Vision Research 164 (2019) 44–52

Contents lists available at ScienceDirect

Vision Research

journal homepage: www.elsevier.com/locate/visres

Objective and quantitative assessment of interocular suppression in strabismic amblyopia based on steady-state motion visual evoked potentials

Xiaowei Zheng[a], Guanghua Xu[a,b,*], Ying Zhi[c], Yunyun Wang[d], Chengcheng Han[a], Bing Wang[c], Sicong Zhang[a], Kai Zhang[a], Renghao Liang[a]

[a] School of Mechanical Engineering, Xi'an Jiaotong University, Xi'an, China
[b] State Key Laboratory for Manufacturing Systems Engineering, Xi'an Jiaotong University, Xi'an, China
[c] Department of Ophthalmology, Xi'an No. 1 Hospital, Xi'an, China
[d] School of Software Engineering, Xi'an Jiaotong University, Xi'an, China

A R T I C L E I N F O

Keywords:
Strabismic amblyopia
Interocular suppression
SSMVEP
Dichoptic viewing

A B S T R A C T

In this study, we aimed to explore an objective, sensitive and quantitative measurement of interocular suppression in strabismic amblyopia. We compared 11 strabismic subjects with 12 normal vision subjects to explore the different response characterizations in normal eyes, nondominant and dominant eyes of strabismic subjects by using steady-state motion visual evoked potentials (SSMVEPs). Stimulation at different temporal frequencies was presented to two eyes by using an interocular dichoptic technique. Furthermore, canonical correlation analysis (CCA), signal-to-noise ratio (SNR) and some statistical methods, such as the paired *t*-test, analysis of variance (ANOVA) and correlation analysis, were used to analyze electroencephalography (EEG) signals. We proposed two indices—divergence J and suppression imbalance (SI) to describe the deficits in interocular suppression—and one index — mask attenuation coefficient (MAC)— to describe the influence of a dichoptic mask from the dominant eyes to nondominant eyes of strabismic subjects. A significant difference was found between nondominant and dominant eyes of strabismic subjects in SSMVEP response and SNR value while no apparent difference was observed between the two eyes in subjects with normal vision. There was a strong linear correlation between divergence J, SI and visual acuity difference of two eyes both in strabismic amblyopia and normal vision. A linear correlation was also found between visual acuity difference and MAC in patients with strabismic amblyopia. Our findings suggest that SSMVEPs can be an objective and quantitative method for measuring the interocular suppression in strabismus and assessing the deficits of strabismic amblyopia.

1. Introduction

Amblyopia, a neurodevelopmental disorder caused by abnormalities in the visual system during early childhood, has a prevalence between 3% and 5% (Chegeni, Khanjani, Rahmatpour, Ahmadi Pishkuhi, & Abdolalian, 2018, Chen et al., 2015). It is mainly manifested as the best corrected visual acuity being lower than that of the normal age-matched eye but having no obvious ocular pathology (Webber & Wood, 2005). The most common predisposing factors for amblyopia are strabismus (affecting the development of binocular vision), refractive error (such as high hyperopia or anisometropia) and form deprivation (such as congenital cataract or ptosis) (Guimaraes et al., 2018).

Monocular deficits and interocular suppression are two underlying mechanisms of amblyopia (Agrawal, Conner, Odom, Schwartz, & Mendola, 2006, Baker, Meese, & Hess, 2008, Chang-Bing, Jiawei, Zhong-Lin, & Yifeng, 2011). Numerous animal experiments have pointed out that monocular visual abnormalities during the critical period of visual development can induce major alterations in the architecture of the visual cortex (Sengpiel, Blakemore, Kind, & Harrad, 1994, Wiesel & Hubel, 1965), weakening the ability of the amblyopic eye to compete for visual pathways, resulting in that visual function connection is dominated by the fellow eye (Crawford, Harwerth, Chino, & Smith, 1996). Moreover, the cells in V1 region cannot synchronize neuronal activities between both eyes when stimuli are presented to the two eyes of an individual with amblyopia (Barnes, Hess, Dumoulin, Achtman, & Pike, 2001, Crawford et al., 1996, Sireteanu, 2000). Recently, a large number of studies have shown that binocular suppression occurs in amblyopia, preventing both the normal fusion of both eyes and the normal perception of the suppressed eye (Baker, Meese, Mansouri, & Hess, 2007, Birch, 2013). To a large extent, amblyopic

* Corresponding author at: School of Mechanical Engineering, Xi'an Jiaotong University, Xi'an, China.
E-mail address: ghxu@xjtu.edu.cn (G. Xu).

https://doi.org/10.1016/j.visres.2019.07.003
Received 10 January 2019; Received in revised form 16 July 2019; Accepted 16 July 2019
Available online 01 October 2019
0042-6989/

suppression is a state that avoids normal integration (Frassle, Sommer, Jansen, Naber, & Einhauser, 2014, Huang, Zhou, Lu, Feng, & Zhou, 2009).

Interocular suppression is clinically diagnosed by the Worth 4-dot test, but this test is not objective and fails to quantitatively measure suppression. Previous studies have used the neutral density filter with the Bagolini striated lens and dichoptic motion coherence threshold tests to assess the degree of interocular suppression in patients with amblyopia (Li et al., 2013, Li et al., 2011, Narasimhan, Harrison, & Giaschi, 2012). Several studies have also suggested that measuring interocular suppression using the dichoptic technique can directly assess the depth of amblyopia (Hess, Mansouri, & Thompson, 2010). However, the subjects must understand the instructions and cooperate with the operators during the dichoptic technique, rendering this method difficult for young children.

Electroencephalography (EEG) offers an alternative method that is more direct and objective for measuring amblyopia interocular suppression. Several studies have reported a lower amplitude and longer latency of visual evoked potentials (VEPs), such as P100, in the amblyopic eye (Banko, Kortvelyes, Weiss, & Vidnyanszky, 2013). Other studies analyzed the steady-state visual evoked potentials (SSVEPs) of amblyopic and fellow eyes to a specific stimulus (Baker, Simard, Saint-Amour, & Hess, 2015, Richard, Chadnova, & Baker, 2018). However, these studies have not provided an exact correlation between the depth of interocular suppression and SSVEP response with no quantitative analysis. The traditional SSVEP paradigm, using a light flicker or pattern reversal stimulation, may also easily cause visual fatigue, and produce more harmonic response, bringing a consequent decrease of signal quality (Han, Xu, Xie, Chen, & Zhang, 2018, Xie, Xu, Wang, Zhang, & Zhang, 2012, Yan, Xu, Xie, Li, & Dan, 2018). Therefore, a quantitative and objective measurement based on steady-state motion visual evoked potentials (SSMVEPs) is a desirable method for assessing interocular suppression in amblyopia, as it can both detect amblyopia and evaluate the effectiveness of amblyopic treatment, especially in children.

2. Methods

2.1. Participants

All participants gave their written informed consent in accordance with a protocol approved by the institutional review board of Xi'an Jiaotong University, and conforming to the tenets of the Declaration of Helsinki.

Eleven strabismic subjects containing three mixed (combined strabismus and anisometropic amblyopia) amblyopic patients from the Xi'an No.1 Hospital (Xi'an, China) participated in the experiments. Subjects were between 8 and 16 years of age (mean age 10.2 years, 6 females). In addition, twelve healthy subjects (ages 10–15 years old, mean age 12.8 years, 3 females), who had normal or corrected to normal vision and no known binocular vision abnormalities participated in this study. All participants wore their best optical correction. In this study, visual acuity referred to the best-corrected visual acuity. Corrected visual acuity was assessed monocularly by the "E" Standard Logarithm Visual Acuity Chart, and the data was transformed into the logarithm of the minimum angle of resolution (logMAR) visual acuity. The clinical details of the strabismic subjects are listed in Table 1. The dominant eye represents the better eye, while the nondominant eye represents the poorer eye, such as the amblyopic or strabismic eye, in strabismus.

2.2. Apparatus

A brain-computer interface (BCI) experimental platform, containing an EEG amplifier, a g.USBamp acquisition and processing system, and an active electrode system g.GAMMAbox (g.tec, Schiedlberg, Austria), was used to collect and process EEG data, as shown in Fig. 1. Six EEG electrodes (PO3, PO4, POz, O1, O2 and Oz) were placed, as shown in Fig. 2, and signals were captured at a sampling rate of 1200 Hz. Before the experiment, the reference electrode, A1, was placed on the left earlobe of the subject and the ground electrode, Fpz, was placed on the forehead. In addition, an online band-pass filter from 2 to 100 Hz was used to remove artifacts, and an offline digital notch filter between 48 and 52 Hz was applied to eliminate the power line interface. An amplitude criterion of ± 200 μV was used to reject trials with other influencing factors, including head movement, frequent blinking, etc., to account for the fact that some children cannot cooperate as well as adults.

2.3. Stimulation and procedure

A circular checkerboard, divided into small grids with the same size and number with black and white color arranged alternatively, was used to realize SSMVEP stimulation in previous BCI design (Han et al., 2018, Zhang, Xu, Xie, & Zhang, 2017). An expansion–contraction process in one stimulation cycle was demonstrated with low adaptation characteristic and less visual discomfort (Bach & Ullrich, 1994, Heinrich & Bach, 2003, Xie et al., 2012). The stimulation paradigm was controlled by MATLAB (MathWorks, Natick, United States) with the Psychophysics Toolbox, and it was presented on a special polarized monitor (LG D2343P, Seoul, Korea) that could realize dichoptic viewing when combined with polarized 3D glasses, as shown in Fig. 1. Before the experiment, the monitor was corrected by a color correction instrument (Spyder 5 Elite, Lawrenceville, United States) and the luminance of the pattern was detected with a luminance meter (SAMPO SM208, Shenzhen, China). The gray background luminance (12.6 cd/m^2) of the pattern remained constant. The luminance of black and white grids was 2.9 and 51.4 cd/m^2, respectively, with a contrast of 89%.

The participants were asked to sit on a comfortable chair in front of the monitor. The visual angle of the stimulation was 5° after adjusting the distance between monitor and seat. As shown in Fig. 3, each subject was requested to finish three conditions in the experimental process. In condition A, two stimulation paradigms with different frequency of 8 Hz and 12 Hz were displayed on the screen. Firstly, the left eye was presented a stimulation frequency of 8 Hz, while the right eye was presented a 12 Hz stimulation. Secondly, the frequencies of the left and right eye were swapped. In condition B, the left eye was presented a stimulation with frequency of 8 Hz, but the right was not presented any stimulation except for a gray background. Then, the right eye was presented the 8 Hz stimulation while the left was presented the gray background. In condition C, the experimental process was the similar to condition B except that the stimulation frequency was 12 Hz instead of 8 Hz. We did not compensate for the squint angle in strabismic amblyopia during the dichoptic stimulation. In addition, there was a small amount of residual cross-talk from the stimulation between both eyes in the condition B and C despite the fact that we adjusted the luminance of the gray background to make it smaller.

Moreover, participants were asked to stare at one of the stimulation paradigms for five seconds per trial for a total of five trials in one stimulation paradigm, with an interval of two seconds between each trial. The participants were subsequently asked to stare at the next paradigm. There were six stimulation paradigms in total, and it took approximately six minutes for a participant to finish this experiment.

2.4. Signal analysis and data process

2.4.1. Canonical correlation analysis (CCA)

CCA is one of the most widely used analysis methods for SSVEP analysis (Hakvoort, Reuderink, & Obbink, 2011, Zhonglin, Changshui, Wei, & Xiaorong, 2006). As a multivariate statistical analysis method, CCA uses the correlations between comprehensive variables to reflect

Table 1
Clinical data of the strabismic subjects. Visual acuity is expressed in logMAR.

Subject No.	Gender	Age	Nondominant eye/Type	Visual Acuity	Optical Correction	Condition	Surgery
A01	F	8	LE/Strab	RE: 0.0 LE: 0.3	RE: +0.50 × 90 LE: +1.50/+0.75 × 95	Left esotropia 10°	None
A02	M	9	LE/Mixed	RE: 0.0 LE: 1.0	RE: +2.00 D LE: −5.50 D	Left exotropia 5°	None
A03	M	16	LE/Strab	RE: 0.1 LE: 0.8	RE: +0.25 D LE: +0.75/+0.50 × 60	Left esotropia 20°	None
A04	F	10	LE/Strab	RE: 0.0 LE: 0.2	RE: none LE: none	Small left esotropia	None
A05	M	8	LE/Strab	RE: 0.1 LE: 0.4	RE: +0.75 D LE: +1.00 D	Left esotropia 10°	2 months ago
A06	F	9	LE/Strab	RE: 0.0 LE: 0.2	RE: +0.50 × 90 LE: −0.25/0.50 × 90	Left exotropia 6°	None
A07	M	9	RE/Strab	RE: 0.3 LE: 0.0	RE: none LE: none	Right exotropia 8°	None
A08	M	9	RE/Mixed	RE: 0.2 LE: 0.1	RE: +3.50/0.75 × 95 LE: +4.00/0.75 × 80	Small right esotropia	None
A09	F	12	LE/Mixed	RE: 0.0 LE: 0.4	RE: +2.25/0.50 × 60 LE: +6.25/+1.25 × 120	Left esotropia 10°	None
A10	F	14	LE/Mixed	RE: 0.0 LE: 0.7	RE: −0.25/+0.50 × 90 LE: +4.00/+1.00 × 160	Small left esotropia	None
A11	F	8	LE/Strab	RE: 0.0 LE: 0.2	RE: +6.50/+2.00 × 60 LE: +7.00/+2.50 × 120	Left esotropia 10°	None

RE = right eye, LE = left eye, Strab = strabismic eye, Mixed = mixed amblyopic eye, M = male, F = female.

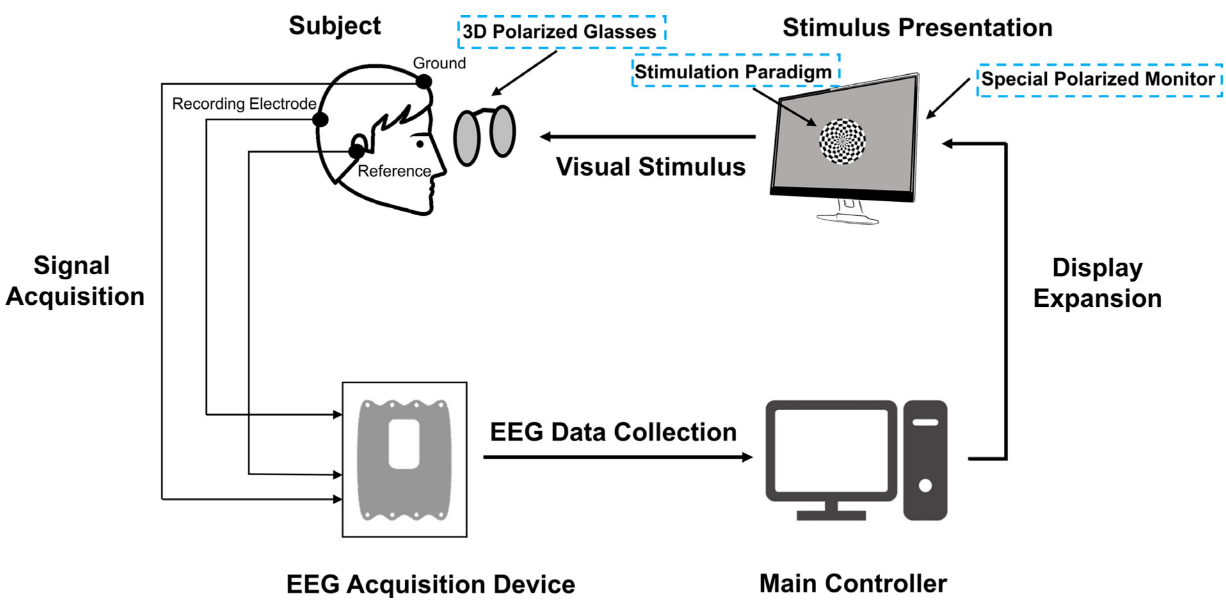

Fig. 1. BCI experimental system.

the overall correlation between two groups of variables (Hotelling, 1936). In this study, one variable is the EEG signals X from six channels, and the other is the reference signal Y_i consisting of sine and cosine pairs with the reference frequency f_i ($i = 1, 2, \ldots, K$,). In addition, Y_i can be constructed as

$$Y_i = \begin{bmatrix} \cos(2\pi f_i t) \\ \sin(2\pi f_i t) \end{bmatrix}, \quad t = \frac{1}{F_s}, \ \cdots, \frac{S}{F_s} \tag{1}$$

where F_s is the sampling rate, and S represents the sample points. Here reference frequency f_i is set to 1.0, 1.1, …, 30.0 Hz (i.e., $K = 291$).

The linear transformations of X and Y_i are $x = w_x{}^T X$ and $y_i = w_{yi}{}^T Y_i$, respectively. CCA can find two linear projection vectors w_x and w_{yi} to maximize the canonical correlation between x and y_i ($i = 1, 2, \ldots, K$). The correlation is calculated by the following formula:

$$\rho_i(x, y_i) = \max_{w_x, w_y} \frac{E[w_x^T X Y_i^T w_{yi}]}{\sqrt{E[w_x^T X X^T w_x] E[w_{yi}^T Y_i Y_i^T w_{yi}]}} \tag{2}$$

where E represents the expected value in statistics, and superscript T indicates the transposition of the matrix. X is the average of five trials in one paradigm from the 6-electrode channel signals. The maximum value ofρ_i, which corresponds to the maximum canonical correlation between X and Y_i, is considered to be the response to the stimulation paradigm of the reference frequency, f_i, in SSMVEPs. Therefore, all the ρ_i and their corresponding frequencies f_i can be plotted as a CCA spectrum.

2.4.2. Signal-to-noise ratio (SNR)

SNR refers to the ratio of signal to noise in a device or system. In this study, the SNR is defined as the ratio of the square of the correlation coefficient at the target stimulation frequency to the mean value of the square of the m adjacent points on the CCA spectrum. Thus,

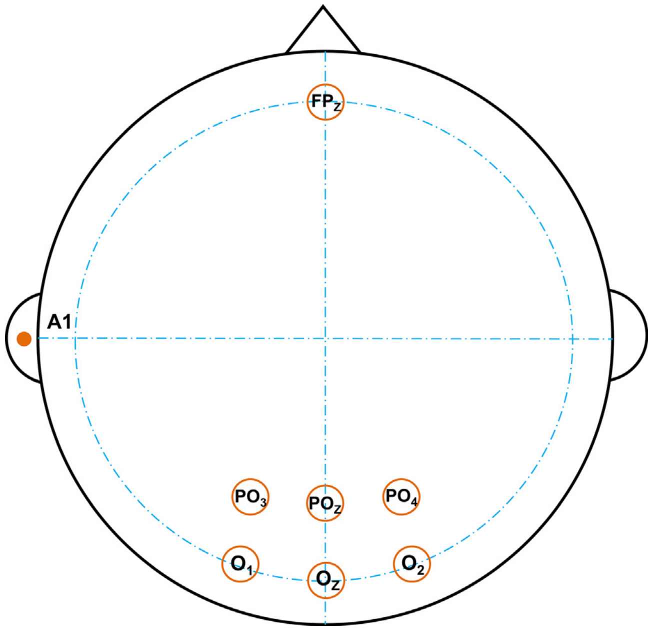

Fig. 2. Electrode locations.

$$SNR = \frac{z(f)^2}{\frac{1}{m} * \sum_{n=1}^{\frac{m}{2}} [z(f + c * n)^2 + z(f - c * n)^2]} \quad (3)$$

where *z(f)* is the CCA spectrum peak at the stimulation frequency. *c* is the scale value of abscissa in the CCA spectrum, which is set to 0.1 Hz in our study. *m* is set to 10.

2.5. Evaluation index

2.5.1. Mask attenuation coefficient (MAC)

The stimulation paradigm presented to one eye can be regarded as the dichoptic mask to the other eye (Baker et al., 2008, Baker et al., 2015). For example, the 12 Hz stimulation displayed to the dominant eye was the mask when the 8 Hz stimulation was presented to the nondominant eye in strabismic subjects, and vice versa. In this study, we put forward the MAC to calculate and quantify the influence of the dichoptic mask from dominant eyes to nondominant eyes in strabismic subjects, and the equation is as follows:

$$MAC = \frac{R_{wom} - R_{wm}}{R_{wom} + R_{wm}} \quad (4)$$

where R_{wom} and R_{wm} denote the SSMVEP response without the mask and with the mask, respectively. A previous study indicated that the R_{wom} is higher than R_{wm} (Baker et al., 2015). So, theoretically, the value of the MAC varies from 0 to 1. The dichoptic mask exerts no effect when MAC is equal to 0. The greater the MAC value, the larger the effect of mask.

2.5.2. Divergence J

Divergence J, a dimensionless index, is used to describe the degree of variation between two variable groups or two variables, irrespective of an exact value. The formula is as follows:

$$J(F_1, F_2) = \frac{1}{2N} \sum_{i=1}^{N} \left(\frac{f_{1i}}{f_{2i}} + \frac{f_{2i}}{f_{1i}} \right) - 1 \quad (5)$$

where f_{1i} and f_{2i} are the *ith* element, respectively, from two variable groups, F_1 and F_2. N is the number of variables in one group. In this study, N is 1 for one pair of eyes, and f_{1i} and f_{2i} are the SSMVEP response of each eye from the same subject. Divergence J varies from 0 to infinity, where 0 represents interocular balance between the two eyes. A larger divergence J value indicates a more severe interocular suppression.

2.5.3. Suppression imbalance (SI)

SI is also used to describe the suppression relation between the two eyes in this study using the following expression (Martins Costa, Almeida Neves Carrega, Nunes, & Tuna, 2017):

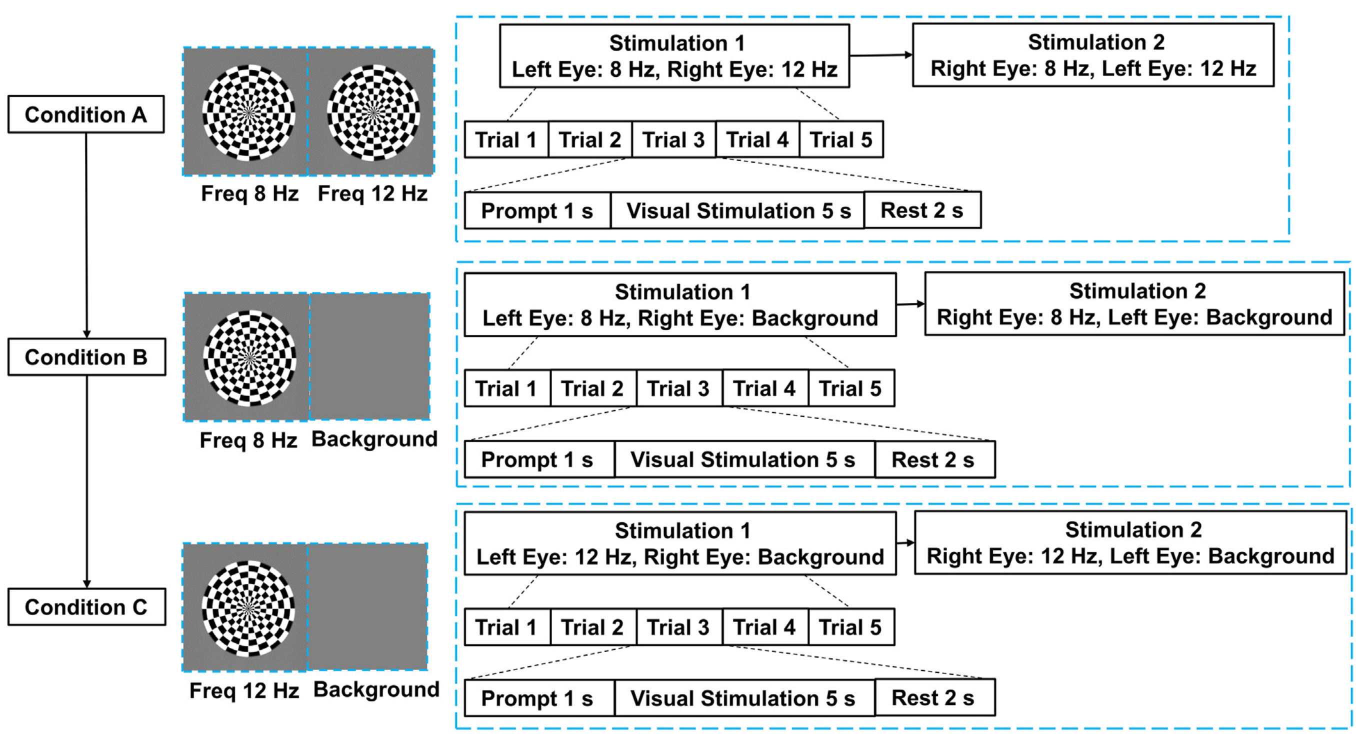

Fig. 3. Experimental Process. Freq = frequency.

$$SI = \frac{R_{RE} - R_{LE}}{R_{RE} + R_{LE}} \quad (6)$$

where R_{RE} and R_{LE} are the SSMVEP response of the right eye and left eye, respectively. SI may vary from -1 to 1, where 0 represents the absence of SI and suggests that interocular balance exists between the two eyes. As SI approaches 0, interocular suppression becomes less evident. The value $1/-1$ indicates a total suppression from one eye. A negative value indicates the dominance of the left eye, whereas a positive value indicates the dominance of the right eye.

2.6. Data processing

Statistical analyses were carried out using SPSS Statistics 22.0 (IBM, Armonk, United States). Paired t-tests, analysis of variance (ANOVA), and correlation analysis were used to analyze the difference and relationships between normal eyes, nondominant eyes, and dominant eyes of strabismic subjects.

3. Results

3.1. SSMVEP response and SNR

Under condition A, an 8 Hz stimulation was presented to one eye, while a 12 Hz stimulation was simultaneously presented to the other eye. SSMVEP response varied between the abnormal and normal binocular functions. As shown in Fig. 4A and B, the SSMVEP response of the dominant eye was larger than that of the nondominant eye in strabismic subjects at the same target frequency. On the contrary, the SSMVEP response of individuals with normal vision had no obvious difference between the two eyes. A typical SSMVEP response of an individual with normal vision was showed in Fig. 4C and D.

A paired *t*-test ($t(10) = -4.854$, $P < 0.001$) found a significant difference between nondominant and dominant eyes in strabismic subjects when an 8 Hz target stimulation with a 12 Hz mask was used. A significant difference was also found when 12 Hz was the target stimulation and 8 Hz was used as the mask ($t(10) = -5.570$, $P < 0.001$). Moreover, no apparent difference was observed between the two eyes of a subject with normal vision ($t(11) = -0.607$, $P = 0.556$, or $t(11) = 0.020$, $P = 0.984$, when the target stimulation was 8 or 12 Hz). Fig. 5 showed the mean SSMVEP response of strabismic and normal subjects under condition A.

The SSMVEP response at target frequencies was statistically significant and not due to noise fluctuations, according to a previous study (Meigen & Bach, 1999). As showed in Figs. 4 and 6, SNR value of the SSMVEPs of the nondominant eyes was higher than that of the dominant eyes in strabismic subjects ($t(10) = -3.757$, $P = 0.004$ when the target frequency was 8 Hz; $t(10) = -4.649$, $P < 0.001$ when the target frequency was 12 Hz). On the contrary, there was not a wide difference in SNR of the SSMVEPs when both eyes had normal vision ($t(11) = -0.160$, $P = 0.876$ when the target frequency was 8 Hz; $t(11) = -0.984$, $P = 0.346$ when the target frequency was 12 Hz).

3.2. Influence of dichoptic mask

As mentioned before, the stimulation to one eye can be regarded as the dichoptic mask to the other eye. Therefore, condition A can be regarded as the "mask" condition, while conditions B and C can be regarded as the "no mask" conditions. The mean SSMVEP response of the nondominant and dominant eyes in strabismic and normal subjects under conditions A, B and C was shown in Fig. 7. There was an obvious difference between the SSMVEP response with and without the dichoptic mask in both the nondominant eyes of strabismic subjects and normal eyes ($P < 0.05$, respectively). Thus, the SSMVEP response of the nondominant eyes in strabismic subjects and normal eyes was attenuated after putting a mask over the other eye. However, no apparent divergence in the dominant eyes of strabismic subjects was found when the nondominant eyes were either masked or unmasked ($P > 0.05$, respectively).

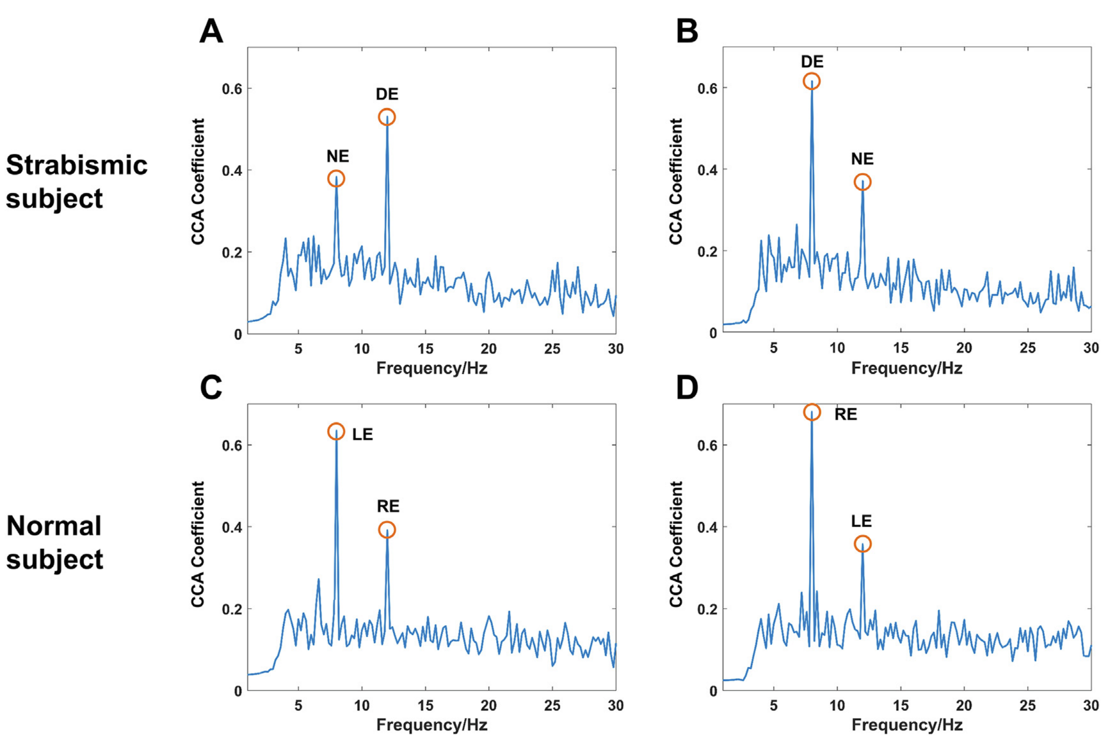

Fig. 4. CCA spectrum and SSMVEP response of strabismic and normal subjects under condition A. (A and B): Strabismic subject A11. (C and D): A normal subject. (A) Nondominant eye: 8 Hz stimulation; Dominant eye: 12 Hz stimulation. (B) Nondominant eye: 12 Hz stimulation; Dominant eye: 8 Hz stimulation. (C) Left eye: 8 Hz stimulation; Right eye: 12 Hz stimulation; (D) Left eye: 12 Hz stimulation; Right eye: 8 Hz stimulation. NE = nondominant eye, DE = dominant eye, LE = left eye, RE = right eye.

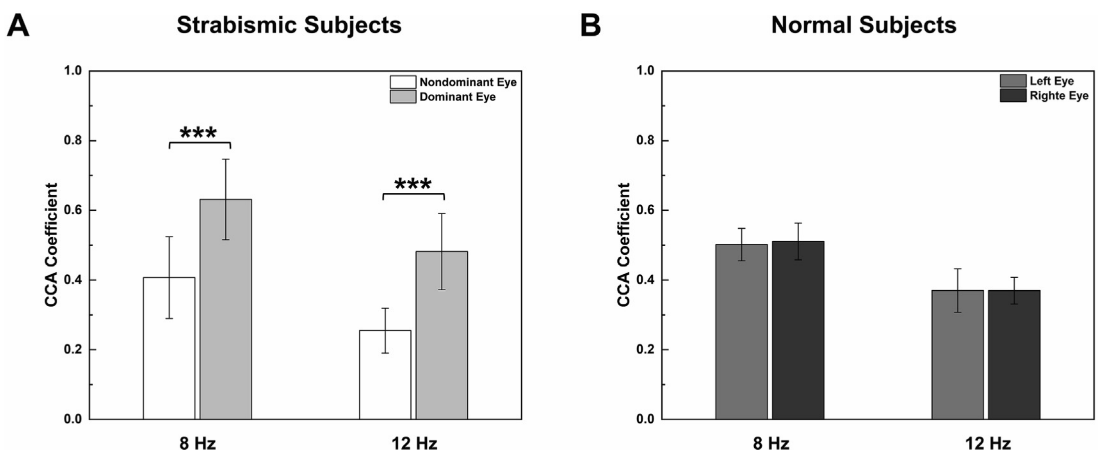

Fig. 5. Mean SSMVEP response of strabismic and normal subjects under condition A. (A) Mean SSMVEP response of nondominant and dominant eyes in strabismic subjects at 8 Hz and 12 Hz stimulation. (B) Mean SSMVEP response of normal subjects at 8 Hz and 12 Hz stimulation. $*P < 0.05$, $**P < 0.01$, $***P < 0.001$. Error bars represent standard deviation.

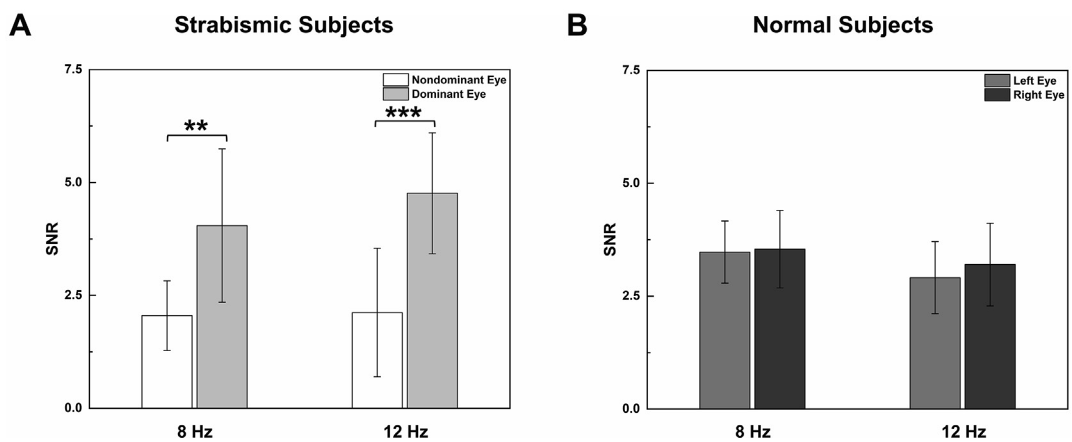

Fig. 6. Mean SNR value of the SSMVEP response of strabismic and normal subjects under condition A. (A) Mean SNR value of the SSMVEP response of the nondominant and dominant eyes in strabismic subjects when stimulated with 8 Hz and 12 Hz frequencies. (B) Mean SNR value of the SSMVEP response of normal subjects when stimulated with 8 Hz and 12 Hz frequencies. $*P < 0.05$, $**P < 0.01$, $***P < 0.001$. Error bars represent standard deviation.

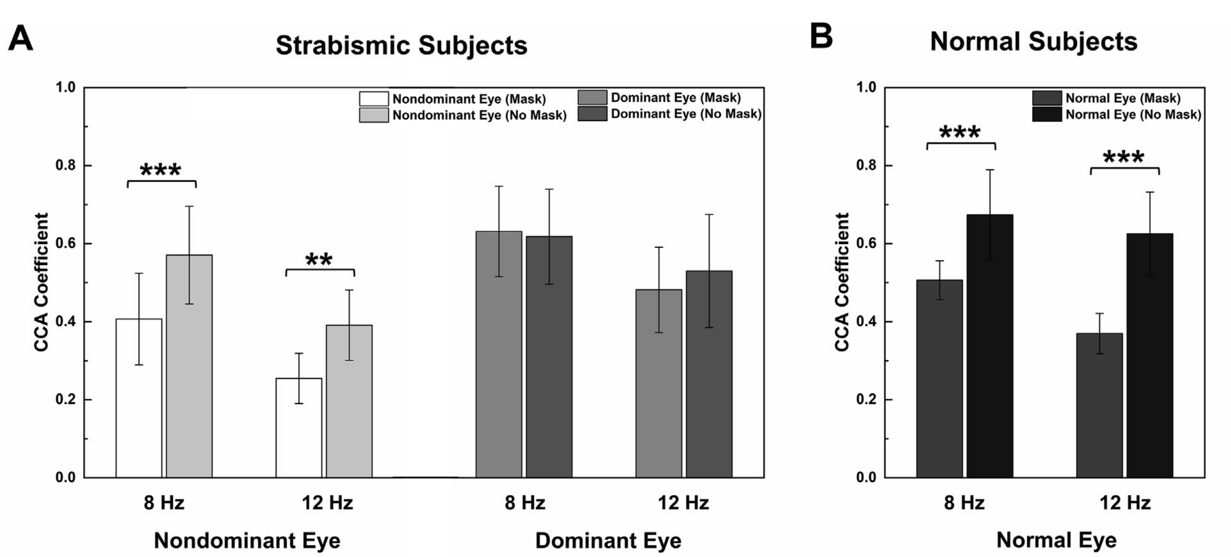

Fig. 7. Mean SSMVEP response of strabismic and normal subjects with or without dichoptic mask under conditions A, B, and C. (A) Mean SSMVEP response of nondominant and dominant eyes in strabismic subjects with or without dichoptic mask when stimulated at 8 Hz and 12 Hz. (B) Mean SSMVEP response of normal subjects at 8 Hz and 12 Hz stimulation. $*P < 0.05$, $**P < 0.01$, $***P < 0.001$. Error bars represent standard deviation.

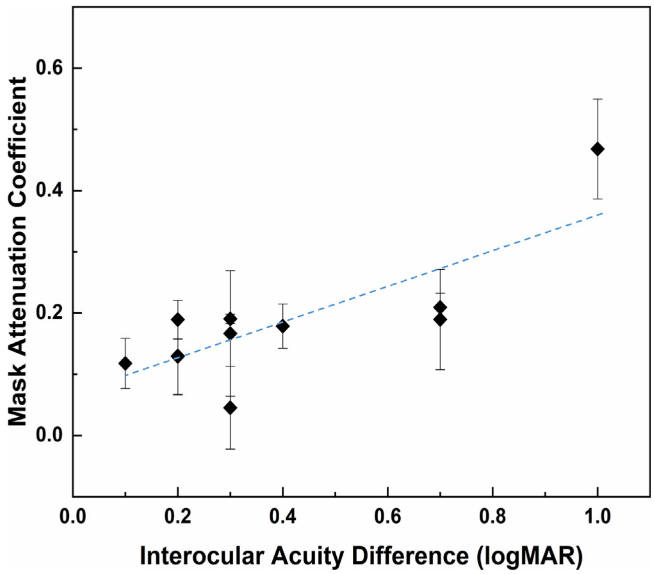

Fig. 8. Correlation between interocular acuity difference and the MAC of nondominant eyes in strabismic subjects. Error bars represent standard deviation.

MAC was used to quantify the influence of the dichoptic mask from the dominant eyes to the nondominant eyes in strabismic subjects. A significant correlation was also found between interocular acuity difference and the MAC of nondominant eyes in strabismic subjects ($r = 0.798$, $P = 0.003$), where the MAC was the average of the MAC values at 8 and 12 Hz, as shown in Fig. 8.

3.3. Quantification of interocular suppression relation

In this study, divergence J was used to describe the difference in the degree of SSMVEP response between the two eyes regardless of which eye was worse. A significant linear correlation was found between divergence J and difference in visual acuity between the two eyes in both strabismic and normal subjects ($r = 0.923$, $P < 0.001$), as shown in Fig. 9A.

SI was also significantly correlated with interocular visual acuity difference of right eye minus left eye in both normal and strabismic subjects ($r = -0.959$, $P < 0.001$), as shown in Fig. 9B.

4. Discussion

We measured SSMVEPs in 11 strabismic amblyopia and 12 normal subjects. In all participants, a peak occurred on CCA spectrum at the target frequency although the response decreased markedly in the nondominant eyes compared with those in dominant eyes of strabismic subjects. In our study, interocular suppression in strabismus was not the same as that in normal vision. This study analyzed interocular suppression in individuals with strabismic amblyopia and normal vision, and then proposed two indices, divergence J and SI, to describe the deficits of interocular suppression, and one index, MAC, to describe the influence of the dichoptic mask from the dominant eyes to the nondominant eyes in strabismic subjects.

4.1. Interocular difference and SSMVEP response

Both strabismic and normal groups differed in terms of interocular visual acuity, which can be considered as an estimate of the severity of suppression (Agrawal et al., 2006, Li et al., 2013). The difference in interocular acuity was larger in strabismus than in normal vision.

The SSMVEP response of the same eye, even monocularly in conditions B and C, was not close to that of different target frequency stimulation, because the absolute CCA peak at the target frequency was related to the stimulation frequency in both strabismic subjects and normal subjects ($t(45) = 4.121$, $P < 0.001$). The response to the 8 Hz stimulation was higher than the stimulation at 12 Hz, but this difference did not influence the results because a dimensionless value was used in our study; therefore the stimulation frequencies were exchanged under each condition.

We found that the SSMVEP response in the nondominant eye decreased significantly when the dichoptic mask of the dominant eye suppressed the nondominant eye in strabismic subjects, as shown in Fig. 7A, but no obvious difference in the dominant eye was found. In addition, the SSMVEP response also decreased after a mask was placed over the other eye in normal vision, although the decrease was not as large as that of the nondominant eye in strabismic subjects. The influence of the dichoptic mask can provide a qualitative method of detecting strabismus. A normal vision may be a condition where the SSMVEP response of the two eyes are affected by the dichoptic mask from the opposite eye. In contrast, a strabismus may be the condition where the SSMVEP response of only one eye is affected, whereas the other eye is almost unaffected by the dichoptic mask from opposite eye.

The reason for the variations in the influence of the mask in strabismic amblyopia may be that the proportion of neurons in the visual cortex driven by nondominant eye is reduced, with a corresponding

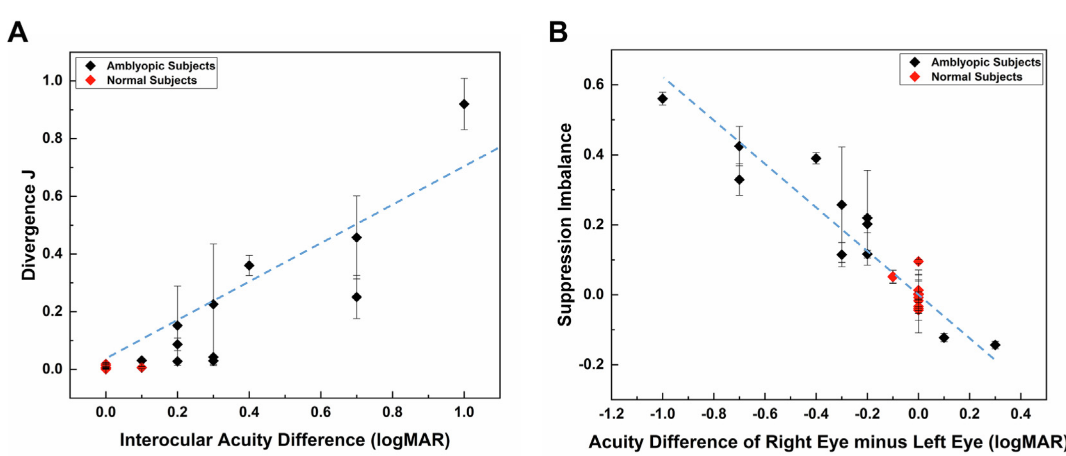

Fig. 9. Correlation between interocular acuity difference and the interocular suppression index — divergence J and SI. (A) Correlation between interocular acuity difference and divergence J. (B) Correlation between acuity difference of right eye minus left eye and SI. Both divergence J and SI were the average value obtained from the 8 and 12 Hz stimulation frequencies of each subject. Error bars represent standard deviation.

increase of neurons responding to the dominant eye when the dichoptic mask is presented to the dominant eye. However, there is no apparent change in the proportion of cells in visual cortex, which is big enough to influence the SSMVEPs when the dominant eye is masked.

4.2. Correlation between suppression and acuity difference in amblyopia

The interocular difference of subjective visual acuity was significantly larger in the strabismic group than that in the normal vision group ($F\,(1, 21) = 24.615$, $P < 0.001$). The difference in visual acuity in amblyopia was correlated with asymmetric interocular suppression, showing a nearly linear association between the severity of suppression and difference in acuity in amblyopia (Li et al., 2011). To verify this statement, divergence J, SI, and MAC were calculated in our study. We found a high correlation between interocular suppression and difference in acuity using divergence J, SI, and MAC. Consequently, our results supported the notion that deeper amblyopia is often accompanied by stronger suppression (Li et al., 2011).

In general, MAC can be an indicator of the effect from the dominant eye to the nondominant eye in strabismic subjects. It can be used when strabismus has already been diagnosed. Divergence J and SI can be used to detect strabismus and quantify interocular suppression because the two indices are suitable for both strabismus and normal vision, as shown in Fig. 9. In addition, a more severe binocular suppression corresponds to a larger divergence J or SI, while normal vision corresponds to a very small value. Thus, we can set a decision threshold, with values above the threshold indicating strabismus and values below the threshold indicating normal vision. However, unlike divergence J, SI can indicate which eye is nondominant and which eye is dominant in strabismic subjects by the sign of the value. Thus, we advocate the use of SI as the index for strabismus.

4.3. Clinical implications

Form deprivation and abnormal binocular interaction are the main reasons for amblyopia, especially during childhood (Guimaraes et al., 2018). The period from birth to 12 years is the most important period for visual development and is highly critical for amblyopia therapy (Lewis & Maurer, 2005). Thus, the earlier the condition is detected, the earlier the cure can be implemented. In addition, the effectiveness and efficiency of treatment are relatively better if they are begun at an early age rather than later in life.

SSMVEPs, as applied in our study, can be used as a technique for the early detection of strabismus, even in young children who typically lack the adequate intelligence needed for cooperating with the traditional strabismic examination. Moreover, SSMVEPs provide an objective and quantitative method for measuring interocular suppression and assessing deficits in strabismic amblyopia. This method can potentially replace traditional suppression detection methods, such as the Worth 4-dot test, which is more subjective and merely qualitative.

5. Conclusion

We used the circular checkerboard stimulation paradigm with dichoptic technique to measure the SSMVEP response in normal eyes, nondominant and dominant eyes of strabismic subjects. Our study provides evidence that interocular suppression plays a vital role in strabismic amblyopia. The influence of the dichoptic mask from the dominant eyes to the nondominant eyes of strabismic subjects calculated by MAC was highly correlated with the difference in visual acuity between the two eyes in strabismic subjects. The depth of interocular suppression, which was calculated by divergence J and SI was highly correlated with difference in visual acuity between the two eyes in both strabismic subjects and normal vision. Our study suggests that SSMVEPs can be used for the detection of strabismic amblyopia and the quantification of interocular suppression.

Acknowledgements

Supported by grants from the National Natural Science Foundation of China (NSFC-51775415) and the Key Research and Development Program of Shaanxi Province of China (2018ZDCXL-GY-06-01).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.visres.2019.07.003.

References

Agrawal, R., Conner, I. P., Odom, J. V., Schwartz, T. L., & Mendola, J. D. (2006). Relating binocular and monocular vision in strabismic and anisometropic amblyopia. *Archives of Ophthalmology, 124*(6), 844–850.

Bach, M., & Ullrich, D. (1994). Motion adaptation governs the shape of motion-evoked cortical potentials. *Vision Research, 34*(12), 1541–1547.

Baker, D. H., Meese, T. S., & Hess, R. F. (2008). Contrast masking in strabismic amblyopia: Attenuation, noise, interocular suppression and binocular summation. *Vision Research, 48*(15), 1625–1640.

Baker, D. H., Meese, T. S., Mansouri, B., & Hess, R. F. (2007). Binocular summation of contrast remains intact in strabismic amblyopia. *Investigative Ophthalmology and Visual Science, 48*(11), 5332–5338.

Baker, D. H., Simard, M., Saint-Amour, D., & Hess, R. F. (2015). Steady-state contrast response functions provide a sensitive and objective index of amblyopic deficits. *Investigative Ophthalmology and Visual Science, 56*(2), 1208–1216.

Banko, E. M., Kortvelyes, J., Weiss, B., & Vidnyanszky, Z. (2013). How the visual cortex handles stimulus noise: Insights from amblyopia. *PLoS One, 8*(6), e66583.

Barnes, G. R., Hess, R. F., Dumoulin, S. O., Achtman, R. L., & Pike, G. B. (2001). The cortical deficit in humans with strabismic amblyopia. *Journal of Physiology, 533*(Pt 1), 281–297.

Birch, E. E. (2013). Amblyopia and binocular vision. *Progress in Retinal and Eye Research, 33*, 67–84.

Chang-Bing, H., Jiawei, Z., Zhong-Lin, L., & Yifeng, Z. (2011). Deficient binocular combination reveals mechanisms of anisometropic amblyopia: Signal attenuation and interocular inhibition. *Journal of Vision, 11*(6), 67–74.

Chegeni, M., Khanjani, N., Rahmatpour, P., Ahmadi Pishkuhi, M., & Abdolalian, N. (2018). The prevalence of amblyopia in Iran: A systematic review. *Journal of Current Ophthalmology*.

Chen, X., Fu, Z., Yu, J., Ding, H., Bai, J., Chen, J., ... Liu, H. (2015). Prevalence of amblyopia and strabismus in Eastern China: Results from screening of preschool children aged 36–72 months. *The British Journal of Ophthalmology,* 100.

Crawford, M. L., Harwerth, R. S., Chino, Y. M., & Smith, E. L., 3rd (1996). Binocularity in prism-reared monkeys. *Eye, 10*(Pt 2), 161–166.

Frassle, S., Sommer, J., Jansen, A., Naber, M., & Einhauser, W. (2014). Binocular rivalry: Frontal activity relates to introspection and action but not to perception. *Journal of Neuroscience, 34*(5), 1738–1747.

Guimaraes, S., Vieira, M., Queiros, T., Soares, A., Costa, P., & Silva, E. (2018). New pediatric risk factors for amblyopia: Strabismic versus refractive. *European Journal of Ophthalmology, 28*(2), 229–233.

Hakvoort, G., Reuderink, B., & Obbink, M. (2011). *Comparison of PSDA and CCA detection methods in a SSVEP-based BCI-system.* Centre for Telematics & Information Technology University of Twente.

Han, C., Xu, G., Xie, J., Chen, C., & Zhang, S. (2018). Highly interactive brain-computer interface based on flicker-free steady-state motion visual evoked potential. *Scientific Reports, 8*(1), 5835.

Heinrich, S. P., & Bach, M. (2003). Adaptation characteristics of steady-state motion visual evoked potentials. *Clinical Neurophysiology, 114*(7), 1359–1366.

Hess, R. F., Mansouri, B., & Thompson, B. (2010). A new binocular approach to the treatment of amblyopia in adults well beyond the critical period of visual development. *Restorative Neurology and Neuroscience, 28*(6), 793–802.

Hotelling, H. (1936). Relations between two sets of variates. *Biometrika, 28*(3/4), 312–377.

Huang, C.-B., Zhou, J., Lu, Z.-L., Feng, L., & Zhou, Y. (2009). Binocular combination in anisometropic amblyopia. *Journal of Vision, 9*(3), 17.11-1716.

Lewis, T. L., & Maurer, D. (2005). Multiple sensitive periods in human visual development: Evidence from visually deprived children. *Developmental Psychobiology, 46*(3), 163–183.

Li, J., Hess, R. F., Chan, L. Y., Deng, D., Yang, X., Chen, X., ... Thompson, B. (2013). Quantitative measurement of interocular suppression in anisometropic amblyopia: A case-control study. *Ophthalmology, 120*(8), 1672–1680.

Li, J., Thompson, B., Lam, C. S., Deng, D., Chan, L. Y., Maehara, G., ... Hess, R. F. (2011). The role of suppression in amblyopia. *Investigative Ophthalmology and Visual Science, 52*(7), 4169–4176.

Martins Costa, M. F. P., Almeida Neves Carrega, F., Nunes, A. M. F., & Tuna, A. R. R. (2017). Interocular suppression. *Third International Conference on Applications of Optics and Photonics,* 108.

Meigen, T., & Bach, M. (1999). On the statistical significance of electrophysiological steady-state responses. *Documenta Ophthalmologica, 98*(3), 207–232.

Narasimhan, S., Harrison, E. R., & Giaschi, D. E. (2012). Quantitative measurement of interocular suppression in children with amblyopia. *Vision Research, 66*, 1–10.

Richard, B., Chadnova, E., & Baker, D. H. (2018). Binocular vision adaptively suppresses delayed monocular signals. *Neuroimage, 172*, 753–765.
Sengpiel, F., Blakemore, C., Kind, P. C., & Harrad, R. (1994). Interocular suppression in the visual cortex of strabismic cats. *Journal of Neuroscience, 14*(11 Pt 2), 6855–6871.
Sireteanu, R. (2000). The binocular visual system in amblyopia. *Strabismus, 8*(1), 39–51.
Webber, A. L., & Wood, J. (2005). Amblyopia: Prevalence, natural history, functional effects and treatment. *Clinical and Experimental Optometry, 88*(6), 365–375.
Wiesel, T. N., & Hubel, D. H. (1965). Comparison of the effects of unilateral and bilateral eye closure on cortical unit responses in kittens. *Journal of Neurophysiology, 28*(6), 1029–1040.
Xie, J., Xu, G., Wang, J., Zhang, F., & Zhang, Y. (2012). Steady-state motion visual evoked potentials produced by oscillating Newton's rings: Implications for brain-computer interfaces. *PLoS One, 7*(6), e39707.
Yan, W., Xu, G., Xie, J., Li, M., & Dan, Z. (2018). Four novel motion paradigms based on steady-state motion visual evoked potential. *IEEE Transactions on Biomedical Engineering,* 1.
Zhang, X., Xu, G., Xie, J., & Zhang, X. (2017). Brain response to luminance-based and motion-based stimulation using inter-modulation frequencies. *PLoS One, 12*(11), e0188073.
Zhonglin, L., Changshui, Z., Wei, W., & Xiaorong, G. (2006). Frequency recognition based on canonical correlation analysis for SSVEP-based BCIs. *IEEE Transactions on Biomedical Engineering, 53*(2), 2610–2614.