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Visual Evoked Potentials Elicited by Pseudorandom Stimulation from Patients with Macular Degeneration

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Purpose: To investigate the effect of a central scotoma on the amplitude, implicit time (IT), and temporal frequency characteristics (TFC) of the visual evoked potentials (VEPs) elicited by a pseudorandom binary sequence (PRBS) stimulus in age-related macular degeneration (AMD) patients.

Methods: Twenty-six patients with AMD, 17 eyes with visual acuity of less than 20/100, and 9 eyes with visual acuity between 20/70 and 20/25, were examined. Nine eyes of age-matched healthy volunteers served as controls. To elicit the PRBS-VEPs, one eye was stimulated with a PRBS stimulus. The first-order kernel was calculated from a cross-correlation between the PRBS and the VEPs. The Fourier transformed first-order kernel was used as the TFC of the visual system.

Results: The mean IT of P2 (second positive peak) of the first-order kernel was significantly delayed (t-test, $P < .05$), and the P2–N2 (peak-to-peak of P2 and second negative peak N2) amplitude was significantly reduced (t-test, $P < .01$) in eyes with AMD. A depression of the TFC values in the 6–18 Hz band was prominent in patients with AMD (t-test, $P < .01$).

Conclusion: PRBS-VEPs demonstrated a prolonged IT and reduced amplitude of the first-order kernel, and reduced TFC with a reduction of visual acuity in patients with macular degeneration. **Jpn J Ophthalmol 2002;46:108–113**

Key Words: Age-related macular degeneration, implicit time, pseudorandom binary sequence, temporal frequency characteristics, visual evoked potential.

Introduction

The temporal frequency characteristics (TFCs) of the human visual system can be obtained by psychophysical methods[1] and by visual evoked potentials (VEPs).[2] We have developed a VEP measurement technique using pseudorandom binary stimulation to elicit the VEPs, and have demonstrated the validity of the TFCs obtained by this technique.[3–5] These studies also demonstrated that this technique was relatively easy to perform and the data could be obtained in a significantly shorter time.

It is generally believed that a central scotoma affects the conventional VEPs significantly.[6] In this study, we recorded the VEPs in patients with age-related macular degeneration (AMD) to determine the influence of a central scotoma of retinal origin on the configuration of the first-order kernel of the pseudorandom binary sequence (PRBS)-VEP and on the derived TFC.

Materials and Methods

Twenty-four patients (26 eyes) with AMD were selected from patients in the outpatient clinic of the Tokyo Medical and Dental University Hospital. They were diagnosed with AMD by ophthalmos-

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copy and fluorescein angiography, and they had no other disease to reduce their visual acuity. Patients with AMD-related retinal changes such as subretinal hemorrhage were included, but patients with other causes of low visual acuity such as dense cataracts, pigmentary retinal dystrophy, or diabetic retinopathy were excluded.

The patients with AMD were classified into two groups by the corrected visual acuity: severe AMD, corrected visual acuity was less than 20/100; and mild AMD, corrected visual acuity was between 20/70 and 20/25 (Table 1). Nine healthy volunteers who were older than 50 years of age and who had no evident retinal disease served as normal controls. The corrected visual acuity of the healthy subjects was 20/20 or better.

The severe AMD group consisted of 13 men and 4 women, and their mean age and SD was 68.9 ± 7.1 years. The mild AMD group consisted of 8 men and 1 woman, and their mean age was 64.7 ±4.5 years. The AMD patients were also classified into two groups according to the diameter of the central scotoma (threshold size was 10°) as measured by Goldmann or Humphrey perimetry (30-2 program). All patients underwent a general ophthalmological examination.

This research conformed to the tenets of the World Medical Association Declaration of Helsinki. Informed consent was obtained from each patient after information on the purpose of the investigation was provided.

Light stimuli were obtained from a 3 × 5 array of red light-emitting diodes (LEDs) with a wavelength of 630 nm (SES107; NEC Medical Systems, Tokyo). The LEDs were mounted on light-proof goggles. The sequence of stimulation was controlled by a personal computer (PC9821NE, NEC, Tokyo), and the LEDs were driven by an electrical power source (NEC Medical Systems). The stimulus duration was 10 milliseconds, and the luminance was 370 cd/m^2. The contrast of the stimulus was 100%, ie, on and off. The light from the LEDs was diffused and made homogeneous by a white filter. The stimuli were delivered monocularly based on 4095 ($= 2^{12} - 1$) PRBS stimuli generated from a 12-bit shift register.

Bipolar VEP recordings were made between Oz (+) and Cz (−), with the right ear grounded. The evoked signals were amplified and band-filtered

Table 1. Measurements in Age-related Macular Degeneration

Class/Number	Age (y)	Sex	Eye	Corrected Visual Acuity	Diameter of Central Scotoma (Degree)	Reference
Severe						
1	65	Female	Right	20/2000	15	
2	72	Male	Right	20/2000	15	
3	79	Male	Right	20/2000	2	
4	70	Female	Right	20/1000	10	
5	78	Male	Left	20/1000	15	
6	68	Female	Right	20/500	5	
7	67	Male	Left	20/400	15	
8	73	Male	Right	20/400	3	
9	72	Male	Left	20/400	10	
10	71	Male	Right	20/290	20	
11	72	Male	Left	20/290	10	
12	69	Male	Right	20/200	8	
13	71	Female	Right	20/200	3	
14	73	Male	Right	20/200	5	
15	52	Male	Right	20/100	10	
16	52	Male	Left	20/100	10	Fellow eye of No. 15
17	67	Male	Right	20/100	5	Fellow eye of No. 7
Mild						
18	70	Female	Right	20/70	2	
19	73	Male	Left	20/70	5	
20	73	Male	Left	20/70	5	
21	63	Male	Right	20/50	0	
22	71	Male	Right	20/50	3	
23	71	Male	Right	20/50	5	
24	72	Male	Right	20/30	0	
25	56	Male	Right	20/25	0	
26	69	Male	Left	20/25	5	

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(1–100 Hz) by a bio-amplifier (MEG-1200, Nihon Koden, Tokyo) and fed to a personal computer (PC9821NE, NEC) through an A/D converter (ADXM-98A; Canopus, Kobe). The one-bit stimulus time was 10 milliseconds, and one sequence of 4095 bits was 40.95 seconds (10 milliseconds × 4095 bit). The VEPs were recorded three times independently and averaged.

An assumption was made that the human visual system is a nonlinear system. The input stimuli driven by a PRBS and the VEP output are shown as x(t) and y(t), respectively (Figure 1a) A cross-correlation function $\phi_{xy}(t)$ between PRBS (x[t]) and PRBS-VEP (y[t]) was calculated, and the first-order kernels were extracted from 1–500 milliseconds of the cross correlation function (Figure 1b). The temporal frequency characteristics (TFC) were then calculated by a Fourier transform of the first-order kernel (Figure 1c).[3–5]

The first-order kernel was obtained for each subject, and the implicit time (IT) and amplitude of the first-order kernel were measured. Two positive peaks and two negative peaks were found in each subject. We identified the positive peak around 90–120 milliseconds as P2, and then determined the next negative peak as N2. The IT of P2 and N2, and the amplitude of P2-N2 were measured (Figure 2) In the severe AMD group, some of the first-order kernels were of low amplitude, but we were able to differentiate the positive peak around 110 milliseconds as P2, and the following trough as N2. A definite peak was detected even in patients with severe AMD, because the stimulus covered the whole field and the responses originating from the peripheral visual field were recorded.

The TFCs were calculated as the power spectrum of the Fourier transform of the first-order kernel, and TFC magnitude was calculated at every 2 Hz.

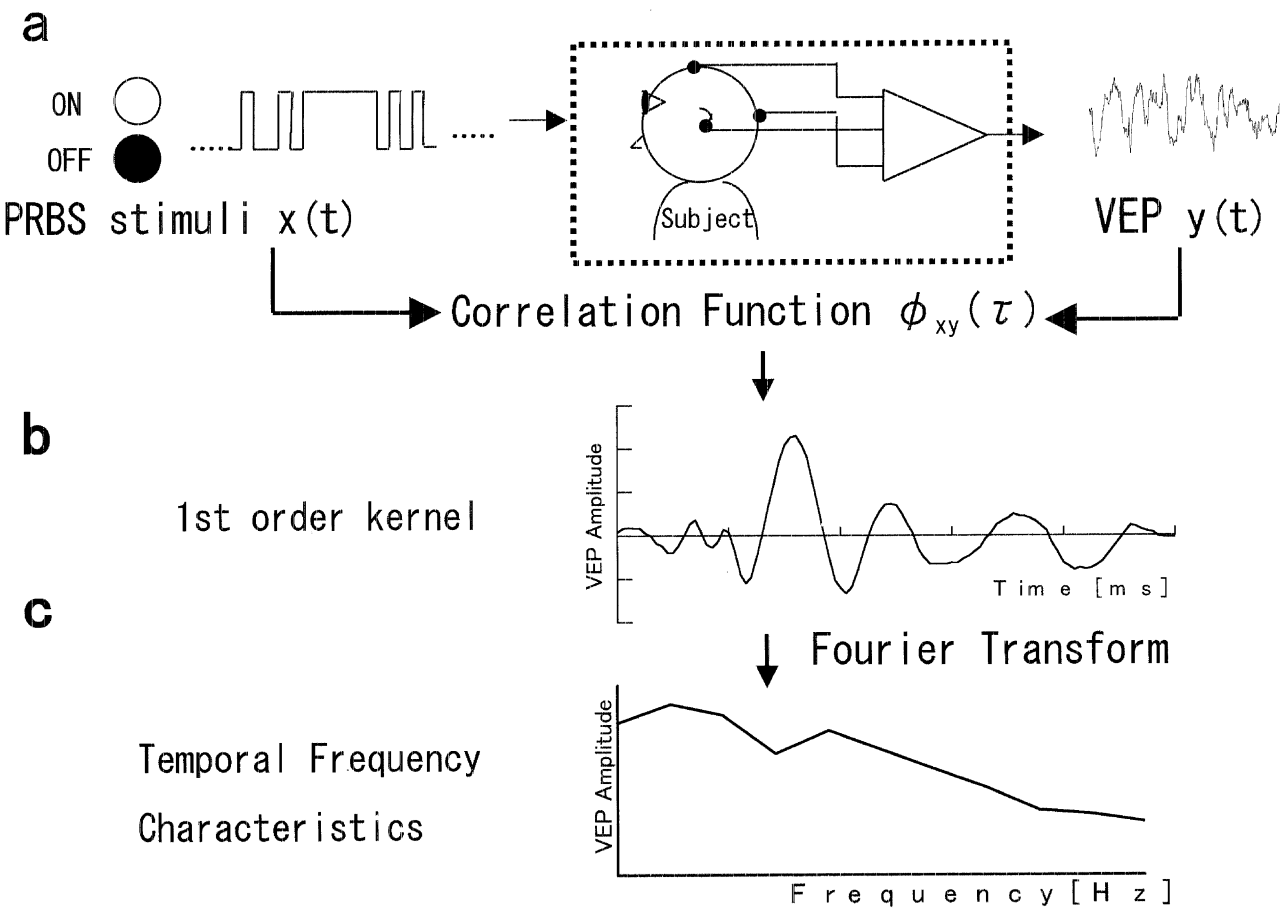

Figure 1. Diagram showing procedure of recording temporal frequency characteristics of visual evoked potentials (VEPs) in age-related macular degeneration (AMD) patients (see Materials and Methods for details). PRBS: pseudorandom binary sequence.

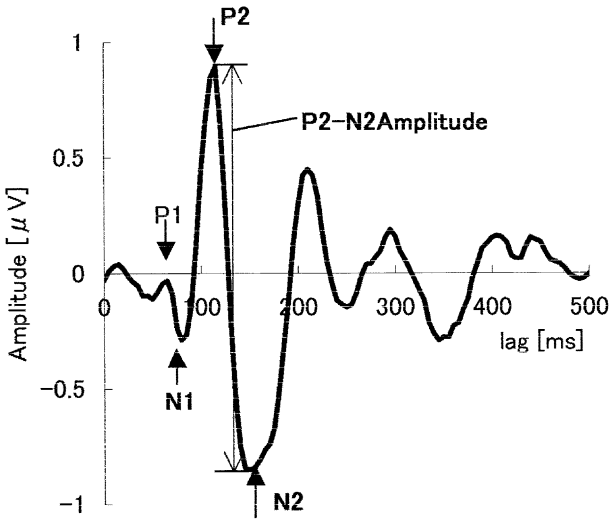

Figure 2. Analysis of first-order kernel of visual evoked potential. First-order kernel of a healthy volunteer.

The difference in the results of the three groups was tested by analysis of variance (ANOVA) with multiple comparisons.

Results

Implicit Times and Amplitudes of First-order Kernel of PRBS-VEP

In normal volunteers, the mean ± SD of the ITs of P2 and N2, and the P2–N2 amplitude were 111.0 ± 4.5 milliseconds, 142.2 ± 7.1 milliseconds, and 2.1 ± 0.7 μV, respectively (Figure 2). For eyes with AMD, the IT of P2 increased as the severity of the AMD increased (ANOVA, $P < .05$). In the severe AMD group, the IT of P2 was significantly longer than that of the normal control (ANOVA, $P < .05$). The IT of N2 had a similar tendency but the delay was not significant (ANOVA, $P = .11$) (Figure 3a).

The P2–N2 amplitude became smaller as the degree of AMD increased (ANOVA, $P < .01$). In both the severe and mild AMD groups, the P2–N2 amplitudes were significantly depressed compared with that of normal control (ANOVA, $P < .01$) (Figure 3b).

The eyes with AMD were divided into two groups according to the diameter of the central scotoma; those eyes with scotoma under 10° and those ≥10°. These two groups showed no significant difference in the IT of P2 and N2, and in the P2–N2 amplitude (*t*-tests).

TFC of VEPs

In the severe AMD group, the TFC of the VEPs was more depressed than in the healthy group at every frequency. The depression was especially apparent between 6 and 18 Hz, and the level of significance was higher than that in mild AMD. On the other hand, the depression of the TFC around 24 Hz was mild and not significant (Figure 4a).

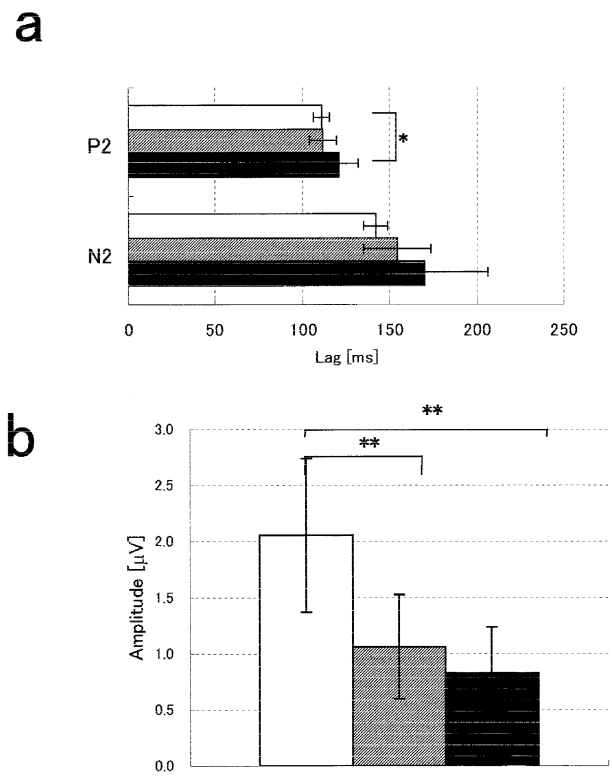

Figure 3. Implicit time (IT) and amplitude of first-order kernel of visual evoked potential (VEP). (**a**) IT of first-order kernel of VEP in normal control and age-related macular degeneration (AMD) patients (*$P < .05$). (**b**) Amplitude of first-order kernel of VEP in normal controls and AMD patients (**$P < .01$). White, hatched, and black areas represent normal control, mild AMD, and severe AMD, respectively.

In the mild AMD group, the TFC of the VEPs was depressed at all frequencies except between 22 and 30 Hz, although the decrease was less than that in severe AMD. Significant differences were found between the mild AMD group and the healthy controls at 6 Hz and between 10 and 20 Hz. The average TFC amplitude of the mild AMD group at 6 Hz was as low as 58% of that of healthy controls (Figure 4b).

The patients with AMD were divided into two groups according to the diameter of the central scotoma. These two groups did not show any significant difference for any frequency by *t*-tests.

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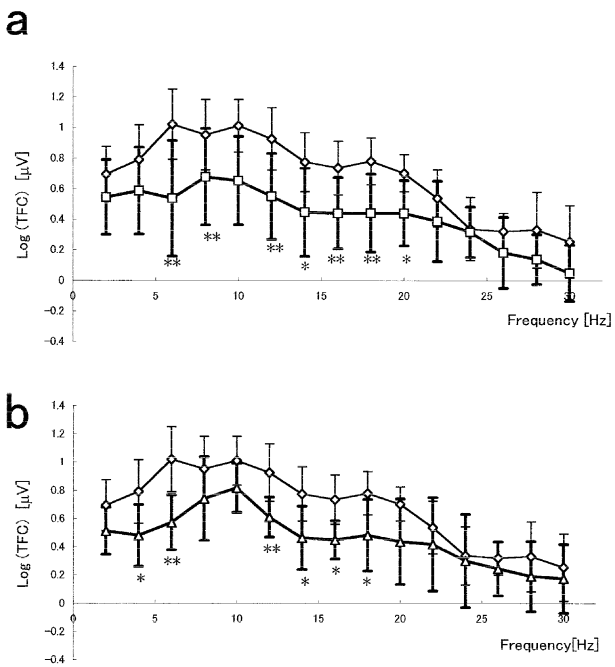

Figure 4. Analysis of temporal frequency characteristics (TFC) of visual evoked potentials (VEPs). (**a**) TFC of severe age-related macular degeneration (AMD). VEPs are depressed at all temporal frequencies. Multiple comparison was performed. $*P < .05$; $**P < .01$. ◇ healthy group, □ severe AMD group. (**b**) TFC of mild AMD patients. VEPs were depressed slightly, and TFCs significantly depressed at 6 and 10–18 Hz bands. Multiple comparison tests were performed. $*P < .05$; $**P < .01$. ◇ healthy group, △ mild AMD group.

Sensitivity and Specificity of VEP Tests

The patients who had VEP values which were out of the normal range, defined by mean ± 1 SD, were classified as being in the positive group of the two AMD groups. In the severe AMD group, the sensitivity (number of positives in the severe AMD/number of severe AMD) of the IT of P2, of the P2–N2 amplitude, and of the TFC was 71% (12/17), 82% (14/17), and 76% (13/17), respectively. In the mild AMD group, the sensitivity of the IT of P2, of the P2-N2 amplitude, and of the TFC was 33% (3/9), 78% (7/9), and 78% (7/9), respectively. For both AMD groups, the sensitivity of IT of P2, of the P2-N2 amplitude, and of the TFC was 58% (15/26), 81% (21/26), and 77% (20/26), respectively.

The patients who showed values within the normal range were classified as being in the negative group in the normal controls. The specificity (number of negative group in normal control/number of normal controls) of the IT of P2, of the P2–N2 amplitude, and the TFC was 89% (8/9), 67% (6/9), and 67% (6/9), respectively.

Discussion

Validity of the Method

VEPs have been used in clinical ophthalmology most commonly for the objective estimation of the properties of the visual pathways from the retina to the cerebral visual cortex. The PRBS method for VEPs can shorten the time to obtain a TFC curve,[7–9] and is useful because stable VEPs corresponding to many temporal frequencies can be derived by one sequence of stimuli.[5,8] The equipment for recording and stimulation used in this study was quite simple and its total weight is about 10 kg. The characteristic features of our instrument are stability of the results and shortened measurement time compared to steady-state VEP measurements, which is the conventional method to obtain the TFC. Although our methodology to obtain the TFC is different from the conventional method, similar results were obtained with normal controls in a previous study.[5] Studies about Fourier transform of pattern VEPs and transient VEPs have been reported,[2,10,11] and the usefulness of Fourier transformation of VEP was presented. In our study, a Fourier transform was applied to the first-order kernels of the VEP which theoretically approximates the waveform of the transient VEP. In the PRBS method, the noise was scattered evenly to all frequency ranges, and the possibility of changes in electrical resistance during repeated measurement is negligible, if depression in a specific frequency occurs.

Change of VEP with Central Scotoma

A prolongation of the IT and depression of the amplitude was more apparent in the AMD group with poor visual acuities. It has been reported that there is a depression of the amplitude and prolongation of the IT of the pattern VEP in macular diseases,[12–14] indicating that pattern VEPs to contrast stimuli represent the responses of the central visual field. Therefore, it is appropriate to assess the macular condition in diseases with a central scotoma and a visual loss. Tumas and Sakamoto reported that the IT was prolonged with visual acuities <20/200 in patients with macular disease.[13] It was suggested that the depression was due to a selective destruction of the slower conducting channels in the center of the retina. The IT of pattern VEPs were also prolonged in healthy volunteers if the contrast or stimulated field were changed.[13] Junghardt et al reported that

the VEP was abolished with an artificial central scotoma of over 10° in normal subjects.[14] These results suggest that the amplitude and IT are affected by a central scotoma and the visual acuity.

In the first-order kernel, high amplitude in the central visual field and low amplitude in the peripheral visual field were measured with the VERIS program, which could detect responses of focal retinal areas by multifocal PRBS stimulation. Baseler and Sutter[15] reported the response of magnocellular (M) and parvocellular (P) pathways with multifocal VEPs with stimuli that changed in pattern and contrast. They assumed that the response of the P pathway is more predominant in a central field than in a peripheral field.[15]

Diffuse, flickering full-field stimuli were used in our study. Flicker VEPs are not commonly used in clinical studies because individual variations are larger than those of the pattern VEPs. Nevertheless, Wright et al reported on the usefulness of both flicker and pattern VEPs for the evaluation of demented patients.[16] This indicated that flash VEPs may reveal a loss of visual function that cannot be detected by pattern VEPs. In this study, although the first-order kernel showed wide variation among subjects, two of the peaks, P2 around 110 milliseconds and N2 around 150 milliseconds, were detected in all subjects. Contamination by the α-waves and P2 of the VEPs can cause a problem in the measurements. We minimized the α-wave contamination by averaging three recordings.

Prolonged IT was related to the visual loss in AMD, with especially prolonged IT in severe AMD. These results are in agreement with the previous results given by pattern VEP studies.

The features of the TFCs that were obtained from Fourier transformation of the first-order kernels of PRBS-VEP were stable among subjects in this study. The TFC is effective in estimating the function of the M and/or the P visual pathways.[2–4] From this point of view, the TFC is useful for evaluating the visual function of AMD patients. The TFCs were depressed in AMD patients at some frequencies, and the band with depressed amplitudes was more widely spread in patients with lower visual acuity because of AMD. Although the distribution of the P or M ganglion cells on the retina is not as clearly defined as that of cones or rods, the density of P ganglion cells is believed to be higher in the macular area.[15] It is suspected that the diminution of the VEP components originating from P ganglion cells is apparently reflecting the distribution of P ganglion cells in the macula.

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