EEG Measurement for Suppression in Refractive Amblyopia and Push-Pull Perception Efficacy

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***Abstract*—In order to evaluate refractive amblyopia suppression and understand the neural mechanism of amblyopia suppression and push-pull perception training, we recorded the EEG of refractive amblyopia children before, during, and after push-pull perception training. We compared the brain activity in different states through the steady-state visual evoked potentials (SSVEPs) response and power topography and compared them with normal children. We found that amblyopic and fellow eyes have different performances in fundamental and harmonic frequency responses. They also show different characteristics when be masked. Push-pull perception training improved the SSVEP performance of amblyopia children by reducing the SSVEP response difference between eyes and improving the intermodulation frequency response. The result of topography showed that push-pull perception reduced the alpha power of occipital and temporal lobes, which was conducive to improving binocular function. The changes of intermodulation response and occipital alpha power were significantly correlated with the clinical indicator. Thus, EEG is a potential method to measure amblyopia suppression and the efficacy of push-pull perception.**

***Index Terms*—Amblyopia, push-pull perception, electroencephalogram (EEG), steady-state visual evoked potential (SSVEP).**

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I. Introduction

The American Academy of Ophthalmology defines *amblyopia* as a unilateral or rarely bilateral reduction in best-corrected vision, which can not be directly attributed to structural eye abnormalities [1], [2]. According to the definition of the strabismus and pediatric ophthalmology branch of the Chinese Medical Association [3], refractive amblyopia means the best-corrected visual acuity of monocular or binocular is lower than that of normal children of the corresponding age. Compared with both healthy eyes of normal children, both amblyopia eyes and fellow eyes of amblyopic children may have deficits in various degrees [4]–[9].

Suppression and rewiring, two theories to explain amblyopia defects, may exist in different courses of amblyopia. When the visual stimuli received by both eyes are inconsistent, suppression often occurs to avoid diplopia and confusion. If the inconsistent visual stimuli exist for some time and suppression is invoked on a more sustained basis, rewiring may occur in the cortex to produce a pathological adaptation. In this case, not only abnormal visual stimuli need to be removed, but visual training, whose time course and extensiveness depend on age and brain plasticity, is also needed [10].

Psychophysical methods are usually used in the clinical evaluation of amblyopia, including most methods that rely on subjective reports [11], such as the contrast sensitivity examination. It is usually difficult for nonverbal or uncooperative subjects (such as infants) to perform such psychophysical vision tests. Even adults, the performance of such tests will be affected by intelligence or malingering [12]. Visual evoked potentials (VEPs) technology provides an objective alternative means for visual function evaluation [13]. The steady-state visual evoked potentials (SSVEPs) have high stability characteristics, so they are favored by many researchers [14], [15]. Most previous studies on amblyopia SSVEP focused more on the fundamental frequency response [16]–[18], lacking consideration of harmonic response. The fundamental and harmonic responses have been proved to originate from different parts of the visual cortex [19], [20]. Therefore, paying attention to both the fundamental frequency response and the harmonic response of amblyopia SSVEP may be helpful for a comprehensive understanding of the function of the amblyopia visual cortex.

As for the treatment of amblyopia, the traditional patching treatment forces the use of amblyopic eyes by covering the dominant eyes of patients. However, the patching treatment has poor efficacy on most amblyopia children, and it is ineffective for adolescent and adult patients most of the time [21]. Perceptual learning technology is also used in the treatment of amblyopia. Through repeated visual stimuli, perceptual learning restores the function of amblyopia, including the improvement of contrast sensitivity, visual acuity, letter recognition ability, and the alleviation of crowding effect [22]. There is evidence that the recovery of visual function is lasting and extensive [23]. Push-pull perception training, one perceptual learning technology, gives amblyopic eyes intense stimulation and fellow eyes weak stimulation [24], [25]. It recalibrates the interocular balance [26], [27] and establishes better binocular visual function [28]. Push-pull perception provides further evidence for the binocular nature of amblyopia, but how push-pull perception affects cortical activities and which brain areas are the key to recovery are still unclear.

Considering the shortcomings of current research, in this study, we used a cosine modulated black-and-white block stimulation to induce SSVEP fundamental frequency responses and harmonic responses of refractive amblyopia children, which could provide a more comprehensive and quantitative description of the function of the amblyopia cortex. We then compared the SSVEP and power topography differences before and after training to measure the efficacy of push-pull perception training and explain its neural mechanism. As a result, refractive amblyopic children showed different characteristics in fundamental frequency and harmonic responses, suggesting some modulation or compensation effect of the advanced visual cortex. Push-pull perception widely inhibited alpha activity in occipital and temporal lobes, and the change of activity in the occipital lobe was correlated with the improvement of binocular balance.

II. Method

A. Participants

Eleven children with refractive amblyopia (ametropia or anisometropia), recruited from the Department of Ophthalmology, Beijing Children's Hospital, Capital Medical University, participated in the experiment. Their clinical details are shown in Table I. They were 4–8 years old (6.1 ± 1.4 years). Three (S2, S3, S9) had binocular disease, and the rest had monocular disease. In our study, the eye with poorer vision was recorded as the amblyopia eye, while the eye with better vision was recorded as the fellow eye. In addition, eight normal children (7.5 ± 3.1 years) also participated in the pre-training measurement of the experiment. All participants wore their best optical correction. Our experiments were approved by the ethics committee of Beijing Children's Hospital.

B. Apparatus

A wireless EEG system (Neusen W, Neuron, Changzhou, China) was used to collect EEG signals in this experiment, and the sampling frequency was 1 kHz. According to the World Health Organization's standard [29], we selected the 64-channel S-size EEG cap (50–54 cm). The reference electrode was placed at the vertex and the ground electrode was located in the midpoint of the FPz and Fz connecting. The other two electrodes were placed at the left and right earlobes for re-reference.

TABLE I
CLINICAL DETAILS OF AMBLYOPIC SUBJECTS

	Age, Gender	Type, Dominant eye	Visual acuity (RE, LE)	BP before PPT (RE, LE)	BP before PPT (RE, LE)
S1	8y7m, M	Ame, LE	(0.6, 0.8)	(6, 8)	(8, 8)
S2	7y9m, M	Ame, LE	(0.5, 0.6)	(6, 8)	(6, 6)
S3	5y4m, M	Ame, LE	(0.5, 0.6)	(6, 6)	(6, 6)
S4	7y4m, M	Ani, LE	(0.4, 1.0)	(7, 8)	(8, 8)
S5	5y8m, M	Ani, LE	(0.5, 0.8)	(6, 3)	(7, 4)
S6	8y4m, M	Ani, RE	(1.0, 0.4)	(8, 6)	(7, 7)
S7	5y2m, M	Ani, RE	(0.8, 0.2)	(8, 1)	(8, 3)
S8	5y2m, M	Ani, RE	(0.8, 0.5)	(8, 8)	(8, 7)
S9	5y4m, M	Ani, RE	(0.6, 0.4)	(8, 3)	(6, 3)
S10	7y8m, M	Ame, RE	(0.8, 0.6)	(8, 3)	(8, 4)
S11	4y7m, M	Ani, RE	(0.9, 0.2)	(8, 1)	(8, 1)

y = Years, m = Months, Ame = Ametropia, Ani = Anisometropia, LE = Left eye, RE = Right eye, BP = Balance point, PPT = Push-pull perception training

C. Experimental Procedure and Stimulation

The experimental flow is shown in the middle panel of Fig. 1. The subjects sat 1.2 m in front of the display and used a headrest to reduce the head movement. They first accepted a 5 min clinical visual function examination, then wore the EEG cap for a 2 min resting state (closing or opening eyes to the white wall) and about 7 min SSVEP signal acquisition, followed by 10 min push-pull perception training. After finishing the training, a similar process was performed, including resting and SSVEP signal acquisition and visual function examination. In order to reduce the interaction between SSVEP stimulation and push-pull perception, a few minutes' rests was conducted before and after push-pull training. The length of rest depends on the subjects. During the experiment, subjects wore polarized glasses (Reedoon, Shanghai, China) to receive the dichoptic stimulation of SSVEP and push-pull training.

1) SSVEP: SSVEP stimulation was presented on a 23-inch polarized display (D2367ph, AOC, Fujian, China) through the Psychophysics Toolbox in MATLAB (MathWorks, Natick, United States). The stimulation target was a square block, whose maximum brightness was about 25 cd/m^2, and the visual angle was about 4° × 4°. Stimulation frequency f_1 was 7 Hz and f_2 was 9 Hz, and the gray level was determined by the cosine function of the targeted frequency. We used a luminance meter (ST-86la, Beijing Shida Photoelectric Technology Co., Beijing, China) to unify the flickering brightness of the two frequencies to reduce the brightness interference.

As shown in the bottom panel of Fig. 1, the SSVEP experiment included six stimulation conditions. Subjects were first stimulated monocularly with two different frequencies. In this case, a flashing square was presented to one eye, and a non-flashing white square was presented to the other eye and then interchanged. After monocular stimulation, the eyes were stimulated binocularly with different frequencies. Each stimulus

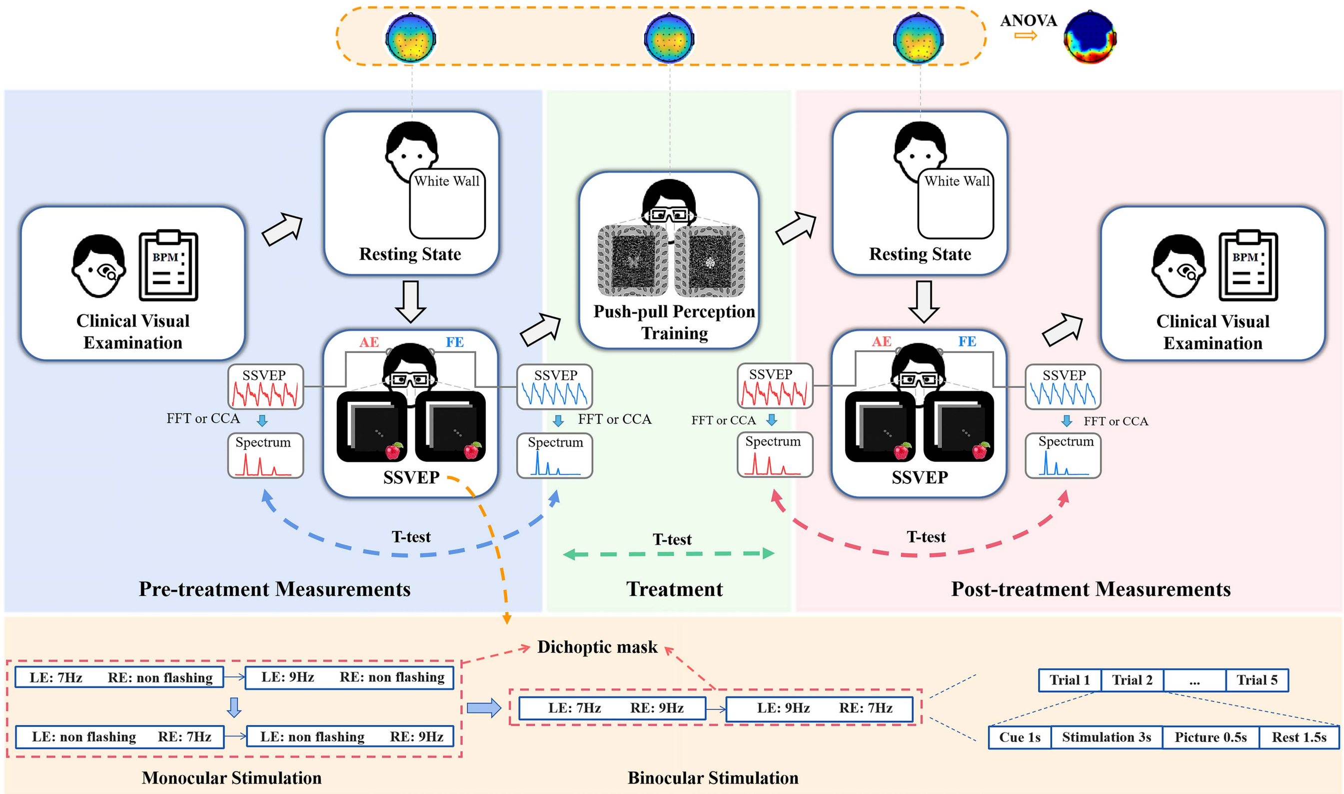


Fig. 1. Experimental flow chart. Subjects were measured for visual function before and after push-pull perception training, including clinical visual function examination and EEG measurement of resting-state and SSVEP. SSVEP experiment included six stimulation conditions, including monocular single-frequency stimulation and binocular different-frequency stimulation. AE = amblyopic eye, FE = fellow eye.

included five trials. Each trial included 1 s cue, 3 s stimulus, 0.5 s fruit picture, and 1.5 s rest. After seeing the fruit picture, the subjects fed back the types of fruit they saw by pressing the key to ensure the effectiveness of the EEG data.

We give a brief description of the above stimulation condition. When the research object is an eye, we will present it with a specific stimulus, such as 7 Hz stimulation, which we call target stimulation; If a different stimulus is presented to the other eye at the same time, such as 9 Hz stimulation, this different stimulus is called masking stimulation.

2) Push-Pull Perception: The push-pull and disinhibition models provided by the National Engineering Research Center for Healthcare Devices (Guangzhou, China) were adopted for push-pull perception training. The stimulation was presented on a 32-inch polarized display (2342p, LG, Seoul, Korea). Subjects adjusted the contrast level of the stimulation for binocular balance before a disinhibition model was added to the stimulation, and they recognized the flickering image received by the amblyopic eye during the training process and pressed the key for feedback. (See supplementary materials for more details.)

D. Signal Processing

All signal processing was completed on MATLAB. We first downsampled the signal to 250 Hz, and then denoised it with a 50 Hz notch filter and a 0.1 Hz–50 Hz band-pass filter. For the signal of the SSVEP experiment, we further removed trials whose absolute value of amplitude was greater than

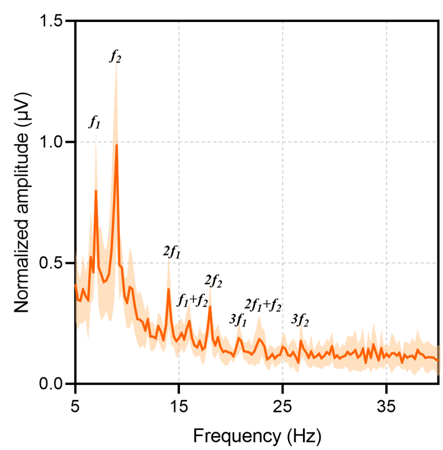


Fig. 2. The average SSVEP Fourier spectrum of dichoptic stimulation. SSVEP response includes fundamental frequency, second and third harmonic response and sum intermodulation frequency response of two stimulation frequencies.

200 μV [30], [31]. For the signals of the resting and push-pull training state, we used the *clean-rawdata* plug-in [32] for further preprocessing and re-referenced the signals to the earlobe in EEGLAB [33], [34].

1) SSVEP: Four occipital electrodes (POz, O1, O2, Oz) were selected to calculate the SSVEP response. The SSVEP paradigm used in this study could induce multiple harmonic responses [35]. Thus, we calculated the SSVEP response of the fundamental frequency, second, third harmonic, and intermodulation frequency of the target frequencies (Fig. 2).

We measured SSVEP response by the signal-to-noise ratio (SNR) [35]–[38] and canonical correlation analysis signal-to-noise ratio (CCA SNR) [18].

SNR is defined as the ratio of the amplitude of the target frequency to the average amplitude of the surrounding frequencies:

$$SNR = \frac{M \cdot F(f)}{\sum_{m=1}^{M/2}[(F(f)-\Delta f \cdot m)+(F(f)+\Delta f \cdot m)]} \quad (1)$$

where f is the stimulation frequency, Δf is the frequency resolution, and $F(f)$ is the Fourier spectrum amplitude at the stimulation frequency. Since the resampling frequency is 250 Hz, Δf is 0.33 Hz. M is set to 6, corresponding to 1 Hz around the target frequency.

CCA is a commonly used signal analysis method in brain-computer interface (BCI) research based on SSVEP [35]–[39]. It is used to calculate the correlation between two groups of variables, one of which is the multi-channel EEG signal X, and the other is the reference signal Y. Y is generally defined by the sinusoidal template:

$$Y_f = \begin{bmatrix} sin(2\pi f t) \\ cos(2\pi f t) \\ \vdots \\ sin(2\pi N_h f t) \\ cos(2\pi N_h f t) \end{bmatrix} \quad (2)$$

where f is the stimulation frequency and N_h is the harmonic number. CCA maximizes the correlation coefficient of its linear combination $x = X^T w_x$ and $y = Y^T w_y$ by finding the weights w_x and w_y:

$$\rho = \frac{E[w_x^T X Y^T w_y^T]}{\sqrt{E[w_x^T X X^T w_x^T] E[w_y^T Y Y^T w_y^T]}} \quad (3)$$

where ρ is the maximum canonical correlation coefficient between variables X and Y. The CCA spectrum consists of the canonical correlation coefficient between X and the reference signal Y with different frequencies (f_i = 0.1, 0.2, 0.3, …, 30.0), and the CCA SNR is defined in the same way as SNR:

$$CCA\,SNR = \frac{N \cdot C(f)}{\sum_{n=1}^{N/2}[(C(f)-\Delta f' \cdot n)+(C(f)+\Delta f' \cdot n)]} \quad (4)$$

where f is the targeted stimulation frequency, $\Delta f'$ is the frequency resolution of the CCA spectrum, set to 0.1. $C(f)$ is the CCA coefficient at the targeted frequency. N is set to correspond to 1Hz around the stimulation frequency.

In order to measure the response time of different eyes to stimulation, we also studied the fundamental frequency phase of SSVEP, calculated by the phase of the Fourier spectrum at the targeted frequency. We averaged the results of all subjects across trials and then channels.

2) Resting and Training State: We used power topography to observe the changes in brain state before, during, and after the push-pull training. Welch's method [40] was used for power calculation. The parameters were set as 1s window length and 50% overlap. The *topoplot* function in EEGLAB was used to draw the relative power data of four frequency bands (delta: 0.1–4 Hz, theta: 4–8 Hz, alpha: 8–14 Hz, beta: 14–30 Hz) into topographic maps.

E. Clinical Data Processing

The balance point (BP) is a common-used index to measure the degree of interocular suppression clinically. It reflects the ability of one eye to resist the suppression of the other eye. The greater BP of an eye, the stronger the anti-suppression ability of that eye; the smaller difference between BP of two eyes, the better interocular balance. (More details about BP are described in the supplementary materials.)

In order to describe the clinical significance of BP more simply, we define the balance point measurement (BPM):

$$BPM = \frac{RBP + LBP}{|RBP - LBP| + k} \quad (5)$$

where RBP and LBP are the BP of the right eye and the left eye, respectively (Table I). k is added to the denominator to avoid the situation that the denominator is 0. The greater BPM, the weaker interocular suppression, and the better interocular balance. If the difference of BPM after and before training is positive, the interocular balance has been improved; conversely, there is no improvement in the interocular balance. In this study, when the value of k was between 0.5 and 5.5, the change of BPM was consistent with the clinical diagnosis results. In the subsequent analysis, we set k to 2.

F. Statistical Analysis

We conducted paired t-test on SSVEP response under various stimulus conditions before or after training. Specifically, as shown in the middle and bottom panel in Fig. 1, we compared the monocular response between eyes to study the differences in response to target stimulation between amblyopic eyes and fellow eyes. The monocular and binocular stimulations were compared to study the response differences with and without masking stimulation. That was to study the masking effect of different eyes. Then we compared the response and masking effect before and after training to measure the efficacy of push-pull perception. In addition, to find the critical brain regions during push-pull perception training, as shown in the upper panel of Fig. 1, we used one-way ANOVA and Tukey-Kramer test to analyze the impact of training stages (before, during, and after training) on power topography. Finally, to find the EEG indexes correlated to interocular suppression, we analyzed the correlation between the change of intermodulation frequency response, power topography, and the change of BPM.

III. Results

A. SSVEP

We recorded a total of 900 trials of SSVEP data, of which 660 trials were from amblyopic children and 240 trials were from normal children. In the preprocessing, we removed 73 trials of amblyopic children and 16 trials of normal children, accounting for 11.06% and 6.67%, respectively.

TABLE II
SSVEP RESPONSE OF AMBLYOPIA CHILDREN BEFORE TRAINING

Before Training	SNR			CCA SNR		
	7 Hz	14Hz	21Hz	7 Hz	14Hz	21Hz
SSVEP Response (Mean ± Std)						
FE	2.196 ± 0.306	2.223 ± 0.404	2.006 ± 0.153	1.531 ± 0.363	1.487 ± 0.445	1.177 ± 0.210
AE	1.919 ± 0.263	2.092 ± 0.376	2.166 ± 0.191	1.312 ± 0.271	1.334 ± 0.443	1.112 ± 0.251
FE(mask)	1.961 ± 0.157	2.074 ± 0.238	2.017 ± 0.229	1.252 ± 0.252	1.249 ± 0.278	1.043 ± 0.133
AE(mask)	2.009 ± 0.207	2.109 ± 0.236	1.892 ± 0.144	1.316 ± 0.186	1.317 ± 0.371	1.118 ± 0.175
T-test Results (t-Value, p Value)						
FE vs. AE	2.433, 0.035*	0.847, 0.417	-2.371, 0.039*	2.463, 0.034*	1.427, 0.184	1.463, 0.174
FE vs. FE(mask)	2.478, 0.033*	1.504, 0.163	-0.139, 0.892	3.407, 0.007**	2.080, 0.064	3.919, 0.003**
AE vs. AE(mask)	-1.184, 0.264	-0.143, 0.889	4.348, 0.001**	-0.044, 0.966	0.129, 0.900	-0.074, 0.942

* $p < 0.05$, ** $p < 0.01$

TABLE III
SSVEP RESPONSE OF AMBLYOPIA CHILDREN AFTER TRAINING

After Training	SNR			CCA SNR		
	7 Hz	14Hz	21Hz	7 Hz	14Hz	21Hz
SSVEP Response (Mean ± Std)						
FE	2.012 ± 0.233	2.145 ± 0.464	2.091 ± 0.453	1.353 ± 0.290	1.402 ± 0.469	1.245 ± 0.491
AE	2.024 ± 0.281	2.119 ± 0.298	2.022 ± 0.303	1.361 ± 0.210	1.310 ± 0.279	1.185 ± 0.371
FE(mask)	2.159 ± 0.323	2.160 ± 0.393	2.117 ± 0.265	1.346 ± 0.316	1.424 ± 0.535	1.130 ± 0.198
AE(mask)	2.046 ± 0.309	2.149 ± 0.325	2.031 ± 0.182	1.243 ± 0.193	1.297 ± 0.386	1.028 ± 0.090
T-test Results (t-Value, p Value)						
FE vs. AE	-0.107, 0.917	0.234, 0.819	0.800, 0.442	-0.150, 0.884	1.122, 0.288	0.931, 0.374
FE vs. FE(mask)	-1.662, 0.127	-0.124, 0.904	-0.189, 0.854	0.097, 0.925	-0.438, 0.670	1.473, 0.172
AE vs. AE(mask)	-0.145, 0.887	-0.514, 0.618	-0.125, 0.903	4.443, 0.001**	0.259, 0.801	1.468, 0.173

* $p < 0.05$, ** $p < 0.01$

Note that 9 Hz is in the alpha band, where children have strong spontaneous oscillation [41], [42]. Thus, spontaneous oscillation easily interfered with the fundamental frequency response at 9 Hz. Although we still put the response results of 9 Hz in the supplementary materials, they may not be accurate enough. Therefore, we mainly analyze the results of 7 Hz below.

The suppression of amblyopia was analyzed through SSVEP results before the push-pull perception training. Table II shows the fundamental and harmonic response of 7 Hz in amblyopic children before training. According to T-test results, the fundamental frequency response of amblyopic eyes (AE) is significantly weaker than that of fellow eyes (FE) at 7 Hz. The fundamental frequency response of fellow eyes is decreased significantly when different frequency stimuli are applied to the other eye, which is the masking effect. At 14 Hz, there is no significant difference in the response between eyes, and there is no significant masking effect either. At 21 Hz, the results of SNR illustrate that the response of amblyopic eyes is stronger than that of fellow eyes and is masked by fellow eyes, while the results of CCA SNR illustrate that amblyopic eyes mask fellow eyes.

Table III shows the fundamental and harmonic response of 7 Hz in amblyopic children after training. At 7 Hz, there is no significant response difference between amblyopic eyes and fellow eyes, and there is no significant response change of fellow eyes when masked, but fellow eyes may mask amblyopic eyes according to the results of CCA SNR. As for 14 Hz and 21 Hz, there is no significant response difference between eyes, and neither eye is masked by the other.

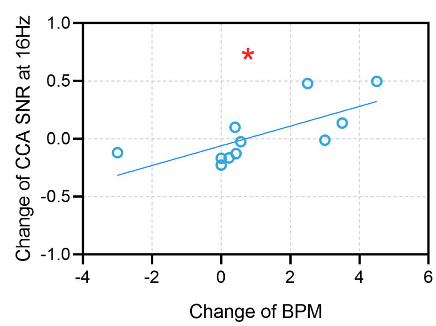


Fig. 3. A scatterplot and correlation analysis of response change at sum intermodulation frequency and BPM change. The asterisks indicate significant difference (* $p < 0.05$).

We also found some significant differences between SSVEP responses before and after training. The results of CCA SNR shows the response of fellow eyes at 7 Hz is decreased significantly ($t_{10} = 2.480$, $p = 0.032$), and the response at the intermodulation frequency 16 Hz is significantly improved ($t_{10} = -2.440$, $p = 0.0348$)). The results of SNR shows the response of amblyopic eyes at 21 Hz is significantly improved ($t_{10} = -2.277$, $p = 0.046$).

TABLE IV
SSVEP RESPONSE OF NORMAL CHILDREN

	SNR			CCA SNR		
	7 Hz	14Hz	21Hz	7 Hz	14Hz	21Hz
SSVEP Response (Mean ± Std)						
LE	2.531 ± 0.346	2.578 ± 0.560	2.058 ± 0.346	1.871 ± 0.436	1.857 ± 0.427	1.393 ± 0.298
RE	2.209 ± 0.513	2.419 ± 0.714	2.189 ± 0.184	1.767 ± 0.477	1.598 ± 0.528	1.198 ± 0.214
LE(mask)	2.258 ± 0.348	2.373 ± 0.527	2.092 ± 0.186	1.490 ± 0.424	1.565 ± 0.464	1.107 ± 0.151
RE(mask)	2.192 ± 0.275	2.331 ± 0.494	2.064 ± 0.29	1.465 ± 0.435	1.434 ± 0.509	1.130 ± 0.312
T-test Results (t-Value, p Value)						
LE vs. RE	1.755, 0.123	0.879, 0.409	-1.173, 0.279	0.836, 0.431	1.837, 0.109	2.984, 0.020*
LE vs. LE(mask)	3.739, 0.007*	0.891, 0.403	-0.278, 0.789	2.868, 0.024*	2.394, 0.048*	2.389, 0.048*
RE vs. RE(mask)	0.132, 0.899	0.518, 0.621	0.906, 0.395	5.961, 0.001**	1.447, 0.191	0.54, 0.606

* p <0.05, ** p <0.01

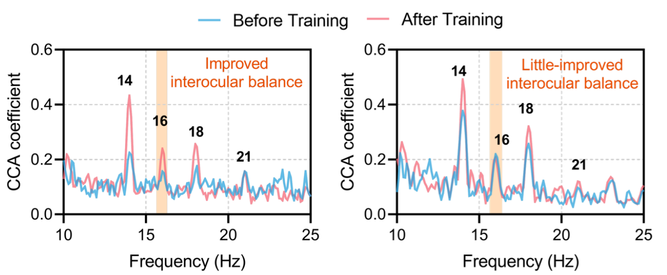


Fig. 4. CCA spectrum of subject S1 with improved interocular balance and subject S5 with little-improved interocular balance. Different subjects have different response changes at 16 Hz before and after training.

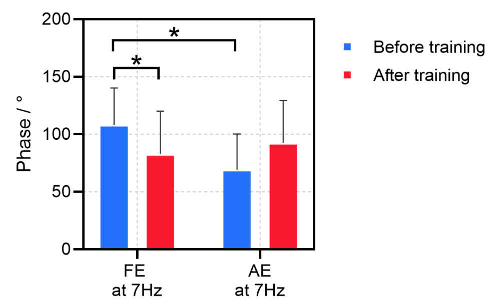


Fig. 5. Comparison of fellow and amblyopic eyes response phases before and after training. The asterisks indicate significant difference (* $p < 0.05$).

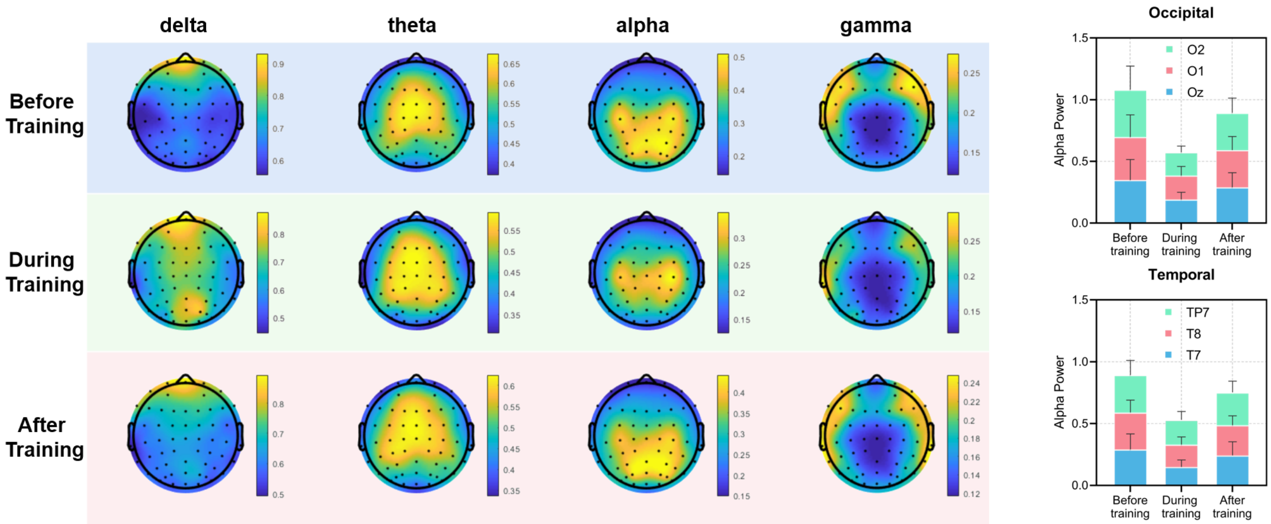
Fig. 4 shows the difference of response at intermodulation frequency 16 Hz after and before training (after training − before training) is significantly positively correlated with the difference of BPM ($\rho = 0.712$, $p = 0.013$), and the value of k in BPM does not affect the results (Fig S3(a)). Fig. 5 shows the frequency spectrum of two subjects under binocular stimulation. The left and the right figures are from subjects S1 and S5, respectively. According to Table I, after training, the BP of S1 is raised from (6,8) to (8,8), and BPM is raised from 3.5 to 8. Correspondingly, his response at 16 Hz is also greatly improved. The BP of S5 is changed from (6,3) to (7,4), and BPM is increased slightly from 1.8 to 2.2. Correspondingly, his response at 16 Hz has little improvement.

Fig. 6 shows that the response phase at 7 Hz of fellow eyes before training is significantly greater than that of weak eyes ($t_{10} = 3.126$, $p = 0.010$). There is no significant difference at the phase between eyes after training ($t_{10} = -0.835$, $p = 0.423$). Compared with before training, the response phase of fellow eyes is decreased significantly after training ($t_{10} = 2.670$, $p = 0.023$).

Table IV shows the fundamental and harmonic response of 7 Hz in normal children after training. As for normal children, there is no significant difference in the fundamental frequency response between left and right eyes, and the masking effect exists in both left and right eyes at 7 Hz. For harmonic response, the results of CCA SNR illustrate that right eyes mask left eyes at 14 Hz; the response of left eyes at 21 Hz is significantly higher than that of right eyes, and right eyes also mask left eyes. In addition, there is no significant difference in the response phase at 7 Hz between eyes of normal children (LE = 98.719° ± 36.169°, RE = 107.000° ± 34.209°, $t_7 = -0.535$, $p = 0.609$).

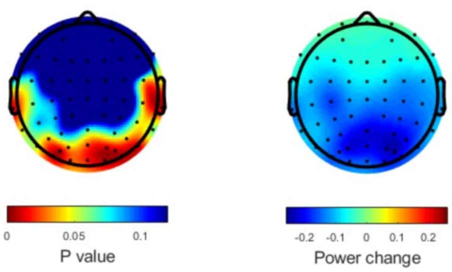
B. Topography

We compared the topography of the four frequency bands before, during, and after training (Fig. 6(a)). The results of ANOVA showed that only the topography of the alpha band had extensive and significant changes. Fig. 7(a) shows the result of ANOVA of the alpha band in a topographic map. According to the color bar, the non-blue areas in the figure have changed significantly (FC6, C6, TP7, P5, P6, P8, POz, PO3, PO4, Oz, O1, $p < 0.05$; T7, T8, PO5, PO6, PO7, PO8, O2, $p < 0.01$). The power of some occipital and temporal lobe areas has changed very significantly. The results of the Tukey-Kramer test showed that significant differences mainly occurred between before and during training. Topography before and during training is compared furtherly (Fig. 7(b)). The power of the areas with significant differences is reduced during training. The power of some electrodes in temporal and occipital regions during training is between the power before and after training (Fig. 6(b)). Results of correlation analysis showed that among these electrodes with significant changes, the changes of alpha power of some electrodes in occipital region are significantly negatively correlated with the changes of BPM (PO4, $\rho = -0.613$, $p = 0.045$; PO6, $\rho = -0.643$, p = 0.032; PO8, $\rho = -0.622$, $p = 0.040$; Oz, $\rho = -0.62$, $p = 0.041$; O2, $\rho = -0.656$, $p = 0.028$), and the correlation



(a) (b)

Fig. 6. (a)Average power topography across amblyopia children of delta, theta, alpha and gamma in different stages and (b)power changes of some occipital and temporal electrodes in alpha band.



(a) (b)

Fig. 7. (a) P-value topography (only areas with $p < 0.05$) and (b) power difference topography between during and before training of the alpha band.

results of PO6 and O2 are not affected by k of BPM (Fig. S3(b)).

IV. Discussion

A. Amblyopia Measurement

In order to understand the visual cortex defects of refractive amblyopic children, we used the fundamental frequency and harmonic response of SSVEP to measure monocular deficits and interocular suppression of amblyopia [43], [44]. As a result, the fundamental frequency response of amblyopic eyes is significantly weaker than that of fellow eyes, but the harmonic response is not necessarily. When amblyopia eyes receive different stimuli, the fundamental response of fellow eyes is decreased significantly, which means amblyopic eyes mask fellow eyes in the fundamental frequency response. However, amblyopic eyes may be masked by fellow eyes in the harmonic response. In addition, the response of amblyopic eyes lags behind that of fellow eyes. These results show the relationship between eyes of refractive amblyopia: first, the amblyopic eyes also receive and process visual information, but the processing efficiency is lower than that of fellow eyes; second, in the process of binocular vision, amblyopic eyes also have a certain impact on fellow eyes.

1) Active Advanced Visual Cortex in Amblyopia: Previous studies have found a neural generator of fundamental frequency response in the primary visual cortex [45], [46], while the harmonic response has been confirmed to occur in other larger areas, such as the second harmonic response limited to the extrastriatal visual area [45]. The fundamental response and harmonic response represent the bottom-up and top-down processes of the brain, respectively [47]. Thus, the fundamental and harmonic responses may represent the primary and advanced visual cortex functions, respectively.

Based on our results, we hold that the weaker response of amblyopic eyes in the fundamental response corresponds to the defects of the primary visual cortex. Defects in the primary visual cortex usually cause the reduced visual acuity of neurons driven by amblyopic eyes [48] and reduced contrast sensitivity [49]. The stronger harmonic response indicates the top-down processing function of the advanced visual cortex, suggesting some modulation or compensation effect from the advanced visual cortex. In addition, some studies have shown that the harmonic response may be related to the regulation of attention [47], [50], so the performance difference between eyes in harmonic response may be related to attention. In this regard, some studies have shown that the attention resources of amblyopia patients are complete [51], [52], while others result that amblyopia children have attention problems [53]. Therefore, it is necessary to improve the experimental paradigm to study the attention problems of different types of amblyopia on SSVEP.

2) Amblyopia Suppression in Advanced Visual Cortex: Under the condition of the dichoptic mask, the fundamental response of fellow eyes is masked by amblyopic eyes, which may be due to the compensatory allocation of neurons driven by fellow eyes to complete the response of amblyopic eyes to different stimuli. On the contrary, fellow eyes may mask amblyopic eyes in the harmonic response, indicating that the interocular suppression from fellow eyes to amblyopic eyes may also occur in the advanced visual cortex. It may provide a reasonable explanation for previous studies believing that the loss of sensitivity in the primary visual cortex is not enough to explain other defects in behavioral measurement [10], [54].

The phenomenon that there is no masking effect in some harmonic responses could be explained by the synchrony hypothesis [16]. This hypothesis points out that a strong stimulus in the other eye can induce binocular neurons to respond synchronously, resulting in an increased response at the target stimulation frequency. Based on this hypothesis, when both eyes are simultaneously stimulated differently, neurons driven by amblyopic eyes in the primary visual cortex are easier to be recruited and enter the synchronous state than those in advanced visual cortex neurons, which results in the improvement of the response of the primary visual cortex so that fellow eyes do not mask them.

3) Response Lag of Amblyopic Eye: Our results show that amblyopic eyes lag behind fellow eyes in the phase of fundamental frequency response, which is not found in normal children. Some studies have also resulted in that [19]. The phase difference between the fellow and amblyopic eyes implies the difference in response time, which may be caused by slower signal transmission in the optic nerve or bundle or slower signal integration of cortical visual neurons. The latency of amblyopic eye signals reaching the cerebral cortex is longer [55], [56], suggesting that the brain may prefer the earlier-reaching signals and then trigger the amblyopia inhibition. [10].

B. Push-Pull Perception Mechanism

1) Recovery of Interocular Balance: Our results show that after training, the fundamental frequency response of fellow eyes is reduced significantly, and the harmonic response of amblyopic eyes when masked is improved significantly. Also, the sum intermodulation frequency response is improved and the interocular response that had significant differences before training becomes insignificant after training. These results show that the interocular response tends to be balanced, and the masking effect becomes weaker after training, indicating that push-pull training has an acute effect on improving amblyopic eye function and reducing interocular suppression. The intermodulation frequency is a sign of the interocular interaction in the cortex [57]. Therefore, the response improvement at intermodulation frequency after training may be related to the recovery of interocular interaction.

As for the correlation results, we found a strong positive correlation between the change of BPM and the response change at the intermodulation frequency. The higher intermodulation frequency change indicates better interocular balance. There is one point that must be illustrated. The only data with negative BPM change in Fig. 4 comes from S8, whose balance point becomes worse (table I) after training. It is pretty rare in practical clinical application. If we eliminate it, the correlation result will become $\rho = 0.780$ (p = 0.008), higher than the previous result. Thus, the response change of SSVEP intermodulation frequency is a potential index to measure the training effect and needs to be verified by large sample data before applied to clinical examination.

In addition, the response phase differences between eyes become insignificant after training, meaning the interocular balance in response speed, which confirms the effectiveness of push-pull perception.

2) Inhibition of Alpha Activity in Visual Cortex: We try to explain the neural mechanism of the push-pull perception model by power topography. As a result, there is a significant reduction in alpha power in the occipital and temporal lobe before and during training, indicating that push-pull perception can effectively modulate the alpha rhythm of the occipital and temporal region of amblyopia. A previous study shows that the push-pull perception model could stimulate the middle temporal lobe (where MT is located) and visual cortex and activate the striate dorsal processing flow [58], which is consistent with our results. The extrastriate cortex such as V2, MT or V5, and V4 shows the neural correlation of relative disparity, thus showing stereoscopic depth perception [59]–[61], which may explain why push-pull perception contributes to the recovery of stereopsis.

Previous studies have shown that active alpha activity is related to reducing visual processing and cognitive activity [62], [63],and minor alpha power is related to the improvement of visual processing [64]. As for attention, push-pull perception is a process of external attention, which selects and adjusts sensory information, including spatial location, time, or specific modal input [65]. Studies have shown that the decrease of alpha power under external attention reflects the increase of excitability of the sensory cortex, thereby enhancing stimulation processing [66]–[70]. Therefore, the extensive decrease of alpha activity in push-pull perception may indicate the improving visual and perceptual function, confirmed by the correlation results of topography. The alpha power of some occipital electrodes indicates whether push-pull training is effective and the recovery of interocular function. Therefore, alpha power change is another potential index to measure the efficacy besides the response change of SSVEP intermodulation frequency.

The duration of push-pull perception training in our experiment is short, which is not enough to make a broad and significant change in power before and after training, accounting for there is no significant difference between the power topography after and before training. Another explanation is that the visual cortex does not need to recruit too many visual-related neurons in the state of resting and opening eyes, and the changes might be found when performing specific tasks. The average power in specific areas after training is between the power before and during training, so the brain state after training may transition from before training to during training. If the subjects are trained for a longer time, the visual cortex may complete the transition, resulting in significant changes, which needs to be further verified.

C. BCI in Amblyopia Examination

In this study, we used some methods of SSVEP-BCI to examine refractive amblyopia. Based on the previous application of CCA coefficient [18], [71], we introduced CCA SNR and compared it with SNR. From the results, the two SNR are not the same, but the conclusions are generally consistent. In terms of intermodulation frequency, CCA SNR seems to get more helpful information. Considering the small number of samples in our study and similar studies [16]–[18], we cannot say which SNR is better. The strategies of the two SNR are different, so the information they get may be complementary.

An inevitable problem in applying SSVEP-BCI is BCI illiteracy, which refers to those who cannot operate the BCI system effectively. The illiteracy of SSVEP-BCI, accounting for about 10% [72], [73], may limit the clinical application of BCI. However, the above rate is calculated under the multi-target task, and our experiment is only a two-target task, which can reduce the rate to a certain extent. A more practical way to solve the problem is to use more complex algorithms. Generally speaking, the training algorithm can extract the subjects' personalized EEG patterns to improve their performance, but it needs data and time to train the model. Such a time-consuming and personalized algorithm seems to be infeasible in clinical examination. However, it is gratifying that with the development of algorithms, the time of training models has been shortened [74]–[76]. In addition, the training-free algorithm is also improving. For example, the algorithm based on chaos theory [77] improves the performance of BCI illiteracy. We believe that BCI illiteracy will not become a significant obstacle in the clinical detection of BCI with the development of algorithms.

The indicators used in clinical examination need strong robustness. At present, the indicators used in amblyopia SSVEP research, such as amplitude, SNR, CCA coefficient, and CCA SNR, are vulnerable to different experimental conditions. Therefore, applying these indicators to clinical examination needs careful consideration and large sample data verification. In further research, we will improve the robustness of BCI indicators by introducing and improving paradigms and algorithms.

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