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Simultaneous recording of multifocal VEP responses to short-wavelength and achromatic stimuli

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Abstract

A paradigm is introduced that allows for simultaneous recording of the pattern-onset multifocal visual evoked potentials (mfVEP) to both short-wavelength (SW) and achromatic (A) stimuli. There were 5 sets of stimulus conditions, each of which is defined by two semi-concurrently presented stimuli, A64/SW (a 64% contrast achromatic stimulus and a short-wavelength stimulus), A64/A8 (64% achromatic/8% achromatic), A0/A8 (0% (gray) achromatic/8% achromatic), A64/A0 and A0/SW. When paired with A64 as part of A64/SW, the SW stimulus yielded mfVEP responses (SWmfVEP) with diminished amplitude in the fovea, consistent with the known sensitivity of the S-cone system. In addition, when A8, which is approximately equal to the L and M cone contribution of the SW stimulus, was recorded alone, the response to A8 was small, but significantly larger than noise. However, when A8 was paired with A64, the response to A8 was reduced to close to noise level, suggesting that the LM cone contribution of the SWmfVEP can be suppressed by A64. When A64 was recorded alone, the response to A64 was about 32% larger than the mfVEP for A64 when paired with the SW. Likewise, the presence of A64 stimulus also reduces the response of SWmfVEP by 35%. Finally, an intense narrow-band yellow background prolonged the latency of SW response for the A0/SW stimulus but not the latency of SW response for the A64/SW stimulus. These results indicate that it is possible to simultaneously record an SWmfVEP with little LM cone contribution along with an achromatic mfVEP.

Keywords

Multifocal VEP; Short wavelength; S-cone; Achromatic

Introduction

It has been proposed that the sensitivity of the short-wavelength (SW) pathway, driven by the short-wavelength (S) cones, may be more sensitive detecting glaucomatous visual defect [5,19]. However, there are several obstacles for using SW paradigms in the clinic. First, the SW automatic perimetry (SWAP) test, the most commonly used test for measuring the function of SW pathway, is more difficult and lengthy than the traditional achromatic static automatic perimetry (SAP) [5]. Second, the SWAP test has been shown to have a poorer test-re-test reliability than the SAP [17]. In addition, learning effects can affect the reliability of the SWAP test [26,31].

The multifocal visual evoked potential (mfVEP) is an objective test of visual function that provides topographical information about local field defects [3,9,11,21]. There is little or no learning effect involved. In addition, the achromatic mfVEP studies have reported sensitivities similar or superior to those for SAP in detecting glaucoma [7]. Therefore, the mfVEP may provide an alternative way to measure the function of the SW pathway. A recent study reported that the blue-yellow mfVEP is more sensitive than the standard achromatic mfVEP for detecting glaucomatous defects [2,20]. Here, we introduce a paradigm for simultaneously recording SW and achromatic mfVEPs. While the presence of the high-contrast achromatic stimulus reduces the LM contamination in the SWmfVEP, it also allows a comparison between the SWmfVEP and achromatic mfVEP.

Methods

Display, conditions and experiments

The spatial characteristic of the stimuli was identical to the 60-sector dartboard mfVEP display provided by VERIS system, which we have used in the past [12,14]. It was 44.5° in diameter and consists of 60 sectors. Each sector contains 16 checks. The size of the individual stimulus sectors, as well as the size of individual checks, was scaled with eccentricity according to a cortical magnification factor [3].

The mean luminance of the achromatic stimulus was 62 cd/m². The maximum intensity for R, G and B guns was 25, 81 and 12 cd/m², respectively. The Michelson contrast of the high-contrast achromatic stimulus was 64%. Increasing contrast beyond 64% does not increase amplitude. In fact, the amplitude can even decrease in some individuals [15].

There were five stimulation conditions. In condition 1 (A64/SW), the 64% achromatic stimulus, which is a pair of colors defined by the relative brightness of the RGB guns: [0.82 0.82 0.82] vs. [0.18 0.18 0.18], was presented with the SW stimulus, which is a pair of colors [0.5 0.5 0] vs. [0.5 0.5 1], where 1 indicates maximum intensity and 0.5 indicates half of the maximum. The color of the background is [0.5 0.5 0.5] or a gray color of 62 cd/m².

Figure 1 illustrates the display when the A64 (left) and SW (right) stimuli appeared. The mfVEPs obtained for this condition are referred to as A64mfVEP and SWmfVEP. In condition 2 (A64/A8), the 64% achromatic stimulus was presented with an 8% achromatic stimulus. The mfVEP response to the 8% achromatic stimulus is referred to as A8mfVEP. In condition 3 (A0/A8), the 8% achromatic stimulus was presented with A0, that is, a blank

gray screen. In condition 4 (A64/A0), the 64% achromatic stimulus was presented with A0. In condition 5 (A0/SW), the SW stimulus was presented with A0.

Three experiments were conducted on separate days. In experiment 1, monocular recording was made twice from both the left eye and right eye, separately, using condition 1. In experiment 2, monocular recording was obtained twice from the dominant eye using conditions 1 to 4. In experiment 3, monocular recording was obtained twice from both the left eye and right eye using conditions 1 and 5. In addition, in experiment 3, the recording was done both with an 80 cd/m² yellow (590 ± 12 nm light-emitting diode (LED)) background (Y80) and without the background (Y0). The intensity of Y80 is similar to that used in the SWAP test. Figure 2 shows the apparatus for applying the Y80, which was superimposed on the stimulus patterns through a 45° semi-transparent mirror. Figure 3 shows the spectra of Y80 (yellow) and cone absorptions (red, green and blue). Since 80 cd/m is greater than the mean luminance of the monitor, it reduced contrast of the LM contrast in the stimulus by at least 50%.

Cone contrast of the stimuli

Although the blue gun of a CRT monitor mainly stimulates the S cones, it also stimulates the L and M cones. Notice that the blue gun's spectrum (cyan in Fig. 3) overlaps with the absorption spectra of L and M cones (red and green in Fig. 3).

The cone excitation contrast to the SW stimulus was determined by converting the CIE chromaticity of the phosphors to cone excitations [29] [33]. The cone contrast to the SW stimulus for the L, M and S cone excitations is 4.8, 8.7 and 86.5%, respectively. Therefore, the SW stimulus introduces a small L and M cone contribution. This contribution is approximated by the A8 stimulus, which has 8% contrast for all cone types.

Multifocal VEP paradigm and temporal parameters

The stimuli were modulated with m-sequences of 1024 steps. The screen refresh rate was 75 Hz or 13.33 ms/frame. Each location and each color were modulated by one of the 120 independent m-sequences. At any frame, either the SW or the achromatic stimuli were presented. The principle behind our approach is almost identical to that previously employed for recording the dichoptic mfVEPs [1,18]. Spatially adjacent stimuli were never presented at the same time, and the minimum temporal interval between adjacent stimuli was 4 screen frames or 53.2 ms. This sparse stimulation approach has been shown to provide mfVEP with high signal to noise ratio [1,18]. For any given sector of the display, the minimum interval between same color stimuli was 16 frames (213 ms). The minimum interval between different colors for a location was 8 frames (106 ms). The duration of the 64% achromatic stimulus was 2 frames (26.6 ms), while the duration of both the SW and 8% achromatic stimuli was 3 frames (40 ms). Each run lasted for 3.6 min. Because during every m-sequence step, or 213 ms, the stimulus only appears with a 50% probability, the effective temporal frequency of a stimulus is about 2.5 Hz.

Recording and data analysis

The mfVEP stimulus presentation and data analysis were performed with custom C++ and MATLAB (MathWorks, Inc, MA) programs. The electrodes that comprised the midline channel were placed at the inion and 4 cm above the inion (active) with a forehead electrode serving as the ground. Additional active electrodes were placed at 4 cm lateral (left or right) to the midline and 1 cm above the inion. The midline active electrode and the two lateral active electrodes were referenced to the inion electrode and created three recording channels. The positions of the active electrodes were based on anatomical considerations and chosen for optimizing mfVEP recording. The mfVEP from the best channels were

analyzed further [13]. The best channel for each location was determined with the average of both the achromatic VEP and SWmfVEP.

The continuous VEP record was amplified with the high- and low-frequency cutoffs set at 3 and 100 Hz (Grass PreAmplifier P511 J, Quincy, MA). The mfVEP responses were further filtered offline with the high- and low-frequency cutoffs set at 3 to 35 Hz using a fast Fourier transformation.

Principal component analysis (PCA)

Multifocal VEP yields 60 local responses. To combine data from different locations and different subjects, we used PCA. Note it is not possible to average mfVEP because both the polarity and the waveform of local responses vary across locations and subjects. The first principal component (PC1) [34] can serve as such an average. This PCA approach assumes that the SWmfVEP and the A64mfVEP for each individual subject originate at the same cortical source. Previous work suggests that the main source of the mfVEP is the primary visual cortex (V1) [34]. V1 has a retinotopic mapping organization [28], i.e., adjacent neurons in V1 have receptive fields that include adjacent portions of the visual field, in an orderly fashion [16]. In other words, the cortical source of the mfVEP is mainly related to the retinal location, not the chromaticity of the stimulus. The cortical source difference between achromatic and chromatic VEP seen in the traditional transient VEP response may be due to the involvement of extra-striate sources.

Subjects

The 6 subjects had normal vision corrected to 20/20, and they ranged in age from 19 to 45. Informed consent was obtained from all subjects before their participation. Procedures adhered to the tenets of the Declaration of Helsinki, and the protocol was approved by the committee of the Institutional Board of Research Associates of Columbia University.

Results

The (A64/SW) condition yields robust achromatic and SWmfVEPs

The (A64/SW) condition yielded robust responses to both the A64mfVEP and SWmfVEP stimuli. Figure 4 shows the mfVEP for one subject. In both panels, blue and red traces present data for the right and left eyes, respectively. In general, the SWmfVEP (lower panel) has approximately the same amplitude as the A64mfVEP (upper panel), except for the center ring. Figure 4 also shows that both the polarity and the shape of the waveforms are similar for both A64mfVEP and SWmfVEP, suggesting that they originated from a similar cortical source. To compare the A64mfVEP to the SWmfVEP, Fig. 5 shows the mfVEPs for three center rings for each subject, after averaging the data for the two eyes. For the rings 4, 5 and 6, not shown in Fig. 5, the relation between the SNR of SWmfVEP and that of A64mfVEP was similar to rings 2 and 3. Figure 6 shows the histograms of the difference in dB between the SNR of the SWmfVEP and that of the A64mfVEP for both the center ring (upper panel) and the other rings (lower panel) combined all the local responses of both eyes and for all the subjects. In the center ring, the SNR of the SWmfVEP is smaller than that of the A64mfVEP, while in the other rings, the difference in the SNR between SWmfVEP and A64mfVEP is distributed around 0.

The amplitude and the latency comparisons between the two mfVEPs are better illustrated in Fig. 7, which shows the PC1 of the mfVEP for each ring. These were obtained from all sectors in the ring, both eyes and all the subjects. Consistent with previous studies (e.g., [8,25,27]), the SWmfVEP (blue) traces are delayed compared to the A64mfVEP (black) traces. Note that in Figs. 5,6,7, the amplitudes of the SWmfVEP are smaller than those of

the A64mfVEP in the fovea, within 2.2° of visual angle. This result is consistent with the decreased effectiveness of SW light in the foveal center due to a high density of macular pigment that differentially absorbs SW light [30] and to the decreased ratio between the density of S cone and those of the L and M cones in the foveal center [4,10,24,32].

The L and M cone contribution to the SWmfVEP

As mentioned in the Methods section, the blue gun of a CRT monitor also activates LM cones. To assess this contribution to the SWmfVEP, we recorded mfVEP responses to an achromatic stimulus with a contrast of 8%. An achromatic contrast of 8% yields LM stimulation that is close to the LM cone contrast in the SWmfVEP. The average SNR of the A8mfVEP recorded with A64mfVEP was 0.04 dB (column 2B, the red line in the A64/A8 panel in Fig. 8), much smaller than 0.40 dB, the SNR of A8mfVEP (column 3B, the red line in the A0/A8 panel in Fig. 8) recorded without A64mfVEP. On the other hand, it is, only 0.27 dB or 7% larger than -0.23 , the SNR of the response to A0mfVEP (no stimulation, column 4B, the green line in A64/A0 panel), probably due to spatial and temporal inhibitory interactions [35]. Note that in our standard mfVEP analysis, the SNR criterion for a reliable mfVEP is 2.3 dB or 70% larger than noise. These results suggest that the L and M component in the SWmfVEP is small.

The effect of the SWmfVEP on the 64% chromatic mfVEP

The SNR of the A64mfVEP recorded to A64/SW (column 1A, the black line in the A64/SW panel of Fig. 8) was 3.26 dB or 32% smaller than the SNR of 4.16 (column 2A, the black line in the A64/A0 panel) when the A64mfVEP was recorded alone. That is, when simultaneously recorded with an SWmfVEP, the A64mfVEP is 32% smaller.

The effect of the A64 stimulus and the yellow background on the SWmfVEP

To further assess the LM component in the SWmfVEP, the SWmfVEP responses were obtained with both the A64/SW condition and the A0/SW condition and both with and without the presence of the Y80 background. Without the yellow background (Y0), the SWmfVEP recorded alone (Fig. 9, column 2B) has a larger SNR than that recorded with A64 stimulus (Fig. 9, column 1B). In other words, obtaining A64mfVEP has a cost of 1.33 dB or 35% signal loss for the SWmfVEP. Comparing the left 4 columns (Y0) vs. the right 4 columns (Y80), yellow background reduces the SNR of mfVEP for all conditions.

Latency is also an important aspect of a VEP response because it is known that S cone response has a longer latency than LM cone response. The effects on latency can be visualized in the PC1 across all subjects in Figure 10. The black lines and black bar of Fig. 10 show that the yellow background prolonged the latency of A64mfVEP as expected because Y80 reduces LM cone contrast of the stimulus. Y80 also prolongs the latency of the SWmfVEP in the A0/SW condition (cyan), indicating that there is a LM cone component in this response, consistent with the overlap of the spectrum of the blue phosphor with the LM cone absorption spectra. In contrast, Y80 does not significantly prolong the latency of SW in the A64/SW condition (blue). Note that the Y80 background reduces the amplitudes for all mfVEPs, presumably because it is intense enough to affect the pupil size and/or produce an inhibitory effect in the cortical level that affects all three cone types.

Discussion

A measure of pure SW pathway function requires the isolation of the contributions of the LM cone system. Ideally, one could obtain a pure SW pathway function using the S-cone-isolated stimulation color pair [6]. Previous research in color vision has shown that the optimal stimulus for isolating a chromatic pathway is an isoluminant sinusoidal grating

stimulus of low-contrast and low temporal frequency with aberration correction [23]. Determining the color for an S-cone-isolated stimulus for each individual is possible but takes time, as well as techniques not universally available in the clinic. In addition, the sinusoidal stimulus does not elicit a robust signal for clinical applications. In this study, we combined two methods to obtain a relatively pure SW mfVEP. First, we set both the red and green gun of CRT at the half maximal intensity for both the yellow and blue colors. Thus, our SW stimulus is simple to produce and yet only contains a weak LM cone component. Second, we use a high-contrast achromatic stimulus to suppress the LM cone component in the SWmfVEP. Although it is difficult to achieve a perfect isolation of one chromatic pathway using a high-contrast checkerboard stimulus, the prolonged and delayed waveform and the attenuated fovea response suggest that the SWmfVEP mainly originates from the SW pathway. We cannot, of course, rule out the possibility that we have not completely isolated the S-cone response. Future work, including experiments with the silent substitution technique, should further test the degree to which isolation was obtained.

In both the behavior test (SWAP) and the full-field VEP [22], obtaining a SW response is achieved by superimposing a SW (blue) stimulus upon a bright yellow background that suppress the LM cone systems. However, this approach is not very feasible for a test based on a CRT display. In this study, we tested whether a yellow background can further remove the LM component in the SWmfVEP. The data show that the yellow background does not alter the latency of the SWmfVEP waveform, supporting our conclusion that there is little or no LM component in the SWmfVEP. It does, however, have the disadvantage of reducing all mfVEP responses and thus is not recommended.

In general, consistent results from multiple tests that target different mechanisms are more reliable for estimating losses in visual function. For example, Delgado et al. [5] compared four different visual field tests including SWAP, frequency doubling technology perimetry (FDT), high-pass resolution perimetry (HPRP) and motion automated perimetry (MAP). They found that the topographies of the visual field obtained from those visual field tests often are not perfectly correlated [5]. However, if, for a location, the visual functions measured with any two tests agree with each other, it is likely that the same result can be obtained with other tests. Our paradigm provides both SW and achromatic mfVEPs with one recording and, therefore, may be more powerful for detecting glaucomatous defects.

Conclusion

MfVEP responses to SW and 64% achromatic stimuli can be recorded simultaneously. The advantage of this paradigm is that the LM cone contribution to the SW stimulus is suppressed by the high-contrast achromatic mfVEP stimulus. This paradigm may provide a way to measure the function of the SW pathway, while simultaneously providing the more typical mfVEP response to an achromatic stimulus.

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Fig. 1.
Examples for the achromatic (*left*) and the SW (*right*) stimuli

Fig. 2.
The apparatus for superimposing the mfVEP stimuli on a yellow background

Fig. 3. Cone fundamentals and the emitting spectra (*red green, blue*) of *yellow* LED light (*yellow*) and blue gun of the CRT monitor (*cyan*). The y axis is the relative intensity

Fig. 4.

The best channel data for the A64mfVEP and the SWmfVEP of one subject. The *red* and *blue* traces present data from the *left* and *right* eyes, respectively. The total recording time for each eye is 7.5 min. *Both panels* have the same scales

Fig. 5.

The best channel data for A64mfVEP and SWmfVEP and for six subjects, averaged for both eyes. The *black* and *blue* traces present data of the A64mfVEP and SWmfVEP, respectively. The *numbers* represent the root mean square amplitude ratio between the A64mfVEP and SWmfVEP in dB units. For example, the value 3 means A64mfVEP is twice as large as the SWmfVEP and the value 0 means they have same amplitude

Fig. 6. The histogram of the SNR difference between SWmfVEP and A64mfVEP for the *center ring* (upper panel) and all periphery rings (lower panel). For a local mfVEP, the data with a SNR for A65 of <2.3 dB were excluded

Fig. 7.

The first principal components (PC1) for 6 rings obtained from both eyes and all the subjects. The *black* traces are the PC1 for the A64mfVEP and the *blue* ones for the SWmfVEP. The numbers in the parenthesis are the radii in visual angle for the rings. The latency differences are all negative, indicating that the A64mfVEP has shorter latency than the SWmfVEP. At the first ring, the SNR of SWmfVEP response is too low for an estimation of the latency

Fig. 8.

The summary of the results for experiment 2. The *upper panel* shows the average and the standard error of the signal to noise ratio (SNR) over the 60 locations. The SNR is in log units (dB). A value 0 dB means that the response (signal plus noise) is equal to the noise level, and a value 3 dB means that it is twice the amplitude of the noise. Each condition provides two sets of mfVEP data, which are presented in *two bars*. The *lower panel* shows the first principal components (PC1) obtained from all the location and all the subjects. The hatched shading groups the data for each condition together

Fig. 9.

The summary of the SNR results for experiment 3. The format is similar to Fig. 8

Fig. 10.

The latency change due to the presence of Y80 (*left panel*) and the first principal components (PC1) obtained from all the location and all the subjects (*right panel*). The *thick lines* present the mfVEP in the Y80 conditions while the *thin lines* present the mfVEP in the Y0 conditions