Binocular interaction of visually evoked cortical potentials elicited by dichoptic binocular stimulation

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To analyze the interaction of cortical potentials elicited by dichoptic stimulation of the dominant and fellow eyes at different frequencies, a pair of programmed power supply units were used to drive a light emitting diode (LED) mounted in the right and left eyes of light-proof goggles to elicit the visually evoked cortical responses (VECPs). The right eye was stimulated at 11.5 Hz and the left eye at 11.0 Hz. Then the stimulation was repeated with the frequency of stimulation switched to the other eyes. The stimulus duration was 5 ms. The sampling rate was 1.0 Hz, and the duration of collection was 200 ms. The VECP of each eye was extracted separately. Individual VECPs could be recorded separately after simultaneous dichoptic stimulation of each eye. The amplitudes of the VECPs were not significantly different after stimulating the dominant eye and the fellow eye separately. The implicit times of negative peak (N-2) and the second positive peak (P-2) were shorter after stimulation of the dominant eye than after stimulation of the fellow eye, but the difference was not significant. However, the implicit time of N-2 elicited by stimulating the dominant eye was significantly shorter when the stimulation rate was 11.5 Hz. The VECPs elicited by stimulating the two eyes can be recorded separately by simultaneous dichoptic stimulation. Dichoptic simultaneous stimulation required a shorter time and may be a more sensitive method of analyzing binocular interactions compared to the classic VECPs using monocular stimulation.

Introduction

The processing of visually evoked cortical responses (VECPs) elicited by stimulating the two eyes has been studied extensively both psychophysically and electrophysiologically in normal humans (Apkarian, Nakayama, & Tyler, 1981; Brown & Norcia, 1997; Lansing, 1964; Lehmann & Fender, 1967; Odom &

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Chao, 1995; Spekreijse, van der Tweel, & Regan, 1972) and patients (Lennerstrand, 1978; Levi & Manny, 1982; Mizota, Hoshino, Adachi-Usami, & Fijimoto, 2004). VECPs have been used to evaluate these signals objectively. The VECPs elicited by monocular stimulation have been compared to those elicited by binocular stimulation, and in general, the binocular VECPs were significantly larger than those elicited by monocular stimulation. However, the degree of interocular interaction varied considerably in the different studies because the methods used had inherent problems. First, the recordings from the two eyes were performed at different sessions, which can alter the responses because of changes in the subjects and environment. Second, two recording sessions were necessary to compare the responses from the two eyes, and the vigilance, awareness, and psychological status might not change for one subject but change for another. Some of the previous studies overcame these two issues using dichoptic stimuli, but their methods were difficult to generalize, too complicated to be used in the clinic, and required relative long recording times. To overcome these disadvantages, we have developed lightproof goggles that can be used to stimulate the two eyes separately. It has enabled us to simultaneous record VEPs elicited by different frequency for each eye in a very short time.

Thus, the aim of this study was to determine whether it was possible to identify the responses elicited from each eye when both eyes were stimulated with our goggle-stimulating system. By stimulating the two eyes at different frequencies, and triggering the collection of cortical potentials by the trigger pulse to each LED, we were able to record the responses elicited from each eye separately.

In addition, we compared the responses elicited from the dominant to those from the nondominant eyes.

Subjects and methods

Subjects

Twenty-five volunteers consisting of nine men and 16 women were tested. The mean age of the volunteers was 22 ± 3 years (± standard deviation) with a range of 21–24 years. None of the subjects had any ocular diseases except for refractive errors, and their best-corrected visual acuity (BCVA) was 20/20 in both eyes. The stereoacuity of all was less than 10.0″ with the Titmus test.

The procedures used conformed to the tenets of the Declaration of Helsinki, and they were approved by the Institutional Review Board of Teikyo University. An informed consent was obtained from all of the subjects after an explanation of the purpose, procedures to be used, and possible complications of the procedure.

Methods

Simultaneous and separate stimulation of two eyes

Dichoptic uniform white field stimulation was done by two high-intensity white light emitting diodes (LXHK-LW3C; Luxeon Star, Quadica Developments Inc., Ontario, Canada). One LED was incorporated into the right and another into the left frame of our specially designed goggles (Figure 1). The LEDs were covered with a diffuser plate to allow uniform stimulation of the eye. The size of the diffuser plate for each eye was 2.5 × 3.5 cm, and the vertical and horizontal angles subtended at the cornea were 90° and 100°, respectively.

The advantage of this type of stimulus is that it is not influenced by inaccurate accommodation, fixation, vergence, or the visual acuity of the subjects. The luminance of the LEDs was modulated rectangularly with the maximum luminace of 1000 cd/m^2. The duration of the pulses was 5 ms. The luminance was measured with a spot photometer (BM-8, Topcon, Tokyo, Japan), and the power supply was adjusted so that each LEDs delivered identical intensities and durations to the two eyes. The modulation and temporal parameters of the stimuli were controlled by a pair of programmable DC power supplies (PBX 40-2.5 Bipolar Power Supply, Kikusui Electronics Corp., Yokohama, Japan). The same pulses that triggered the LEDs also triggered the VECP data acquisition computer. With these goggles, flash stimuli were given to one eye at 11.0 Hz and to the fellow eye at 11.5 Hz. The stimuli were delivered to each eye to elicit responses of the visual cortex from the two eyes separately (Figure 1).

Recording VEPs elicited from stimulating two eyes individually

The subjects were preadapted to the room lighting before beginning the recordings, and then they were instructed to try not to blink during the VECP recordings. First, the left eye was covered by an eye patch under the goggles, and the VECPs elicited by stimulating the right eye at 11.5 Hz were recorded. Second, the right eye was covered by an eye patch, the VECPs elicited by stimulating the left eye at 11.0 Hz were recorded. And third, the VECPs elicited by dichoptic stimulation of the right eye at 11.5 Hz and left eye at 11.0 Hz were recorded.

The recording electrode was placed on the inion (Oz), and the reference electrode was placed at Fz. The ground electrode was placed on the right earlobe. Signals were amplified 4,000 times (Synafit 2100, GE Yokogawa,

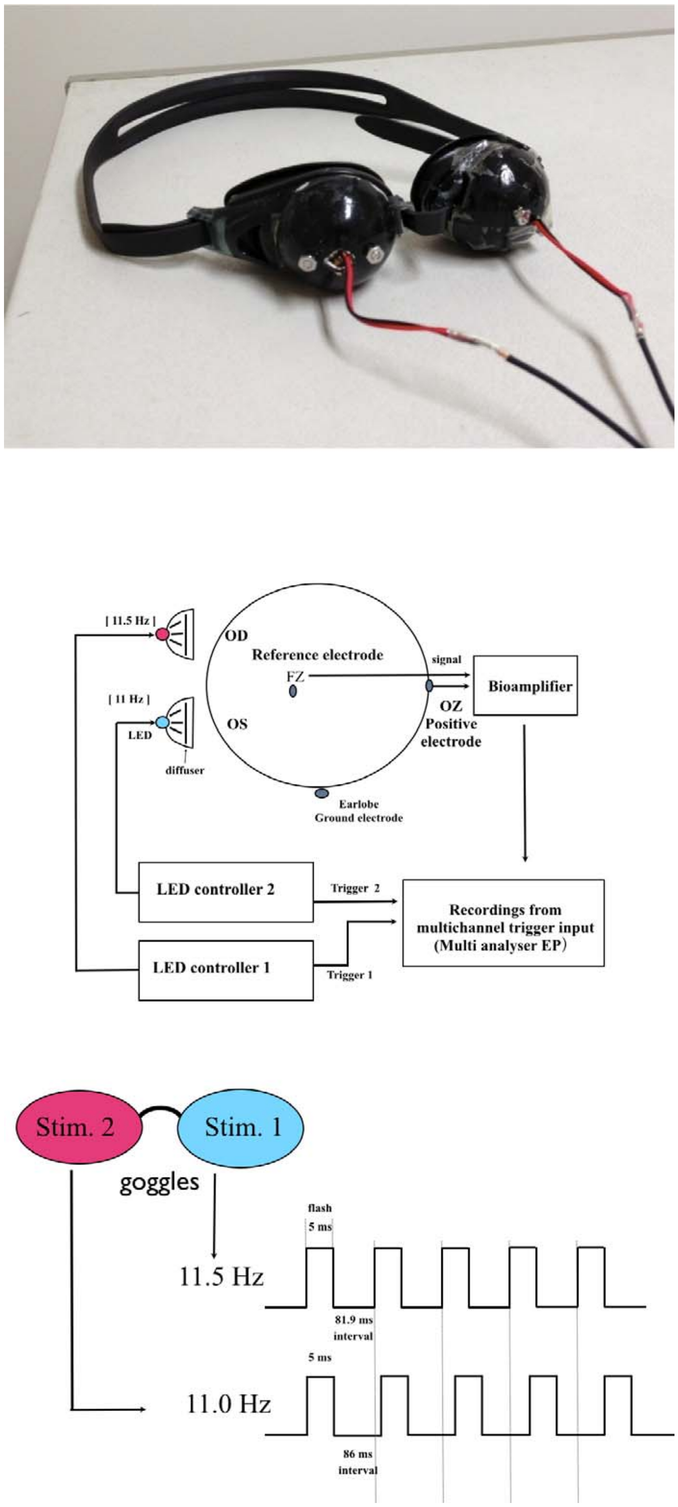


Figure 1. Schematic diagram of the VECP recording system. VECPs were elicited by dichoptic stimulation of the two eyes with lightproof goggles. Top: Photograph of the lightproof goggles. Middle: Dichoptic uniform field stimuli were delivered to the two eyes using a pair of LEDs, which were mounted in the goggles. An LED was placed in the right and left frames of lightproof goggles. Modulation and temporal parameters of the stimulus were controlled by a pair of programmable power supplies that triggered the LEDs and VEP data acquisition computer. Bottom: The flash stimulation with different frequencies, i.e., 11.5 Hz to the right eye and 11.0 Hz to the left eye. The stimuli were simultaneously delivered to the two eyes to elicit responses from the two eyes separately. Note that the colors in the illustration are only used to label right and left eye. They are not color filters.

Tokyo, Japan), and the responses were band-pass filtered from 1.0 to 100 Hz. The sampling rate was 1.0 kHz, and the recording time was 200 ms. One hundred twenty-eight responses were averaged. The recordings were performed at least twice to determine the repeatability. Because the recordings were performed until 128 acceptable recordings were collected, it took approximately 1 min for one session. In addition, the measurements for each subject were performed twice within one week to determine the inter-measurement variability.

The amplitude of the VEPs was measured from the trough of the N2 wave to the following positive P2 peak. The implicit times were measured from the start of the flash stimuli to the peak of N2 and the peak of P2. All of the amplitudes and implicit times were collected and measured by computer software (Multi Analyser EP, MTS, Tokyo). All of the results are expressed as means ± standard deviation (SDs).

Determination of dominant and nondominant eye

The dominant eye was determined by the Dolman method (Dolman, 1920). In brief, the subject was given a card with a small hole in the middle and instructed to hold it with both hands. The subject was then instructed to view a distant object through the hole with both eyes open. The subject then alternated closing one eye and reported which eye was viewing the object. Alternatively, the subject slowly pulled the card back to the face while keeping the object in view, and whichever eye was viewing the object was the dominant eye (Cheng, Yen, Lin, Hsia, & Hsu, 2004).

Results

Recordings of VECPs following monocular and dichoptic stimulation

The VECPs recorded following monocular and dichoptic stimulation indicated that the individual VECPs could be recorded separately following the dichoptic stimulation (Figure 2). When the VECPs elicited by monocular stimulation of the right and left eyes were compared, no significant differences were found in the amplitude and the implicit times of N2 and

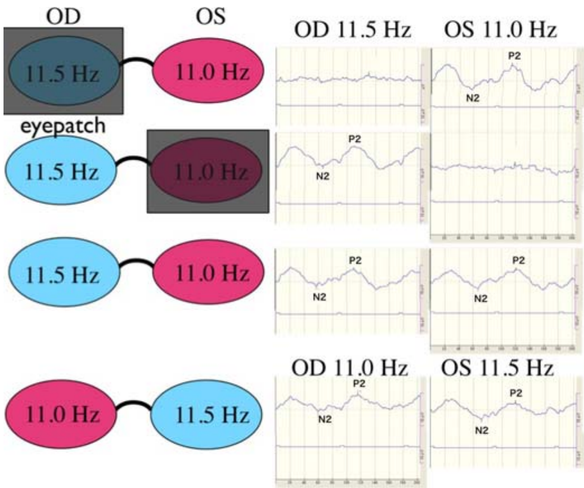
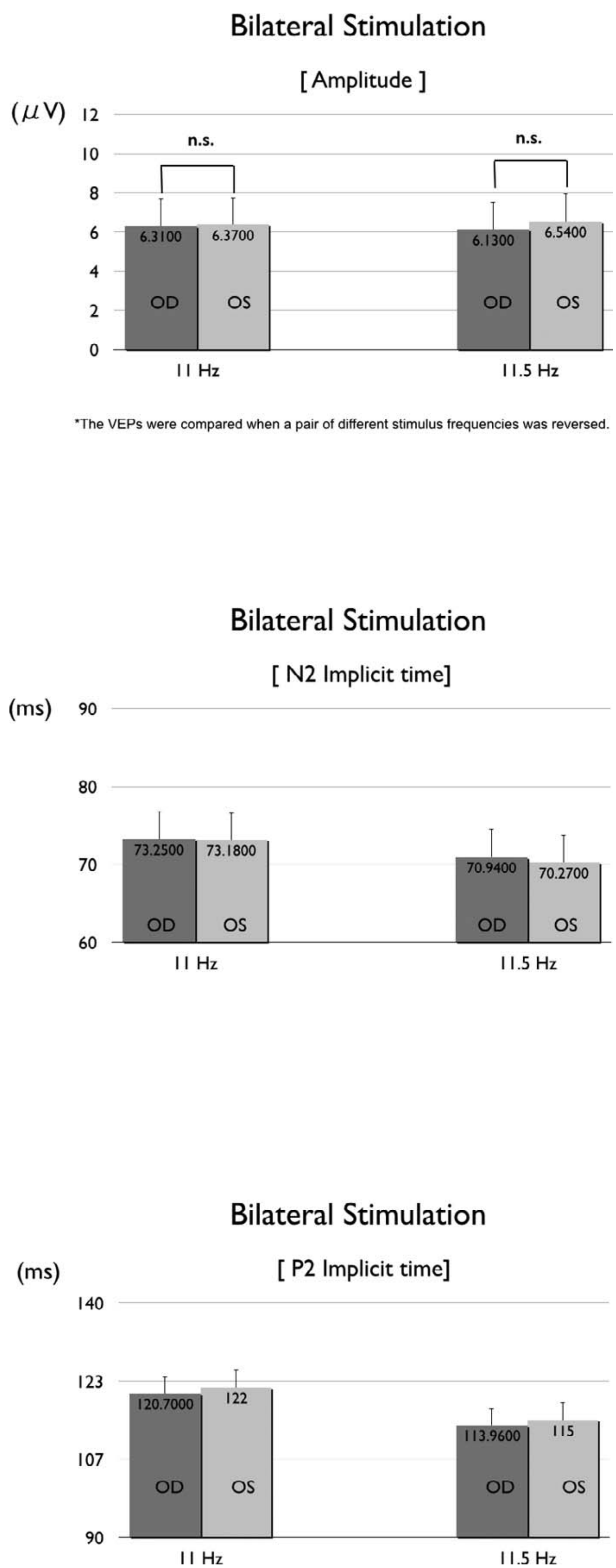


Figure 2. Representative VECPs recorded after monocular and binocular stimulation of the right and left eye. First and second rows: When one eye was covered with an eye patch, and the monocular stimulation as a conventional way elicited flash VECPs while nonstimulated fellow eye showed noise level in the VECP. The third and fourth rows: The individual VECP could be recorded separately following dichoptic simultaneous stimuli; 11.5 Hz to the right eye and 11.0 Hz to the left eye in the third row and vice versa for the fourth row.



P2. When the VECPs recorded by dichoptic stimulation were compared, again no significant differences were found between the right and left eyes in the amplitudes and implicit times of N2 and P2 (Figure 3).

Comparison of VECPs elicited by monocular stimulation of dominant and nondominant eyes

The right eye was dominant in 15 subjects and the left eye in 10 subjects. When the VECPs recorded after monocular stimulation of the dominant or nondominant eyes were compared, the implicit times of the N2 and P2 of the dominant eye were shorter than those of the nondominant eye, but the differences were not significant (Figure 4). When the VECPs were elicited by dichoptic stimulation, the implicit times of the N2 and P2 of the dominant eye were shorter than those of nondominant eye but the differences were also not significant (Figure 4). However, the implicit time of N2 was significantly shorter when flash stimuli were delivered at 11.5 Hz to the dominant eye than that of the nondominant eye (Figure 4).

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Figure 3. Comparisons of the VECPs recorded after monocular and binocular stimulation of the right and left eyes. No significant differences were found in the amplitudes and in the implicit times of the N2 and P2 between the right and left eyes.

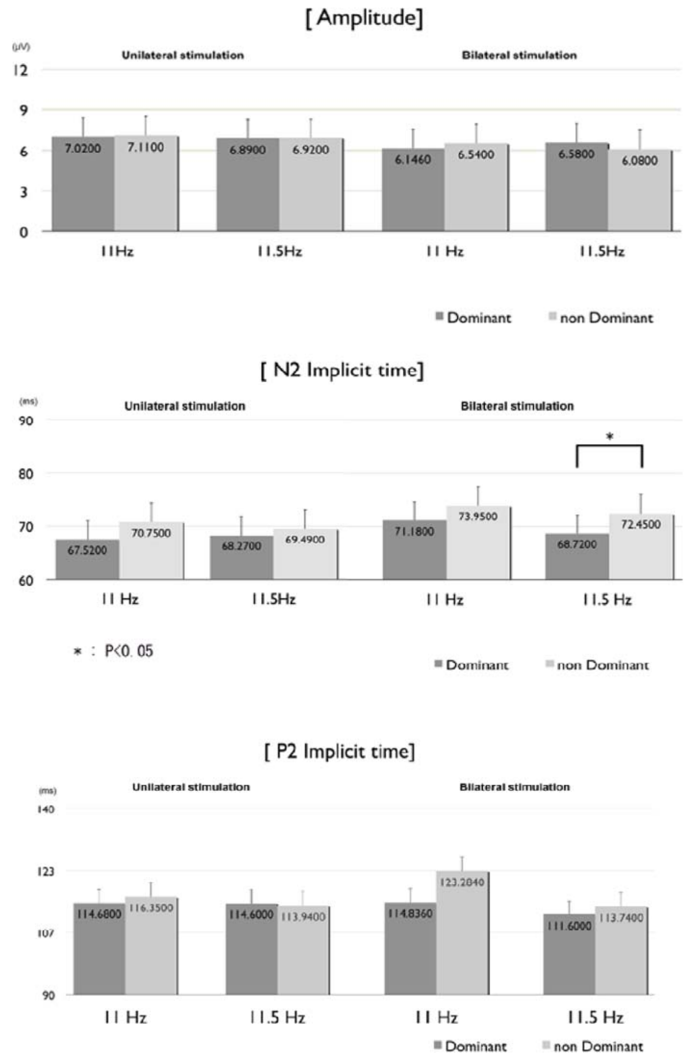

Figure 4. Comparisons of VECPs recorded after monocular and binocular stimuli between dominant and nondominant eyes Top: N2-P2 amplitude. Middle: N2 implicit time. Bottom: P2 implicit time. Left two columns: Comparisons of VECPs recorded after monocular stimuli between dominant and nondominant eyes. The implicit times of the N2 and P2 elicited by stimulation of the dominant eye are shorter than those elicited by stimulation of the nondominant eye but the difference was not significant. Right two columns: Comparisons of VECPs recorded after binocular stimuli between dominant and nondominant eyes. In general, there was a tendency for the implicit times of N2 and P2 of the dominant eye to be shorter than those of the nondominant eye. The N2 implicit time was significantly shorter when flash stimuli were delivered at 11.5 Hz frequency rate in the dominant eye than that in the nondominant eye. The error bars are the standard deviation.

Comparison of VECPs elicited by monocular and dichoptic stimulation

The mean amplitudes for the N2-P2 was smaller and the peak times of N2 and P2 were longer with dichoptic stimulation except the implicit time of the P2 elicited by 11.5 Hz stimulation. But the difference was not statistically significant for each comparison (Figure 4).

Discussion

Sherrington (1904) compared the threshold frequency when repetitive flashes were presented simultaneously to both eyes to that when the flashes were presented alternately to the two eyes. He used this method to study the interactions of the monocular signals in the human brain. The main conclusion he made was that there was little binocular interaction for square wave flicker because thresholds for in-phase and 180° out-of-phase flicker were approximately the same. His psychophysical work was explored extensively by others (Cavonius, 1979; Odom & Chao, 1995; van der Tweel, Spekreijse, & Regan, 1970), who noted dichoptic phase differences in flicker (van der Tweel, Spekreijse, & Regan, 1970) and concluded that the observations were attributable to time differences in visual subsystems (Cavonius, 1979; Odom & Chao, 1995). Like their works, more refined, systems analysis approaches have been used to try to understand the nature of binocular interactions. Stereopsis and motion perception have been studied by examining the binocular interactions of the VECPs (Jeffreys, 1996; Lankheet & Lennie, 1996; Livingstone, 1996). Several investigators have reported that the amplitude of the monocular VECPs decreases when the contralateral eye is steadily illuminated or when the image in the fellow eyes moves on the retina (Lehmann & Fender, 1967; Lennerstrand, 1978; Sato, Taniai, Mizota, & Adachi-Usami, 2002; Spekreijse, van der Tweel & Regan, 1972). This decrease has been termed interocular suppression, and the degree of suppression increased as the complexity, e.g., luminance, frequency, checker pattern size, of the contralateral stimulus increased.

Different types of binocular interactions, such as facilitation (McKerral et al., 1995; Shimoyama et al., 1998), summation (Bearse & Freeman, 1994; Geer & Spafford, 1994; Shimoyama et al., 1998; Sutija, Ficarra, Paley, Zhang, & Solan, 1990; Tobimatsu & Kato, 1996; White & Bonelli, 1970), and suppression (Eysteinsson, Barns, Denny, & Frumkes, 1993; Heravian-Shandiz, Douthwaite, & Jenkins, 1992) have been studied. Generally, stationary or pattern-reversal stimuli (Jakobsson & Lennerstrand, 1985; Johansson & Jakobsson, 1993, 2000; Mizota et al., 2004; Sato et al., 2002; Schmeisser & Dawson, 1982; Spekreijse, van der Tweel, & Regan, 1972; Wijeakumar, Shahani, McCulloch, & Simpson, 2012; Zemon & Ratliff, 1982) have been used, and studies using VECPs elicited by transient flashes

Study	Stimulus: Type	Stimulus: Delivering instrument	Stimulus: Profile	Active electrode
Lennerstrand (1978)	checkerboard pattern	transparent screen	bilaterally different reversal rate pattern 10R/7L (Hz)	2.5–3 cm cranial to the inion
Levi and Manny (1982)	**luminance***	monitor (Tektronix 608 with P45 Phosphor)	PRBS	not clear
Baitch and Levi (1988)	**luminance***	a pair of LED goggles	**bilaterally different frequency*** 6R/8L, 12R/14L, 18R/20L (Hz)	O1, O2, Oz, and Pz
Odom and Chao (1995)	**luminance***	a pair of LED goggles	bilaterally different phase	2.5 cm above the inion
Sato et al. (2002)	**luminance***	**LEDs integrated in the lightproof goggles***	PRBS	**Oz***
Current study	luminance*	LEDs integrated in the lightproof goggles*	bilaterally different frequency* 11.0 and 11.5 Hz	Oz*

Table 1. Previous studies on binocular interaction with visually evoked cortical potentials elicited by dichoptic binocular stimulation. *Notes*: VER: visual evoked responses; PRBS: pseudorandom binary sequence; LED: light emitting diode; P110: major positive peak at 110 ms; N2: second negative peak of steady state flash VEP; P2: second positive peak of steady state flash VEP. *Note that the common points with the current study set in bold text are limited. #The data were fit by a model that had two binocular pathways, one that summed monocular nonlinear elements and a second that had a nonlinearity following the combination of monocular linear elements.

are rare (Regan, 1976; Shimoyama et al., 1998). However, most stimuli in daily life are transient.

Because there are substantial variations in the VECP amplitudes when elicited monocularly from an eye (Srebro, 1978), it is not suitable for the assessment of binocular interactions. In routine flash VECP recordings, the responses elicited from the two eyes are recorded separately because it has been thought that there is no other way to identify the responses from both eyes separately. Our method of using dichoptic stimuli with LED goggles enabled us to analyze binocular vision in one recording session and was suitable for studying binocular interactions in humans. Comparison of the present study and several previous studies on binocular interaction with visually evoked cortical potentials elicited by dichoptic binocular stimulation are presented in Table 1.

Our results showed that although the VECPs elicited by stimulating the dominant eye had shorter implicit times than that of the nondominant eye; however, the differences were not significant. But the implicit time of N2 was significantly shorter when the VECPs were elicited by stimulating the dominant eye than in nondominant eye. We suggest that the difference is because simultaneous stimulation simulates the ordinary binocular interactions more exactly. It has been reported that the dominant eye activates a larger area of the primary visual cortex than the nondominant eye from the functional MRI findings (Rombouts, Barkhof, Sprenger, Valk, & Scheltens, 1996). Our results did not show any differences in the amplitudes of N2 and P2 elicited by stimulation of the dominant and nondominant eyes. But a shorter implicit time in the response from the dominant eye following either monocular or binocular stimulation is in good accordance with the earlier findings.

Sato, Taniai, Mizota, and Adachi-Usami (2002) reported on another way to investigate binocular interactions in normal subjects by using multi-input stimuli with pseudorandom binary sequence (PRBS). They applied the PRBS method to temporally modulate dichoptic flash stimuli, and developed a stimulating

Subject	Analysis procedure	Interested parameter	Findings
stereoblind case	**raw wave analysis***	**amplitude***	The VER of each eye to binocular stimulation were reduced to half or less of the monocular value in normal subjects. The response of the sominant eye was the same for monocular and binocular stimulation in stereoblind subjects.
amblyopia	Fourier analysis	temporal frequency	reduced S/N ratio in midtemporal frequency range in a severe amblyopic eye
stereoblind case	Fourier analysis	temporal tuning of a 2 Hz beat response	reduction of nonlinear components in the stereoblind subject
volunteers with normal vision*	standardized first and second harmonic waves	relative amplitudes as a function of interocular phase difference#	The pathway that summed nonlinear monocular elements and the pathway that combined monocular linear elements prior to a binocular nonlinear element were identified with the magnocellular and parvocellular pathways, respectively.
volunteers with normal vision*	**raw wave analysis***	**implicit times of P110***	When two eyes were bilaterally exposed to two PRBS stimuli of the same luminosity, the P110 amplitudes of both eyes were decreased by the same amount from that obtained by stimulating only one eye.
dominant and nondominant eyes	raw wave analysis*	amplitude and implicit times	Significant difference between dominant and nondominant eyes in an implicit time of N2 and P2.

Table 1. Extended.

system for simultaneous recording the VECPs elicited from the two eyes. They did not investigate whether there is a difference between dominant and nondominant eye. Although they showed clear cortical responses resembling standard VECPs, further investigations are needed to determine whether the VECPs are comparable to and can be interpreted as standard VECPs.

Our study has several limitations. Simultaneous but separate stimulation of the two eyes may not be suitable for detecting binocular interactions. A larger sample size may detect significant difference between dominant and nondominant eyes. But our results showed the feasibility in recording VECPs simultaneously elicited by different dichoptic stimulation rates.

In conclusion, binocular interactions were found in the VECPs elicited by LEDs following dichopitic flash stimuli. Our system has the advantage of lessening the variations in the VECPs caused by recording eyes separately. In addition, a much shorter time is needed to record the VECPs from the two eyes by our system than the conventional transient flash VECP method. Therefore, our system can be useful, practical, and time saving when applied to patients.

Keywords: binocular interaction, visually evoked cortical potential, dominant eye, hole in card test

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