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Low Vision Rehabilitation

Perceptual Learning Based on the Lateral Masking Paradigm in Anisometropic Amblyopia With or Without a Patching History

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Purpose: Perceptual learning (PL) has shown promising performance in restoring visual function in adolescent amblyopes. We retrospectively compared the effect of a well-accepted PL paradigm on patients with anisometropic amblyopia with or without a patching therapy history (patching therapy [PT] group versus no patching therapy [NPT] group).

Methods: Eighteen PT and 13 NPT patients with anisometropic amblyopia underwent monocular PL for 3 months. During training, patients practiced a Gabor detection task following the lateral masking paradigm by applying a temporal two-alternative forced choice procedure with the amblyopic eye. Monocular contrast sensitivity functions (CSF), visual acuity, interocular differences in visual function metrics, and stereoacuity were compared before and after training.

Results: PL improved the visual acuity of the amblyopia eyes by 0.5 lines on average in the PT group and 1.5 lines in the NPT group. A significant reduction in the interocular difference in visual acuity was observed in the NPT group ($P < 0.01$) but not in the PT group ($P = 0.05$). Regarding CSF metrics, the area under the log CSF and cutoff in the amblyopic eyes of the NPT groups increased after training ($P < 0.05$). In addition, the interocular differences of the CSF metrics ($P < 0.05$) in the NPT group were significantly reduced. However, in the PT group, all the CSF metrics were unchanged after training. A total of 27 of 31 patients in both groups had no measurable stereopsis pretraining, and recovery after training was not significant.

Conclusions: PL based on a lateral masking training paradigm improved visual function in anisometropic amblyopia. Patients without a patching history achieved greater benefits.

Translational Relevance: PL based on a lateral masking training paradigm could be a new treatment for amblyopia.

Introduction

Amblyopia is a developmental disorder of the central nervous system that results from the abnormal processing of visual images during critical years and that leads to reduced visual acuity, contrast sensitivity, and binocular vision.[1] Anisometropic amblyopia is one of the most common forms of amblyopia, and optical correction combined with patching has been considered the gold standard treatment. However, patching therapy is less effective in older children and adults with amblyopia.[2] Many studies have shown that visual perceptual learning (PL) can improve visual experience in older children and even adults because their brains still retain residual neural plasticity.[3–5] Therefore, various forms of PL are increasingly used in clinical practice as complementary treatments for amblyopes beyond the critical period and tend to be more acceptable to older patients because they present with fewer socioemotional effects than traditional patching therapy.[6]

PL is a way to practice visual tasks to improve performance, including position discrimination, contrast detection with or without flankers, contrast discrimination, etc.[7] In PL based on the lateral masking paradigm, the stimuli include a series of Gabor patches with two flanking Gabors, which have been shown to enhance the stimulation and activation of receptive fields in the visual cortex and induce improvement in visual function by facilitating neuronal connections at the cortical level.[8] Polat et al. (1994) first reported that the lateral masking paradigm could improve visual function in adult patients with amblyopia, including visual acuity and contrast sensitivity; since then, this training paradigm has also been applied in the treatment of different types of amblyopia as well as other eye diseases, such as myopia, macular degeneration, and glaucoma.[9–12] In Polat's study, after training, the subjects' cortical spatial range of lateral interactions increased by a factor of six.[13] Yalcin et al. used this method to train adults with hypermetropic anisometropic amblyopia, and the average visual acuity improved by 2.6 lines (logMAR) after training.[14] Children with deprivation amblyopia due to limbal dermoids showed improvements in visual acuity by 3.1 lines after 6 months of training intervention.[15] Battaglini et al. found improvement in contrast threshold in patients with albinism and bilateral amblyopia, and a positive training effect could transfer to other visual functions, such as Vernier acuity, contrast sensitivity function, and foveal crowding.[16] Overall, the effectiveness of PL based on the lateral masking paradigm in the treatment of amblyopia has been widely recognized.

Patients with amblyopia who had previously undergone patching gained little benefit when they repeated the procedure.[17] This means that depending on their history of patching, patients with amblyopia respond differently to re-treatment, as well as to different PL therapies. Liu et al. found that regardless of whether the dichoptic training paradigm of a contrast discrimination task or the monocular training paradigm of an orientation discrimination task was used in PL, patients with amblyopia with a history of patching consistently achieved fewer gains.[18,19] This may suggest that patching history does affect plasticity interactions in PL. Because there are differences in the treatment effects for different paradigms of PL, we wanted to investigate the effect of patching history on lateral paradigm training. Here, we used a retrospective approach by screening patients with anisometropic amblyopia who underwent monocular PL based on the lateral masking paradigm from April 1, 2020, to December 1, 2021, in the Uniting Functions in Ophthalmology and Optometry (UFOs) database.[20–22] Then, they were grouped according to whether or not they had a history of patching, and the differences in visual acuity, contrast sensitivity function, interocular difference, and stereoacuity between the two groups before and after training were assessed.

Methods

Participants

We input the proposed criteria, including "diagnosis: anisometropic amblyopia," "age: older than 9 years," "training: perceptual learning," "paradigm: lateral masking paradigm,"[23] "training duration: 3 months," "testing: clinical visual function testing and quick contrast sensitivity function (qCSF)," and "date: from April 1, 2020, to December 1, 2021," into the UFOs database. Anisometropic amblyopia was defined as an interocular difference $\geq$ 1.00 diopters (D) in spherical equivalent or/and $\geq$1.50 D interocular difference in astigmatism between any meridians according to the Preferred Practice Pattern from the American Academy of Ophthalmology[24] when they were first diagnosed. A total of 170 patients with lateral masking paradigm training records were screened from the time range, and 37 patients with anisometropic amblyopia who had complete baseline data, including qCSF, were finally included. Among them, 4 patients (10.8%) were unable to complete follow-up due to the coronavirus

Table 1. Demographics of Patients With Amblyopia in the PT Group

			Refractive Error		Visual Acuity		Stereoacuity			
Patient	Age (y)	Sex	AE	FE	AE	FE	Near	Far	Training Duration (Mo)	Age at the Beginning of Patching (Y)
PT1	12	F	+4.75/−1.00*165	+1.00	0.58	0.00	>400″	>400″	3	9
PT2	16	F	+3.75/−0.75*165	−0.75/−1.00*175	0.20	0.00	500″	400″	3	13
PT3	14	M	+1.25	−1.25*165	0.74	−0.10	>400″	>400″	3	10
PT4	12	M	+4.75/−0.50*170	+2.75/−0.50*180	0.24	−0.04	>400″	>400″	3	7
PT5	14	M	+4.00/−2.00*5	−0.75*180	0.16	−0.10	>400″	>400″	3	10
PT6	9	M	+1.50/−1.25*10	+0.25	0.46	0.00	>400″	>400″	3	6
PT7	9	F	+2.00/−0.50*90	−0.25	0.14	−0.04	250″	200″	3	7
PT8	16	F	+1.50/−1.50*110	plano	0.90	0.00	>400″	>400″	3	13
PT9	9	M	−1.50/−0.50*25	+0.25/−0.75*170	0.20	0.08	>400″	>400″	3	5
PT10	10	M	+6.50/−1.25*25	+2.25/−0.5*170	0.18	−0.10	>400″	>400″	3	7
PT11	9	F	−1.00	+1.00	0.26	−0.02	>400″	>400″	3	3
PT12	10	M	+6.00/−1.25*170	+4.00/−1.50*10	0.32	0.00	>400″	>400″	3	6
PT13	9	M	+2.75/−1.25*165	+1.00/−0.75*180	0.26	−0.04	>400″	>400″	3	7
PT14	15	M	+6.25/−1.75*120	−1.00	0.76	−0.04	>400″	>400″	3	5
PT15	10	M	−14.00	plano	1.00	−0.04	>400″	>400″	3	9
PT16	9	M	−3.00/−0.75*50	+1.25/−0.50*180	0.76	0.00	>400″	>400″	3	3
PT17	18	F	+3.75	+0.25	0.16	0.00	>400″	>400″	3	4
PT18	10	F	−1.00*180	−2.25/−1.75*180	0.54	0.02	>400″	>400″	3	4

PT, patching history group; M, male; F, female; AE, amblyopic eye; FE, fellow eye.

Table 2. Demographics of Patients With Amblyopia in the NPT Group

			Refractive Error		Visual Acuity		Stereoacuity		
Patient	Age (Y)	Sex	AE	FE	AE	FE	Near	Far	Training Duration (Mo)
NPT1	19	M	+6.50/−0.75*160	−0.50/−0.50*5	0.80	−0.10	>400″	>400″	3
NPT2	11	M	+3.00/−1.00*165	+0.75/−0.50*10	0.76	0.00	>400″	>400″	3
NPT3	9	F	−11.25/−5.50*170	−9.00/−5.50*170	0.30	0.20	>400″	>400″	3
NPT4	13	M	+5.50/−0.50*165	+0.25	0.50	−0.10	>400″	>400″	3
NPT5	10	M	+2.75/−0.50*53	−1.00	0.74	−0.10	>400″	>400″	3
NPT6	11	F	−7.00/−4.50*180	−5.75/−1.75*10	0.60	0.20	>400″	>400″	3
NPT7	17	M	+3.75/−0.75*25	−0.75	0.40	−0.10	>400″	>400″	3
NPT8	14	M	+7.50/−1.50*120	+1.00	0.74	0.00	>400″	>400″	3
NPT9	14	F	+7.50/−1.50*13	−1.50/−0.50*20	0.98	−0.08	>400″	>400″	3
NPT10	9	M	+4.50/−2.50*180	+0.50/−0.50*165	0.30	−0.10	>400″	>400″	3
NPT11	11	F	+6.25/−0.50*35	Plano	0.74	−0.10	>400″	>400″	3
NPT12	9	M	+2.00/−0.25*170	+0.50/−0.25*172	0.26	0.00	63″	100″	3
NPT13	9	F	+5.75/−0.75*175	+2.75/−0.25*160	0.16	0.00	200″	>400″	3

NPT, No patching therapy history group; M, male; F, female; AE, amblyopic eye; FE, fellow eye.

disease 2019 (COVID-19) pandemic. Additionally, 2 patients (5.4%) were unable to complete the training due to poor compliance, and 31 patients were included in the final statistical analysis. The average age was 11.97 ± 3.14 years, and the training interval was 3 months. Patients were divided into two groups based on previous amblyopia treatment before training: (1) the patching therapy (PT) group, who had a previous patching history, and (2) the no patching therapy (NPT) group, who did not have a previous patching history. Patients in the PT group had a patching history average of 1 to 2 years. Detailed information on baseline characteristics of the participants is provided in Tables 1 and 2. Written informed consent was obtained from each participant. This study adhered to the tenets of the Declaration of Helsinki, and the experimental protocol was reviewed and approved by the Zhongshan Ophthalmic Center Ethics Committee. The following tests were carried out before and after training.

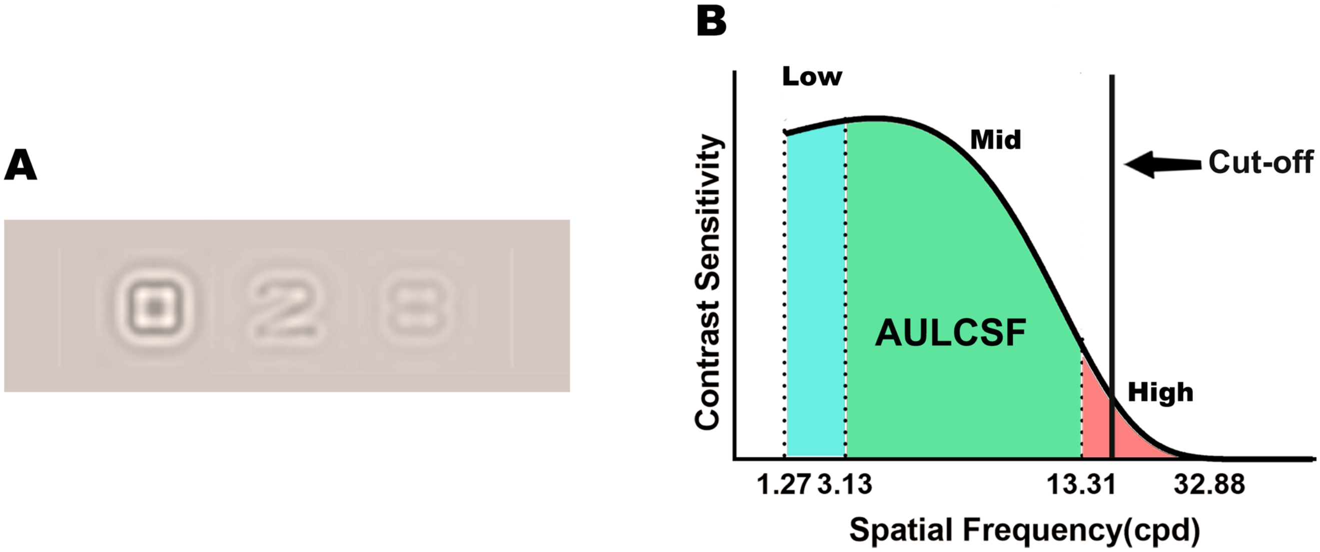

Figure 1. (**A**) Three spatial frequency bandpass-filtered digits with different contrasts, with contrast decreasing from left to right. (**B**) The *black curve* is the contrast sensitivity function curve; the *blue* area represents the low-spatial frequency part of the area under the curve (1.27-3.13 cpd); the *green* area represents the mid-spatial frequency part of the area under the curve (3.13-13.31 cpd); the *red* area represents the high-spatial frequency part of the area under the curve (13.31-32.88 cpd); and the *black straight line* represents the cutoff spatial frequency.

Measurements of Visual Function Metrics

Visual Acuity

Best-corrected visual acuity (BCVA) was assessed with a Thumbing-E Early Treatment Diabetic Retinopathy Study (EDTRS) chart (WEHEN Vision, Guangzhou, Guangdong, China) from a distance of 4 m at a luminance of 200 cd/m^2 and expressed in logMAR units. The charts consist of 5 optotypes per line for a total of 12 lines, with optotype size increasing from −0.3 logMAR to 1.0 logMAR in steps of 0.1 logMAR. Each falsely identified optotype will add 0.02 logMAR in visual acuity.

Contrast Sensitivity Function

Contrast sensitivity function (CSF) was measured using the qCSF method (Manifold Contrast Vision Meter, Adapative Sensory Technology, Inc., San Diego, CA, USA), a Bayesian adaptive active learning procedure for quantitative CSF (qCSF) assessment.[25–28] The qCSF algorithm selects the optimal test stimulus from a total of 2432 possible stimuli in each trial; these stimuli consisted of 3 spatial frequency bandpass-filtered digits with different contrasts and were presented on a gamma-corrected 46-inch LCD monitor (Model: NEC LCD P463, luminance: 50 cd/m^2, 60 Hz) with a resolution of 1920 × 1080 pixels. Subjects needed to identify the numbers shown on the screen from a distance of 4.5 m in a dark room (Fig. 1A) in each trial after their refractive error had been best corrected. The qCSF algorithm controls the contrast and spatial frequency of the stimuli in each trial in response to the result of the feedback of each subject; specifically, the change in spatial frequency is represented by resizing the digits. A new trial started 500 ms after the subject's response. Each test consisted of 35 trials and took approximately 3 to 5 minutes.

The test generated 21 raw data points in each visit: the monocular contrast sensitivities at 19 spatial frequencies (1.27, 1.57, 1.82, 2.18, 2.61, 3.13, 3.75, 4.5, 5.39, 6.46, 7.47, 9.27, 11.11, 13.31, 15.95, 19.11, 22.9, 27.44, and 32.88 cpd), the area under the log CSF (AULCSF), and the cutoff spatial frequency for individual eyes. The cutoff spatial frequency characterizes the high-frequency resolution of the visual system and is defined as the spatial frequency where the contrast threshold is 50%. We used the trapezoid method to calculate the AULCSF in 4 different frequency ranges to represent different aspects of visual performance,[29] from 1.27 cpd to 3.13 cpd for the AULCSF of low spatial frequency, from 3.13 cpd to 13.31 cpd for the AULCSF of middle spatial frequency, and from 13.31 cpd to 32.88 cpd for the AULCSF of high spatial frequency.[30] Finally, the overall AULCSF was calculated as a broad measure of spatial vision as a summary metric based on the curve for the entire frequency range, which was from 1.27 to 32.88 cpd in this study (Fig. 1B).

Stereoacuity

Near stereoacuity was measured with the Random Dot Stereo Acuity Test (Vision Assessment Corpora-

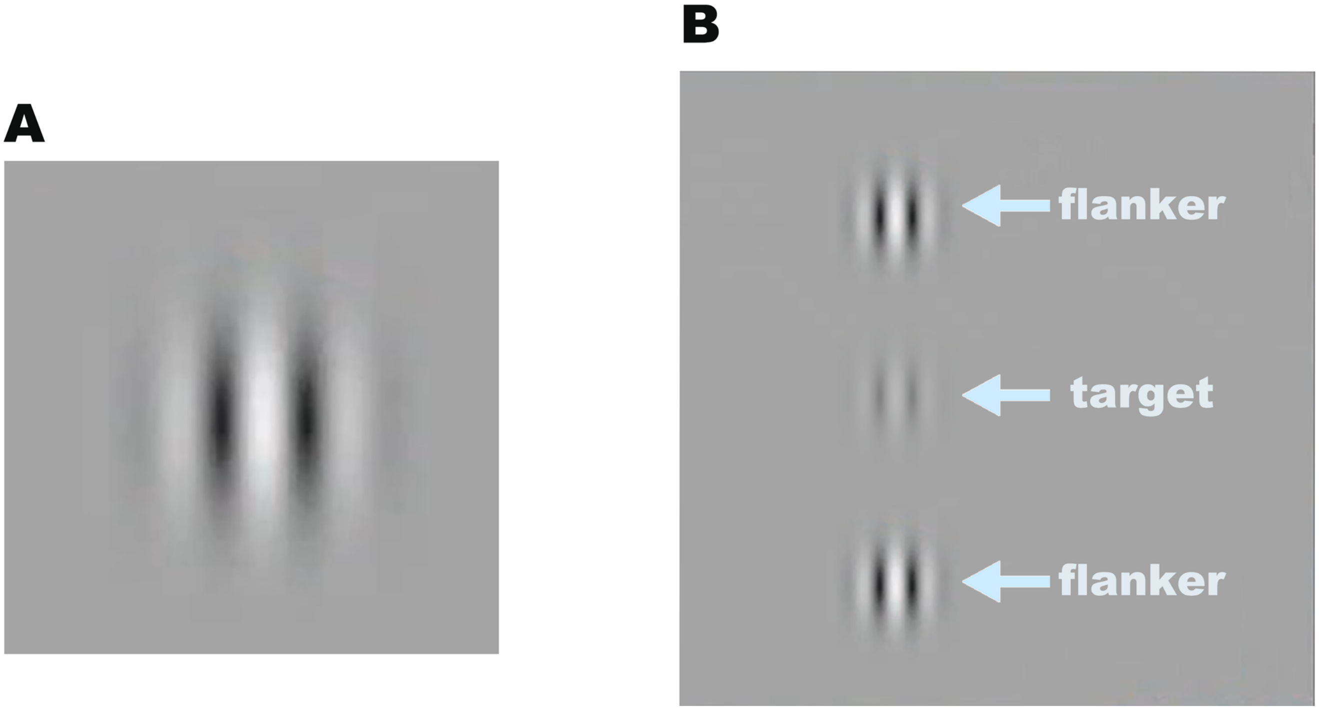

Figure 2. Stimuli in perceptual learning. (**A**) The single Gabor patch was used as the basic stimulus in perceptual learning. (**B**) One fixation Gabor patch placed in the center of the screen and two high-contrast collinear Gabor patches flanking the fixation patch comprised the entire stimulus set.

tion, Elk Grove Village, IL, USA) at a distance of 40 cm using sections B and C with disparities ranging from 12.5 to 400 arc-seconds, which was made up of contour-based circle and symbol targets with monocular cues. The distance stereoacuity was measured using the Randot Stereoacuity Tests (Stereo Optical Co., Inc., Chicago, IL, USA) at a distance of 4 m, including disparities ranging from 60 to 400 arc-seconds with no monocular cues. All observers wore polarizing glasses, and the refractive error was corrected during the test. Each measurement was repeated twice. Nil stereopsis was recorded as 10,000 arc-seconds.

Perceptual Learning Procedure (Lateral Masking Paradigm)

All patients had stable visual acuity for 6 months before training and wore fully corrected glasses during training. Patients trained every other day (40 sessions per procedure) with the PL based on the lateral masking paradigm (RevitalVision, Talshir, Israel) for 3 months. Each day, the training consisted of 9 sessions, including 900 trials, for a total duration of 35 to 45 minutes. The first week of training was conducted in the hospital, and the remaining sessions were conducted at home via a home personal computer (PC), all of which were connected to the central server through the network. The stimuli were displayed on an LCD monitor (refresh rate of 60 Hz) with a luminance resolution of 8 bits and a training distance of 150 cm. Calibration was performed before each training session to ensure that the stimuli were correctly presented. The basic stimuli were Gabor patches produced by a cosinusoidal model, with the edge blurred by a stationary Gaussian (Fig. 2A). The stimulus set was composed of one central Gabor patch with relatively low contrast located in the central fixation area and two collinear high-contrast Gabor patches with relatively high contrast sensitivity distributed on the flanks of the central stimulus above and below (Fig. 2B).

The Gabor patches in the test were used in different configurations with different spatial frequencies, contrasts, orientations, spatial locations, distances, and displacements, which changed according to the patient's feedback throughout the training session. The participant's mouse interaction during the training served as a basis for the algorithm to adjust the distance between the central Gabor and the flankers to maximize the contrast response. This algorithm runs on a central server and can calculate the performance of each subject and send it back to the appropriate station to tailor the training plan. The training contrast threshold was measured using the three-down/one-up staircase and the temporal two-alternative forced choice (2AFC) procedure. The stimulation duration varied from 80 to 320 ms for each stimulus appearance (starting from 320 ms) and was reduced depending on the patient's performance. During this period, there were two intervals (first and second), only one of which would contain a central low-contrast Gabor patch and two collinear high-contrast Gabor patches. In the other interval, only the two collinear high-contrast Gabor patches were displayed. Participants were asked to choose which interval contained a foveally presented low-contrast Gabor patch. The fellow eye was masked during the training.[23,31]

Statistical Analysis

Statistical analyses were performed with SPSS version 25 (SPSS, Inc., Chicago, IL, USA), and plots were produced using GraphPad Prism 9 (GraphPad Software, La Jolla, CA, USA). The $\chi 2$ test was used to compare the sex distribution in the PT and NPT groups. The normality of the data was assessed with the Shapiro–Wilk test. All metrics measured before and after training were compared with paired *t*-tests or paired nonparametric tests based on the data distribution. The independent-samples *t*-test or independent nonparametric test was used to compare the data difference between the two groups. Pearson's test was applied to assess correlations. Baseline calibration was performed using multivariate linear regression to eliminate any possible effect of the possible imbalance of baseline data.[32] A P value of less than 0.05 was considered to indicate statistical significance for all tests.

Results

The average age was 11.72 ± 3.01 years (range from 9 to 18 years) for the PT group and 12.00 ± 3.24 years (range from 9 to 19 years) for the NPT group, with no significant difference between the 2 groups ($P = 0.81$). The sex distribution between the two groups was not significantly different using the $\chi 2$ test ($P = 0.21$). Comparing visual function before training, there was no significant difference between the two groups in the baseline BCVA, the area under the log CSF, cutoff spatial frequency, the AULCSF of low, middle, and high spatial frequency of the amblyopic eyes or in stereoacuity (all $P > 0.05$). In addition, we compared the interocular differences in the various metrics between the amblyopia eye and the fellow eye, calculated as the value of the fellow eye minus the value of the amblyopic eye. However, all baseline interocular differences, including those of BCVA, AULCSF, cutoff spatial frequency, and the AULCSF of low, middle, and high spatial frequency, respectively, were not significantly different between the two groups (all $P > 0.05$; Table 3). The reported P values in Table 3 represent the results of the comparison between the two groups.

Visual Acuity Changes After Monocular Lateral Masking Training

Table 3 shows the pre- and post-training changes in visual acuity for the PT and NPT groups. The change in visual acuity in amblyopic eyes was calculated as the visual acuity at the end of training minus the visual acuity before training. After 3 months of training, the BCVA of the amblyopic eyes in the PT group improved from 0.44 ± 0.29 logMAR before training to 0.39 ± 0.28 logMAR after training ($P = 0.01$; Fig. 3A). The BCVA of the amblyopic eyes in the NPT group improved from 0.56 ± 0.26 logMAR before training to 0.41 ± 0.22 logMAR after training ($P < 0.01$; Fig. 3B). Thirty-three percent of the amblyopic eyes in the PT group and 69% of the amblyopic eyes in the NPT group had more than 1 line of visual acuity improvement after training. The visual acuity improvement after training was more significant in the NPT group than in the PT group, and there was a significant difference in average BCVA improvement between the two groups ($P < 0.05$; Fig. 3C). In both groups, the BCVA at the end of training remained stable at 6 months after follow-up, respectively (Supplementary Table S1).

To assess the role of interocular differences in visual function in the treatment of anisometropic amblyopia, we further analyzed the changes in the interocular difference in visual acuity between the two eyes. The change in the interocular difference of best corrected visual acuity (IOD BCVA) was calculated as the IOD of the BCVA at the end of training minus the IOD of the BCVA before training: a larger reduction in IOD or a smaller IOD after training means a better training effect. The IOD of the BCVA in the PT group did not change significantly, from −0.46 ± 0.29 before training to −0.42 ± 0.29 after training ($P > 0.05$; Fig. 4A). The IOD of the BCVA in the NPT group decreased significantly, from −0.58 ± 0.30 before training to −0.43 ± 0.24 after training ($P < 0.01$; Fig. 4B). Although there was no significant difference in the IOD of the BCVA at baseline between the two groups (see Table 3), there was a significant difference in the change in the IOD of the BCVA between the two groups after training ($P < 0.01$; Fig. 4C).

The improvement of visual acuity in the amblyopic eye was significantly correlated with pretraining visual acuity in the NPT group ($r = -0.68$, $P = 0.01$; Fig. 5C)

Table 3. Detailed Information About the Two Groups

Variable	PT Group	NPT Group	*P* Value
Total (*n*)	18	13	
SED-IODabs (Diopters)	2.39 ± 1.83	3.05 ± 1.51	0.404
Sex (male/female)	13/8	8/5	0.209
Age (y)	11.72 ± 3.01	12.00 ± 3.24	0.810
Baseline measurement			
BCVA (logMAR) AE	0.44 ± 0.29	0.56 ± 0.26	0.183
AULCSF AE	0.96 ± 0.50	0.84 ± 0.33	0.395
Low-SF AULCSF AE	0.55 ± 0.19	0.57 ± 0.11	0.747
Mid-SF AULCSF AE	0.40 ± 0.32	0.27 ± 0.23	0.213
High-SF AULCSF AE	0.01 ± 0.01	0.00 ± 0.01	0.178
Cutoff AE	8.39 ± 4.37	6.57 ± 3.29	0.215
BCVA (logMAR) IOD	−0.46 ± 0.29	−0.58 ± 0.30	0.332
AULCSF IOD	0.60 ± 0.57	0.72 ± 0.34	0.533
Cutoff IOD	11.34 ± 6.15	13.19 ± 5.15	0.215
Low-SF AULCSF IOD	0.16 ± 0.23	0.13 ± 0.13	0.708
Mid-SF AULCSF IOD	0.47 ± 0.35	0.59 ± 0.26	0.300
High-SF AULCSF IOD	0.12 ± 0.10	0.12 ± 0.08	0.953
Near stereoacuity	3.84 ± 0.47	3.70 ± 0.74	0.529
Distance stereoacuity	3.83 ± 0.50	3.85 ± 0.55	0.926
Training effect			
Improvement in BCVA (logMAR) AE	−0.05 ± 0.07	−0.15 ± 0.07	0.045*
Improvement in AULCSF AE	0.01 ± 0.17	0.18 ± 0.19	0.019*
Improvement in low-SF AULCSF AE	0.00 ± 0.07	0.05 ± 0.07	0.069
Improvement in mid-SF AULCSF AE	0.01 ± 0.12	0.12 ± 0.13	0.035*
Improvement in high-SF AULCSF AE	0.00 ± 0.01	0.01 ± 0.04	0.140
Improvement in cutoff AE	−0.20 ± 1.34	1.37 ± 1.37	0.009*
Reduction in BCVA (logMAR) IOD	0.04 ± 0.08	0.15 ± 0.10	0.002*
Reduction in AULCSF IOD	−0.05 ± 0.22	−0.27 ± 0.31	0.040*
Reduction in low-SF AULCSF IOD	−0.01 ± 0.08	−0.04 ± 0.10	0.247
Reduction in mid-SF AULCSF IOD	−0.04 ± 0.15	−0.18 ± 0.21	0.036*
Reduction in high-SF AULCSF IOD	−0.01 ± 0.08	−0.05 ± 0.10	0.215
Reduction in cutoff IOD	−0.07 ± 4.52	−2.94 ± 4.46	0.131

SED, spherical equivalent diopter; it is numerically equal to the spherical diopter plus half of the cylindrical diopter; AE, amblyopic eye; BCVA, best corrected visual acuity; LogMAR, logarithm of the minimum angle of resolution; AULCSF, area under the log contrast sensitivity function; SF, spatial frequency; IOD, interocular difference between two eyes.

*Significance at 0.05.

but not in the PT group ($r = 0.17$, $P = 0.50$; Fig. 5A). Improvement in visual acuity in the amblyopic eye is negatively correlated with pre-training visual acuity in the NPT group. It suggested that the worse the pre-training visual acuity, the more significant the improvement in training, and it may be correlated with the large treatment space with poorer baseline values,[4] which aligned with previous researches.[19,33,34] In addition, the reduction in interocular acuity difference was significantly correlated with the pretraining IOD of the BCVA in the NPT group ($r = -0.73$, $P < 0.01$; Fig. 5D); this phenomenon was not observed in the PT group ($r = -0.10$, $P = 0.68$; Fig. 5B). Furthermore, this reduction was not correlated with age or sex in either the NPT (age: $r = -0.35$, $P = 0.24$ and sex: $r = 0.26$, $P = 0.40$) or PT group (age: $r = 0.14$, $P = 0.59$ and sex: $r = -0.03$, $P = 0.90$).

Overall, PL resulted in a certain degree of improvement in the visual acuity of the amblyopic eyes in both groups, but the visual acuity improvement, as well as the reduction in the interocular visual acuity difference, were more pronounced in the NPT group. The poorer

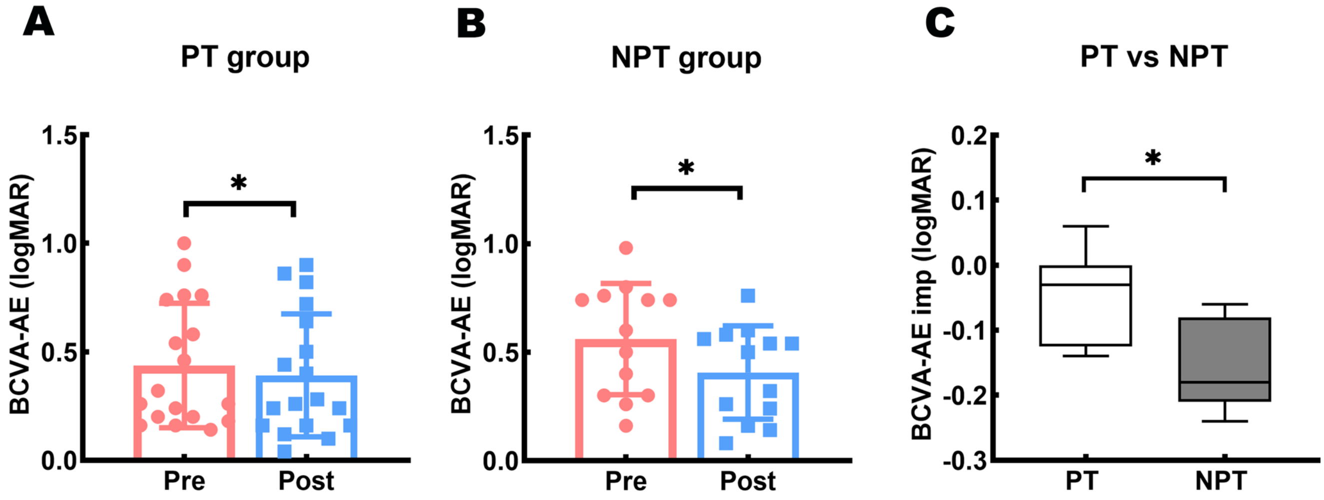

Figure 3. (**A**) Visual acuity in amblyopic eyes before and after training in the PT group. Points represent individual values. Error bars represent one standard error of the mean. (**B**) Visual acuity in amblyopic eyes before and after training in the NPT group. Points represent individual values. Error bars represent one standard error of the mean. (**C**) Average visual acuity improvement in amblyopic eyes between the PT and NPT groups. The *solid line* within the box represents the median. Error bars represent maximum and minimum values. * Indicates statistical significance at 0.05; ns indicates no statistical significance at 0.05.

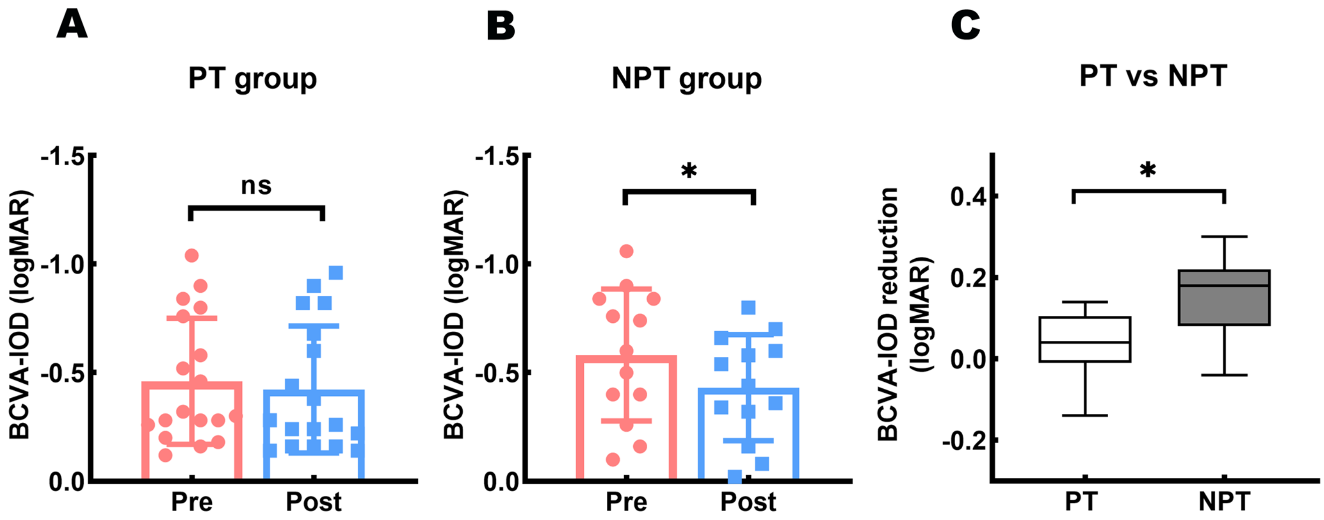

Figure 4. (**A**) Interocular difference in visual acuity before and after training in the PT group. Points represent individual values. Error bars represent one standard error of the mean. (**B**) Interocular difference in visual acuity before and after training in the NPT group. Points represent individual values. Error bars represent one standard error of the mean. (**C**) The average reduction in interocular differences in visual acuity between the PT and NPT groups. The *solid line* within the box represents the median. Error bars represent maximum and minimum values. * Indicates statistical significance at 0.05; ns indicates no statistical significance at 0.05.

the pretraining visual acuity and the greater the IOD visual acuity were, the more significant the improvement in visual acuity after training.

CSF Changes After Monocular Lateral Masking Training

The pre- and post-training CSF were measured separately for each eye. The mean value of the CSF metric changes in the 2 groups is shown in Table 3. In the PT group, there was no significant change in the average cutoff of the amblyopic eyes, which remained at 8.19 ± 4.08 cpd after training, compared to 8.39 ± 4.37 cpd before training ($P = 0.54$; Fig. 6A). Similarly, the CSF metrics of the amblyopic eyes in the PT group, including overall AULCSF (0.96 ± 0.50 vs. 0.97 ± 0.49), AULCSF of low spatial frequency (0.55 ± 0.19 vs. 0.55 ± 0.19), AULCSF of middle spatial frequency (0.40 ± 0.32 vs. 0.41 ± 0.31), and AULCSF of high

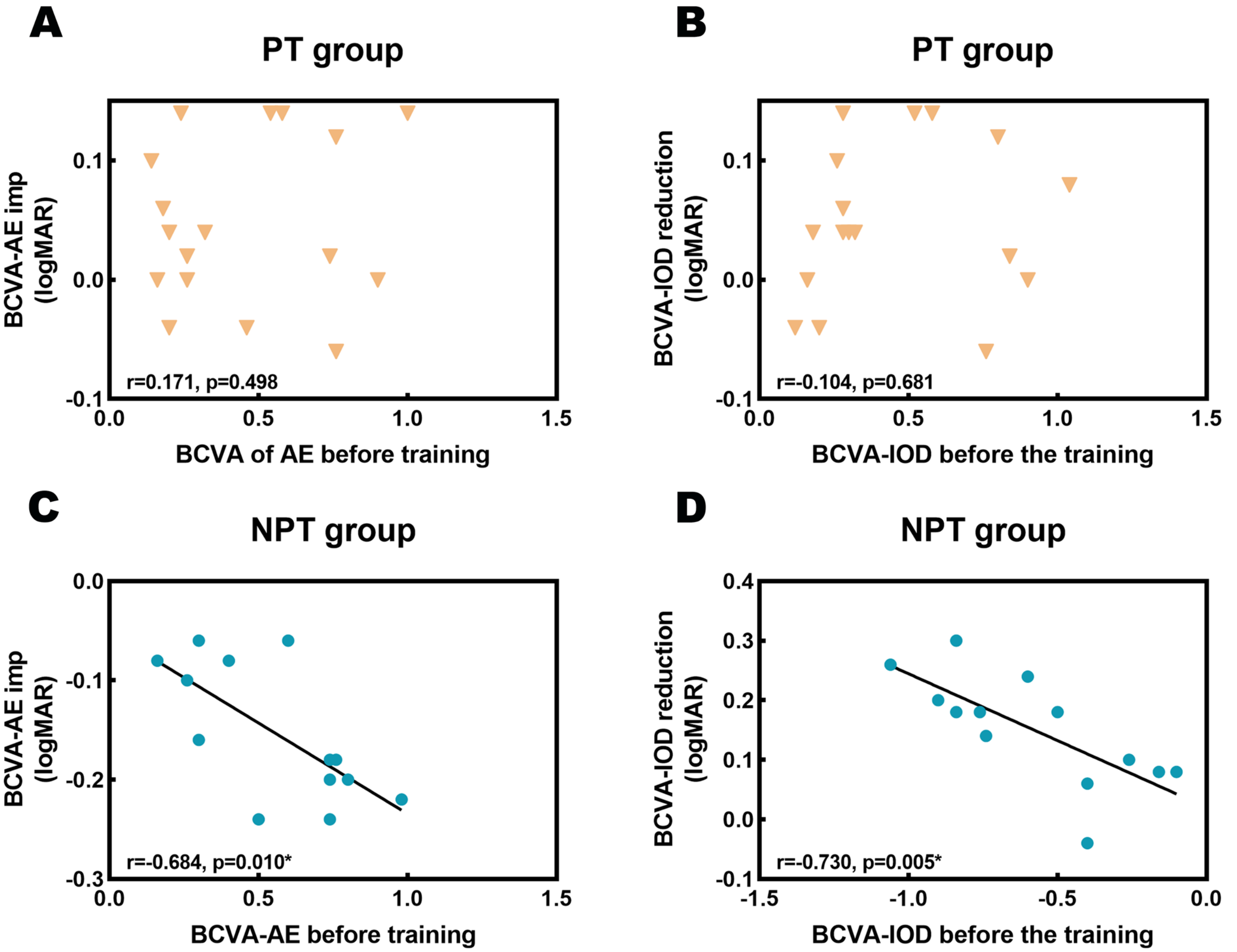

Figure 5. (**A**) Improvement in the BCVA of AEs as a function of the pretraining BCVA of AEs in the PT group. (**B**) Reduction in the interocular difference in BCVA as a function of the pretraining interocular BCVA difference in the PT group. (**C**) Improvement in BCVA of AEs as a function of the pretraining BCVA of AEs in the NPT group. (**D**) Reduction in interocular difference in BCVA as a function of the pretraining interocular BCVA difference in the NPT group.

spatial frequency (0.01 ± 0.01 vs. 0.00 ± 0.01), did not show significant differences after training (all $P > 0.05$; Fig 6C). On the other hand, in the NPT group, the average cutoff spatial frequency of the amblyopic eye increased from 6.57 ± 3.29 cpd to 7.94 ± 3.51 cpd after training ($P < 0.01$; Fig 6B). The CSF metrics of the amblyopic eyes in the NPT group, including the overall AULCSF (0.84 ± 0.31 vs. 1.02 ± 0.40), AULCSF of low spatial frequency (0.57 ± 0.12 vs. 0.62 ± 0.09), and AULCSF of middle spatial frequency (0.27 ± 0.23 vs. 0.39 ± 0.26), showed significant improvements after training (all $P < 0.05$), whereas the AULCSF of high spatial frequency did not show a significant change ($P = 0.22$; Fig. 6D). Overall, all CSF metrics in the amblyopic eyes of the NPT groups increased significantly after training, except for the AULCSF of high spatial frequency.

Comparing the changes in CSF metrics after training between the PT and NPT groups, there were significant differences in the cutoff spatial frequency ($P < 0.01$; Fig. 7A), AULCSF ($P = 0.02$), and AULCSF of the middle spatial frequency ($P = 0.04$) in the amblyopic eyes of the two groups, whereas there were no significant differences in the AULCSF of low spatial frequency ($P = 0.07$) and AULCSF of high spatial frequency ($P = 0.14$; Fig. 7B). No correlations were observed between the improvements in CSF metrics and visual acuity in the amblyopic eyes in the NPT group (cutoff: $r = -0.05$, $P = 0.88$; AULCSF: $r = 0.27$, $P = 0.37$; low-SF-AULCSF: $r = 0.23$, $P = 0.44$, mid-SF-AULCSF: $r = 0.16$, $P = 0.61$).

In the PT group, there was no significant difference in the average IOD in the cutoff spatial frequency, which remained at 11.28 ± 6.99 cpd after training,

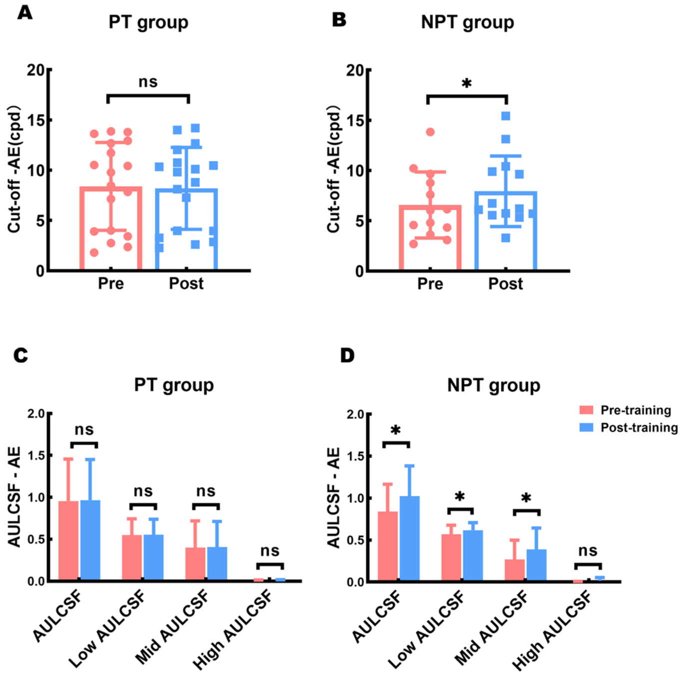

Figure 6. (**A**) Change in the cutoff spatial frequency of the AEs before and after perceptual learning in the PT group. (**B**) Change in the cutoff spatial frequency of the AEs before and after perceptual Learning in the NPT group. (**C**) AULCSF of the AEs before and after training in the PT group. (**D**) AULCSF of the AEs before and after training in the NPT group. Points represent individual values. Error bars represent one standard error of the mean. * Indicates statistical significance; ns indicates no statistical significance.

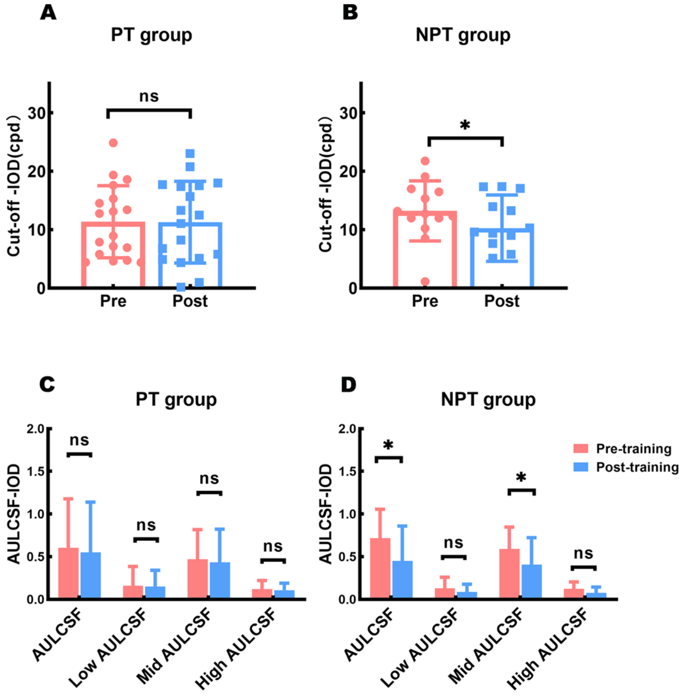

Figure 8. (**A**) Interocular difference in the cutoff spatial frequency before and after training in the PT group. (**B**) Interocular difference in the cutoff spatial frequency before and after training in the NPT group. (**C**) Interocular difference in the AULCSF before and after training in the PT group. (**D**) Interocular difference in the AULCSF before and after training in the PT group. Points represent individual values. Error bars represent one standard error of the mean. * Indicates statistical significance at 0.05; ns indicates no statistical significance at 0.05.

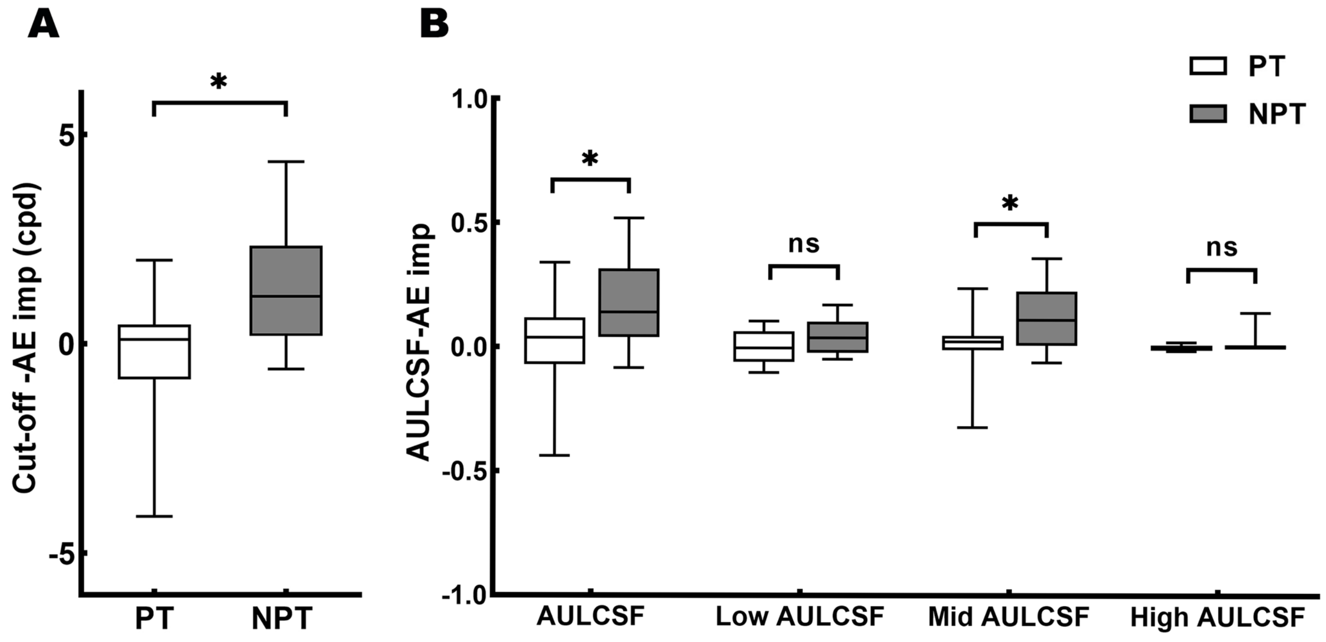

Figure 7. (**A**) Amount of improvement in the cutoff spatial frequency of the AEs between the PT and NPT groups. (**B**) Amount of improvement in the AULCSF of the AEs between the PT and NPT groups. The *solid line* within the box represents the median values. Error bars represent maximum and minimum values. * Indicates statistical significance at 0.05; ns indicates no statistical significance at 0.05.

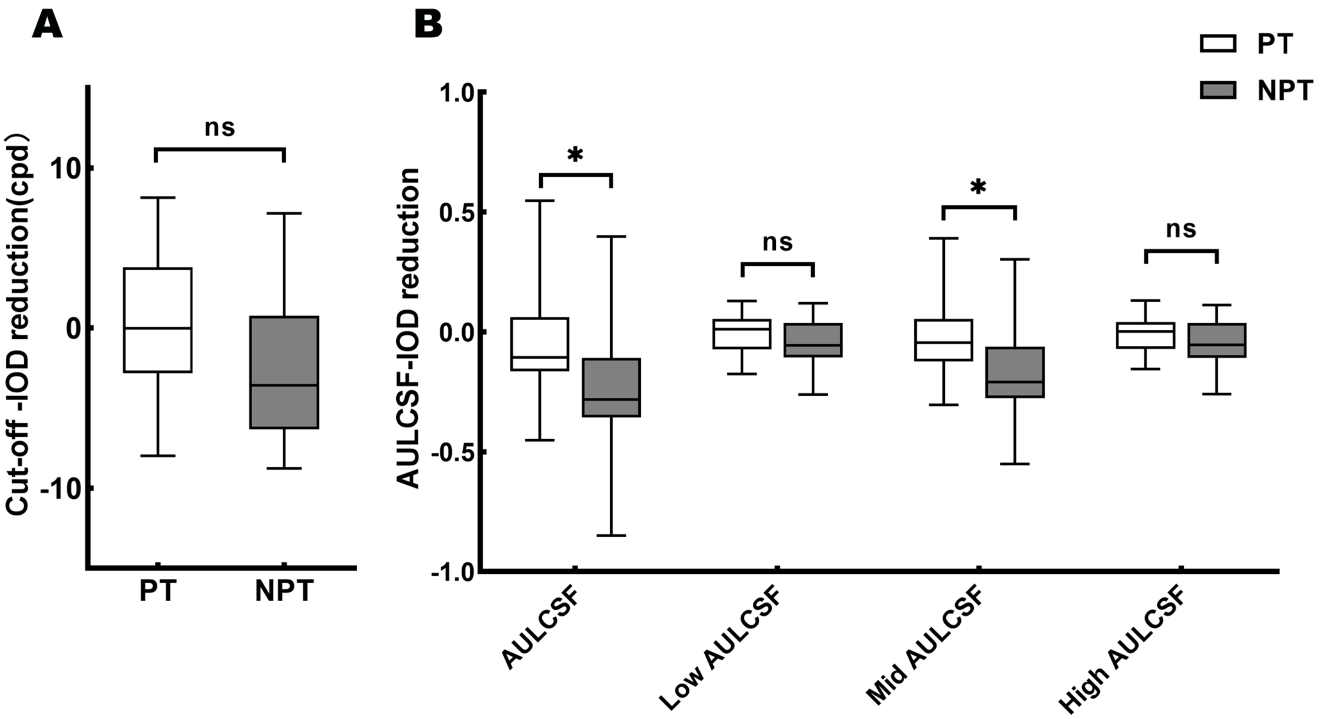

Figure 9. (**A**) Amount of improvement in the interocular difference in the cutoff SE between the PT and NPT groups. (**B**) Improvement in the interocular differences in the AULCSF metrics between the PT and NPT groups. The *solid line* within the box represents the median. Error bars represent maximum and minimum values. * Indicates statistical significance; ns indicates no statistical significance at 0.05.

compared to 11.34 ± 6.16 cpd before training ($P = 0.95$; Fig. 8A). Similarly, the IODs in the CSF metrics in the PT group, including AULCSF (0.60 ± 0.13 vs. 0.55 ± 0.14), AULCSF of low spatial frequency (0.16 ± 0.05 vs. 0.15 ± 0.05), AULCSF of middle spatial frequency (0.47 ± 0.08 vs. 0.43 ± 0.09), and AULCSF of high spatial frequency (0.12 ± 0.02 vs. 0.11 ± 0.08), did not show significant changes after training (all $P > 0.05$; Fig. 8C). On the other hand, in the NPT group, the average IOD in the cutoff spatial frequency decreased from 13.19 ± 1.43 cpd to 10.25 ± 1.58 cpd after training ($P = 0.04$; Fig. 8B). The IODs in the CSF metrics in the NPT group, including AULCSF (0.72 ± 0.09 vs. 0.45 ± 0.11) and AULCSF of middle spatial frequency (0.59 ± 0.07 vs. 0.41 ± 0.09), showed significant reductions after training (all $P < 0.01$), whereas the IOD in the AULCSF of low spatial frequency (0.13 ± 0.04 vs. 0.09 ± 0.03) and AULCSF of high spatial frequency (0.12 ± 0.02 vs. 0.08 ± 0.02) did not show significant changes (all $P > 0.05$; Fig. 8D).

When comparing the changes in the IODs in the CSF metrics after training between the PT and NPT groups, there were significant differences in the IODs in the AULCSF and AULCSF of middle spatial frequency (both $P = 0.04$; Fig. 9B), whereas there were no significant differences in the IODs in the cutoff spatial frequency, AULCSF of low and high spatial frequency (all $P > 0.05$; Figs. 9A, 9B).

Stereoacuity

Most of the participants in our study did not have measurable pretraining stereoacuity. Among the 18 patients in the PT group, only 2 (PT2 and PT7) had stereoacuity before training, and only PT7 also showed near and distance stereoacuity improvement. Among the 13 patients in the NPT group, only 2 (NPT12 and NPT13) had stereoacuity before training, and only NPT13 also showed improved distance stereoacuity. None of those who had no stereopsis before training regained stereoacuity through training.

Discussion

In this research, we reviewed the UFOs database in a tertiary eye center to explore the effects of monocular PL based on the lateral masking paradigm on patients with anisometropic amblyopia with or without patching history. PL based on the lateral masking paradigm resulted in visual acuity improvement in both the PT and NPT groups; however, the improvements are more significant in the NPT group, and this advantage in NPT is also shown in the contrast sensitivity function. After 6 months of follow-up, the visual acuity progress of PL training in patients remains stable.

Previous studies indicated that re-applying patching therapy to juvenile patients with amblyopia who had previously received patching or suppression treatment did not lead to a significant improvement in visual acuity.[17] In our study, the PT group, which has an average of 1 to 2-year patching therapy history, still showed some modest improvement in visual acuity. However, the improvement was limited (0.5 lines), considering a 3-month training period. Patients without a patching history in the NPT group achieved greater improvements in the visual acuity (1.5 lines) of their amblyopic eyes with this training paradigm. As observed from the training effects of PT and NPT results, although we could not obtain the visual acuity improvement that benefited from the patching therapy history in the PT group, it seems that the PT group may have reached a plateau in visual acuity before training. As a retrospective study, to minimize the potential effect of the possible imbalance of the baseline data before training between two groups due to the non-normal distribution of parameters with a limited sample size. We used multivariate linear regression to eliminate the effect of the baseline raw data. After statistical correction, the improvement in visual function after training was indeed more significant in the NPT group than in the PT group. Therefore, the possibility that limited visual function plasticity leads to little further PL training performance in the PT group also cannot be excluded.[35]

The quantitative computerized quantitative contrast acuity function is a more comprehensive method of response to visual function in amblyopia than visual acuity. The qCSF testing offers a broader observation of human visual function under diverse contrast conditions, showcasing our visual quality in different environmental contexts more related to the real world.[36] In our study, although there was a slight improvement in visual acuity in the PT group, their CSF function still did not recover, whereas in the NPT group, in addition to a more pronounced improvement in visual acuity, the CSF metrics were all improved except for the high spatial frequency. This aligns with the findings from Liu's study.[18,19] In fact, recovery of high-frequency bands in amblyopia is difficult. Many previous studies have demonstrated that even in patients with successfully treated amblyopia with 1.0 visual acuity, CSF is still deficient at high spatial frequencies.[21,34] In amblyopia that has not been fully treated, as in our study, this defect would be more serious. In the NPT group, the improvement in CSF was more significant in the middle spatial frequency (mid-SF AULCSF). This may be attributed to the fact that the amblyopic deficit in CSF is primarily concentrated in the middle and high frequencies.[21] As a result, when the overall CSF is restored, the middle spatial frequency also exhibits more pronounced improvements. Previous PL studies have found that the effects of training can be interconverted between different training tasks[4–6]; however, from the PT and NPT visual acuity and CSF results, the trained CSF function gains seemed to transfer to visual acuity in the NPT group but not in the PT group, and there did not seem to be a tendency for the gains to expand from lower spatial frequencies to higher spatial frequencies from the training effects, even though we did not set a fixed training cutoff frequency. This could be that the dissemination of learning may occur unidirectionally, propagating from spatial frequencies near the acuity limit (as practiced by Huang et al.'s observers) to lower spatial frequencies, but not in the reverse direction.[35,37]

For binocular function, PL did show some improvement in stereoacuity in patients with amblyopia in some previous studies.[37,38] However, in our study, few patients in either the PT or the NPT group showed improvement in stereoacuity. Even the observed reduction in both visual acuity and CSF IOD in the NPT group did not improve stereopsis recovery, suggesting that these visual function recoveries are not directly interconvertible. Previous studies have shown that approximately three-quarters of anisometropic children still have binocular visual deficits after treatment.[39,40] On the one hand, anisometropic amblyopia as unilateral amblyopia causes great damage to binocular function, especially stereoacuity, and on the other hand, the stereoacuity methods we use are threshold-based, making it difficult to accurately quantitatively measure some of the patients who may potentially have binocular vision. It seems that training with binocular PL is more beneficial than monocular training in improving stereoacuity,[41,42] and dichoptic training has the potential to yield additional improvements in stereoacuity for adults with amblyopia following extended periods of monocular training.[43]

There are also some limitations in our study. First, this was a single-center, small-cohort retrospective review. Second, although we did not observe significant visual function improvement in the PT group as in the NPT group, this might be constrained by the small sample size. Therefore, further exploration is necessary. Next, almost all of the patients improved with training, but two patients (PT2 and PT6) still regressed in visual function at the end of the training. Although the training was conducted under parental supervision at home, we were not able to obtain actual patient compliance.

In conclusion, PL based on the lateral masking paradigm as a convenient home-based amblyopia training method could restore visual function amblyopes beyond the critical period, and more significant improvement was observed in patients with no patching history. This finding can help in the development of a more personalized treatment plan based on patching history and further optimize the clinical amblyopia treatment procedure.

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