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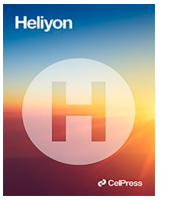

Characteristics and predictive factors of visual function improvements after monocular perceptual learning in amblyopia

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ABSTRACT

Monocular perceptual learning has shown promising performance in restoring visual function in amblyopes beyond the critical period in the laboratory. However, the treatment outcome is variable and indeterminate in actual clinical and neuroscientific practice. We aimed to explore the efficacy of monocular perceptual learning in the clinical setting. By combining continuous monitoring of perceptual learning and clinical measurements, we evaluated the efficacy and characteristics of visual acuity and contrast sensitivity function improvement and further explored the individualized effect after perceptual learning. Amblyopes (average age:17 ± 7 years old) were trained in a monocular two-alternative forced choice identification task at the 50% contrast threshold of the amblyopic eye for 10–15 days. We found that monocular perceptual learning improves both visual acuity and contrast sensitivity function in amblyopia. The broader activation of spatial contrast sensitivity, with a significant improvement in lower spatial frequencies, contributed to improving visual acuity. Visual acuity changes in the early stage can predict the endpoint treatment outcomes. Our results confirm the efficacy of monocular perceptual learning and suggest potential predictors of training outcomes to assist in the future management of clinical intervention and vision neuroscience research in amblyopia beyond the critical period of visual plasticity.

1. Introduction

Amblyopia is a common neuro-visual disorder resulting from developmental abnormality [1,2] impairing multiple visual functions [spatial vision such as visual acuity (VA), contrast sensitivity (CS), and binocular vision] [3–5].

Optical correction [6,7] combined with occlusion or penalization [8–10] have been considered as the gold standard treatment for amblyopia. These approaches have demonstrated improved VA outcomes in young children [11]. However, the efficacy of traditional therapies reduces significantly in older children and adults with amblyopia [12,13]. As neuroplasticity still appears evident in adult

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human cortices [14], novel therapies that employ perceptual learning to restore vision loss in older patients beyond the critical period of vision development have been investigated [15–23]. Perceptual learning refers to the phenomenon that practicing visually demanding tasks can lead to remarkable and consistent improvements in the training task [24]. A wide range of perceptual learning strategies have been developed, including position discrimination [14,25,26], contrast detection with or without flankers [15,16,27–30], and contrast discrimination [31,32], etc. Improvements have been reported in VA, binocular summation, stereopsis, motion perception of the amblyopic and even the fellow eye after comprehensive training in trained and untrained tasks [16,17,32–36]. However, the response varied and limited transfer to different stimuli tasks were also observed [14,37–40]. The specificity and transfer of perceptual learning are still under debate.

Recently, monocular perceptual learning with spatial frequency (SF) cut-off tasks [16,24,34] has been implemented as a supplementary therapy for amblyopes beyond the critical period. A broader bandwidth of training in amblyopia has been reported compared to normal participants [27], and the binocular function improved both in psychophysics and electroencephalogram testing paradigms [31,32,41]. Nevertheless, laboratory training performance is satisfactory but limited to small-scale studies, and the improvement varied substantially between tasks and individuals [42–45]. Subjects in these studies mainly included anisometropic, strabismic, or mixed amblyopia, and the training outcome showed quite promising results among a wide age range from 4- to 70-year-olds [33,46]. More systematic individualized effect exploring rigorous randomized clinical trials is needed to eventually translate perceptual learning therapy into more widely accepted clinical practice [3]. In addition, previous studies employed various theories to explain the transferring effect of clinical testing from contrast detection to other visual functions. CS is considered a fundamental characteristic of the visual system. Training in contrast detection facilitates performance in high-level tasks such as VA [35]. However, how exactly the contrast sensitivity function (CSF) reconstruction affects VA improvement remains unclear.

In this study, we aimed to explore the efficacy of monocular SF cut-off training in the clinical setting. We included amblyopia participants beyond the critical period who received monocular SF cut-off training as a supplementary intervention. We utilized three comprehensive clinical measures: monocular VA, monocular CSF and stereopsis. All these clinical tests were measured before and after training. VA was monitored daily to understand longitudinal changes during the training cycle (Fig. 1). For the complete analysis of CS with computerized threshold data output, we separated the area into low, mid, and high SFs as evaluation indicators to better reflect changes in different SF ranges for amblyopia patients. We further grouped patients with different clinical effectiveness to investigate characteristics of treatment outcomes by comparing a series of comprehensive visual clinical measurements.

Here, we hypothesized that monocular perceptual learning at SF cut-off improves clinical visual functions such as VA, and CSF in amblyopes beyond the critical period. Furthermore, the response at the early stage could predict the endpoint treatment outcomes.

2. Materials and methods

2.1. Participants

Forty-nine amblyopes (average age:17 ± 7 years old) participated in this study. All participants were recruited from Zhongshan Ophthalmic Center (ZOC), a major tertiary eye hospital at Sun Yat-sen University, Guangzhou, China, from July 2019 to August 2021. The diagnosis and classification of amblyopia were established based on their first visit records from the hospital according to the American Academy of Ophthalmology Preferred Practice Pattern [47]. Specifically, anisometropic amblyopia was defined as an

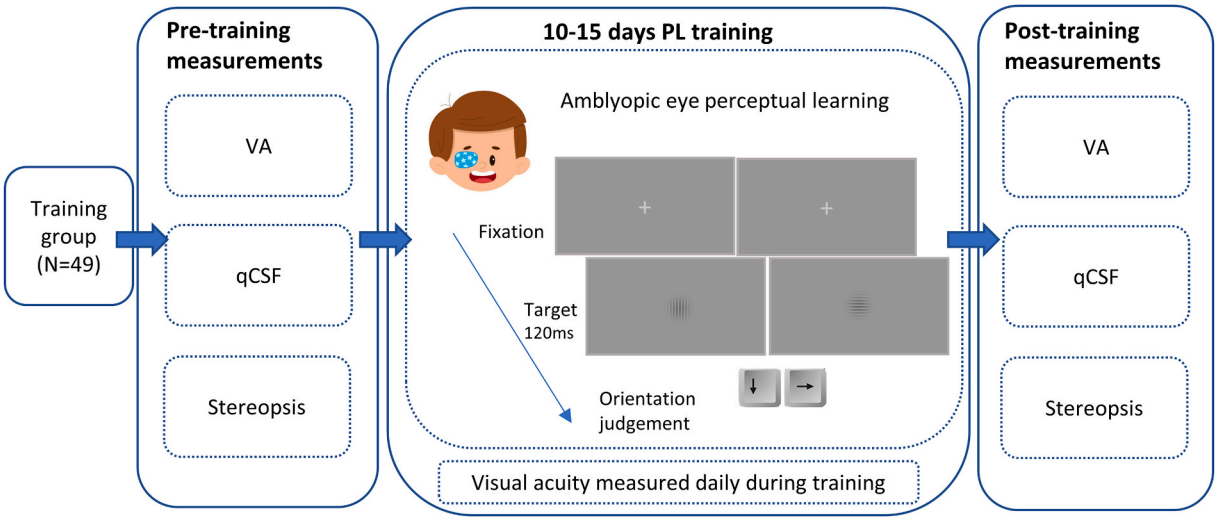

Fig. 1. Experimental Procedure. Subjects in the training group were trained in a monocular two-alternative forced choice (2AFC) identification task in the amblyopic eye for 10–15 days [16,27,32]. We measured monocular visual acuity, monocular contrast sensitivity function, and stereopsis before and after training. Monocular visual acuity was monitored every day during training. See Table S1 for clinical details.

interocular difference in spherical equivalent of ≥1.00 D between eyes and/or ≥1.50 D difference in astigmatism between the two eyes in any meridians and an interocular best corrected visual acuity (BCVA) difference of at least 0.20 logMAR. Isoametropic amblyopia was defined as >3.00 D in spherical equivalent or >2.00 D of astigmatism in both eyes with BCVA worse than the age-specific cut-off values as defined by the Preferred Practice Pattern [47]. The 4^{Δ} base-out test was performed to exclude micro strabismus at the initial visit. Strabismic amblyopia was defined as the presence of a heterotropia on examination at distance or near (with or without optical correction), with more than 4^{Δ} measured using the prism cover/uncover test at near fixation, or a documented history of strabismus that is no longer present, but presenting with an interocular BCVA difference of at least 0.20 logMAR. Detailed baseline characteristics is provided under Table S1. Both anterior (by slit-lamp examination) and posterior (by direct ophthalmoscopy) segments were examined to exclude organic causes of vision loss. All refractive corrections were assessed by cycloplegic refraction at their first visit. All subjects were naïve observers to the experimental stimulus. All participants obtained prior informed consent. If the participant was younger than 18 years old, the informed consent was obtained from both the child and their parents/guardians. No compensation was provided. The research adhered to the tenets of the Declaration of Helsinki and the experimental protocol was reviewed and approved by the ZOC Ethics Committee (2017KYPJ006).

2.2. Apparatus and setup

CSF was assessed using the quick contrast sensitivity function (qCSF) method. Stimuli were digits presented on a gamma-corrected 46-inch LCD monitor (Model: NEC LCD P463) with a resolution of 1920 × 1080 pixels, a mean luminance of 50 cd/m^2 and a 60 Hz vertical refresh rate. Subjects first viewed the display in a dark room from a distance of 4 m.

Monocular perceptual learning used a desktop computer (ASUS 3.60 GHz Intel Core i3-8100) running MATLAB R2016a (MathWorks, USA). It was presented at a viewing distance of 150 cm on a Gamma-calibrated 27-inch color CRT monitor (refresh rate = 85 Hz) at a 10.8 bits monochromatic mode to ensure high grayscale resolution. The mean luminance was 50 cd/m^2.

2.3. Procedure

2.3.1. Monocular perceptual learning

During perceptual learning, the participants completed a 2AFC orientation identification task near the SF cut-off in their amblyopic eye with the fellow eye patched [27]. Gabor patch was used as the stimuli, with its edge being blurred by a half-Gaussian 0.5° ramp. The initial contrast of the Gabor patches was 30%. The SF was fixed, and the contrast varied based on the participant's response. The training distance was 150 cm, and the patch took up 2° of the visual angle. Each trial started with a 259-ms fixation cross displayed at the center of the monitor. Each stimulus was oriented horizontally or vertically and presented at an interval of 120 ms. Participants were instructed to input its orientation using a computer keyboard. A correct identification of orientation indicated that the participant could see the patch. A three-down, one-up staircase procedure decreased signal contrast by 10% after every three consecutive correct responses and increased signal contrast by 10% after every incorrect response, converging to a performance level of 79.3% correct. Each participant performed ten training sessions a day, and each session consisted of 80 trials. The average of the last four reversal CS values was calculated as the CS threshold of each session. The whole course lasted for a consecutive 10–15 days, amounting to 8000 to 12,000 training trials. Participants were allowed to take breaks at the end of each training session to avoid fatigue effects.

2.4. Clinical measurements

2.4.1. Visual acuity

VA was measured with a Tumbling-E EDTRS chart from a 4 m distance and expressed in logMAR units. The luminance was 200 cd/m^2. The chart consisted of 5 optotypes per line with 14 lines decreasing from 1.0 logMAR to −0.3 logMAR. Baseline BCVA was measured before training. Best-corrected VAs were assessed every day after each training throughout their training cycle.

2.4.2. Quick contrast sensitivity function (qCSF)

The qCSF method with digits was applied to assess CSF [48,49]. The Arabic numeral set, 0–9, was modified to follow the specifications of Sloan optotypes and filtered with a raised cosine filter. The SF and contrast of the stimuli in each trial were controlled by the qCSF algorithm based on the patient's response, and the digits were resized according to the corresponding spatial frequency. Patients were instructed to read out the Arabic number that appeared on the center of the screen from a distance of 4 m in a dark room. The experimenter entered the subjects' reports as numbers via a keyboard. No feedback was provided. A new trial started 500 ms after the response. Each eye was examined separately in 35 trials with three digits stimuli in each trial. The entire examination took approximately 20 min. Baseline qCSF was measured before training.

2.4.3. Stereoacuity

Near stereoacuity was measured with the Random Dot Stereo Acuity Test (Vision Assessment Corporation, Elk Grove Village, Illinois, USA) at 40 cm, and distance stereoacuity was measured using the Randot Stereoacuity Test (Stereo Optical Co., Inc., Chicago, IL, USA) at 3 m. The tests were administered following the manufacturer's instructions. The near Random Dot Stereo Test consisted of sections B and C using random dot patterned circle and symbol targets with disparities ranging from 12.5 to 400 arc seconds. The distance Randot Stereo Test included disparities ranging from 60 to 400 arc-seconds without monocular cues. Each measurement was repeated twice. Baseline stereopsis was measured before training.

3. Quantification and statistical analysis

We designed our task to evaluate changes in VA, stereopsis, and CSF metrics (including the area under log contrast sensitivity function [AULCSF]; SF cut-off; low, mid, and high spatial frequencies of the area under log contrast sensitivity function [low, mid, high–SF–AULCSF]) from baseline. Considering that there was no intervention during the training cycle in the fellow eye, our analysis mainly focused on changes in the trained eye.

VA was scored per letter correct (0.02 logMAR per letter). Near and distance stereopsis were scored by minimal detectable disparity. Nil stereopsis was recorded as 5000 arc secs.

CSF was presented as an estimated CSF curve. AULCSF was calculated from 1.5cpd to 18cpd as a summary metric. Low, mid, and

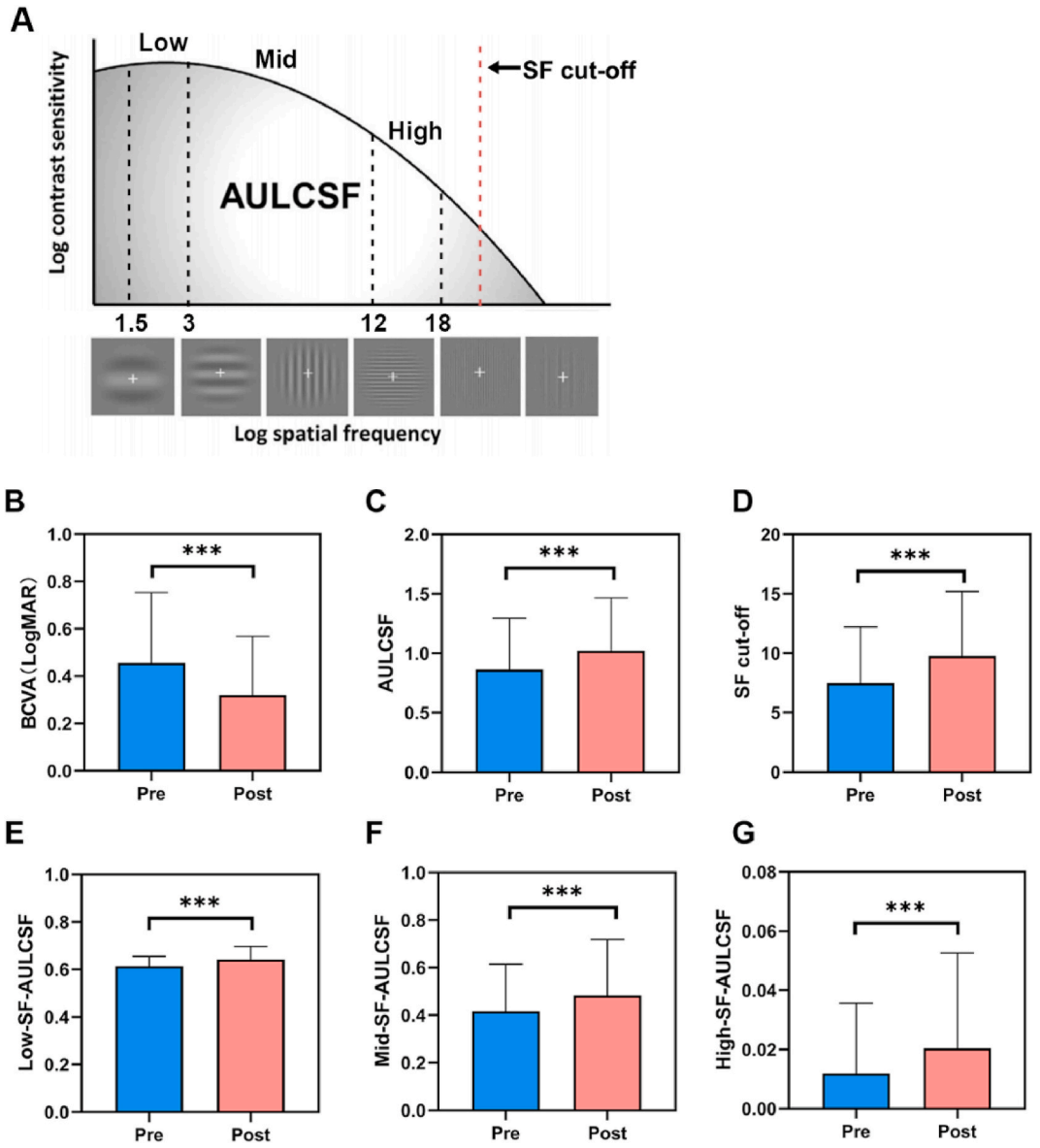

Fig. 2. Illustration of CSF and comparison of monocular visual function before and after training of all participants. Schematic diagram of the CSF metrics: the black curve in the figure is the contrast sensitivity curve; AULCSF is a broad measure of spatial vision from 1.5 to 18cpd as a summary metric of CSF; the AULCSF was further separated into three parts represent different frequency range spatial vision [50]: 1) Low–SF–AULCSF from 1.5 to 3cpd; 2) Mid–SF–AULCSF from 3 to 12cpd; 3) High–SF–AULCSF from 12 to 18cpd. The red dash line shows the spatial frequency cut-off representing the high-frequency resolution of the visual system. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

The average value of monocular visual functions before and after training: (B) BCVA, (C) AULCSF, (D) SF Cut-off, (E) Low–SF–AULCSF, (F) Mid–SF–AULCSF, (G) High–SF–AULCSF. Three asterisks indicate a significance level of $p < 0.001$.

high–SF–AULCSF were integrated from 1.5cpd to 3cpd, from 3cpd to 12cpd, and from 12cpd to 18cpd, respectively [50]. The contrast threshold was defined as the lowest contrast limit at which the visual system resolved the spatial details of the pattern. SF cut-off was defined as the SF where the contrast threshold was 50% (See Fig. 2A), representing the high-frequency resolution of the visual system. The improvement curve was obtained by subtracting the pre-from the post-training CSF function, normalizing SF to the training frequency, fitted by a Gaussian function (See Fig. 7A). SF at maximum contrast sensitivity improvement (SF of max CS) was defined as the SF where the peak value of the improvement curve existed. The bandwidth of perceptual learning was estimated from the improvement curve as below [27].

$$\log\left[CS_{post-training}(f)\right] - \log\left[CS_{pre-training}(f)\right] = a exp\left[-\left(\frac{log\ 2(f) - log\ 2(f_0)}{\sigma}\right)^2\right]$$

$$Bandwidth = 2\sqrt{ln\ 2}\sigma$$

Notes: a refers to the amplitude of the improvement. f refers to the normalized spatial frequency. f_0 refers to the spatial frequency with the max improvement. σ refers to the standard deviation of the Gaussian function [27].

Statistical analyses were performed with SPSS 26.0 (IBM Corporation, Armok, NY). Descriptive statistics were used to summarize participant demographics. Categorical variables were expressed as frequencies (percentage) and continuous variables as mean and SD or median and quartiles. The normality of data was assessed with the Shapiro-Wilks test. All the metrics measured before and after training was compared with paired *t*-test or paired nonparametric test based on data distribution. An Independent *t*-test or independent nonparametric test was used to compare the data difference between the two groups. To assess the relationship between VA improvement during the first three days of training and endpoint improvement in VA and CSF metrics, Pearson's correlation coefficient was computed to indicate the linear relationship and its strength. A p-value of less than 0.05 was considered statistically significant for all tests.

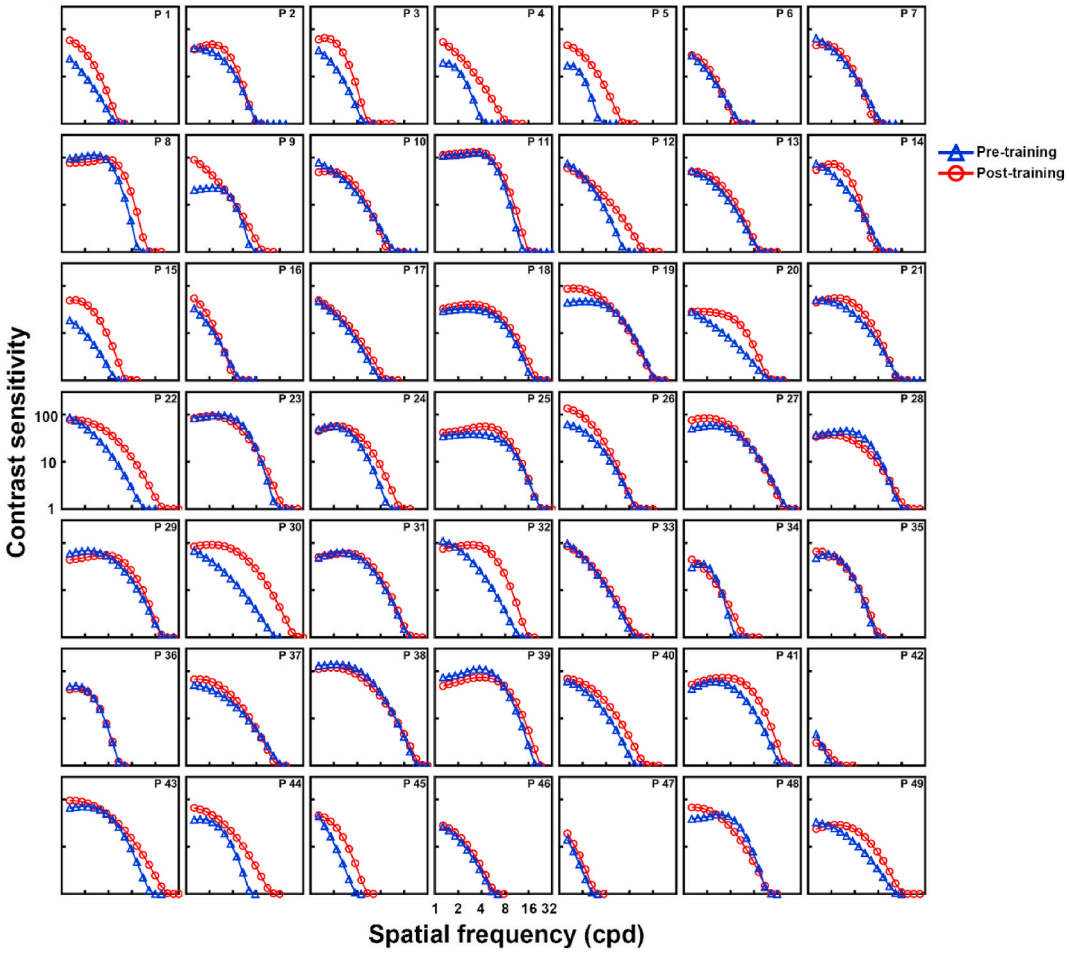

Fig. 3. CSF curves before and after perceptual training in the amblyopic eyes of individuals.
The blue triangles and lines represent the pre-training CSF; The red circles and lines represent the post-training CSF.

4. Results

A total of forty-nine amblyopic patients (36 anisometropic, nine isoametropic, and four strabismic amblyopes) were included in this study, and all patients had a history of one or more types of amblyopia treatment (see Table S1 for details). The training duration was 13 ± 2 days.

4.1. Does monocular cut-off spatial frequency training generalize the improvement of all the clinical measurements?

We compared post-training and the baseline BCVA and found an average improvement of 1.4 ± 1.2 lines in the trained eye at the end of training (Fig. 2B). All the CSF metrics, including AULCSF, SF cut-off, low, mid, and high–SF–AULCSF, exhibited significant improvement from baseline (Fig. 2C–G, Table S2). Individual CSF function before and after training is shown in Fig. 3. Only 21 participants completed the stereoacuity test and were included in the final analysis. However, both near and distance stereoacuity showed no improvement after training (Figs. S1A and B). Overall, monocular perceptual learning significantly improved visual function in the amblyopic eye. Further analysis of the relevance of these improvement indicators revealed that VA correlated with baseline BCVA (Pearson's $r = -0.579$, $r^2 = 0.323$, $p < 0.001$, Fig. 4A) and baseline spherical equivalent diopter (SED) (Pearson's $r = 0.337$, $r^2 = 0.114$, $p = 0.018$, Fig. 4B). Here we used absolute values, considering only a few myopic amblyopes enrolled in this study. It shows that the worse the baseline VA and the higher the refractive error of the amblyopic eye, the more significant the improvement after training. This trend remained significant if the outlier (−15D) was ignored. If signs of refractive error were not ignored, the improvement in BCVA has no statistically significant correlation to the SED, whether the outlier (−15D) was ignored or not. Also, there was a significant correlation between pre- and post-training BCVA (Pearson's $r = 0.913$, $r^2 = 0.834$, $p < 0.001$, Fig. S2). The training yielded a significant training effect in the anisometropic and isoametropic groups, while the strabismic group exhibited little improvement (Table S3). In the fellow eye, no significant difference was found in VA and CSF (AULCSF and SF cut-off) before and after training (BCVA: [0.02 ± 0.18)] vs [0.02 ± 0.17)], Wilcoxon signed-rank test: $z = -0.36$, $p = 0.81$; AULCSF: [1.37 ± 0.40] vs [1.39 ± 0.36], Wilcoxon signed-rank test: z = -0.83, $p = 0.41$; cut-off: [18.56 ± 7.99] vs [18.89 ± 7.41], Wilcoxon signed-rank test: $z = -0.46$, $p = 0.65$).

4.2. Do patients with different post-training visual acuities differ in other clinical measurements?

We divided participants into two groups for further analysis based on training effects on clinical VA improvement. Participants whose BCVA improved by up to 1 line (0.1 logMAR) or more were defined as the effective group, while others were defined as the ineffective group. In the effective group, CSF metrics including AULCSF, SF cut-off, low–SF–AULCSF, mid–SF–AULCSF and high–SF–AULCSF all improved from baseline (Fig. 5A–E, Table S2). In the ineffective group, although there was no noticeable improvement in VA, their AULCSF, SF cut-off, mid–SF–AULCSF, and high–SF–AULCSF all improved except for low–SF–AULCSF from baseline (Fig. 6A–E, Table S2).

Detailed information about the two groups is provided in Table 1. There was a statistically significant difference in baseline BCVA and baseline SED between the two groups, with the effective group having significantly worse baseline BCVA and lower SED than the ineffective group (all $p < 0.05$). If the absolute value of the outlier (−15D) was ignored, the statistical difference remained. For SED with the sign, there was no significantly statistical difference between the effective and ineffective group, whether the outlier (−15D) was ignored or not. There was no statistical difference between the two groups at baseline AULCSF, SF cut-off, low–SF–AULCSF, mid–SF–AULCSF, high–SF–AULCSF, and stereoacuity (all $p > 0.05$). Although there was a significant difference in VA improvement between the two groups after training, we compared the two groups to further understand whether there was also a corresponding

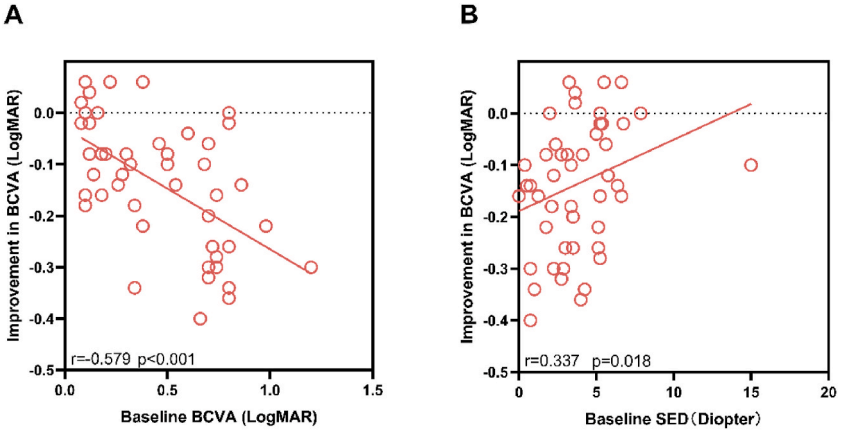

Fig. 4. (A) Relationship between the improvement of BCVA and baseline visual acuity. (B) Relationship between the improvement of BCVA and baseline spherical equivalent diopter.

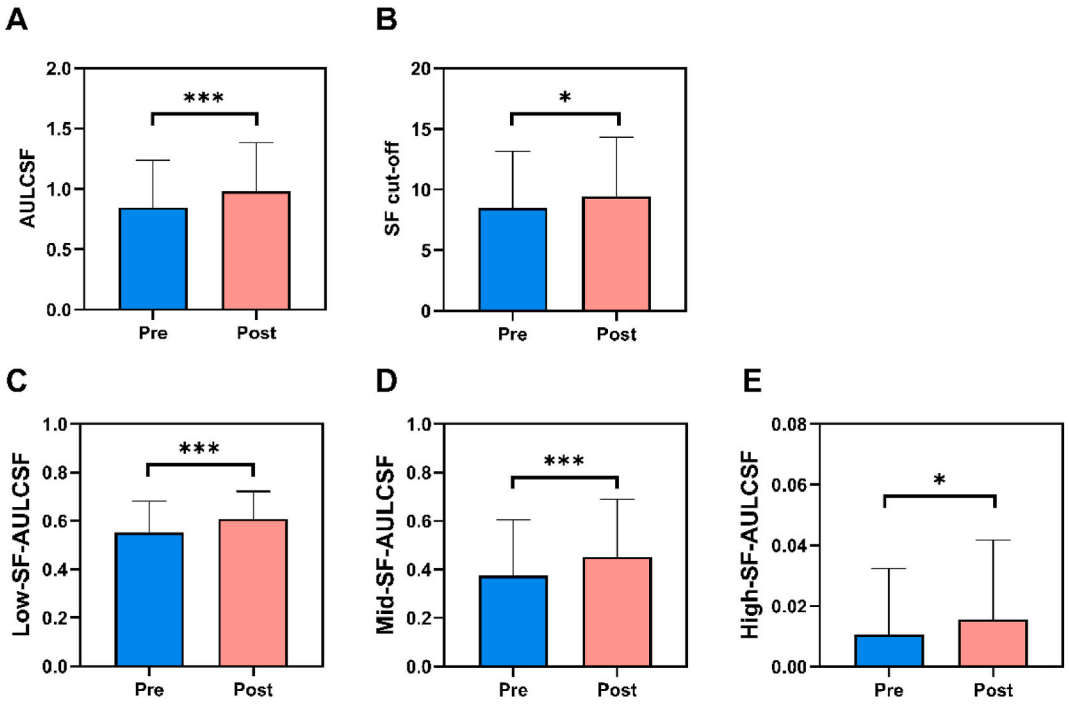

Fig. 5. Summary of CSF metrics before and after training in effective group (A) AULCSF. (B) SF Cut-off, (C) Low- SF- AULCSF. (D) Mid–SF–AULCSF. (E) High–SF–AULCSF. Notes: A single asterisk indicates a significance level of $p < 0.05$. Three asterisks indicate a significance of $p < 0.001$.

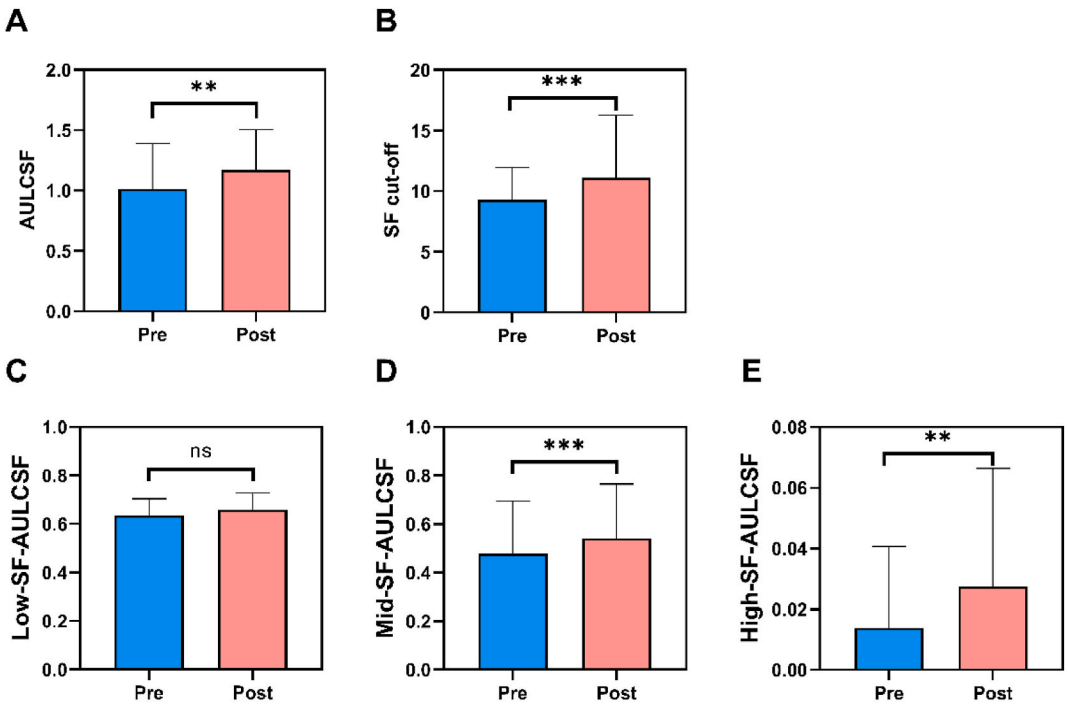

Fig. 6. Summary of CSF metrics before and after training in the ineffective group. (A) AULCSF. (B) SF Cut-off, (C) Low- SF-AULCSF, (D) Mid–SF–AULCSF, (E) High–SF–AULCSF. *Notes:* ns indicates no significance. Two asterisk indicates a significant level of $p < 0.01$. Three asterisks indicate a significance level of $p < 0.001$.

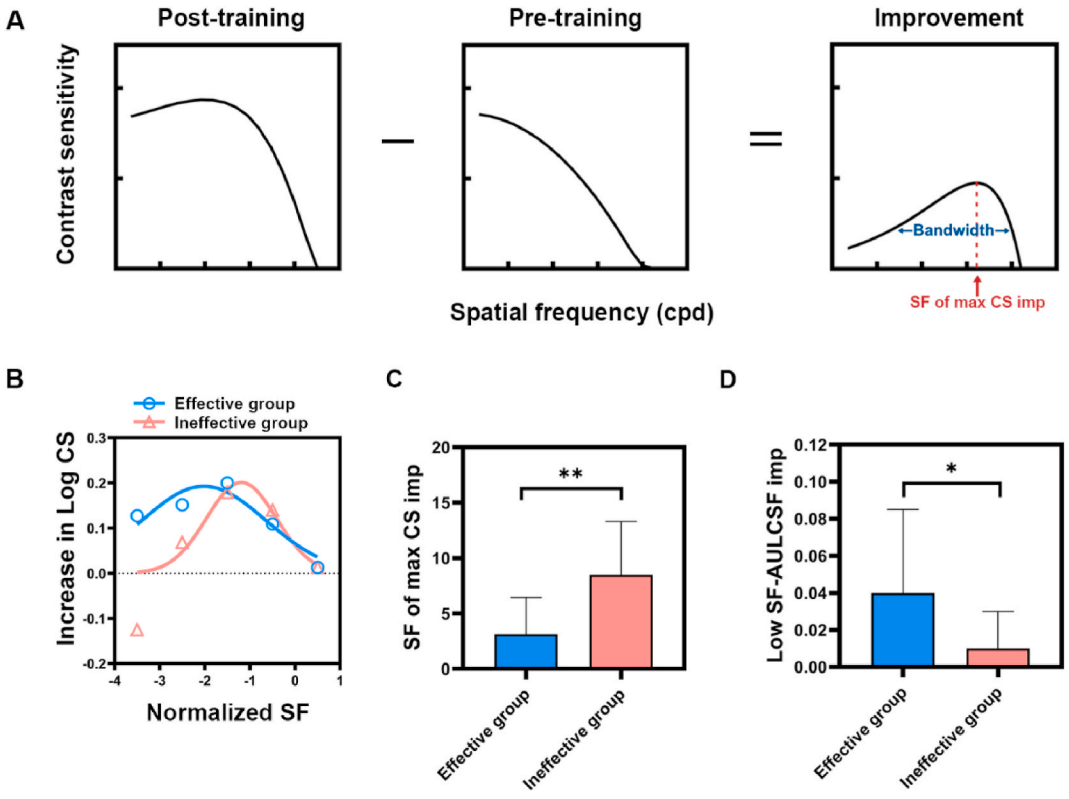

Fig. 7. (A) Illustrations of bandwidth and spatial frequency of maximum contrast sensitivity improvement (SF of max CS improvement): the bandwidth of perceptual learning is used here as an improvement value that can be estimated by subtracting the pre-training CSF from the post-training CSF [27]; the SF of max CS improvement refers to the spatial frequency in which the contrast sensitivity gains maximum improvement after training. (B) Bandwidth in two groups. Average contrast sensitivity improvements were plotted as a function of spatial frequency. The spatial frequencies were normalized to the training frequency. The green circles and lines represent the effective group; The orange triangles and lines represent the ineffective group. Although there is no statistically significant difference in the bandwidth between the two groups ($p > 0.05$), the curve still shows that the effective group has a wider bandwidth range after training and covers the broader low spatial frequencies. (C) Comparison of the SF of max CS improvement in the two groups. (D) Comparison of the improvement of low- SF-AULCSF in the two groups. Notes: A single asterisk indicates a significance level of $p < 0.05$. Two asterisks indicate a significance of $p < 0.01$. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

improvement in each indicator of CSF, including training-related metrics such as bandwidth and SF of max CS (Fig. 7A and B). We found there was a significant difference in improvement between the effective and ineffective groups between the two indicators, low–SF–AULCSF and SF of max CS (all $p < 0.05$, see Fig. 7C and D), while there was no difference in improvement in other metrics, such as overall AULCSF, SF cut-off, mid–SF–AULCSF, high–SF–AULCSF and bandwidth of PL (all $p > 0.05$). The difference between the two groups suggested that the CSF improvement in the effective group with significantly improved VA was more significant in the lower frequency. Although there was no significant correlation between the magnitudes of improvements in low–SF–AULCSF and improvement in VA, the former was significantly correlated with the change in overall AULCSF, a metric representing overall CSF function ($r = 0.654$, $r^2 = 0.428$, $p < 0.001$, see Fig. 8A). Worse initial low–SF–AULCSF correlated with better low–SF–AULCSF improvement ($r = -0.440$, $r^2 = 0.194$, $p = 0.002$, see Fig. 8B). Furthermore, both pre-and post-training VA correlated with pre-and post-training low–SF–AULCSF, respectively (see Fig. 8C and D).

4.3. Can early-stage visual acuity changes predict the outcome of the endpoint?

To better understand how VA improvement emerged throughout training, we reviewed VA assessment performed on the first three days and the last days of training. Individual VA is shown in Fig. 9. The VA improvement noted on the first training day correlated with the final training effect on VA (Pearson's $r = 0.699$, $r^2 = 0.488$, $p < 0.001$, see Fig. 10A). This correlation was even more significant as training went on (Pearson's $r = 0.727$, $r^2 = 0.528$, $p < 0.001$, see Fig. 10B; Pearson's $r = 0.780$, $r^2 = 0.608$, $p < 0.001$, see Fig. 10C). A significant VA improvement at the beginning of training could signal better prognosis. There were 83.67% of patients who maintained improved VA for at least three months follow up after their training ceased. We investigated whether these early changes in VA data could also predict CSF function at the end of the training. But there was no significant correlation observed between changes in VA during the first three days and endpoint improvement in CSF metrics, including AULCSF, SF cut-off, low-, mid- and high–SF–AULCSF,

Table 1
Detailed information about the two groups.

Variable	Effective group (≥1line)	Ineffective group (< 1line)	Chi-square	t value	z value	P-value	Cohen's d
Total (n)	29	20	–	–	–	–	–
Type			1.28			0.61	
Anisometropic amblyopia	22 (75.86%)	14 (70%)	–	–	–	–	–
Isoametropic amblyopia	4 (13.79%)	5 (25%)	–	–	–	–	–
Strabismic amblyopia	3 (10.34%)	1 (5%)	–	–	–	–	–
Sex (male/female)	19/10	11/9	0.55	–	–	0.56	–
Age (yrs)	18 ± 7	16 ± 7	–	−0.92	–	0.36	0.27
Training duration (days)	12 ± 2	13 ± 1	–	0.84	–	0.40	0.25
SED (Diopter)	3.40 ± 2.93	4.30 ± 1.74	–	–	−1.96	0.049*	0.59
Baseline Measurement (AE)							
BCVA (logMAR)	0.55 ± 0.29	0.30 ± 0.25	–	−3.19	–	0.003*	0.91
AULCSF	0.84 ± 0.40	1.02 ± 0.48	–	1.41	–	0.17	0.42
Low–SF–AULCSF	0.55 ± 0.13	0.59 ± 0.18	–	–	−1.67	0.10	0.49
Mid–SF–AULCSF	0.37 ± 0.23	0.47 ± 0.27	–	1.29	–	0.20	0.41
High–SF–AULCSF	0.01 ± 0.02	0.01 ± 0.03	–	–	−0.88	0.38	0.25
SF Cut-off	8.48 ± 4.70	9.29 ± 4.91	–	–	−0.88	0.39	0.25
Near Stereoacuity (arc second)	5000 (5000-5000) N = 11	5000 (5000-5000) N = 10	–	–	−0.95	0.76	0.28
Distance Stereoacuity (arc second)	5000 (5000-5000) N = 11	5000 (5000-5000) N = 10	–	–	0	1	0
Training effect on CSF (AE)							
Improvement in AULCSF	0.14 ± 0.14	0.13 ± 0.18	–	–	−0.36	0.74	0.10
Improvement in low–SF–AULCSF	0.06 ± 0.07	0.03 ± 0.07	–	–	−2.18	0.029*	0.66
Improvement in mid–SF–AULCSF	0.08 ± 0.09	0.08 ± 0.11	–	–	−0.45	0.67	0.13
Improvement in high–SF–AULCSF	0.01 ± 0.01	0.01 ± 0.02	–	–	−1.36	0.18	0.40
Improvement in cut-off	0.95 ± 2.09	2.07 ± 2.33	–	–	−1.43	0.16	0.42
Bandwidth of PL	2.03 ± 1.37	2.21 ± 1.99	–	–	−0.10	0.93	0.03
SF of max CS improvement	4.89 ± 3.49	8.20 ± 5.34	–	–	−2.59	0.009*	0.80

Data are mean (SD), median (quartiles) or n (%). logMAR = logarithm of the minimum angle of resolution; SED = absolute value of spherical equivalent refraction; AULCSF = the area under the log contrast sensitivity function; AE = Amblyopic eye; A single asterisk indicates a significance level of $p < 0.05$.

respectively. (All $p > 0.05$).

5. Discussion

Perceptual learning is currently being adopted as a complementary intervention for amblyopia, especially for older patients beyond their critical period of visual development. Its effectiveness, however, remains variable and unpredictable. This study shows that older amblyopes who underwent monocular perceptual training with a contrast adjusted target tuned to their SF cut-off could benefit from a significant training effect, showing meaningful improvements in VA and contrast sensitivity. A poor baseline VA and broad stimulation of contrast sensitivity identification task at SF cut-off during perceptual training may signal better training outcomes in VA. Early VA improvement may likely serve as a marker of endpoint VA gain.

Previous studies have demonstrated that perceptual learning can improve multiple visual functions in amblyopes. Overall, our patients showed significant improvement in VA by 1.4 lines, comparable to previous studies [3]. CSF metrics also improved, including AULCSF, SF cut-off, low, mid, and high–SF–AULCSF. In line with Polat et al. [15] and Zhou et al. [16], most of our patients maintained improved VA within the three-month follow-up, implying a potential in perceptual learning affecting long-term modification of cortical circuits [51]. However, no training effect was noted in near and distance stereopsis. Although some research reported improvement in stereopsis following monocular perceptual learning [35,52], it is debatable whether it can improve binocular processing, including stereopsis [41,53]. Our negative results may partly be attributed to the individualized outcome of stereopsis after perceptual learning. For example, there were a few individual cases who had remarkable improvement such as Patient 1 who showed no initial distance stereopsis improved to 100 arc s, and Patient 44 improved to 400 arc s. Patient 31 failed the initial near stereopsis improved to 400 arc s, while Patient 44 improved from 100 arc s to 20 arc s. Other patients remained to have limited to no stereopsis even after training. Our results are consistent with Liu's study who had only one participant with no measurable baseline stereopsis with a previous treatment history gaining measurable improvement in stereopsis after monocular training [54]. It may be ascribed to the reason that both distance and near stereopsis tests employed in our study have a maximum disparity of 400 arc s. Participants who failed to detect this disparity endpoint were labeled as having no stereopsis. Their stereopsis may have partially improved after training, but not to the detectable level. For individuals, responses to monocular SF cut-off training are variable, with various combination of improvement in VA, contrast sensitivity among different spatial frequency band, and stereopsis [45]. Training strategy should be modified according to individual characteristics to boost the efficacy.

Several participants failed to gain notable improvement in VA. Further investigation indicated that poor baseline VA correlated with better training outcomes, consistent with that reviewed by Tsirlin et al. [46]. As VA reflects the spatial resolution at high contrast, while CSF provides a more comprehensive assessment of spatial vision, this study separated the AULCSF into three segments to

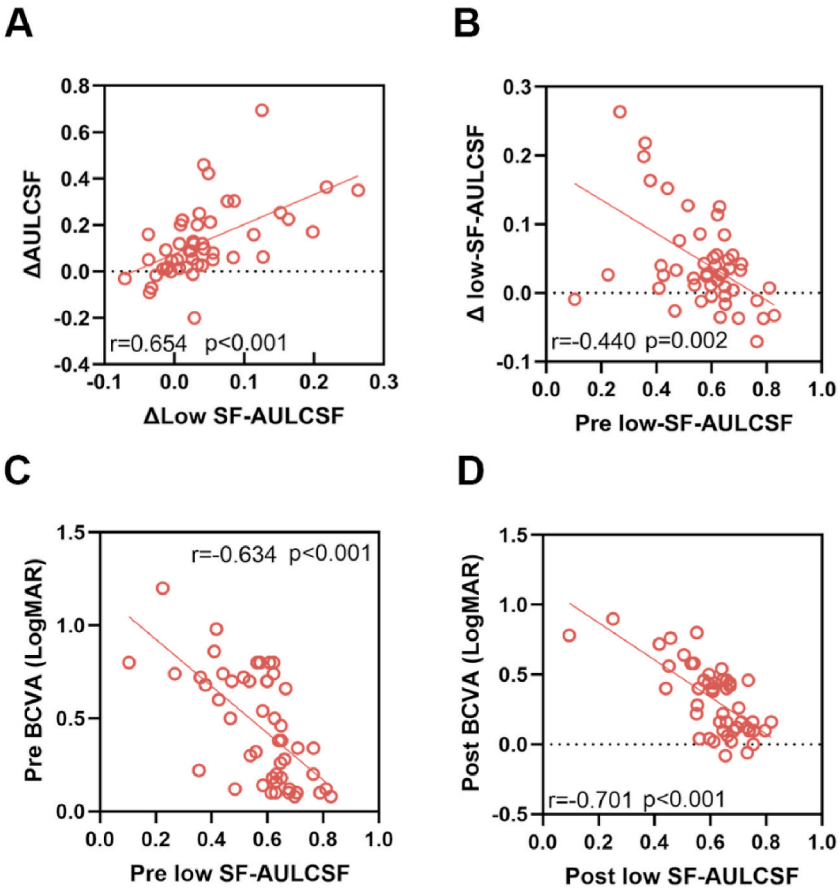

Fig. 8. (A) Relationship between the changes in low- SF-AULCSF after training and AULCSF after training. (B) Relationship between pre-training low–SF–AULCSF and improvement in low- SF-AULCSF. (C) Relationship between pre-training visual acuity and pre-training low- SF-AULCSF. (D) Relationship between post-training visual acuity and post-training low- SF-AULCSF.

comprehensively quantify the low, mid, and high spatial frequency spectrum area [50]. Each spectrum might reveal the holistic CSF function in the corresponding frequency band. Comparable bandwidths of the two groups indicated a similar range of spatial frequencies impacted by perceptual learning [27], but different patterns of CSF reconstruction were found in the two groups. The effective group showed significant improvement in low–SF–AULCSF, while the ineffective group did not. The maximum improvement of CSF lies at a lower SF in the effective group versus the ineffective group where a low–SF–AULCSF correlates with VA. Considering these, we suggest that activating a broader SF contrast spectrum after perceptual learning in amblyopia contributes to VA improvement. It is widely believed that high SF information reflects the ability to resolve fine details. As a result, improvement in high SF should be correlated with VA improvements. However, optotypes in the EDTRS chart are broadband and scale variant. Individuals with different VA use different object frequencies to identify the letter. The actual retinal spatial frequency is lower than the assumed frequency directly transformed from VA [55]. Additionally, neuroscience research revealed that low SF information may reach high-order areas rapidly, sending feedback to the occipito-temporal cortex, and facilitating high spatial frequency-based analysis [56]. Future research with daily CSF assessment may help illustrate the exact mechanism of how the reconstruction of CSF transfer to VA improvement.

Similar to previous research [16,27,34], our study mainly recruited anisometropic amblyopia, and the training outcome is satisfactory in this subgroup. With the relatively small number of participants, the isoametropic group also exhibited significant improvement in VA and CSF metrics, while the strabismic group seemed to benefit little from training. As reviewed by Tsirlin et al. [46] and Rodán et al. [57], the effect of monocular perceptual learning strategy had never been explored in isoametropic amblyopia before. We believe our study provides a new perspective on perceptual learning therapy in isoametropic amblyopia. More participants are needed to prove the training efficacy in different etiologies in future studies.

Previous studies focused only on the starting and endpoints rarely on the relationship between early training process changes and the endpoints. In this study, we found that VA and CSF metrics improvements correlate with each other, especially in the low frequencies band, and that changes in VA in the first three days can serve as a marker of final VA improvement. The early VA changes may fail to predict CSF improvement because of the lack of recognized translation between the two metrics. Perceptual learning in different disciplines share commonalities, and auditory perceptual learning research reveals that the vast majority of the early and fast

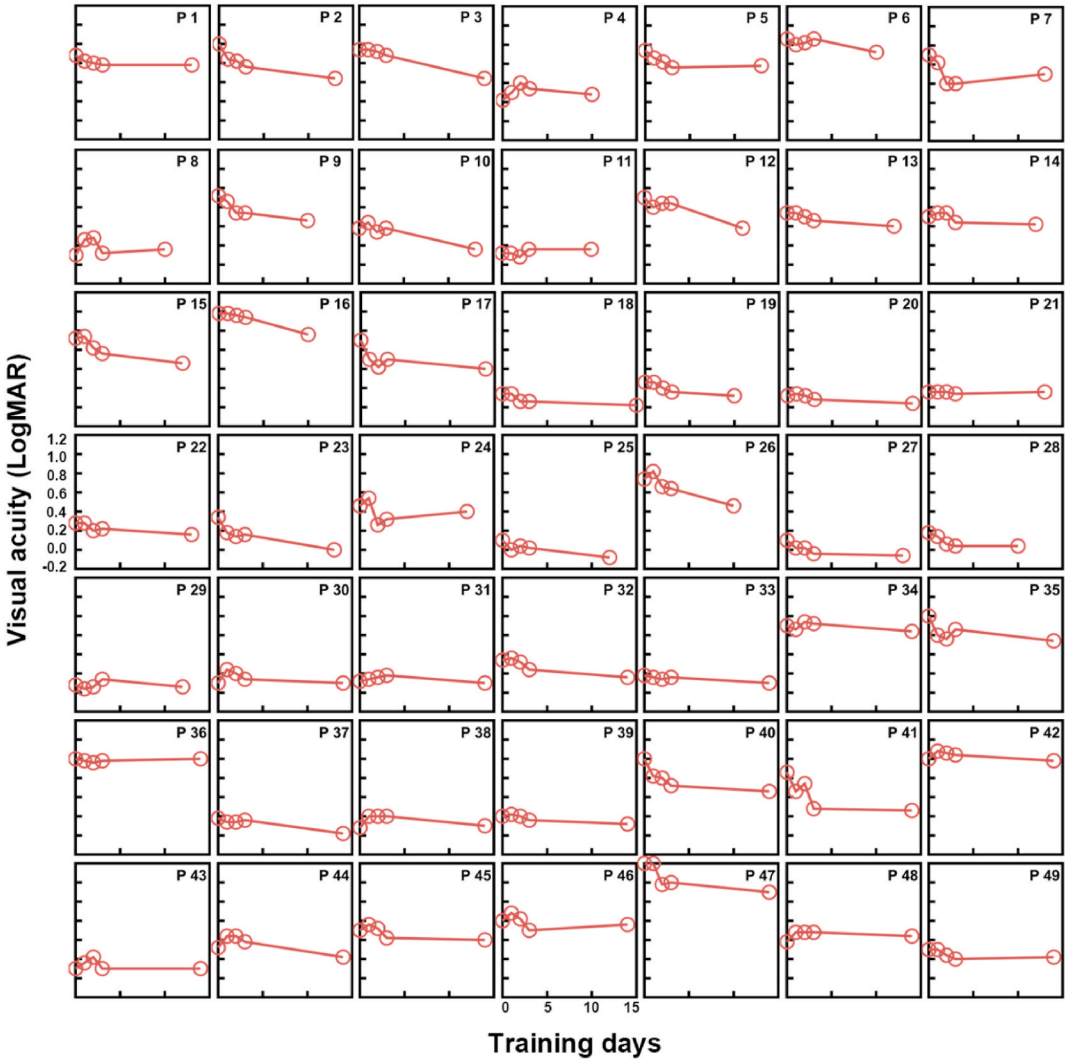

Fig. 9. Visual acuity (logMAR) tested before training, during the first three days after training sessions, and the last day after training sessions in the trained eyes of all participants.

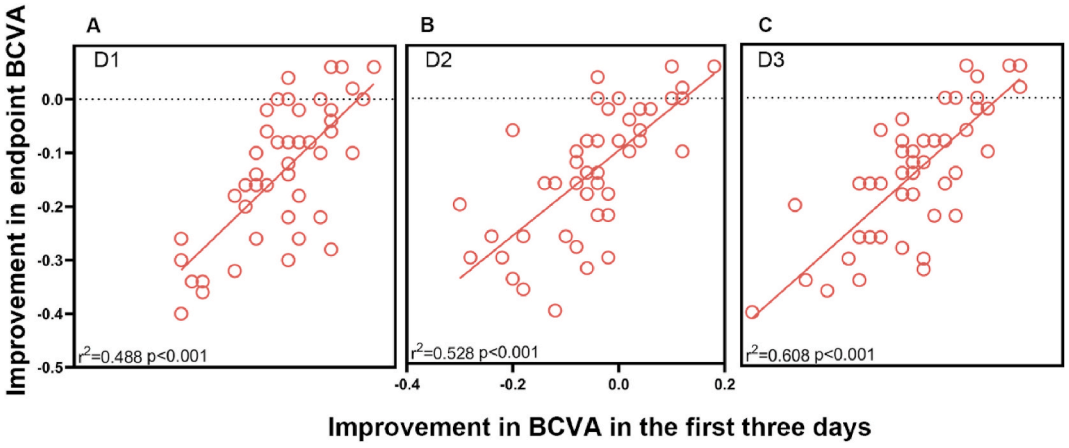

Fig. 10. Relationship between improvement in visual acuity in the first three days and the endpoint. Correlation between visual acuity improvement after one day (A), two days (B) and three days (C) of training and endpoint visual acuity improvement, respectively.

improvement in the learning task can be attributed to perceptual learning effect per se [58]. Also, the individual learning ability was deemed a determining factor of training effect [59], for which monitoring VA changes in the initial stage may provide some hints to facilitate the prediction of participants' responses to perceptual learning and adjust the management in clinical and neuroscience research practice in amblyopia.

5.1. Limitations of the study

In our study, the predominant subtype of amblyopia was anisometropic amblyopia, and the sample of isoametropic and strabismic amblyopia was relatively small. Most of the patients had no measurable baseline stereopsis, which limited the training effect on stereopsis in participants with better stereopsis. Thus, to explore the general training effect of monocular perceptual learning, more participants from different groups, with different levels of stereopsis should be recruited in future studies. We did not collect CSF data daily during training because VA was the most accessible measurement in clinical practice. Therefore, we failed to investigate the relationship between early response and endpoint outcome in CSF metrics, despite our study's close relationship between VA and CSF. Our previous study demonstrated that CSF could reflect more subtle visual function changes than VA [60], and future work could be conducted to monitor CSF during perceptual learning and further evaluate whether it may be a more sensitive indicator to predict the final learning effect. Other measurements such as suppression can also be added to future studies to help better explore the neural mechanisms underlying perceptual learning in amblyopia.

Resource availability

Lead contact

Further information and requests for resources should be directed to and will be fulfilled the lead contact, Jinrong Li (lijingr3@mail.sysu.edu.cn).

Data and code availability

All data supporting findings of this work are provided within the manuscript and its supplemental information section. Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

Author contribution statement

Yunsi He: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Lei Feng: Performed the experiments; Analyzed and interpreted the data.

Yusong Zhou: Yijing Zhuang: Zixuan Xu: Ying Yao: Xiaolan Chen: Rengang Jiang: Junpeng Yuan: Qingqing Ye: Yun Wen: Yu Jia: Performed the experiments.

Jing Liu: Jinrong Li: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e17281.

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