Original Article

Significance of binocular fusion in enhancing visual acuity during amblyopia treatment

Zongyue Lv[1], Zhengyang Tao[2], Guorui Hu[1], Hongwei Deng[2]

[1]Department of Ophthalmology, The Second Clinical Medical College, Jinan University, Shenzhen, China; [2]Department of Strabismus and Pediatric Ophthalmology, Shenzhen Eye Hospital, Jinan University, Shenzhen, China

Contributions: (I) Conception and design: H Deng, Z Lv; (II) Administrative support: H Deng; (III) Provision of study materials or patients: Z Lv, Z Tao; (IV) Collection and assembly of data: G Hu; (V) Data analysis and interpretation: Z Lv, G Hu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Hongwei Deng, PhD. Department of Strabismus and Pediatric Ophthalmology, Shenzhen Eye Hospital, No. 18 Zetian Road, Futian District, Shenzhen 518000, China. Email: dhw110@126.com.

Background: Currently, the exploration of amblyopia treatment methods is gradually shifting to the restoration of binocular visual perceptual function. Binocular fusion function, as an important component of binocular visual function, mainly reflects the patient's ability to integrate the signals received from both eyes. In this study, we investigated the relationship between binocular fusion function and improvement in visual acuity during amblyopia treatment.

Methods: A retrospective analysis was conducted on a cohort of patients with amblyopia, aged 3–14 years old, who visited an outpatient clinic in Shenzhen Eye Hospital between May 2021 and January 2023. The investigation included 105 patients (210 eyes) with isometropic or anisometropic amblyopia. All participants underwent cycloplegic refraction examination and binocular fusion function measurement. All patients underwent standard amblyopia treatment, and those with the best-corrected visual acuity (BCVA) of 0.6 or higher in the amblyopic eye of both eyes received binocular fusion training using a computer platform.

Results: A statistically significant negative correlation (−0.263, P=0.007) was observed between the absolute difference in binocular BCVA and binocular fusion function at the start of treatment (baseline). Linear regression analysis revealed that the improvement in BCVA in the amblyopic eye exhibited correlations with several factors, including the baseline binocular BCVA difference, baseline BCVA of the amblyopic eye, improvement in binocular fusion function, and the number of fusion training sessions (regression coefficients: −0.463, −0.771, 0.007, and 0.063, respectively; all P<0.05). Two patterns of binocular fusion function development during treatment were identified using group-based trajectory modeling (GBTM): the slow growth pattern and the rapid growth pattern. The results of a multivariate logistic regression model indicated a statistically significant link between fusion training and the development pattern of binocular fusion function [odds ratio (OR): 5.219, 95% confidence interval (CI): 2.045–13.323].

Conclusions: Enhancing binocular fusion function may result in an improvement of BCVA in the amblyopic eye of patients with amblyopia. The frequency of binocular fusion training is crucial for rapid improvement in binocular fusion function.

Keywords: Amblyopia; binocular fusion function; binocular visual function; group-based trajectory modeling; refractive errors

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Introduction

Amblyopia is the most prevalent cause of visual impairment in children (1). Traditional amblyopia treatments focus on refractive adaptation and suppression of the dominant eye to enhance vision in the amblyopic eye (2). For patients aged 3–5 years, the lower limit is 0.5, and for those over 6 years, the lower limit is 0.7. An eye with vision below this value is defined as an amblyopic eye. As an initial amblyopia treatment, refractive adaptation or optical treatment enhances vision in approximately 70% of patients by more than 0.2 logarithm of the minimum angle of resolution using eye patching or atropine penalization on the dominant eye (3). However, compliance with occlusion therapy is low, approximately 48%. Children prescribed 3–6 hours of occlusion daily often adhere to only half of the prescribed time. The primary cause of this occlusion, which results in reduced visual quality and has an impact on appearance and daily activities, ultimately leading to peer teasing (4,5).

Recent research indicates that visual impairment in amblyopia may be secondary to abnormal binocular inhibition, referring to a phenomenon where the neural processing of visual information from both eyes is suppressed or inhibited. There has been speculation that monocular amblyopia may arise from anomalies in binocular visual function as well; consequently, approaches to treat amblyopia have shifted to prioritize the restoration of binocular visual perceptual function (6). Binocular fusion, which is crucial in binocular visual function, involves integrating images from each eye in the brain to create stereoscopic vision (7). Furthermore, binocular fusion function may reveal the balance of contrast sensitivity between both eyes (8). Binocular fusion function is a component of binocular vision function, while best-corrected visual acuity (BCVA) reflects whether the patient is currently in a state of amblyopia. The focus of this research is the modification of binocular fusion function in the context of conventional amblyopia treatment. Additionally, we investigated in this study the correlation between enhancing binocular fusion function through training and improvements in the BCVA of the amblyopic eye. We present this article in accordance with the STROBE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-24-125/rc).

Highlight box

Key findings

- Enhancing binocular fusion function may result in an improvement of best-corrected visual acuity (BCVA) in the amblyopic eye of patients with amblyopia. The frequency of binocular fusion training is crucial for rapid improvement in binocular fusion function.

What is known and what is new?

- Refractive correction and occlusion are currently effective methods for treating amblyopia, but the poor compliance of most people results in the actual treatment effect not meeting expectations.
- The restoration of binocular fusion function can promote the improvement of BCVA in both eyes of amblyopia patients.

What is the implication, and what should change now?

- Dual eye fusion training can be used as a supplementary method for treating amblyopia, in conjunction with traditional amblyopia treatment methods.

Methods

General information

Patients aged 3–14 years who visited the pediatric ophthalmology outpatient clinic at Shenzhen Eye Hospital between May 2021 and January 2023 were included in this retrospective study. A total of 105 patients (210 eyes) who had been diagnosed with either isometropic or anisometropic amblyopia were selected at random. The diagnostic criteria for isometropic amblyopia and anisometropic amblyopia were made according to the "Consensus on the Prevention and Treatment of Amblyopia in Chinese Children" (2021). With a BCVA below the age group average, isometropic amblyopia was defined as a spherical lens power above 3D or a cylindrical lens power over 2D. In addition to a two-line BCVA discrepancy, anisometropic amblyopia was characterized by a difference in spherical lens power of 1.5D or in cylindrical lens power of 1D between the eyes. After their initial visit, patients would undergo two follow-up examinations, with each exam spaced 3 months apart, resulting in a total time span of 6 months between the first and last assessments. All patients underwent refractive adaptation treatment during each visit. Individuals whose BCVA disparity between the amblyopic eyes exceeded two lines received two hours of daily occlusion therapy for the eye with relatively better vision. The SJ-RS-WL2015 multimedia visual function training therapy system (developed by Guangzhou Shijing Medical Software Co., Ltd., China) was utilized by patients with a BCVA of 0.6 or higher to conduct fusion training via its online platform.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and approved by the Institutional Ethics Committee of Shenzhen Eye Hospital (No. 20211009-02). Written informed consent was obtained from patients' legal guardians prior to enrolment.

Inclusion and exclusion criteria

Inclusion criteria: (I) individuals aged 3 to 14 years; (II) absence of neurological disorders in the past; (III) no organic lesions in the eyes; (IV) no color vision deficiencies; (V) absence of ocular misalignment, including strabismus and nystagmus; (VI) ability to comprehend instructions and cooperate in completing quantitative binocular separation and fusion function tests using a computer platform; (VII) minimum of two follow-up visits with complete data.

Exclusion criteria: (I) incomplete data in retrospective records; (II) presence of ocular misalignment; (III) during follow-up, diagnosis of new ocular or systemic diseases, such as neurological or psychiatric disorders.

Examination methods

General ophthalmic examination

Each patient underwent an anterior segment examination using a Topcon SL-2G slit-lamp biomicroscope (Japan) in conjunction with a medical flashlight. Ocular alignment and ocular motility assessments were conducted by experienced clinical physicians using eye movement tests, corneal light reflex tests, and alternate cover tests to assess the patient's eye position and motility. Fundus examinations were conducted following cycloplegic refraction using a handheld WelchAllyn-12851 direct ophthalmoscope (USA).

Examination of BCVA and refractive status

A standard logarithmic chart (Jiangsu Suhong Medical Instruments Co., Ltd., China) placed 5 meters from the patient was utilized to evaluate visual acuity. Compound tropicamide eye drops (Shenyang Xingqi Pharmaceutical Co., Ltd., China) were administered every 10 minutes, three times, to patients over the age of six to dilate the pupils and paralyze the ciliary muscles. A 1% atropine gel (Shenyang Xingqi Pharmaceutical Co., Ltd.) was applied twice daily for three days in children under the age of six in order to induce sufficient pupil dilation (loss of pupillary light reflex). BCVA and lens prescriptions were recorded following retinoscopy (YZ6E model, 66 Vision Tech Co., Ltd., Suzhou, China) with dilated pupils. During the administration of 1% atropine for pupil dilation, we also advise the family members to help the child become familiar with recognizing the E-chart. All patients underwent retinoscopy under pupil dilation using the YZ6E retinoscope (66 Vision Tech Co., Ltd.), and their spherical and cylindrical lenses were recorded. The BCVA of the patients was measured using the decimal counting method.

Computer platform-assisted binocular fusion function examination and training

The examination and training were conducted using the online platform of the SJ-RS-WL2015 multimedia visual function training therapy system (Guangzhou Shijing Medical Software Co., Ltd.). The computer processor and operating system are: Intel(R) N95 1.70 GHz processor, Windows 10 Home Chinese Edition 64-bit operating system. The tests were conducted in a 3 m × 5 m room with 200 lux illumination. The random dot fusion images measuring 305 px × 305 px were observed on a Windows 10 PC with a 1,920×1,080 resolution and 60 Hz refresh rate. Participants wore red-blue spectacles and observed the monitor from about 46 cm away. Initially, the monitor displayed fully overlapped red and blue images (*Figure 1A*). Participants identified the direction of an arrow in the image, causing the images to separate progressively by 0.54° angles until they were unable to distinguish the arrow direction. Correct answers to the separation function test shifted the blue dot image to the right and the red dot image to the left. Inversely, the convergence function test was conducted. The examination concluded upon receiving three faulty responses. The divergence distance in pixels (px) between the red and blue random dot images was converted to fusion function values using a tangent function. The sum of the absolute separation and convergence function values was the binocular fusion range. Normal values are >6.5 for the separation function and >15 for the convergence function. Patients are required to complete the entire training procedure through the use of a computer-based online platform while wearing red-blue glasses. The training consists of two sections: "Find the Same" and "Line Fusion", with each section practiced once a day for 15 minutes. In the "Find the Same" section, the patient is asked to find the image that matches the central figure from 16 surrounding figures. Clicking with the mouse will change the displayed patterns. In the "Line Fusion" section, two line patterns gradually separate, and when the patient sees both images, pressing the spacebar will move on to the next pattern. The daily training progress of each patient

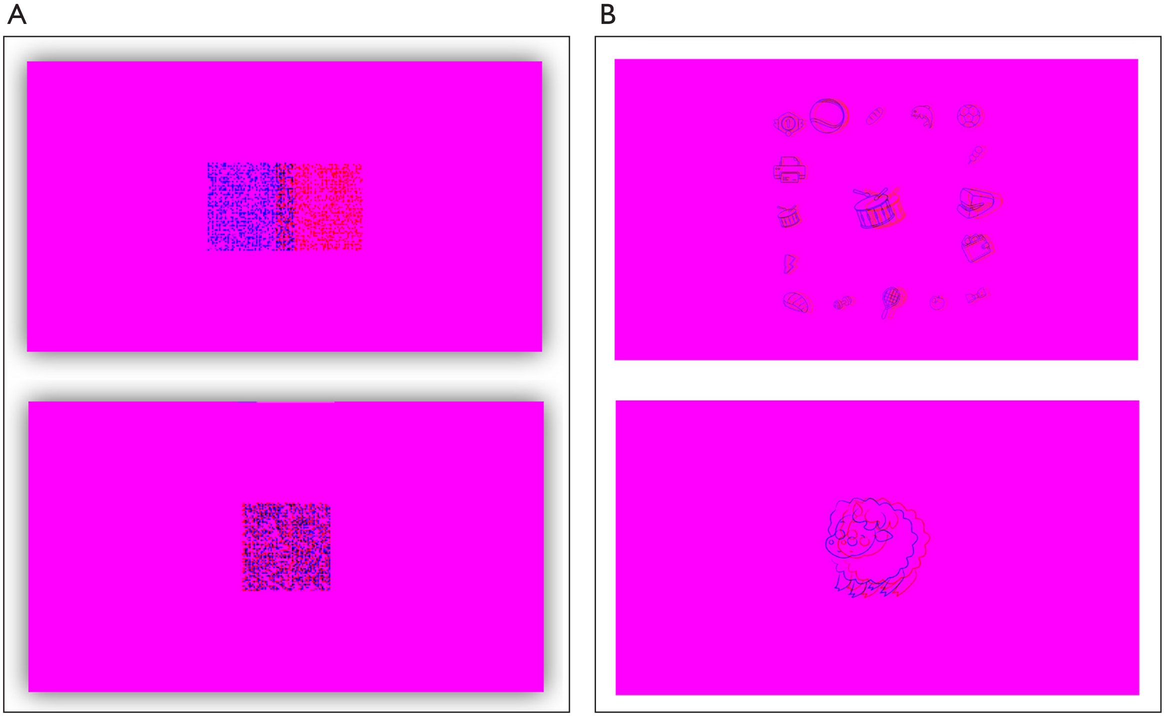

Figure 1 Overview image of binocular fusion function assessment and training. (A) Diagram of binocular fusion function measurement. (B) Binocular fusion function training screenshot.

was monitored, and the total number of completed training sessions was recorded by the system's infrastructure. The content viewed by patients during the binocular fusion function training is shown in *Figure 1B*.

Statistical methods

The statistical analyses were performed using the *R* software (version 4.2.2). The continuous data with normal distribution were represented as mean ± standard deviation or median (Q1, Q3) with non-normal distribution. The *t*-test for normal distribution continuous data, or Wilcoxon rank-sum test for non-normal distribution continuous data, was used for between-group comparisons. Categorical data were presented as n (%) and Fisher's exact test was used for comparison in two groups or Chi-squared test was used for comparisons in three or more groups.

Spearman's analysis

The Spearman's correlation coefficient calculated the correlation between the binocular fusion function and the difference in binocular BCVA.

Linear regression analysis

Univariate and multivariate linear regression models were both employed. Those that showed significance in the univariate analysis were included in the multivariate linear regression model. Stepwise selection method was used to screen the variables and build the fitted model, and Akaike's Information Criterion (AIC) was used as a criterion to determine the strength of the model (9).

The BCVA improvement model: the dependent variable was the BCVA improvement in the amblyopic eye at the second follow-up. Independent variables included patient age, gender, amblyopia type, baseline BCVA of the amblyopic eye, absolute baseline BCVA difference between eyes, baseline binocular fusion function, and binocular fusion function training. Variables significant at $P<0.05$ in the univariate analysis were incorporated into the multivariate model. The optimal model was identified using a stepwise selection approach with minimum AIC as the model selection criterion.

The absolute difference in binocular BCVA model: the dependent variable was the absolute difference in binocular BCVA. Amblyopia type, baseline BCVA of the amblyopic

Table 1 Basic information of enrolled patients

Characteristic	Isometropic (n=72)	Anisometropic (n=33)	Total
Female, n	36	17	53
Age at first visit, y, median (range)	5.0 (5.0, 6.0)	6.0 (5.0, 7.0)	5.0 (5.0,6.0)
Sphere >0	71	32	103
With cylinder <2.00 D	44	27	71
With cylinder ≥2.00 D	27	5	32
Sphere <0	1	1	2
With cylinder <2.00 D	1	1	2
With cylinder ≥2.00 D	0	0	0

D, diopter.

Table 2 Refractive status and baseline binocular fusion function of the patients

Variable	Right eye	Left eye
Sphere, D	3.81±3.10	4.11±2.96
Cylinder, D	−1.44±1.29	−1.65±1.11
BCVA	0.59±0.24	0.54±0.25
Binocular divergence, px	0.67±1.52	
Binocular convergence, px	0.72±1.84	

Data are presented as mean ± standard deviation. D, diopter; BCVA, best-corrected visual acuity.

eye, absolute binocular BCVA difference, and binocular fusion function were independent variables. Variables with P<0.05 in the univariate model were included in the multivariate model. We used a stepwise selection method with minimum AIC to identify the best-fit model.

Group-based trajectory modeling (GBTM) analysis

A semi-parametric trajectory grouping strategy is used by GBTM, which hypothesizes the existence of multiple latent trajectories within the population. The model calculates the posterior probability of each individual belonging to different trajectories. Individuals are classified based on their highest posterior probability corresponding to a specific growth trajectory, enabling group clustering. Each latent trajectory represents a subclass with unique growth patterns. The initial model starts with a single latent class, to which classes are added repeatedly. Each latent class trajectory begins with a linear polynomial function, which can be extended to a quartic polynomial function. The GBTM model identifies latent trajectories with similar fusion patterns by analyzing dynamic changes in separation and convergence indicators at baseline, the first follow-up, and the second follow-up. The model selection is guided by two core principles: a superior fit is indicated by a smaller absolute value of the Bayesian Information Criterion (BIC), and the average posterior probability (AvePP) for each trajectory group should exceed 0.7 to signify high internal group coherence.

Logistic regression analysis with GBTM trajectory

After establishing GBTM groups, univariate and multivariate logistic regression analyses examined associations between different fusion patterns and baseline variables (BCVA of the amblyopic eye, absolute difference in binocular BCVA, baseline binocular fusion function, and the number of fusion training sessions). Variables with P<0.05 in univariate logistic regression were integrated into the multivariate model. The optimal model for the fusion function was determined using a stepwise selection method with minimum AIC.

Results

Composition of patients in the retrospective study

A total of 72 patients (68.6%) with isometropic amblyopia and 33 patients (31.4%) with anisometropic amblyopia were enrolled in the study. All patients had central fixation and no additional ocular organic diseases (*Tables 1,2*).

Relationship between binocular BCVA imbalance and fusion function

The Spearman's correlation coefficients between the difference in binocular BCVA and binocular fusion function at baseline, the first follow-up, and the second follow-up were r=−0.237 to −0.263 (*Figure 2*), −0.266 to −0.314 (*Figure 3*), and −0.241 to −0.266 (*Figure 4*), respectively (all P<0.05). A consistent negative correlation is indicated by these values.

Analysis of factors influencing BCVA improvement in the weakest eye

Multivariate linear regression at the second follow-up revealed a negative correlation between the improvement in BCVA in the weakest eye and both the baseline BCVA

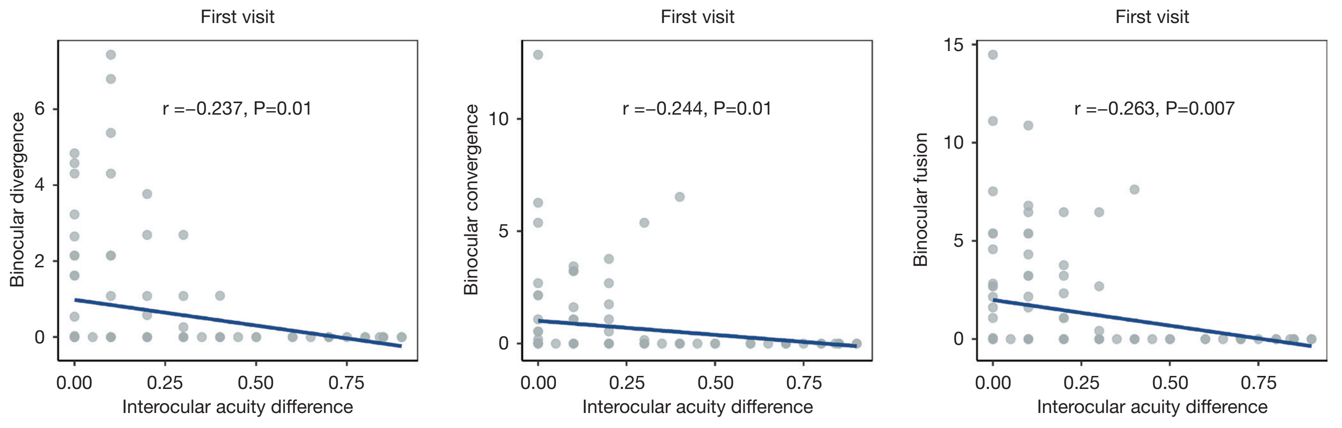

Figure 2 Correlation curves between baseline binocular fusion function and the difference in binocular BCVA. BCVA, best-corrected visual acuity.

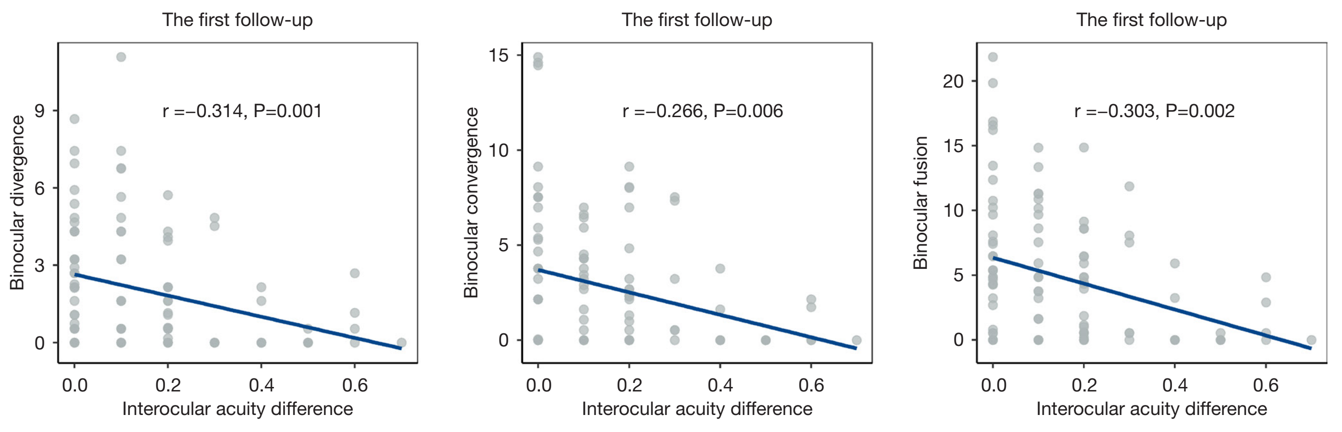

Figure 3 Correlation curves between binocular fusion function and the difference in binocular BCVA at the first follow-up. BCVA, best-corrected visual acuity.

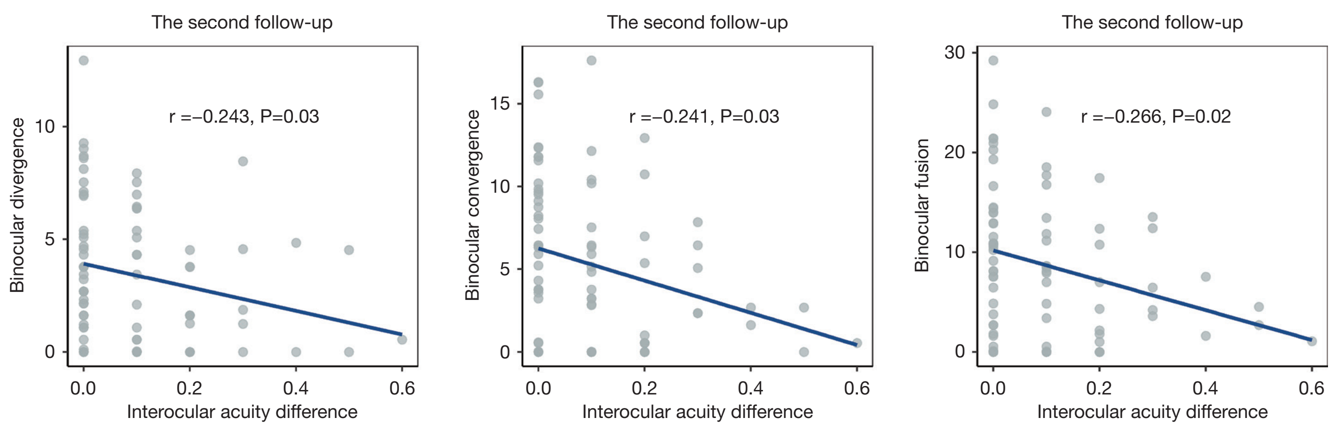

Figure 4 Correlation curves between binocular fusion function and the difference in binocular BCVA at the second follow-up. BCVA, best-corrected visual acuity.

Table 3 Grouping criteria for binocular fusion function growth patterns in GBTM

Group	The polynomial degree of group trajectories	AIC	BIC	Minimum AvePP in groups
1	1-Linear	2,774.196	2,799.981	1.000
	2-Quadratic	2,774.196	2,799.981	1.000
	3-Cubic	2,774.196	2,799.981	1.000
	4-Quartic	2,774.196	2,799.981	1.000
2	1-Linear	2,331.416	2,386.670	0.991
	2-Quadratic	2,332.522	2,395.142	0.988
	3-Cubic	2,332.522	2,395.142	0.988
	4-Quartic	2,332.522	2,395.142	0.988

GBTM, group-based trajectory modeling; AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; AvePP, average posterior probability.

difference between eyes and the baseline BCVA of the weakest eye. The regression coefficients were −0.463 (t=−4.975, Df=77, P<0.001) and −0.771 (t=−7.511, Df=77, P<0.001), respectively. Conversely, positive correlations were observed with the improvement in binocular fusion function and the number of binocular fusion training sessions. The coefficients for these correlations were 0.007 (t=4.869, Df=77, P<0.001) and 0.063 (t=2.508, Df=77, P=0.01), respectively. For each unit increase in the baseline BCVA difference between the eyes, the corresponding improvement in BCVA decreases by 0.463.

Analysis of factors affecting the difference in binocular BCVA

Univariate analysis did not reveal a statistically significant correlation between improvement in binocular fusion function and the difference in binocular BCVA (regression coefficient =−0.003, t=−0.739, Df=77, P=0.463).

Analysis of factors influencing the growth trend of binocular fusion function

Models with one to seven groups were tested for GBTM grouping of binocular fusion function growth patterns, with limitations fitting three or more groups. The two-group model with a first-order polynomial function had the lowest BIC value (2,386.67; *Table 3*), identifying slow growth (31.4%%, AvePP =0.991) and rapid growth (68.6%, AvePP =0.998) pattern groups (*Figure 5*).

Univariate logistic regression linked a high growth rate in separation and convergence to the baseline BCVA of the weakest eye [odds ratio (OR): 9.624, 95% confidence interval (CI): 1.203–77.023] and to fusion function training (OR: 5.219, 95% CI: 2.045–13.323) (*Table 4*). The relationship between fusion function training and the rapid growth pattern was further validated through multivariate logistic regression (OR: 5.219, 95% CI: 2.045–13.323). The probability of experiencing rapid improvement in fusion function after training is 5.219 times greater than the probability of experiencing rapid improvement without training.

Discussion

Currently, refractive adaptation, eye patches, or atropine penalization of the dominant eye are the most common treatments for amblyopia (10,11). Although these methods are effective, 15–50% of patients do not achieve normal vision after extended conventional treatment (12). Furthermore, approximately 25% of patients with amblyopia experience a relapse within a year following the cessation of treatment (13). Binocular pathway has been used as a treatment for amblyopia (14-18). A significant limitation of traditional amblyopia therapy is its exclusive emphasis on modifying the monocular visual pathway, thereby overlooking the potential contribution of binocular visual function to treatment efficacy.

A correlation was identified between the absolute difference in binocular BCVA and binocular fusion range in the retrospective analysis of our study. Severe impairment in binocular fusion function was correlated with a larger

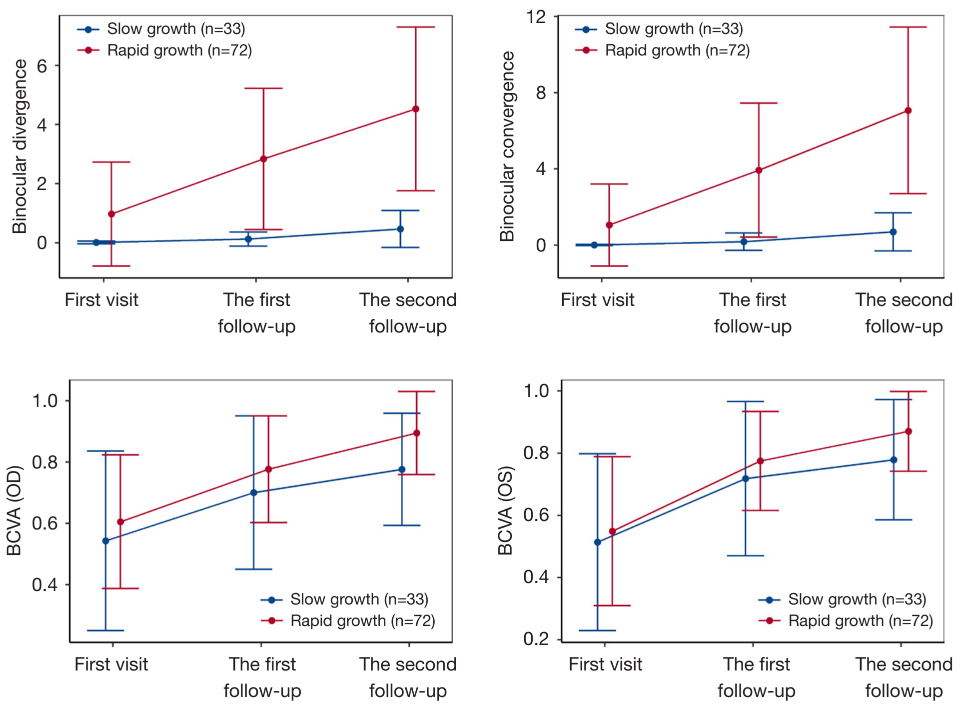

Figure 5 Grouping of binocular separation function and binocular convergence function ascending patterns. BCVA, best-corrected visual acuity; OD, oculus dexter; OS, oculus sinister.

Table 4 The result of growth trend of binocular fusion function univariate logistic model

Variable	Estimate	Standard error	Z	P value	OR (95% CI)
Age	0.225	0.146	1.538	0.12	1.252 (0.940–1.668)
Gender	–0.238	0.422	–0.564	0.57	0.788 (0.345–1.801)
Amblyopia type	0.077	0.455	0.168	0.86	1.080 (0.442–2.636)
Binocular divergence	3.231	2.278	1.418	0.15	25.296 (0.291–2,196.754)
Binocular convergence	4.784	3.763	1.271	0.20	119.572 (0.075–190,856.753)
Baseline BCVA of the weakest eye	2.264	1.061	2.134	0.03	9.624 (1.203–77.023)
Difference in Binocular BCVA	–1.102	0.768	–1.435	0.15	0.332 (0.074–1.497)
Train	0.734	0.280	2.622	0.009	2.083 (1.204–3.607)
Number of trainings	1.652	0.478	3.456	<0.001	5.219 (2.045–13.323)

OR, odds ratio; CI, confidence interval; BCVA, best-corrected visual acuity.

disparity in binocular BCVA.

It is worth noting that normal binocular BCVA in relation to age does not necessarily indicate normal binocular fusion function. Our analysis of two follow-up visits indicated that improvements in the BCVA of the weakest eye were related to its baseline BCVA, the initial BCVA disparity between eyes, and the expansion of the binocular fusion range (or fusion function improvement). This finding indicates that patients with better baseline vision, less disparity between eyes, and a broader range of binocular fusion before treatment are more likely to experience a significant improvement in BCVA in the weakest eye post-treatment.

The patients in our investigation were categorized into groups with slow and rapid growth in binocular fusion function using GBTM. We observed that the rapid increase in fusion range correlated with the number of fusion training sessions and the baseline BCVA of the amblyopic eye in amblyopia; however, no such correlation was observed with the absolute difference in binocular BCVA. This may be attributed to the baseline vision of the amblyopic eye, indicating its level of suppression in the brain. Reduced initial visual acuity indicates heightened suppression, which complicates efforts to enhance binocular fusion function (19). Although refractive adaptation or occlusion may enhance the BCVA of the amblyopic eye and reduce BCVA disparity, the suppression of the amblyopic eye frequently persists, resulting in impaired binocular fusion function.

The current clinical standard for successful amblyopia treatment is age-related normal BCVA in both eyes. However, the level of binocular visual perceptual function is given less importance. In the 2019 American Academy of Ophthalmology guidelines, only five of the twenty studies encompassing binocular vision perceptual training for amblyopia treatment reported improvements in patients' stereoscopic acuity. Furthermore, all of these studies focused on BCVA improvement as their primary effectiveness metric (20). This highlights a gap in a unified, comprehensive standard for assessing the binocular visual perceptual function of patients with amblyopia.

Our research underscores the vital role of binocular fusion function training in the treatment of amblyopia, as it facilitates the improvement of BCVA in the amblyopic eye and aids in the restoration of fusion function. Binocular fusion training can rapidly enhance fusion function, providing data support for amblyopia rehabilitation through binocular visual function training.

This retrospective study encompasses a diverse age range among patients, potentially introducing variability due to the differing cooperation levels, particularly among younger children, during computer-assisted platform examinations.

The BCVA results were determined using a compound optometric correction. The prospective intervals for follow-up, particularly 3 and 6 months post-treatment, may have been influenced by changes in pupil dilation, which could have had an impact on the results of BCVA.

None of the individuals in our patient cohort achieved a normal state of binocular fusion function post-treatment for amblyopia. We hypothesize that this may contribute to residual amblyopia or relapse. However, due to the retrospective nature of this study, we do not have sufficient statistical evidence to substantiate this hypothesis. Future research will focus on patients who achieve normal binocular BCVA but still exhibit impairments in fusion function. The objective is to further investigate the connection between binocular fusion function and the recurrence of amblyopia.

Conclusions

Enhancing binocular fusion function may result in an improvement of BCVA in the amblyopic eye of patients with amblyopia. The frequency of binocular fusion training is crucial for rapid improvement in binocular fusion function.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-24-125/rc

Data Sharing Statement: Available at https://tp.amegroups.com/article/view/10.21037/tp-24-125/dss

Peer Review File: Available at https://tp.amegroups.com/article/view/10.21037/tp-24-125/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-24-125/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and approved by Institutional Ethics

Committee of Shenzhen Eye Hospital (No. 20211009-02). Written informed consent was obtained from patients' legal guardians prior to enrolment.

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