The Therapeutic Impact of Perceptual Learning on Juvenile Amblyopia with or without Previous Patching Treatment

Xiang-Yun Liu,[3] Ting Zhang, Yan-Lei Jia, Ning-Li Wang, and Cong Yu**

PURPOSE. To investigate the therapeutic impact of perceptual learning on juvenile amblyopia that is no longer responsive to patching treatment (group) or was never patch treated (N group).

METHODS. Ten and 3 N subjects aged 8 to 7 years were trained with a grating acuity task for 0 to 60 sessions. Half in each group were further trained with single or crowded tumbling acuity tasks for 8 to 0 sessions.

RESULTS. Training improved grating acuity by – % in the eyes and 36 % in the N eyes, along with a boost of single and crowded acuities by 0.9 or 0.7 lines in the eyes and 2-and lines in the N eyes, in contrast to a nearly 2-line improvement in the same eyes after previous patching treatment. Stereoacuity was improved in some and N eyes. The single and crowded acuity improvements were not significantly dependent on the pretraining acuity. The single and crowded acuity and stereoacuity improvements were uncorrelated with grating acuity improvement, suggesting some random training impacts on different tasks and individuals. Further direct single and crowded acuity training generated an additional 0. - and 0. -line boost for eyes and a 0. - and 0.2-line boost for N eyes, resulting in overall single and crowded acuity gains of and 0. lines for eyes and and 8 lines for N eyes.

CONCLUSIONS. Perceptual learning has a small but significant therapeutic impact on both and N juvenile eyes, which is most likely to have clinical values for eyes with mild amblyopia. Early diagnosis and treatment are most important and effective. (*Invest Ophthalmol Vis Sci.* 0 ;5 : 3 - 38) DOI:10. 67/iovs. 0-63

Amblyopia is an eye condition associated with anisometropia, strabismus, or compromised form vision in early childhood and is typically diagnosed by significantly reduced visual acuity without detectable structural or pathologic causes.[–3] Conventional patching treatment is most effective in treating amblyopia when the child is younger than 6 or 7 years (the sensitive period). Recent studies have shown that amblyopic vision can be improved through perceptual learning in older children and adults. Perceptual learning refers to improvement, through practice, in discrimination of many basic visual features, such as contrast, orientation, Vernier acuity, and texture.[–7] Levi and Polat[8] and Levi et al[9] first reported that training in Vernier acuity improves performance in adult amblyopes, which also leads to improved visual acuity. Later studies found perceptual learning in tasks such as contrast detection and position discrimination in juvenile and adult amblyopes, and learning also transfers in various degrees to visual acuity.[0–7] These findings raise the hope that perceptual learning could become a new therapeutic means for treating amblyopia beyond the sensitive period.

In the present study, we investigated the impact of perceptual learning on juvenile amblyopia for two specific goals. First, although conventional patching can greatly improve amblyopic vision in young children,[8] visual acuity may not always be fully restored.[9] It is important to know whether the residual visual acuity loss in amblyopic eyes that are no longer responsive to patching treatment can be further recovered by perceptual learning. Second, it is still uncertain how much juvenile amblyopic eyes that have never undergone patching treatment can benefit from perceptual learning. Li et al[3] recently reported that extended positional acuity training leads to a substantial recovery of visual acuity in two previously untreated juvenile amblyopic eyes. A larger sample is needed to establish the therapeutic value of perceptual learning in never-treated juvenile amblyopia.

juvenile amblyopic eyes, which is most likely to have clinical value in treating juvenile eyes with mild amblyopia.

METHODS

Observers

Twenty three amblyopic subjects aged 8 to 7 years were trained in the engzhou Central eople's Hospital, engzhou City, or the Zaozhuang Municipal Hospital, Zaozhuang City, in the Shandong province of China. en subjects (7 boys, 8 ± 0 9 years, able , the error bars indicate SD M) had been patch treated for more than years, starting at the age of 7 ± years, by the first and third authors, who are ophthalmologists. heir visual acuity had improved by 0 9[illegible] ± 0 088 log units or 9[illegible] ± 0 88 lines on a logarithmic visual acuity chart (averaged from nine subjects' data, with subject SYs prepatching visual acuity missing), but there had been no acuity improvement in the [illegible] months before the current training started. hese 0 subjects formed the patch-treated ( ) group. he other 3 subjects (0 boys, [illegible] ± 0 9 years, able) had never had patch treatment. hey formed the never patch-treated (N) group. ach subject's vision was best corrected before training by the first and third authors who supervised the current training. he training frequency ranged from two to five daily sessions per week, which was more frequent during summer and winter breaks and varied among subjects. he training lasted [illegible] months on average, ranging from 3 to 0 months. In addition, we obtained the pre- and postpatching visual acuity data of [illegible] juvenile amblyopes from the medical archives at the eijing ongren Hospital. hese amblyopes received 9[illegible] ± 3[illegible] hours of patching treatment starting at similar ages (0 ± 0 [illegible] years, age-matched control group). he study adhered to the tenets of the Declaration of Helsinki and was approved by the ethnics committees of both hospitals. Informed consent was obtained from each subject's parents after an explanation of the nature and possible consequences of the study.

Apparatus

he stimuli were generated by computer (Mat ab-based WinVis program, Neurometrics Institute, akland, CA) and presented by one of two -in C monitors (model [illegible]0, Sony, okyo, Japan, or model S 0 A, N S , Shanghai, China) at 0 × 768 pixels, 0 37 × 0 37 mm per pixel, 8[illegible]Hz frame rate, for grating acuity and contrast sensitivity testing and at 0 8 × [illegible]3[illegible] pixels, 0 9 × 0 9 mm per pixel, [illegible]0Hz frame rate, for acuity testing. he luminance of the monitors was linearized by an 8-bit look-up table for acuity testing and by a -bit look-up table with a video attenuator for grating acuity and contrast sensitivity testing. he mean luminances of the Sony and the N S monitors were [illegible]7 and 7 [illegible]/m , respectively, with the 8-bit look-up table, and 7 0 and 0 [illegible]/m , respectively, with the -bit look-up table. Viewing was monocular with the fellow eye covered by a black eye patch. A chin-and-head rest was used to stabilize the head. xperiments were run in a dimly lit room. In addition, a andot Stereo est (Stereo ptical Co, Inc., Chicago, I) was used to test stereoacuity under normal room lighting.

Stimuli

rating acuity was tested with a ° × ° sharp-edged, full-contrast, square-wave grating tilted ± [illegible]° from vertical (ig a).

Contrast sensitivity was measured with a abor stimulus (aussian windowed sinusoidal grating). he spatial frequencies of the abor were ,3/ , / , / , and / [illegible] times the cutoff spatial frequency of the contrast sensitivity function predetermined with the grating acuity task. he SD was 0 9°, and the orientation was tilted ± [illegible]° from vertical. or both the grating acuity and contrast sensitivity tasks, the viewing distance was 8 m with the use of a front-surface mirror. ach contrast sensitivity function was fitted with a difference of aussian functions $y = A e^{-(x/\sigma)} - A e^{-(x/\sigma)}$, where y is the contrast sensitivity, x is the spatial frequency of the grating, A and A are the amplitudes of the aussians, and σ and σ are the standard deviations of the aussians.

Single acuity was tested with one tumbling letter (a minimal-luminance black letter on a full-luminance white background, see ig 3a). Crowded acuity was tested with a tumbling letter target surrounded by four additional same-sized tumbling letters on four sides at an edge-to-edge gap of one letter size (see ig 3b). he crowded acuity was functionally similar to the conventional visual chart acuity, since both may be influenced by the crowding effect. he stroke and opening width of the letters were one fifth of the letter height. he viewing distance was [illegible]m.

Procedures

ach subject practiced the grating acuity task (ig a) with the amblyopic eye for 0 to [illegible]0 -hour sessions (mean = [illegible] [illegible] ± 9 sessions for the

TABLE 1. he Characteristics of the Amblyopic and ellow yes in the roup

Subject	Age (y)	Sex	Type	Strabismus (Dist)	Eye: Refractive Error	Line Acuity	Patch Treatment Starting Age∣Starting Acuity∣Length (y)
S	0 8	M	Aniso	None	plano + [illegible]0/+0 7[illegible]×9	[illegible]/[illegible] [illegible]/ 0	[illegible]8∣[illegible]/ 0∣
XC	0 3	M	Aniso	None	+[illegible]0/+0 7[illegible]×3 + [illegible]0	[illegible]/ 0 [illegible]/	7 8∣[illegible]/ 0∣ [illegible]
XC	[illegible]0	M	Aniso	None	−0 [illegible]0/−0 × +0 [illegible]0/−0 [illegible]× [illegible]	[illegible]/ [illegible]/ ⁻	3 [illegible]∣[illegible]/ ∣ [illegible]
SY	[illegible]	M	Aniso	None	+ 7[illegible] −0 [illegible]0	[illegible]/ [illegible] [illegible]/7 [illegible]	3 [illegible]∣unknown∣
MA	7	M	Ametr	None	+[illegible]0 +[illegible]00	[illegible]/ [illegible] [illegible]/7 [illegible]	0∣[illegible]/ 0∣7 7
XX	8 [illegible]		Strab Aniso	30Δ so	+ 00 +[illegible]00	[illegible]/[illegible] [illegible]/ ⁻	0∣[illegible]/ 0∣ [illegible]
X	8	M	Ametr	None	+[illegible] [illegible]/+0 [illegible]0×70 +[illegible]00	[illegible]/[illegible]⁻ [illegible]/ 0	[illegible]0∣[illegible]/[illegible]0∣3
D	8 [illegible]		Aniso	None	+[illegible]00 +[illegible]00	[illegible]/[illegible] [illegible]/ 0⁻	0∣[illegible]/ 0∣ [illegible]
CY	0 8	M	Aniso	None	+0 [illegible]0 +3 00	[illegible]/[illegible] [illegible]/7 [illegible]	7 [illegible]∣[illegible]/ 0∣3
Y	0 [illegible]		Aniso	None	+ 00 + 00	[illegible]/[illegible] [illegible]/	7 9∣[illegible]/30∣ [illegible]

Aniso, anisometropia; ametr, ametropia; strab, strabismus.

TABLE 2. he Characteristics of the Amblyopic and ellow yes in the N roup

Subject	Age	Sex	Type	Strabismus (Dist)	Eye: Refractive Error	Line Acuity	Patch Treatment
M	8 0		Aniso	None	+5 00	6/ 0$^-$	None
					plano	6/6	
ZC	5	M	Aniso	None	− 50	6/6	None
					+0 50/+ 00×85	6/ 5	
ZL	3	M	Aniso	None	plano	6/5$^+$	None
					+3 00/− 00× 5	6/37 5	
M	6	M	Aniso	None	plano	6/5	None
					+3 00/+ 50× 35	6/60	
MZ	8 0	M	Aniso	None	+ 50/+ 00×65	6/	None
					+ 0 75	6/6	
M	9 0	M	Aniso	None	− 5/−0 50×80	6/ $^+$	None
					−0 75/−0 5×5	6/7 5	
YC	8 5	M	Aniso	None	+0 75	6/5	None
					+3 00/+ 50×80	6/ $^+$	
X			Strab	60$^\Delta$ so	+6 00	6/50$^-$	None
			Aniso		plano	6/6	
Y	8 0	M	Ametr	None	+ 50	6/ 0$^+$	None
					+ 00	6/7 5	
C	3	M	Aniso	None	plano	6/	None
					+3 75/+0 75×90	6/30$^-$	
XY	8	M	Ametr	None	plano	6/5^{-3}	None
			Astig		+ 00×80	6/	
MX	0 9	M	Strab	0$^\Delta$ so	+ 5× 00	6/ $^+$	None
			Ametr		5/+0 50×60	6/6$^-$	
C	7 5		Aniso	None	plano	6/6	None
					+3 00	6/ 0	

Aniso, anisometropia; ametr, ametropia; strab, strabismus; astig, astigmatism

group and 579 ± 6 sessions for the N group), 6 to staircases per session, and one session on a given day he single acuity and stereoacuity were measured every 0 sessions throughout the training courses efore and after training, the contrast sensitivity function and the single and crowded acuities in both eyes and the stereoacuity were measured

he grating acuity, contrast sensitivity, and acuities were all measured with a one-interval, forced-choice staircase procedure he stimulus was presented for an unlimited time until a key press by the subject he subject's task was to judge the orientation of the grating (tilted left or right from vertical) or the tumbling (left, right, up, or down) Auditory feedback was given on incorrect responses

ach staircase followed the 3-down- -up rule, which converged on a 79 % correct level on the underlying psychometric function ecause of the young age of many subjects, each staircase was short and consisted of two preliminary reversals and four experimental reversals (~ 5–30 trials) he step size of the staircase was 0 05, 0 05, and 0 03 log units for grating acuity, contrast sensitivity, and acuity measurements, respectively he geometric mean of the experimental reversals was taken as the threshold

RESULTS

Experiment 1: Perceptual Learning of Grating Acuity and Its Impact on Contrast Sensitivity Function, E Acuities, and Stereoacuity

Perceptual Learning of the Grating Acuity Task. he eyes had better pretraining grating acuity on average than did the N eyes (5 ± 5cyc/deg vs 7 5± 8cyc/deg, $P =$ 0 005, two-tailed parametric *t*-test) After training, the grating acuity of the eyes changed insignificantly, from 5 ± 5 to 5± 6cyc/deg (mean percentage improvement [M I] = − % ± 3 6%, $P =$ 0 9, one-tailed paired *t*-test, which was used to calculate the *P* values throughout the study, except where specified otherwise; igs b–d) his insignificant change indicated that the previous patching treatment had recovered grating acuity to its upper limit However, the posttraining grating acuity of the eyes was still lower than that of the fellow eyes (3 7 ± 7cyc/deg, $P =$ 0 0 8)

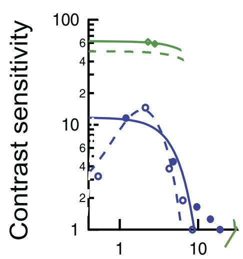
rating acuity improved significantly in the N eyes, from 7 5± 8cyc/deg before training to 5± 9cyc/deg after training (M I = 37 % ± 3 %, $P =$ 0 008; igs b, c, e) he observed improvement was mainly contributed by six N subjects whose grating acuity improved by 5% or more (M I = 7 8% ± 9 9%, $P =$ 0 007; igs b, e) he session-by-session training results of these subjects indicated varied learning speed, taking 0 to 0 sessions for learning to maximize (ig e) he M I of the remaining seven subjects was 5 % ± 3 7% ($P =$ 0 098) verall, the grating acuity improvement had a strong correlation with the pretraining acuity (earson $r =$ 0 83, $P <$ 0 00) in the N eyes hose with poorer pretraining acuity tended to have more room for grating acuity improvement he posttraining grating acuity of the N eyes was also lower than that of the fellow eyes (3 5± 6cyc/deg, $P <$ 0 00)

Contrast Sensitivity Changes after Grating Acuity Training. Contrast sensitivity functions (CS s) were measured in both eyes of each subject, with abor stimuli before and after grating acuity training he abor spatial frequencies were , 3/ , / , / , and / 6 times the pre- or post-training cutoff spatial frequency measured in the previous grating acuity task o compare the pre- and post-training CS functions between the amblyopic and fellow eyes, the sensitivities at spatial frequencies of , , , 8, 6, and 3 cyc/deg were calculated on the basis of data fitting (the sensitivity was set to 0 beyond the cutoff frequency) In the eyes, the CS functions of the amblyopic eyes were similar to those of the fellow eyes before grating acuity training ($F_{,9}$ = 0 68, $P =$ 0 69 , repeated-measures ANOVA) and were not significantly changed after grating acuity training ($F_{,9}$ = 0 509, $P =$ 0 9 ; examples shown in ig a) In the N eyes, the CS functions of the amblyopic eyes were significantly different from those of the fellow eyes before grating acuity training (F , = 9 6, $P =$ 0 0) and were changed marginally significantly after training

(a)

Contrast sensitivi

(b) NPT



better subgroup did not differ signific... the ... sub... worse subgroup in the ... eyes (single ... improvement 0 ... ± ... 0 0 ... vs 0 08 ± 0 0 ... log units, *P* = 0 ... 0, however ... improvement ... 0 0 ... ± 0 0 ... vs 0 09 ± 0 0 ... log units, *P* = 0 3 ... , two-tailed parametric *t*-test, *n* = ... in each subgroup) Nor did the improvements differ between the better and the w...

subject C, who had a median pretraining single acuity of 3 0 arcmin and crowded acuity of 8 arcmin) hese results imply that only eyes with mild amblyopia stand a good chance of regaining normal vision after perceptual learning

When compared with the trained and N amblyopic eyes, the untrained fellow eyes showed similar gains in crowded acuity (F , o = 7, P = 0 , ig 3c), suggesting that some general learning may be responsible for the visual acuity improvement he trained amblyopic eyes showed more gains in single acuity than did the fellow eyes (F , o = 3 7, P = 0 00), probably because the amblyopic eyes practiced single acuity during grating acuity training (every 0 sessions)

We found that the acuities tended to be improved more at a younger age in the N eyes (ig 3d) his trend was insignificant between age and single acuity improvement (r = −0 7, P = 0 38), but was significant between age and crowded acuity improvement (r = −0 6, P = 0 0 7) No such trend was evident in the eyes However, we could not find a direct link between acuity improvement and grating acuity improvement oth single and crowded acuity improvements did not correlate with grating acuity improvement (r = 0 07 and −0 0 , respectively, igs 3e, 3f)

Stereoacuity Changes after Grating Acuity Training. he stereoacuity was improved by 7 % ± 3 % (P = 0) in the eyes and 8 0% ± 0 7% (P < 0 00) in the N eyes (igs a, b) he improvement was contributed by three of the nine subjects (33 3%) and 9 of the N subjects (8 8%) Among them, one and one N subject who failed the initial stereoacuity test (marked by a lowercase f in ig a) showed restored stereoacuity up to 0 arc sec (ig a) or the convenience of data analysis, the stereoacuity for those who failed the and ot Stereo est was set at 00 arc sec, the lowest score

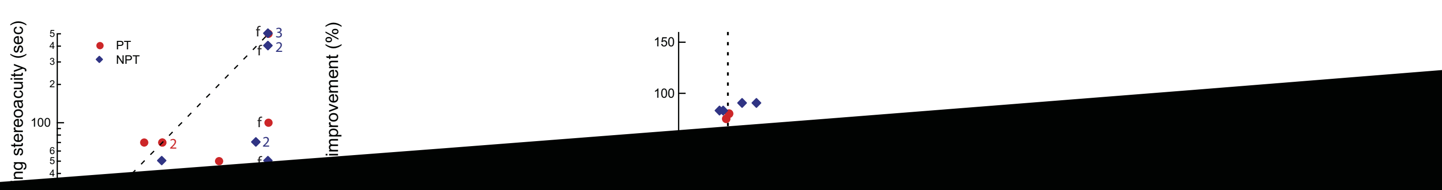
ike acuities, the stereoacuity improvement observed in the three and nine N subjects did not correlate with grating acuity improvement in the amblyopic eyes (r = −0 , P = 0 09, ig c) It did not correlate with single acuity improvement (r = 0 7, P = 0 , ig d) and crowded acuity improvement (r = 0 , P = 0 6 , ig e) in the amblyopic eyes nor with the improvement in interocular acuity difference (r = 0 6, P = 0 , ig f)

Experiment 2: Further Direct Perceptual Learning of Single and Crowded E Acuities

In the previous grating acuity training, the stimuli were ° and 3 ° tilted square-wave gratings hese stimuli were made of oblique bars that were different from the horizontal and vertical bars of the tumbling s Moreover, the tumbling s were often much smaller than the ° × ° gratings used in grating acuity training (e g , the size of a 6/ tumbling = 0 × 0 arcmin), so that the test results were potentially influenced by spatial uncertainty, especially at very small stimulus sizes ecause the transfer of perceptual learning is proportional to the similarity between the trained and tested tasks, these difference between the grating stimuli and tumbling s might have contributed to the relatively small improvements in acuities in the previous experiment

o achieve the best training efficiency, we continued to train the subjects directly with the single and crowded acuity tasks We were able to call back half the subjects in each group (five s and seven N s) and had them practice the single and crowded acuity tasks in alternating blocks of trials (staircases) for 8 to 0 hour daily sessions

After this additional training, the single and crowded acuities in the five eyes were nearly unchanged (single , 0 0 ± 0 03 log units, P = 0 9 , igs a, crowded , 0 0 ± 0 0 log units, P = 0 8, igs b, d) he overall improvement after grating acuity and acuity training was 0 log units for the single acuity (ig b) and 0 0 log units for the crowded acuity (ig d), equivalent to and lines on a visual acuity chart, respectively In contrast, the single and crowded acuities in the seven N eyes (igs a, c) improved significantly (0 0 ± 0 03 log units, P = 0 0 0, and 0 0 ± 0 0 log units, P = 0 00 , respectively, igs b, d) hese improvements added to the initial acuity improvements after grating training, so that the combined training improved single acuity by 0 log units or lines (ig b) and crowded acuity by 0 8 log units or 8 lines (ig d)



[redacted]

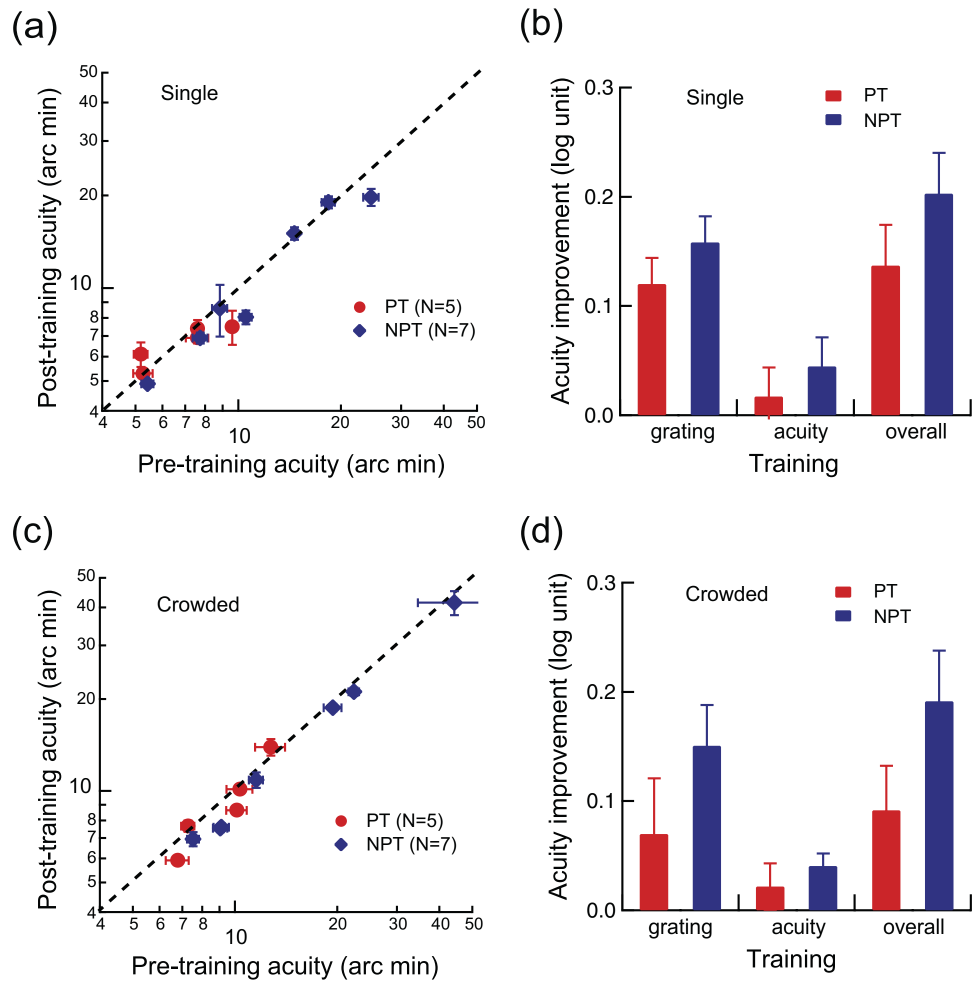


FIGURE 5. he impact of direct acuity training after earlier grating acuity training (a) Single acuity before and after direct acuity training (b) Single acuity improvement after earlier grating training, subsequent acuity training, and the overall improvement (c) Crowded acuities before and after direct acuity training (d) Crowded acuity improvement after earlier grating training, subsequent acuity training and the overall improvement

Follow-up Measurements

We remeasured the visual acuities in seven eyes and eight N eyes year after training (mean, ± 0 7 months) Among them, some received grating acuity training only and some received combined grating acuity and acuity training he visual acuities of the eyes regressed by 0 0 ± 0 0 log units ($P = 0$) he visual acuities of the N eyes regressed by 0 0 ± 0 03 log units ($P = 0$ 39) hese results indicate that training-induced visual acuity improvements persisted for nearly year after the training had stopped

DISCUSSION

In this study, grating acuity training had a small but significant therapeutic impact on the visual acuities of and N eyes and the impact was slightly larger if the grating acuity training is combined with direct acuity training ecause of the relatively small sample size, our results are better regarded as preliminary, and the therapeutic value of perceptual learning on adolescent amblyopia should be further evaluated in larger sample sizes and by meta-analyses of results of multiple studies

he combined grating acuity and acuity training improved single and crowded acuities by 0 and 0 0 log units in the eyes his effect, although small, may bear clinical significance when added to previous visual acuity gains after patching, especially with the consideration that these eyes are no longer responsive to further patching treatment he effect of combined training is larger in the N eyes (0 versus 0 8 log units), which is comparable to the outcomes of previous perceptual-learning studies Many studies have shown visual acuity improvements in the neighborhood of 0 to 0 3 log units[8- , 7, 0] A few others showed either larger[,] or smaller[, 3] effects he visual acuity improvements we obtained from the and N eyes are relatively small in magnitude and do not seem to correlate with pretraining acuities his result suggests that perceptual learning may be most beneficial for treating mild amblyopia in juveniles and adults

In our results, grating acuity learning was evident in only some of the N eyes but not in the eyes (ig), and that grating acuity improvement did not predict acuity improvement (ig 3) rating acuity trained the contrast sensitivity to the cutoff spatial frequency, which was higher than 8 cyc/deg and in many cases ~ 0 to 30 cyc/deg in the and N eyes before training (ig b) n the other hand, it is possible that an observer can make correct judgment of the gap orientation of near-acuity tumbling s on the basis of frequency components that are much lower than the cutoff frequency or example, the subject may use the low-order geometric moment information, such as the skewness of the light distribution of the tumbling images (i e , which side of the image is lighter) to judge gap orientation ecause different visual processes may have been involved, grating acuity learning (as well as many other types of perceptual learning) in theory should have minimal transfer to acuity, because of the task specificity in perceptual learning [ ] Alternatively, perceptual learning could improve the overall responsiveness of the amblyopic visual system to recover visual acuity indirectly. However, this potential improvement in responsiveness is probably small enough that only mild amblyopia could benefit from it for full vision recovery.

Because amblyopia is characterized by visual acuity loss that has no detectable structural or pathologic cause, it would be ideal to train visual acuity directly to gain the maximum therapeutic impact on amblyopic vision, rather than to rely on the often partial transfer of perceptual learning of other visual tasks. As mentioned, the commonly observed task specificity often makes the transfer of perceptual learning difficult or even unlikely. However, no such direct visual acuity training in amblyopic eyes has been performed in previous studies. Our second experiment trained acuities directly, but the impact was not straightforward because of the earlier grating acuity training. A new study with exclusive visual acuity training is necessary to clarify this issue.

The small visual acuity gain from perceptual training may result at least partially from a general learning process, as the crowded acuity was not significantly more improved in the