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Nonlinear Characteristics of Visual Evoked Potential in Glaucoma patients and Their Correlation with the Visual Responses on Magnocellular and Parvocellular Pathways

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Abstract— **Purpose was to investigate the linear and nonlinear characteristics of VEPs, and their correlation with the visual parvocellular and magnocellular systems. The VEPs were elicited by pseudorandom luminance modulated stimulation from patients with primary open angle glaucoma and compared with normal subjects. VEPs were recorded from 26 eyes with primary open angle glaucoma (POAG) and 10 eyes of age-matched normal volunteers. To acquire the VEPs, the eye was stimulated with a pseudorandom binary sequence (PRBS) stimulus of 40 sec duration. The first (linear) and second-order (nonlinear) binary kernels were determined by a cross-correlation function between PRBS and VEP. The amplitudes of the first- and second-order kernels decreased with the advancement of POAG. Positive peak latencies around 120 ms of first slice of second-order kernels increased with the advancement of POAG, while the second slice amplitudes were not different in normal, early POAG and moderate POAG patients. These results support the observations in previous studies that the first and second slice response functions reflect the response of the M- and P-pathways, respectively.**

I. Introduction

Nonlinear system identification method has been used to analyze the biological stimulation-response system, i.e., the visual system with an input signal of visual stimulation and an output of responses. When the pseudorandom binary sequence (PRBS) stimulation is used as input signal, by cross-correlating responses with the PRBS, the *n*th order binary kernels describing the nonlinear system can be derived [1][2]. This method has been applied to describing the relationship between the color and/or pattern stimulus and the visual evoked potential (VEP) [3]-[5]. The VEP is derived from the occipital lobe of the head when visual stimulation is applied. VEP has been the common technique to study the human visual system objectively and non-invasively. The binary kernels may be correlated with the human visual system function, and expect to be some indices for the clinical testing. In fact, the physiological and clinical efficacy of analyzing the kernels has been shown in earlier studies [6]-[8].

Mathematically, the first-order kernel corresponds approximately to the linear component and the second and higher order kernels describe the non-linearity of the system being tested. Although the physiological and clinical efficacy of analyzing the kernels has been shown in earlier studies [2][5], physiological or biological meaning of kernels is still controversial.

The human visual system is composed of parvocellular (P) and magnocellular (M) pathways. P pathway responds mainly to low temporal and high spatial frequency stimulation, respectively, while M pathway respond to high temporal and low spatial frequency stimulation. In several optic nerve disorders, one of the pathways is preferentially damaged. For example, in the early stage of glaucoma, M-cells are preferentially damaged [9] and the amplitude of VEP response to high flicker frequency is reduced [10]. Therefore, measurement of the responses on each pathway of the human visual system is believed to be effective for screening such disorders. It has been previously reported that the first and second slice of binary kernels reflect the response of the parvocellular and magnocellular pathways, respectively [7][8][11][12].

In this study, to investigate the linear and nonlinear characteristics of VEPs, and their correlation with the visual parvocellular and magnocellular systems, the VEPs were elicited by pseudorandom luminance modulated stimulation from patients with primary open angle glaucoma and compared with normal subjects.

II. Method

A. Binary Kernel

The human visual system can be assumed to be a nonlinear system with one input and one output, the light stimulus, $x(t)$, and the VEPs, $y(t)$, respectively. The input-output relationship can be described by their binary expansions [1][2] so long as the input, $x(t)$, is a binary (-1 or +1) sequence,

$$y(t) = \sum_{n=0}^{N} \sum_{\tau_n=\tau_{n-1}+1}^{R} \cdots \sum_{\tau_1=0}^{R} b_n(\tau_1,\cdots,\tau_n)\, x(t-\tau_1)\cdots x(t-\tau_n) \quad (1)$$

where τ_n is a time delay and $b_n(\tau_1,\ldots\tau_n)$ is the nth-order binary kernel. When PRBS used as input, $x(t)$, these sliced kernels of all orders are lined up along the first-order cross-correlation cycle between the PRBS (m-sequence) $x(t)$ and the corresponding system response, $y(t)$. The first and the second-order kernels can be extracted from a first-order cross

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correlation function between PRBS and PRBS-VEP by the m-transform method [2].

B. Subjects

VEPs were recorded from 26 eyes with primary open angle glaucoma (POAG) and 10 eyes of age-matched normal volunteers. Twenty six eyes of 26 glaucoma patients were studied. Their visual acuity and visual field defect were also measured. The glaucomatous eyes were classified into 3 groups according to their visual field defect [13]: stage 0-1 (early), stage 2-4 (moderate) and stage 5-6 (severe).

This research was conducted in accordance with the tenets of the Declaration of Helsinki, and written informed consent was obtained from all subjects.

C. Visual Stimulation

Light stimuli were provided by light-proof goggles lined with an array of 3 x 5 red light-emitting diodes (LEDs) with a wavelength of 630 nm. The LEDs were covered with thin white paper to obtain unpatterned light stimuli. The mean luminance of the stimulation was about 180 cd/m^2. In all measurements, the stimuli were monocularly given to open eyes. LEDs were driven by PRBS of 40,950 ms generated by a 12-bit shift register with a clock interval of 10 ms [12][14]-[16].

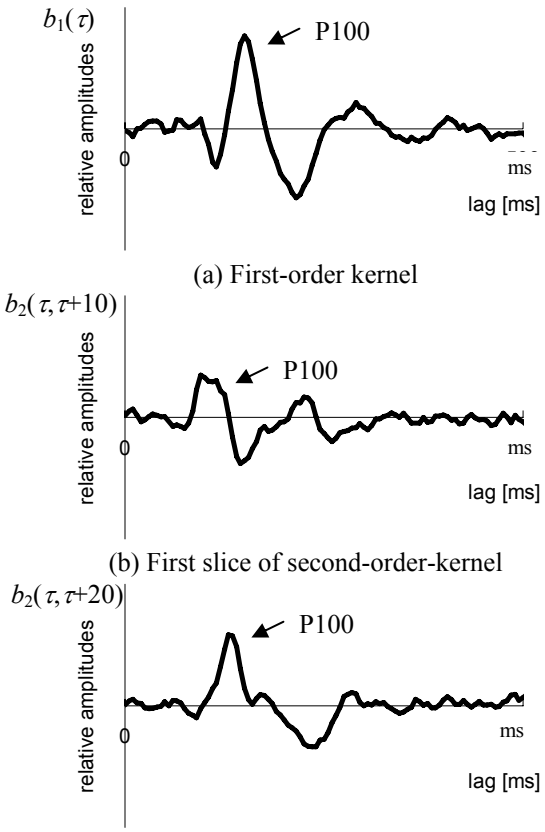
D. VEP Measurements and analysis

Bipolar EEG recordings were made between Oz (+) and Cz (-), with grounding at the right ear. The EEG signal was amplified and band-filtered (1-100 Hz) by a bio-amplifier, then applied to an A/D converter in which the sampling frequency was 200 Hz. PRBS stimulation was repeated at least three times at intervals of about 30 seconds. Three EEG responses without artifact were collected and averaged.

First and second-order kernels were estimated by calculating the first-order cross-correlation function between the PRBS and the PRBS-VEP [2]. Root mean squared amplitudes of 0-300 ms and positive peak latency around 110 ms of first-order and second-order kernel slices were evaluated.

III. Results

Waveforms of the kernels obtained from an early POAG patient are shown in Fig. 1. As shown in the figure, positive peak was found in each slice. Although the amplitudes of the peaks decreased with the advancement of the glaucoma, their latencies can be detected in the patients' data. The amplitudes (RMS) of the first- and second-order kernels decreased with the advancement of POAG (Fig. 2). Positive peak latencies around 110 ms of first slice of second-order kernels increased with the advancement of POAG, while the second slice amplitudes were almost equal in normal, early POAG and

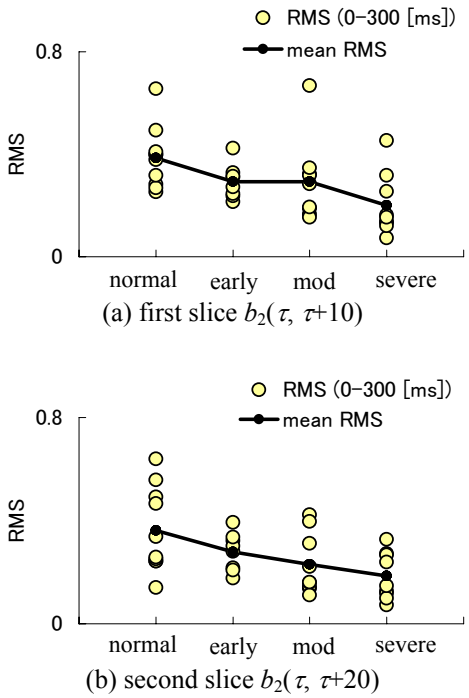


(a) First-order kernel

(b) First slice of second-order-kernel

(c) Second slice of second-order kernel

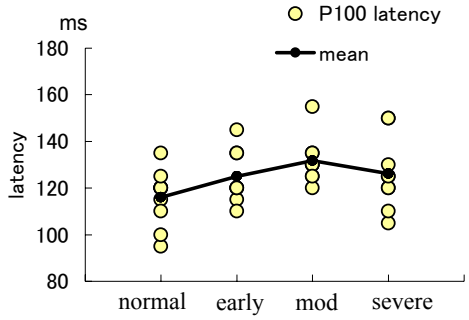
Fig. 1. First and second-order kernels obtained from a POAG patient in early group.



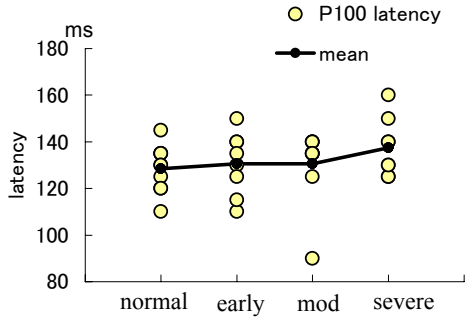
(a) first slice $b_2(\tau,\ \tau+10)$

(b) second slice $b_2(\tau,\ \tau+20)$

Fig. 2. RMS of second-order kernels changes according to the advancement of POAG.



(a) first slice



(b) second slice

Fig. 3. P100 latencies of second-order kernels changes according to the advancement of POAG.

moderate POAG patients (Fig. 3).

IV. Discussion

A predominant loss of the M axons has been shown histopathologically [9], and several VEP studies have demonstrated depression of the responses to high flicker stimulation in early glaucomatous patients [10][15][16]. For PRBS-VEP, Klistorner *et al*, have examined the effect of variation of luminance contrast on first and second-order kernels, and presented that contrast function of second-order kernel first slice and second slice mimic those of the M and P neurons, respectively [7]. Graham *et al*, presented the low second-order kernels in early glaucomatous patients, demonstrating that first slice reflects M-pathway responses [5]. Momose *et al*, measured VEP to checkerboard pattern reversing based on PRBS, and showed that P150 latencies of first and second slices reflected the high and low temporal responses, respectively [15].

Results in this study support the previous physiological interpretation of second-order kernel slices shown above. Increasing of P100 latencies of first slice with the advancement POAG (Fig. 3(a)) would be related to the predominant M-cells loss in early and moderate groups. In contrast, no significant difference among the groups was found in second slices (Fig. 3(b)). RMS of some kernels in severe group were low and their waveform was distorted. This may be the reason for the decreasing of the latencies in severe group. These results indicated the second-order kernel slices can be a good index for testing M/P pathways function. Methodology for VEP measurement and kernel estimation with high S/N is necessary because of low amplitudes of higher slices especially in patients.

V. Conclusion

First and second slices of second-order kernels of the VEPs were elicited by pseudorandom luminance modulated stimulation from patients with primary open angle glaucoma and compared with normal subjects. Results indicated that the first and second slices reflected the M and P pathway responses, respectively, agreeing with the previous studies.

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References

[1] P.D. Marmarelis and V.Z. Marmarelis, Analysis of physiological systems. New York: Plenum Press, 1978.

[2] E.E. Sutter, "A deterministic approach to nonlinear systems analysis," in Nonlinear Vision (Pinter R B, Nabet B. Ed.), CRC Press, pp.171-220, 1992.

[3] K. Momose, "Extraction of color response from visual evoked potentials using the binary kernel method," *IEICE Trans. on Info. & Sys*, vol. E81-D, pp. 124-131, 1998.

[4] K. Momose K, K. Komiya and A. Uchiyama, "Nonlinear analysis of visual evoked potential elicited by color stimulation," *Method of Information in Medicine*, vol. 36, pp. 315-318, 1997.

[5] N. Nemoto, K. Momose, M. Kiyosawa, H. Mori, and M. Mochizuki, "Characteristics of first and second order kernels of visually evoked potentials elicited by pseudorandom stimulation," *Doc Ophthalmol.*, vol.108, no.2, pp.157-163, 2004.

[6] S.L. Graham, A. Klistorner, J.R. Grigg and F.A. Billson, "Objective VEP perimetry in glaucoma: asymmetry analysis to identify early deficits," *J Glaucoma*, vol.9, pp.10-19, 2000.

[7] A. Klistorner, D.P. Crewther and S.G. Crewther, "Separate magnocellular and parvocellular contributions from temporal analysis of the multifocal VEP," *Vision Res* vol.37, P.2161-2169, 1997.

[8] A. Klistorner and S.L. Graham, "Early magnocellular loss in glaucoma demonstrated using the pseudorandomly stimulated flash visual evoked potential," *J Glaucoma* vol.8, P.140-148, 1999.

[9] H.A. Quigley, R.M. Sanchez, G.R. Dunkelburger, N.L. Henaut and T.A. Baginski "Chronic glaucoma selectively damages large optic nerve fibers," *Invest Ophathalmol Vis Sci*, vol.28, P.913-918, 1987.

[10] E. T. Schmeisser and T.J. Smith, "High-frequency flicker visual evoked potential losses in glaucoma," *Ophthalmology* vol.96, pp.620-623, 1989.

[11] K. Momose, and S. Kasahara, "Nonlinear characteristics of visual evoked potential and their correlation with the visual responses on magnocellular and parvocellular pathways," *Proceedings of the 25th Annual International Conference of the IEEE EMBS,* 2003 Cancun, Mexico. 784.

[12] K. Momose, N. Nemoto, H. Mori, M. Kiyosawa, M. Mochizuki, "VEP elicited by Pseudorandom Binary Stimuli from patients with Macular

Degeneration," *The Proceedings of the 22nd Annual International Conference of the IEEE EMBS* (CD-ROM), TU-CXH-45, 2000.

[13] E. Aulhorn, "Comparative visual field study in patients with primary open angle glaucoma and another ischemic optic neuropathy," *Docum. Ophthalmolo. Proc. Series*, vol.22, 1980.

[14] K. Momose, M. Kiyosawa, N. Nemoto, Y. Kimura, F. Okuyama, and M. Senda, "Visual temporal frequency characteristics determined by pseudorandom binary stimuli," *Invest. Ophthalmol. & Vis. Sci.*, vol.40, no.1, pp.50-54, 1999.

[15] J. J. Yu, M. Kiyosawa, N. Nemoto, K. Momose, H. Mori, and M. Mochizuki, "Correlation between frequency doubling technology perimetry and Temporal Frequency characteristics in early glaucoma," *Doc Ophthalmol.*, vol.107, no.2, pp.93-99, 2003.

[16] K. Momose, M. Kiyosawa, N. Nemoto, H. Mori, M. Mochizuki, and J. J. Yu, "PRBS-determined temporal frequency characteristics of VEP in glaucoma," *Doc Ophthalmol*., vol.108, no.1, pp.41-46, 2004.