance of the fellow nonamblyopic eyes (gray curve). It is worth noting that for zero noise, the posttraining thresholds were still higher than the thresholds of the fellow eye (AL: 88.3%; SG: 9.9%), but the difference was substantially decreased compared with the pretraining curve.

Our TvN analysis shows that the improvement in positional acuity can be attributed primarily to a very marked increase in sampling efficiency. Sampling efficiency increased by a factor of 6.6 (red circle: from 2.1% to 13.8%) for AL, and by a factor of 3.2 (blue square: from 5.5% to 17.9%) for SG (Fig. 2E), indicating that an increased number of target patches were extracted and used for positional processing and averaging after the course of training. In other words, after training, the observers were able to sample visual information more efficiently from the visual stimulus. This improvement, as a result of extended perceptual learning, is substantially greater than the approximately 1.33-fold (33%) improvements, as indicated by the black dashed line (Fig. 2E), we have reported in earlier studies in a dozen amblyopes (five children and seven adults as shown by the filled symbols in Fig. 2E) after 7 to 10 training sessions.[23,26] In the present study, we also observed about a 20% decrease (from 2.1 to 1.6 arcmin) of additive internal spatial noise, or perceptual distortion, in observer SG (Fig. 2F, blue square).

Generalized Transfer of Learning to Letter Recognition and Depth Perception

We observed fast recovery of visual acuity over sessions in both observers (Fig. 3A). Before the commencement of visual training, their isolated letter acuities were nearly identical (~20/80), and both observers showed crowding[27] Their isolated-letter acuity (open symbols) was better than their crowded line letter acuity (solid symbols). Both crowded and isolated letter acuities improved significantly while the observers were practicing position-discrimination tasks. The results are replotted as percent improvement versus cumulative training hours for crowded and isolated letters in Figures 3B and 3C, respectively. The solid lines show the exponential function fit to the visual acuity data in the figures.

Observer AL showed a ~60% improvement (approximately 0.4 log unit or 4 letter lines on a logMAR letter chart), whereas SG showed a ~37% improvement (2 letter lines) in both isolated and crowded letter acuities after 25 sessions (40–50 hours of training). An important question is whether this improvement can be simply attributed to the 40 to 50 hours of occlusion that accompanied the perceptual learning. Although we cannot rule this explanation out, we can compare the present results with the well-documented effects of occlusion. As noted earlier, the dose–response rate for occlusion (in patients aged 3–8 years) is ~0.1 log unit/120 hours of occlusion,[5] shown by the dashed in Figure 3B. Observer SG's acuity improvement fell very close to the predicted effects of occlusion alone, but we note that SG (12 years old) was older than the original study group in Stewart et al.[5] On the other hand, based on the dose–response curve for occlusion, it would require approximately 350 hours of occlusion alone to obtain the same amount of improvement demonstrated by AL in about one seventh of the time.

As is evident in Figure 3B, the improvement in acuity of both observers in the first 20 hours was comparable to that of the dozen observers who participated in our previous studies[26,28]: mean improvements of 27% and 33% for both childhood (Xs, 7–10 years old; $n = 5$) and adult (filled squares, 21–55 years old; $n = 7$) amblyopes, respectively. Note that all the childhood amblyopes in the earlier studies had already completed occlusion therapy before starting the learning experiments.

Figure 2. Perceptual learning of position discrimination. (**A**, **B**) Positional threshold as a function of training session. With practice, thresholds for all four noise levels (0–2.67 arcmin) decreased gradually across sessions, which means that the observers were able to detect a smaller offset (or misalignment) between the two Gabor patch groupings and reached a performance plateau after approximately 25 sessions. At the beginning, fewer positional noise levels and trials were required from observer AL because of his younger age. Starting from session 31, he was also tested at all four noise levels and more trials to maximize the improvement; however, no further improvement was observed across sessions. (**C**, **D**) Positional threshold as a function of external positional noise levels across sessions (s). With practice, the curves shifted downward (increased efficiency) gradually and also leftward, from session to session. *Blue* and *red solid lines*: the pretraining and plateau TvN curves, respectively. *Gray line*: the TvN function for the nonamblyopic eye (NAE). For clarity, the data points are presented only for the pre- and posttraining sessions. Error bars, SEM. (**E**, **F**) Mechanisms of perceptual learning. Both observers showed a remarkable increase in sampling efficiency (AL: increased by 560%; SG: increased by 224%), with observer SG showing a 20% decrease in internal spatial distortion. *Shaded areas*: decreased internal noise and increased efficiency in posttraining measurement when compared with pretraining measurement. *Dashed line*: mean data of five child and seven adult observers (*filled symbols*) from our previous studies for comparison: a 14% decrease in internal spatial noise and 33% increase in efficiency.[23,26] Note that the five child observers in the previous study had already completed occlusion therapy (OT) before they began the perceptual learning treatment.

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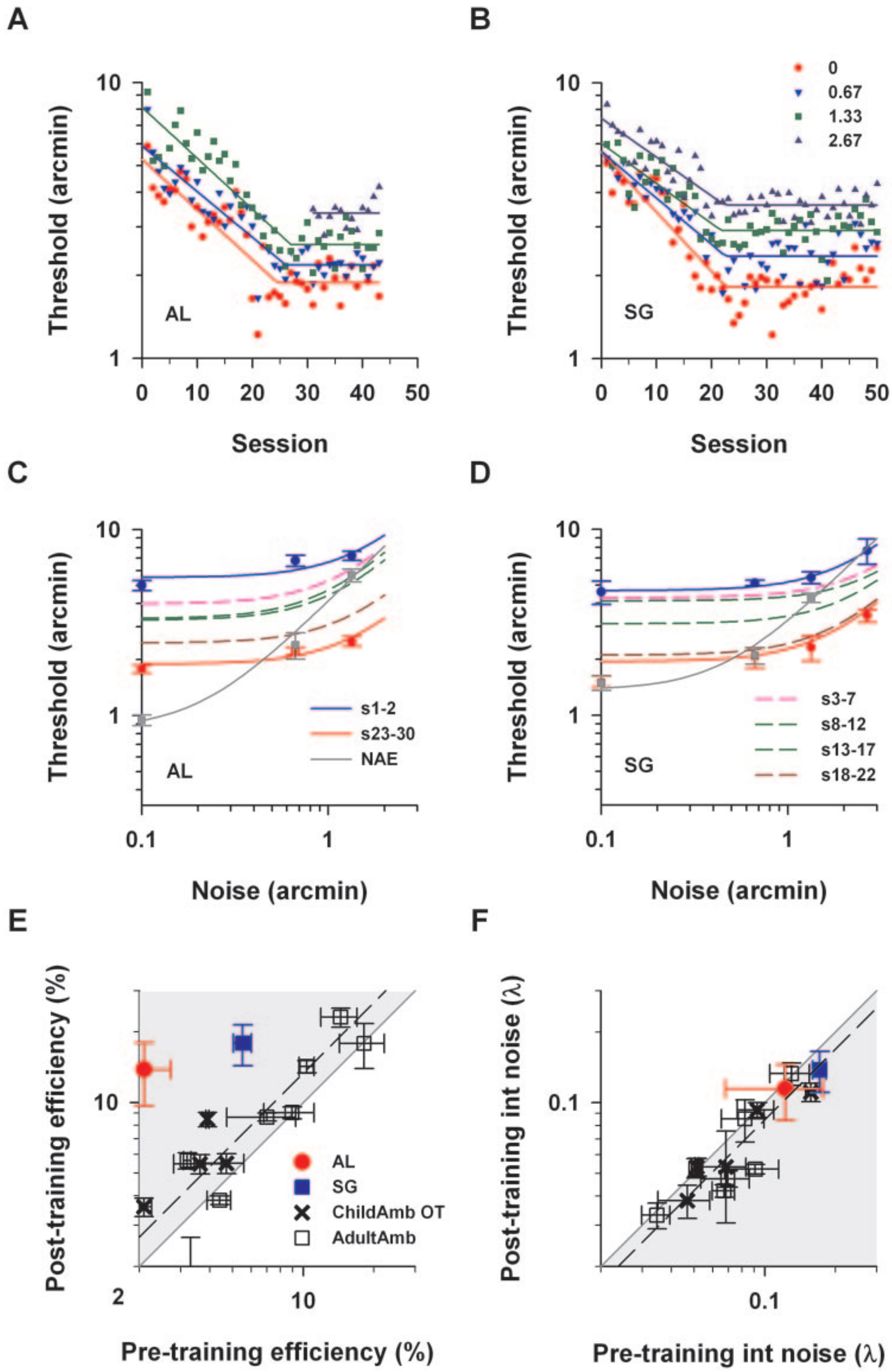
A comparison of Figures 3B and 3C suggests that single-letter acuity (Fig. 3C) recovered faster than did crowded-letter acuity (Fig. 3B), and this observation is borne out by the time constants of the best fit exponential functions (solid lines). In the first 30 hours, the mean recovery rates were 15% per 10 hours for isolated letters and 12% per 10 hours for crowded letters (AL: 20.7%; SG: 9.4% for isolated and AL: 15.1%; SG: 8.6% for crowded). Each 15% improvement represents about 1 logMAR chart line. The time constants for isolated letters (AL: 10.1 hours; SG: 20.4 hours) were significantly shorter than those for crowded letters (AL: 25 hours; SG: 32.3 hours), implying that two different limiting mechanisms are involved and that more time is needed for the effects of crowding to be resolved.

To evaluate the long-term stability of the visual acuity outcome, we remeasured the visual acuity of AL after cessation of treatment and found that most of the acuity improvement was maintained 7 months after the training was completed (Fig. 3A, gray arrows).

Of interest, after practicing position discrimination, both observers also demonstrated measurable stereopsis (AL: 70 arcsec; SG: 85 arcsec). Note that neither demonstrated mea-



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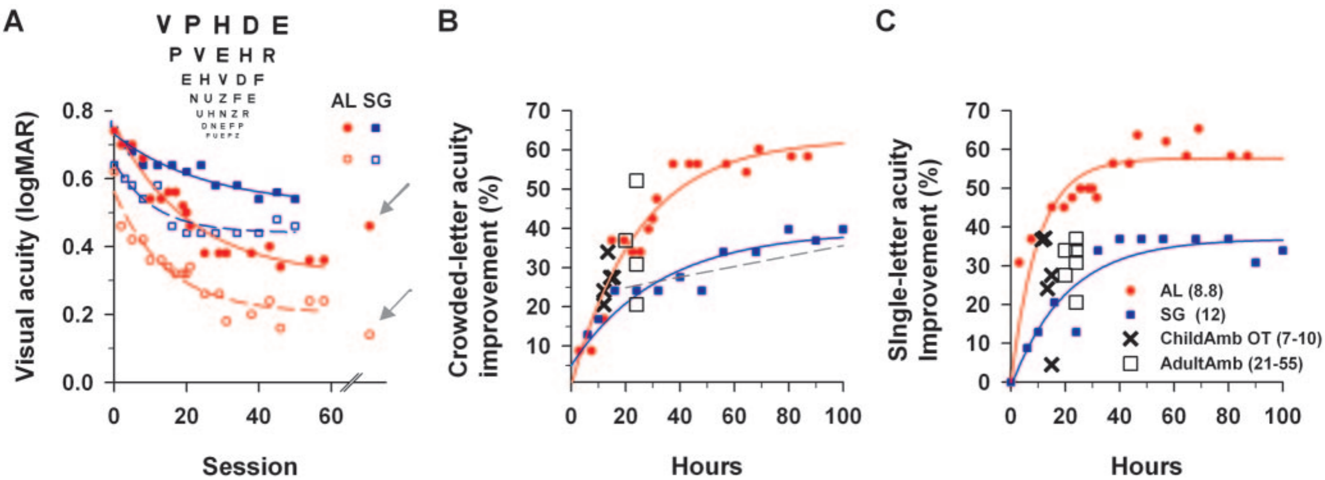

FIGURE 3. (**A**) Fast recovery of visual acuity. Solid and open symbols indicate crowded-letter acuity and single-letter acuity, respectively. *Arrows*: maintenance data 7 months after the last day of training. *Inset*: a logMAR visual acuity letter chart; each 0.1 logMAR unit represents 1 letter line. The acuity improvement almost reached the plateau level at session 30. Training with high spatial frequency stimuli could further maximize the improvement; therefore, AL was tested at 4 m from sessions 31 to 45. However, no significant change in positional (data not shown) and visual acuities was observed across those sessions. (**B**, **C**) Percentage improvement in visual acuity as a function of training hours. The plateau improvement of observer AL was much greater than that of the children previously with occlusion therapy (OT) in the same age range (*cross*) and adults (*open squares*) reported in our studies.[23,26] For comparison, the *gray dashed line* shows the dose–response data of occlusion therapy from a recent study of 94 amblyopic children (3–8 years old).[5]

surable stereoacuity (or >400 arcsec) before the commencement of the experiments.

Discussion

Our results showed that the reduced vision in the two children with amblyopia was substantially recovered after intensive perceptual learning. Both positional and Snellen acuities were substantially improved, but not entirely normalized, after the children practiced position discrimination. The present study differs in two important ways from previous studies of perceptual learning in childhood amblyopia. First, the two observers in the present study were "fresh" (previously untreated) amblyopes. Previous studies have trained children who had already undergone substantial occlusion and had reached a plateau in their response to occlusion. Second, previous studies involved far fewer hours of practice, typically 15 to 25.

Position Acuity

Both observers showed substantial improvement (~60%) in position acuity at plateau, considerably greater than in our previous studies. In our previous study, using identical methods, we found that four of the five children showed improvements in position acuity, which averaged approximately 30%. Since the roughly 30% improvement in the first 15 hours in the present study was similar to that of previously treated amblyopes, we attribute the large increase at plateau to prolonged learning. As noted in Figure 2, asymptotic learning was not achieved until ~25 sessions (40–50 hours). This substantial improvement reflects primarily a three- to sixfold increase in sampling efficiency, much greater than observed in our earlier study. An important finding was that after learning, performance of the amblyopic eye was almost as good as (low noise) or better than (high noise) that of the fellow eye.

We postulate that the use of positional noise with feedback given to the observers' responses could contribute to the reweighting of neural connections[28] and the modest recalibration of the spatially distorted visual system. It would be interesting to record the retuning dynamics of behavioral receptive fields in amblyopic vision with the use of an efficient reverse-correlation technique.[29]

Letter Acuity

Similar to the results of our previous study, we found that the improvement in position acuity transferred to letter acuity. The plateau improvement in both isolated and crowded-letter acuity was considerably larger for AL than for SG. Amblyopes differ substantially in their individual responses to treatment, so we can only speculate about why our observers differed in their responses. It is worth noting that AL is considered to be still within, or at the limit of, the critical period, whereas SG is not. We suspect that the difference in their responses could be due in part to the age difference, since in prior studies, investigators have reported that the most effective timing of treatment may interact with the age at presentation.[12,30]

Comparing the present results with our previous studies,[23,26] the rates of improvement were comparable to those of both amblyopic children and adults. However, the plateau improvements in position acuity for both observers, and in visual acuity for AL, are considerably greater. Thus, it is clear that more than the 10 sessions used in our previous studies[23,26] are needed to reach steady plateau performance in patients with amblyopia. The present findings suggest that extended training sessions (>50 hours for severe amblyopia) are indicated for successful amblyopia treatment and maximizing visual outcomes.

Does Perceptual Learning Provide an Added Benefit?

Occlusion therapy is the "gold standard" method for treating amblyopia. In the present study, and all previous perceptual learning studies, the subjects wore occlusion while performing the visual task, and so it is reasonable to ask whether "active" perceptual learning actually provides an added benefit over occlusion alone.

We argue that perceptual learning does indeed provide an added benefit for the following reasons. First, in our previous study,[23] we found that perceptual learning improved both position discrimination and letter acuity in amblyopes who were no longer responsive, or were nonresponsive, to occlusion, and demonstrated that even after occlusion therapy was terminated, room remained for visual improvement with perceptual learning. This finding reveals neural plasticity that

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might not be "taken up" completely by occlusion therapy. Second, a previous study showed that the dose–response rate for occlusion (in patients aged 3–8 years) is ~0.1 log unit/120 hours of occlusion[5] and to the extent that we can use it as a basis for comparison, it would require approximately 350 hours of occlusion alone to obtain the ~0.4 log unit improvement demonstrated by AL in approximately one seventh of the time. It is important to note that there are individual differences in responding to occlusion therapy; 2 of 72 patients in the study by Stewart et al.[5] showed recovery of as much as 4 and 8 chart lines after a cumulative dose of 100 hours of occlusion. Although we cannot rule out the possibility that AL was one of these rare "superresponders," we think it is more likely that the combination of occlusion and perceptual learning sped up his response. Finally, the effects of occlusion alone on position acuity have been shown to be modest,[31] whereas the effects noted in this study were substantial.

We suggest that this new approach, combining occlusion with perceptual learning, may be a useful method for obtaining the optimal treatment outcome in the shortest possible time. Eliminating or reducing the need to wear an eye patch in public would eliminate, or at the very least reduce, the emotional stress that often accompanies occlusion therapy.[32] We note that the in-house training itself is labor intensive and requires considerable parental dedication. Ultimately, a home-based training version involving the Internet may help to lessen the time commitment and the financial burden on parents. However, before this perceptual learning approach is used to treat amblyopia clinically, there are still many questions to be addressed. Only two amblyopic patients participated in the present study, and the response to treatment is likely to vary among individuals. Therefore a large-scale clinical study is needed to determine the dose–response function and compare that to the dose–response function of occlusion alone as well as to evaluate the prognosis for different types and depths of amblyopia.

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References

1. Levi DM, Carkeet A. Amblyopia: A consequence of abnormal visual development. In: Simons K, ed. *Early Visual Development, Normal and Abnormal.* Oxford, UK: Oxford University Press; 1993:391–408.
2. Levi DM. Visual processing in amblyopia: human studies. *Strabismus*. 2006;14:11–19.
3. Pediatric Eye Disease Investigator Group. A randomized trial to evaluate 2 hours of daily patching for strabismic and anisometropic amblyopia in children. *Ophthalmology.* 2006;113:904–912.
4. Pediatric Eye Disease Investigator Group. A randomized trial of patching regimens for treatment of severe amblyopia in children. *Ophthalmology.* 2003;110:2057–2087.
5. Stewart CE, Moseley MJ, Stephens DA, Fielder AR. Treatment dose-response in amblyopia therapy: the Monitored Occlusion Treatment of Amblyopia Study (MOTAS). *Invest Ophthalmol Vis Sci*. 2004;45:3048–3054.
6. Awan M, Proudlock FA, Gottlob I. A randomized controlled trial of unilateral strabismic and mixed amblyopia using occlusion dose monitors to record compliance. *Invest Ophthalmol Vis Sci*. 2005;46:1435–1439.
7. Repka MX, Beck RW, Holmes JM, et al. A randomized trial of patching regimens for treatment of moderate amblyopia in children. *Arch Ophthalmol*. 2003;121:603–611.
8. Pediatric Eye Disease Investigator Group. A comparison of atropine and patching treatments for moderate amblyopia by patient age, cause of amblyopia, depth of amblyopia, and other factors. *Ophthalmology.* 2003;110:1632–1638.
9. Bhola R, Keech RV, Kutschke P, Pfeifer W, Scott WE. Recurrence of amblyopia after occlusion therapy. *Ophthalmology*. 2006;113:2097–2100.
10. Stankovic B, Milenkovic S. Continuous full-time occlusion of the sound eye vs full-time occlusion of the sound eye periodically alternating with occlusion of the amblyopic eye in treatment of amblyopia: a prospective randomized study. *Eur J Ophthalmol*. 2007;17:11–19.
11. Dorey SE, Adams GG, Lee JP, Sloper JJ. Intensive occlusion therapy for amblyopia. *Br J Ophthalmol*. 2001;85:310–313.
12. Stewart CE, Fielder AR, Stephens DA, Moseley MJ. Treatment of unilateral amblyopia: factors influencing visual outcome. *Invest Ophthalmol Vis Sci*. 2005;46:3152–3160.
13. Cleary M. Efficacy of occlusion for strabismic amblyopia: can an optimal duration be identified? *Br J Ophthalmol*. 2000;84:572–578.
14. Loudon SE, Polling JR, Simonsz HJ. Electronically measured compliance with occlusion therapy for amblyopia is related to visual acuity increase. *Graefes Arch Clin Exp Ophthalmol*. 2003;241:176–178.
15. Levi DM, Polat U. Neural plasticity in adults with amblyopia. *Proc Natl Acad Sci USA*. 1996;93:6830–6834.
16. Levi DM, Polat U, Hu YS. Improvement in vernier acuity in adults with amblyopia: practice makes better. *Invest Ophthalmol Vis Sci*. 1997;38:1493–1510.
17. Sireteanu R, Lagreze WD, Constantinescu DH. Distortions in two-dimensional visual space perception in strabismic observers. *Vision Res*. 1993;33:677–690.
18. Polat U, Ma-Naim T, Belkin M, Sagi D. Improving vision in adult amblyopia by perceptual learning. *Proc Natl Acad Sci USA*. 2004;101:6692–6697.
19. Zhou Y, Huang C, Xu P, et al. Perceptual learning improves contrast sensitivity and visual acuity in adults with anisometropic amblyopia. *Vision Res*. 2006;46:739–750.
20. Fronius M, Cirina L, Kuhli C, Cordey A, Ohrloff C. Training the adult amblyopic eye with "perceptual learning" after vision loss in the non-amblyopic eye. *Strabismus*. 2006;14:75–79.
21. Levi DM. Perceptual learning in adults with amblyopia: a reevaluation of critical periods in human vision. *Dev Psychobiol*. 2005;46:222–232.
22. Chung STL, Li RW, Levi DM. Identification of contrast-defined letters in adults with amblyopia benefits from perceptual learning. *Vision Res*. 2006;46:3853–3861.
23. Li RW, Young KG, Hoenig P, Levi DM. Perceptual learning improves visual perception in juvenile amblyopia. *Invest Ophthalmol Vis Sci*. 2005;46:3161–3168.
24. Morad Y, Werker E, Nemet P. Visual acuity tests using chart, line, and single optotype in healthy and amblyopic children. *J AAPOS*. 1999;3:94–97.
25. Wickens TD. *Elementary Signal Detection Theory.* Oxford, UK: Oxford University Press; 2002.
26. Li RW, Levi DM. Characterizing the mechanisms of improvement for position discrimination in adult amblyopia. *J Vis*. 2004;6:476–487.
27. Chung STL, Li RW, Levi DM. Crowding between first- and second-order letter stimuli in normal foveal and peripheral vision. *J Vis*. 2007;7:1–13.
28. Li RW, Levi DM, Klein SA. Perceptual learning improves efficiency by re-tuning the "template" for position discrimination. *Nat Neurosci*. 2004;7:178–183.
29. Li RW, Levi DM, Klein SA. The receptive field and internal noise for position acuity change with feature separation. *J Vis*. 2006;6:311–321.
30. Pediatric Eye Disease Investigator Group. Randomized trial of treatment of amblyopia in children aged 7 to 17 years. *Arch Ophthalmol.* 2005;123:437–447.
31. Simmers AJ, Gray LS, McGraw PV, Winn B. Functional visual loss in amblyopia and the effect of occlusion therapy. *Invest Ophthalmol Vis Sci*. 1999;40:2859–2871.
32. Koklanis K, Abel LA, Aroni R. Psychosocial impact of amblyopia and its treatment: a multidisciplinary study. *Clin Exp Ophthalmol*. 2006;34:743–750.

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