• Clinical Research •

Making stereopsis related to the ability of ocular deviation: a new paradigm for assessment of intermittent exotropia

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Received: 2024-02-21 Accepted: 2024-08-23

Abstract

● **AIM:** To investigate the underlying factors by establishing a new paradigm for assessing control ability under stereopsis testing conditions.

● **METHODS:** This was a prospective observational study. We evaluated the control ability of intermittent exotropia (IXT) patients in three conditions: natural 2D optotype viewing, 2D optotype viewing with polarized glasses, and 3D optotype viewing with polarized glasses. Recording with a smartphone, we captured videos to analyze the accurate time of spontaneous exodeviation and subsequent realignment before and after breaking fusion. Additionally, the correlation of stereopsis were also analyzed.

● **RESULTS:** A total of 48 patients (age range: 4-33y; 54.17% male) participated in the study. When viewing 3D optotypes with polarized glasses, their median control scores were 1 (interquartile range, 0-4) at distance and 0 (0-1) at near. These scores were significantly better than those observed under natural viewing conditions, which were 2.5 (1-5) at a distance and 1 (0-3) at near (Friedman test, *P*=0.049). Furthermore, those subjects who exhibited exophoria (realignment within 2 seconds) while viewing 3D optotypes with polarized glasses were more likely to have measurable stereo vision (Kendall's τ_b=-0.344, *P*=0.018).

● **CONCLUSION:** IXT patients exhibit enhanced control ability when using polarized glasses to view 3D optotypes, notably improving realignment capabilities. This expands our understanding of current tests and offers a potentially sensitive method for assessing IXT severity.

● **KEYWORDS:** intermittent exotropia; stereopsis; control ability

DOI:10.18240/ijo.2025.02.15

Citation: Li JB, Kong WT, Shen T, Yuan YG, Chen CL, Peng DM, Liang MT, He X, Luo D, Su JY, Wang W, Wang RX, Yu XP. Making stereopsis related to the ability of ocular deviation: a new paradigm for assessment of intermittent exotropia. *Int J Ophthalmol* 2025;18(2):308-314

INTRODUCTION

Intermittent exotropia (IXT) accounts for a quarter of strabismus worldwide and affects 3.3%-3.9% of children[1-2]. IXT patients manifest intermittent divergent exodeviation, experience a decline in their ability to maintain alignment control, and ultimately suffer from impairment in binocular sensory function[3]. Both control ability and binocular stereopsis are crucial factors in intervention decision-making[4-9]. However, current clinical assessments have failed to consistently establish a correlation between these two factors and, at times, have produced contradictory results. The Pediatric Eye Disease Investigator Group's analysis of 652 IXT participants, indicates that varying levels of stereoacuity may coexist with varying degrees of control[10]. This poses a substantial challenge in evaluating the severity of IXT, making it difficult to manage.

The underlying reasons for this contradiction remain largely unexplored, possibly due to the intricate variability of control abilities[11]. Intermittent exodeviation is a complex condition influenced by uncertain factors such as fatigue and lack of concentration[12-13], while the existing detection methods fall short in accurately reflecting the spectrum of control ability variations. Intriguingly, we have observed specific cases in which individuals exhibit poorer control over exodeviation during natural viewing but demonstrate measurable stereopsis. Upon closer scrutiny, these patients consistently exhibited at least brief periods of ocular alignment during stereopsis measurements. This phenomenon has piqued our curiosity: Does control ability indeed undergo changes during stereopsis measurements, and is control ability in this context more inherently related to stereopsis?

In this study, we set a new paradigm that assessing the control ability of the same cohort of IXT patients under different conditions: natural viewing and stereopsis measurement. Given that stereopsis measurements involve two influencing factors—polarized glasses and stereoscopic targets[14]—we introduced an additional condition where only polarized glasses were worn. With the use of smartphones, we precisely documented alterations in eye position both before and after breaking fusion, including the time of spontaneous exotropia or realignment. Furthermore, we investigated the correlation between stereopsis and the time taken for changes in eye position within these novel setups. Our objective was to determine that whether evaluating realignment performance under different levels of stereoscopic stimulus stimulation can hold promise as a sensitive approach for assessments of IXT severity, and providing new explanations for the contradictions within existing clinical assessment indicators.

PARTICIPANTS AND METHODS

Ethical Approval This study was approved by the Institutional Review Board/Ethics Committee of the Zhongshan Ophthalmic Center (ZOC) (2022KYPJ101), Sun Yat-sen University. Informed written consent was obtained from at least one legal guardian of each participating child, and the tenets of the Declaration of Helsinki were followed throughout this study.

Inclusion and Exclusion Criteria All the study participants were recruited at the Zhongshan Ophthalmic Center, Guangzhou, China, from March to April 2022. Patients were considered eligible if they were diagnosed with IXT. Exclusion criteria were as follows: 1) convergence insufficiency (near angle more than 10 prism diopters (PD) greater than distance); 2) high accommodative convergence to accommodation (AC/A) ratio (exclude >6:1 by gradient method)[15]; 3) younger than four years with poor coordination; 4) prior strabismus surgery or botulinum toxin injection.

Study Design Figures 1-2 illustrated the novel work paradigm of our data collection process. All patients were assessed for control ability under three conditions: Condition 1: natural viewing, looking at the matching-2D optotype without wearing polarized glasses; Condition 2: looking at the matching-2D optotype with polarized glasses; Condition 3: looking at the 3D optotype with polarized glasses.

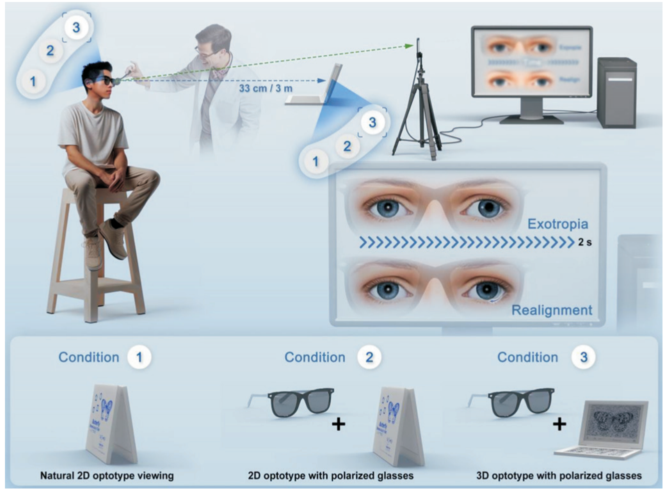

Figure 1 The workflow of the novel paradigm The same cohort underwent control ability assessments under three conditions. We used smartphones to capture videos of eye positions. We recorded and analyzed the spontaneous strabismus eye positions before covering or breaking fusion and the subsequent realignment.

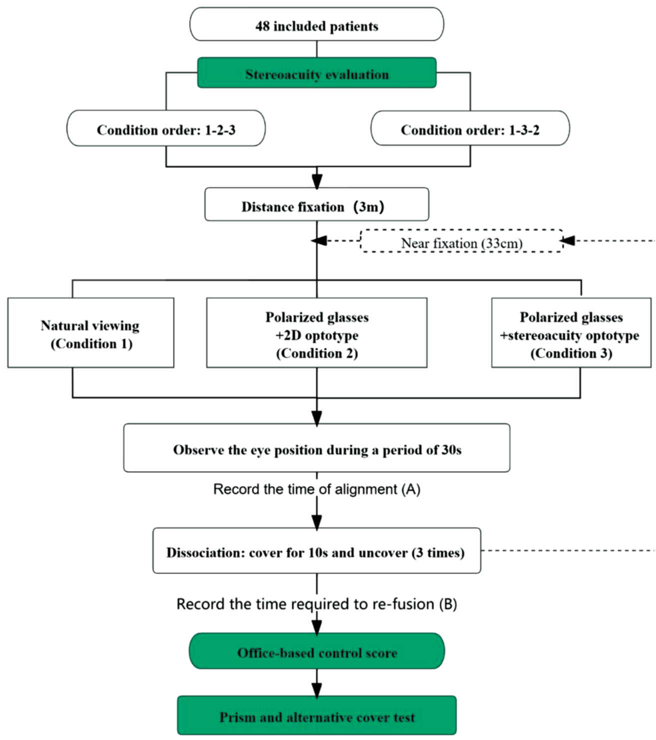

Figure 2 Study design Flowchart summarizing the study design and indicators used.

The 2D optotypes were on the back cover of the stereoacuity book, and we picked the matched one for testing. All the patients were divided into two groups and received different orders of conditions: 1-2-3 and 1-3-2. We set an interval of >12h between condition 1 and the other two, while the interval between conditions 2 and 3 was 1h. Moreover, prior to condition 1, an assessment of stereoacuity was conducted, and subsequent to condition 3, the deviation angle was measured using the prism and alternate cover test. This sequencing aimed to mitigate potential impacts on the control score.

Following is a brief description of the steps taken to record the office-based control score[5]. In particular, this office-based score was categorized as 0-2 (no exotropia unless dissociated) and 3-5 (tropia). We started the measurement at distance fixation (3 m). The participants were asked to look at an optotype for 30s. The time of spontaneous exotropia before dissociation was recorded as indicator A. Then, the cover-uncover test was conducted to dissociate. The covering lasted 10s and was repeated three times. Eye blinking and focusing attention were allowed to help re-align the eyes, and the longest time required to re-fuse was recorded as indicator B (30s max). The control score is determined using indicators A and B. Specifically, for A, the assessment criteria are set as follows: A=30s (score 5), 15s≤A<30s (score 4), and A<15s (score 3). In cases where A is recorded as 0s, the scoring depends on indicator B values: B>5s (score 2), 1s≤B≤5s (score 1), and B<1s (score 0). This evaluation is conducted separately for near and distance fixation conditions, resulting in scores ranging from 0 to 5 for each condition.

Record of the Time of Deviation and Alignment We used a smartphone to record the participants' eye position during this process. We set the smartphone to stay coaxial with the visual target, and more than 5 cm deviations were avoided, either vertical or horizontal. Adobe Prime software (USA) was used to check the video frame by frame. In particular, monocular fixation served as the baseline eye position, with spontaneous strabismus time recorded as the duration of deviation from this baseline eye position. Recovery time was measured as the time taken to return from the maximum deviated eye position to the baseline eye position upon cover-uncovering. The time between keyframes was recorded for subsequent statistical analysis (Supplementary Video 1). The data of condition 1, 2, and 3 were analyzed by Kong WT, Liang MT, and He X respectively.

Relevant Ophthalmic Assessment Stereoacuity was evaluated using the Distance Randot test at distance fixation (3 m) and the Stereo Butterfly test at near fixation (33 cm). Log arcsec conversion was used (ranging from 1.3 to 3.3 log arcsec); nil stereoacuity was arbitrarily assigned a log arcsec value of 4[16]. Ocular deviation was measured using a prism and the alternate cover test at distance (5 m) and near (33 cm) fixation.

Statistical Analyses For the statistical analysis, the difference between the three related samples (condition 1, condition 2 and condition 3) were compared using Friedman's non-parametric two-way analysis of variance since the data were not normally distributed or ordinal and Bonferroni correction was used for multiple comparison. Correlations between office-based scores and the stereoacuity or angle of deviation were explored with Spearman's correlation, while Kendall's tau correlation was employed for analyzing ordinal data variables, and no *P*-value adjustments were applied. *P*-values of <0.05 were considered significant. Statistical analysis was conducted using SPSS 19.0 (Chicago, IL, USA) and GraphPad Prism 8.0.0 (San Diego, CA, USA).

RESULTS

Patient Demographics and Clinical Characteristics Forty-eight patients met the inclusion criteria. Of these, 26 were male (54.17%), and 22 were female (45.83%). The mean age of the patients was 13.8y (range, 4-33y). The mean near exodeviation was 37.3±11.1 PD, (range, 15-63), and the mean distant exodeviation was 40.1±10.3 PD (range, 20-75). The mean log arcsec of stereoacuity was 3.2±0.9 (3 m) and 2.4±1.0 (33 cm). The control scores at baseline (the condition 1) were 2.7±2.1 (3 m) and 1.5±1.7 (33 cm). The patient characteristics were listed in Table 1. The office-based control ability was analyzed in all subjects under three different conditions.

Changes in Control Scores in Each Condition The primary outcome of this study was the control score, where a higher score indicates worse control. At distance fixation, the median control score was 2.5 in condition 1, 1.0 in condition 2, and 1.0 in condition 3. At near fixation, the median control score was 1.0 in condition 1, 0.5 in condition 2, and 0 in condition 3 (Table 2). There was a significant difference between condition 1-3 ($P<0.05$) at both distance ($P=0.007$) and near fixation ($P=0.000$). After conducting multiple comparisons, it was observed that the control score exhibited a significant decrease in condition 3 compared to condition 1 at near fixation ($P=0.049$, after Bonferroni correction; Figure 3A). However, this significance was not present at distance fixation ($P=0.140$, after Bonferroni correction; Figure 3B). There were no significant differences found between condition 2 and condition 1, nor between condition 2 and condition 3, as revealed by pairwise comparisons of the control score or recovery time (data not shown).

Figure 3C-3D illustrated the trends in control scores when comparing condition 3 to condition 1. Among the 48 patients examined, 16 individuals (33.33%) demonstrated an improved control ability at distance fixation, as indicated by a downward arrow in Figure 2C. Conversely, 29 subjects (60.42%) exhibited no change in their scores, while 3 subjects (6.25%) saw an increase in their scores in condition 3. At near fixation (Figure 2D), the distribution of subjects with decreased, unchanged and increased scores were 39.58% (19/48), 56.25% (27/48), and 4.17% (2/48) respectively. Furthermore, the control score showed notable improvement of at least 2 points

Table 1 Patient demographics and clinical characteristics

Characteristics	Data
Age (y)	4-33 (13.8±3.0)
Gender, *n* (%)	
Male	26 (54.1)
Female	22 (45.9)
Refractive error (diopters, D)	
OD	-10.00 to +2.50 (-3.00±0.75)
OS	-10.00 to +2.50 (-3.00±0.75)
Deviation (prism diopters, PD)	
Distance	20-75 (40.1±10.3)
Near	15-63 (37.3±11.1)
Stereoacuity, *n* (%)	
Distance	
Normal (<100")	12 (24.8)
Subnormal (120"-400")	6 (12.3)
None (>400")	30 (62.5)
Near	
Normal (100")	17 (35.4)
Subnormal (120"-400")	12 (25)
None (>400")	19 (39.5)

Values represent mean±SD. OD: *Oculus Dexter*; OS: *Oculus Sinister*.

in 8 subjects (16.67%) at distance fixation and 10 subjects (20.83%) at near fixation. Additionally, 14.58% (7/48) of patients improved from tropia (score 3-5) to phoria (scoring 0-2) at distance fixation, and 20.83% (10/48) exhibited the same improvement at near fixation, while only 2.08% (1/48) at distance and no patient at near changed from phoria to tropia.

Changes in Recovery Time for Each Condition Result shows no significant change in the time of exotropia in all conditions, but the recovery time significantly changed after the cover-uncover test. At distance fixation, the median recovery time was 9s in condition 1, 1.58s in condition 2, and 1.42s in condition 3. At near fixation, the median recovery time was 1.17 in condition 1, 0.92 in condition 2, and 0.66 in condition 3 (Table 2). It should be noted that the shorter recovery time suggested a greater ability of alignment control. There was a significant difference between condition 3 and condition 1 at both distance fixation (*P*=0.009, after Bonferroni correction; Figure 4A) and near fixation (*P*=0.015, after Bonferroni correction; Figure 4B).

Figure 4C-4D showed the change trends of the recovery time in conditions 3 and 1. At distance fixation, of 48 patients, 26 (54.17%) showed improved control ability, as indicated by a downward arrow in Figure 4C, while 16 (33.33%) and 6 (12.50%) showed unchanged or deteriorated recovery times respectively. At near fixation, the rates were 22 (45.83%), 22 (45.83%), and 4 (8.33%) respectively (Figure 4D). Among the patients with increased speed of realignment, 12.50% (6/48) and 16.67% (8/48) reduced the recovery time by more

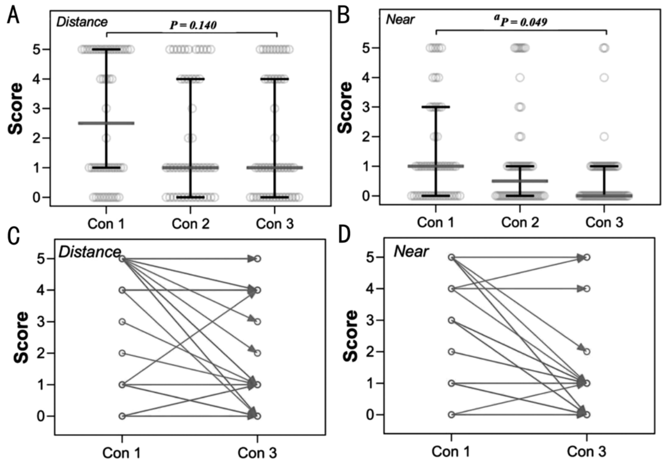

Figure 3 The control scores in each condition A, B: Box and whiskers plots showing the control scores. Lines show upper quartile, median, and lower quartile values; C, D: The two segments of the arrow are the same subject, and the downward arrow indicates that the subject's control ability improved in condition 3. Con 1: Natural viewing condition; Con 2: Polarized glasses condition; Con 3: Polarized glasses + 3D optotype; Distance fixation (3 m); Near fixation (33 cm). [a]*P*<0.05; [b]*P*<0.01 after Bonferroni correction.

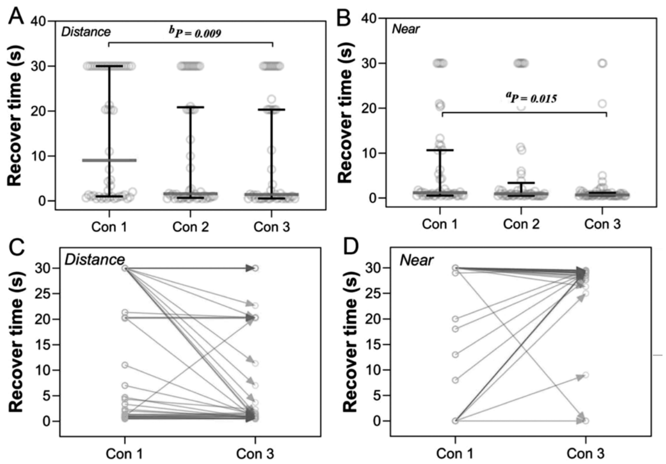

Figure 4 Analysis of recovery time in each condition A-B: Box and whiskers plots showing the recovery time. Lines show upper quartile, median, and lower quartile values; C-D: The two segments of the arrow are the same subject, and the downward arrow indicates that the subject's recovery time decreased in the condition 3. Con 1: Natural viewing condition; Con 2: Polarized glasses condition; Con 3: Polarized glasses + 3D optotype; Distance fixation (3 m); Near fixation (33 cm). [a]*P*<0.05; [b]*P*<0.01 after Bonferroni correction.

than 10s at distance fixation and near fixation respectively. Additionally, at distance fixation, 33.33% (16/48), and at near fixation, 47.92% (23/48) were able to recover within 2s in condition 3.

Correlation Between Stereoacuity and Control Score There was no monotonic relationship between stereoacuity and the control score by drawing a scatterplot. Spearman rank correlation analysis show that there was no significant correlation between log stereoacuity and the control score

Table 2 Comparison of study outcomes

Items	Condition 1	Condition 2	Condition 3	P[1]	P[2] (condition 3 *vs* 1)
Distance					
A	0 (0-30)	0 (0-30)	0 (0-30)	0.617	
B	9 (1-30)	1.6 (0.7-20.8)	1.42 (0.5-20.3)	0.001[b]	0.009[b]
M	2.5 (1-5)	1 (0-4)	1 (0-4)	0.007[b]	0.140
Near					
A	0 (0-0.75)	0 (0-0.75)	0 (0-0)	0.463	
B	1.2 (0.5-10.7)	0.9 (0.5-3.4)	0.66 (0.5-1.1)	0.001[b]	0.015[a]
M	1 (0-3)	0.5 (0-1)	0 (0-1)	0.000[b]	0.049[a]

Values represent the median (interquartile range). A: The time of extropia (s); B: The time of recovery (s); M: The Mayo Clinic Medicine College control score. Condition 1: Natural viewing; Condition 2: Polarized glasses+normal optotype; Condition 3: Polarized glasses+stereoscopy. [1]Friedman test of three conditions; [2]Pairwise comparisons between condition 3 and 1 (Bonferroni correction). In all cases, there was no significant difference between condition 2 and 1 or between condition 2 and 3. [a]$P<0.05$; [b]$P<0.01$.

Table 3 Correlation analysis of the stereoacuity and control

Items	Condition 1	Condition 2	Condition 3
Recovery time, ≤2s=0, >2s=1	-0.213, 0.144	-0.334, 0.022[a]	-0.378, 0.01[b]
Control score, <3 point=0, ≥3 point=1	-0.25, 0.087	-3.44, 0.018[b]	-3.44, 0.018[b]

Values represent the Kendall-Tau-b and *P*. Kendall's tau correlation was employed for analyzing ordinal data variables, and no *P*-value adjustments were applied. [a]$P<0.05$; [b]$P<0.01$. Stereoacuity nil=0, none nil=1.

at either distance fixation and near fixation natural viewing condition (distance: RS=0.212, P=0.20; near: RS=0, P=0.99). Likewise, polarized glasses condition or stereo geometric shapes condition did not show any correlation.

However, the statistical tests revealed an correlation after categorisation (at distance fixation): for stereoacuity, nil=0 and not nil=1; for recovery time, ≤2s=0 and >2s=1; and for the control score, <3 points=0 and ≥3 points=1. The stereoacuity showed a negative correlation with the recovery time in condition 2 (Kendall's τ_b=−0.334, P=0.022) and condition 3 (Kendall's τ_b=−0.378, P=0.01). Similarly, stereoacuity showed a correlation with the control score in condition 2 (Kendall's τ_b=−0.344, P=0.018) and condition 3 (Kendall's τ_b=−0.344, P=0.018) but not in condition 1 (Table 3). At near fixation, no statistically significant correlation was observed for all indicators.

The correlation between the control score and the angle of deviation (PD) was also evaluated. The results show that the control score and the angle of deviation have a mild correlation (P=0.0275 and RS=0.31, Spearman test only in condition 3 with near fixation).

DISCUSSION

Accurately assessing the deterioration of IXT has posed a longstanding challenge for clinicians, particularly when two existing evaluation indicators, stereopsis, and control ability, yield inconsistent results. In our study, we placed a special focus on evaluating control ability while patients were fixating on 3D optotype using polarized glasses. We discovered a significant improvement in control ability compared to the natural viewing condition. These findings enhance our understanding of the observed inconsistency between the conventional clinical assessments of stereopsis and alignment ability. Additionally, our research yielded a surprising revelation: subjects who could rapidly realign within 2s after fusion disruption were more likely to exhibit stereopsis in the new paradigm. This discovery holds the potential to open novel insights for assessing disease progression in the future.

Herein, we discovered that IXT patients showed improved control scores and quicker realignment times when wearing polarized glasses and focusing on 3D optotype, notably, a finding not attributable to control variability. Control in IXT can fluctuate over short periods, switching between phoric and tropic states. A previous investigation found that 24% of patients tested twice within 5min experienced control changes, with 6% shifting from tropia to phoria at a distance and 18% transitioning from phoria to tropia up close[12]. Our data revealed a higher percentage, with 39.6% (19/48) exhibiting score changes, including 14.58% improving from tropia to phoria at a distance and 20.83% at near fixation, while only one patient shifted from phoria to tropia at a distance. To mitigate these variations, we introduced a minimum 1-hour washout phase and followed a fixed testing order (distance before near, control group before experimental group) to reduce fatigue and other moderating factors' impact on results. We also employed video recording and precise frame analysis (0.01s sensitivity) to calculate the onset of eye position changes, which proved more accurate than traditional methods. Consequently, our data elucidate specific phenomena that partially explain the lack of correlation between conventional stereopsis assessments and control ability.

Currently, there are new methods that have been introduced, incorporating advancements in technology and principles. For instance, similar to Holter evaluation for 24-hour electrocardiography monitoring, a portable eye tracker was used to record changes in a patient's eye position throughout the day[17]. The results revealed a correlation between the frequency of strabismus and the degree of deviation. Another involved study that delve into the disease principle of interocular suppression. The study produced correlational findings, such as the relationship between the fusion maintenance score (indicating the ability to maintain normal sensorimotor fusion) and the control score[18]. These findings underscore the central challenge in evaluating IXT, which stems from limitations in technological advancements and an incomplete understanding of disease principles. Further research in this direction holds significant promise.

Remarkably, our correlation analysis revealed a new finding: subjects with shorter recovery times (≤2s after uncovering) showed a correlation with measurable stereopsis, particularly at a distance, a phenomenon not previously documented. We dissected two components of the control score: one focused on the duration of spontaneous exotropia during binocular fixation, and the other on the duration of binocular realignment after breaking fusion. Our results indicated that patients with IXT achieved faster realignment, rather than a reduction in spontaneous exotropia. This intriguing outcome suggests that receiving binocular cues (viewing 3D optotype with polarized glasses) may stimulate the motor fusion mechanism rather than maintain the fusion.

Both binocular fusion and stereopsis share a common neural basis[19-20]. Stereoscopic vision is mediated by neurons in the visual cortex that respond to the same (or similar) positions in visual space through both eyes and selectively encode specific disparities[21-22]. Current neural circuits tip on the relationship between eye position and stereopsis, like response selectivity for binocular disparity[23-24], interocular matching of orientation preference[25], and ocular dominance in response magnitude[25-26]. The average onset age for patients with IXT is around 4 years old[27], and most individuals already possess the ability to align their eyes and perceive depth. Even though binocular alignment is generally considered a prerequisite for stereovision, it is still uncertain whether the loss of stereoacuity is a cause or a consequence of the loss of control. Our data reveals that individuals who still have stereoscopic vision show a significant improvement in their realignment ability when exposed to binocular stimulation. Conversely, individuals without stereovision cannot realign even when exposed to binocular stimulation. We qualitatively confirmed that providing binocular stimuli can promote fusion before a complete loss of stereopsis occurs. Therefore, investigating realignment response selectivity for binocular stimulation may measure the sensitivity of neurons to disparities perceived by both eyes, offering promise for assessing the severity of stereopsis.

Our study has some limitations. First, we utilized fixed stimuli (400" random dots for distance and 100" outlines for near vision). However, further quantification of stimulus intensity is needed. Second, we did not repeat the controlled assessment at different times of the day. Previous studies have shown that measuring three times at other times of the day or measuring five consecutive times can improve the stability of the score[28]. Third, polarized glasses were used instead of red and green glasses (in the TNO test). Compared with polarized glasses, red and green glasses may have a more significant impact on interocular suppression, so whether our research results can be deduced to TNO test results is unclear. In addition, testing the depth of suppression[29-30], considering adding studies with Bagolini filter bar in the future study may provide a better understanding of the relationship of interocular suppression and sensory or motor fusion in IXT.

Our data provide a new perspective to clarify the absence of a relationship observed in current clinical assessments of IXT parameters. Significantly, control abilities, especially realignment capabilities, showed marked improvement when viewing 3D optotypes with polarized glasses. Evaluating realignment performance under different levels of stereoscopic stimulus stimulation may hold promise as a sensitive approach for future assessments of IXT severity.

ACKNOWLEDGEMENTS

The authors thank Professor Xiang Chen, Jiawei Zhou and Mingleung Ma for providing insightful comments.

Foundations: Supported by the National Natural Science Foundation of China (No.82070995; No.82301256); Youth S&T Talent Support Programme of Guangdong Provincial Association for Science and Technology.

Conflicts of Interest: Li JB, None; **Kong WT,** None; **Shen T,** None; **Yuan YG,** None; **Chen CL,** None; **Peng DM,** None; **Liang MT,** None; **He X,** None; **Luo D,** None; **Su JY,** None; **Wang W,** None; **Wang RX,** None; **Yu XP,** None.

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