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Dual-directional optokinetic nystagmus elicited by the intermittent display of gratings in primary open-angle glaucoma and normal eyes

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Abstract

Purpose. To compare optokinetic nystagmus (OKN) responses to the intermittent display of stimuli between normal subjects and patients with primary open-angle glaucoma (POAG).

Methods. Optokinetic nystagmus (OKN) was recorded in 9 glaucomatous patients and 7 normal subjects. The computer-generated stimuli displayed sinusoidal luminance gratings (16 cd/m^2 mean luminance, 0.5 cyc/deg) with a $\pi/2$ phase shift between successive stimulus gratings. These stimulus gratings were separated by an interstimulus interval (ISI), during which a homogeneous luminance field of 16 cd/m^2 was presented. The ISI duration and the luminance contrast were set at different values.

Results. For normal subjects, dual-directional alternating OKN could be evoked in the ISI range from 33 to 100 ms. The dual-directional alternating OKN was defined as that OKN slow phase alternatively tracked in the direction of $\pi/2$ shift (forward OKN) and against the $\pi/2$ shift (reverse OKN). By contrast, for most glaucomatous eyes, nearly no reverse OKN could be evoked at any ISI value.

Conclusions. The lack of reverse OKN in POAG patients in the present experiments is a meaningful finding. The occurrence of reverse OKN during a certain range of ISI duration could be related to the biphasic characteristics of the temporal impulse response in normal subjects, whereas, the lack of reverse OKN might suggest the plausible damage of magnocellular cells in POAG.

Keywords: optokinetic nystagmus; primary open-angle glaucoma; intermittent display; visual temporal impulse response

Introduction

Primary open-angle glaucoma (POAG) is a progressive optic neuropathy, in which loss of optic nerve fibers occurs under open iridocorneal angle conditions and concurrent with the chronically raised intraocular pressure (IOP). Histological evidence has shown the selective loss of larger diameter magnocellular (M-) ganglion cells in early POAG,[1–3] although some recent studies also indicated the glaucomatous loss of parvocellular (P-) cells.[4–6] In correspondence with the vulnerability of larger ganglion cells in glaucoma, psychophysical tasks isolating functions of magnocellular (M-) cells have been employed for detecting the early glaucomatous visual damage, such as motion perception and flicker sensitivity.[7–12] Recently, the frequency-doubling technology (FDT) perimetry has been demonstrated to be effective for diagnosing early glaucoma, because FD illusion reflects the nonlinear characteristic of a subgroup of M-cells, the Y-like M cells.[13–18]

From an engineering viewpoint, the characteristics of a "system" can be sufficiently characterized by the impulse response, which is defined as a system's output for a given impulse signal input. Through the impulse response, one can describe how the system responds to any stimuli by

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convolving the system's input with the system's impulse response.[19] This impulse response concept has been adopted to investigate temporal characteristics of the visual system as the visual temporal impulse response by many psychophysical studies.[20–25] These results have demonstrated that the visual temporal impulse response to the luminance pulse is biphasic, a positive lobe followed by a negative lobe (see Fig. 5a for a schematic diagram of biphasic temporal impulse response), whereas the impulse response to the isoluminant chromatic pulse is monophasic, or a single positive lobe.[23–25] Correspondingly, electrophysiological recordings from ganglion cells in macaque monkeys demonstrate that M-cells are sensitive to the luminance modulation stimuli and show a biphasic temporal impulse response; on the contrary, P-cells are sensitive to chromatic modulation and show a monophasic temporal impulse response.[26,27]

Further psychophysical investigations reported that single-step movement could evoke motion perception opposite to the direction of physical shift under certain interstimulus interval (ISI) conditions and suggested that the reverse motion perception is related to the biphasic temporal impulse response.[28–30] Therefore, for the normal subjects, it would be a reasonable conjecture that the intermittent display of stimulus gratings with successive $\pi/2$ phase shift could elicit the reverse motion perception against the direction of $\pi/2$ phase shift, as well as the forward motion perception in the direction of $\pi/2$ phase shift. The two perceived opposite motions will result in the alternation of motion perception, as well as the corresponding optokinetic nystagmus (OKN).[31–34] Considering the losses of large ganglion cells in glaucomatous eyes,[1–3] we presume that the temporal impulse response might be impaired by POAG, thus, the plausible impaired temporal impulse response might corrupt the alternation of motion perception and related OKN responses. In the present experiments, we employ intermittently displayed stimuli to compare OKN responses between normal subjects and POAG patients. We attempt to probe whether the present OKN method would be helpful for the diagnosis of POAG.

Materials and methods

In our experiments, seven normal subjects underwent testing of both eyes (14 normal eyes in all). Nine patients underwent testing in the glaucomatous eyes (11 glaucomatous eyes in all). The POAG patients had typical glaucomatous optic nerve heads and reproducible visual field defects on the Ocotpus1-2-3 automated perimetry (Interzeag, Schlieren, Switzerland). Eyes were considered to be glaucomatous if they had a minimum cluster of four adjacent points decreased at least 5 dB with one of the points decreased at least 10 dB, or three adjacent points decreased at least 10 dB. Our criteria conformed to the strict criterion of Caprioli.[35] The cup-to-disc (C/D) ratio in the glaucomatous eye ≥ 0.6. All but three patients had a history of IOP > 21 mm Hg. The unaided or corrected visual acuity of each patient was at least 20/40. The age range of POAG group was from 50 to 76 years. All healthy subjects had normal IOP, normal visual field, normal C/D ratio, and 20/40 visual acuity or better. The age range of the normal group was from 51 to 74 years, with the exception of one subject who was younger than 40 years. There was no significant age difference between the POAG patients and the normal controls ($P > 0.2$, Mann-Whitney test). The experimental protocol was approved by the Medical Ethics Committee of Zhongshan Hospital of Shanghai Medical University and followed the tenets of the Declaration of Helsinki. Each subject provided signed written consent before the experiments.

The intermittent display of luminance gratings (white/black) was presented on a ViewSonic PT813 monitor at a frame rate of 60 Hz. At a viewing distance of 57 cm, vertical sinusoidal gratings (16 cd/m^2 mean luminance, 0.5 cyc/deg) subtended a visual angle of 40° × 30°. The stimuli were displayed in the following sequence: first, a luminance grating was presented for approximately 17 ms (1 video frame at 60 Hz); second, an interstimulus interval (ISI), in which a homogeneous luminance field (16 cd/m^2, equal to the average luminance of the stimulus grating) was presented; then, a luminance grating with $\pi/2$ (90°) phase shift with respect to the previous grating was presented for 17 ms, and the ISI again. In accordance with this sequence, these repetitive $\pi/2$ phase-shift gratings with ISI were employed for each trial (see Fig. 5b as an example).

In the OKN experiments with different ISI, the ISI duration was randomly selected from approximately 17, 33, 50, 67, 83, 100 ms (1, 2, 3, 4, 5, or 6 video frames) for each trial, while the luminance contrast level of the stimulus grating was fixed at 10%. In the OKN experiments with different contrasts, the stimulus contrast was randomly set at several levels: 2%, 5%, 10% and 50% for each trial, while the ISI was fixed at an optimum value, with which the reverse OKN was vigorously evoked in the OKN experiments with different ISI. To ensure that all subjects in the present experiments had relatively normal oculomotor behavior, the conventional OKN for each subject was checked by the continuously moving gratings at 12°/s.

The eye movements were measured with either the electro-oculographic (EOG) technique,[36] or the magnetic scleral search coil technique,[32,37] in which an annulus of silicone rubber with an induction coil (Skalar Medical BV, Netherlands) was adhered to the subject's eye. The subjects sat in a dark room with the head stabilized by a chin rest. They were instructed to passively stare at the screen with the tested eye, while the untested eye was covered by an eye patch. Each trial was presented for 20 seconds and repeated at least three times. The data was sampled at 100 Hz and stored on a PC computer for off-line analysis. The recorded data of eye movements was parsed into three components: the forward OKN corresponding with the direction of $\pi/2$ phase shift, the reverse OKN opposite to the $\pi/2$ phase shift, and no-OKN occurrence. The percentage time of each OKN component was defined as the cumulative occurring duration of the component divided by the trial time.

Results

OKN response to conventional continuously moving gratings

When a large field (40° × 30°) moving grating stimuli (12°/s) was presented to the subjects, OKN eye movements could be evoked on both normal controls and POAG patients (Fig. 1). This indicated that the oculomotor response were relatively normal for all patients in this experiments.

OKN response to stimulus with different ISI duration

Typical OKN recordings of normal subjects are illustrated in Figure 2a. Under the short ISI (17 ms), the evoked OKN only tracked in the direction of the π/2 phase shift (forward OKN). When the ISI reached 33 ms, the reverse OKN opposite to the direction of π/2 phase shift appeared, thus, the slow phase of OKN alternated between forward and reverse direction, i.e., the dual-directional alternating OKN occurred. The percentage time of OKN, averaged for normal subjects, as a function of ISI duration was plotted in Figure 3a. Samples of OKN recordings of POAG subjects were illustrated in Figure 2b. Contrary to the observation in normal subjects, nearly all of the glaucomatous eyes exhibited forward OKN and little reverse OKN, except for one instance in which the minimal reverse OKN occurred when the ISI increased to about 83 ms. Moreover, with increasing ISI, the percentage time of forward OKN of all POAG patients deteriorated more rapidly compared with the results of normal subjects (Fig. 3b).

OKN response to stimulus with different luminance contrast

For normal controls, both percentage time of forward and reverse OKN rapidly increased with the enhancement of contrast, and the percentage time reached its maximum value and saturated at the luminance contrast of 5% for forward OKN and at 10% for reverse OKN, respectively (see Fig. 4a). However, for the glaucomatous patients, the forward OKN eye movements were obviously evoked only at contrast levels higher than 10%. More importantly, the reverse OKN was scarcely evoked at any contrast level (see Fig. 4b).

Discussion

In the present investigation, significant differences of OKN features were found between normal and POAG eyes. For the normal subjects, the reverse OKN occurred and resulted in the dual-directional alternating OKN when the ISI duration fell into a certain range, whereas for most of the POAG patients, no reverse OKN could be evoked.

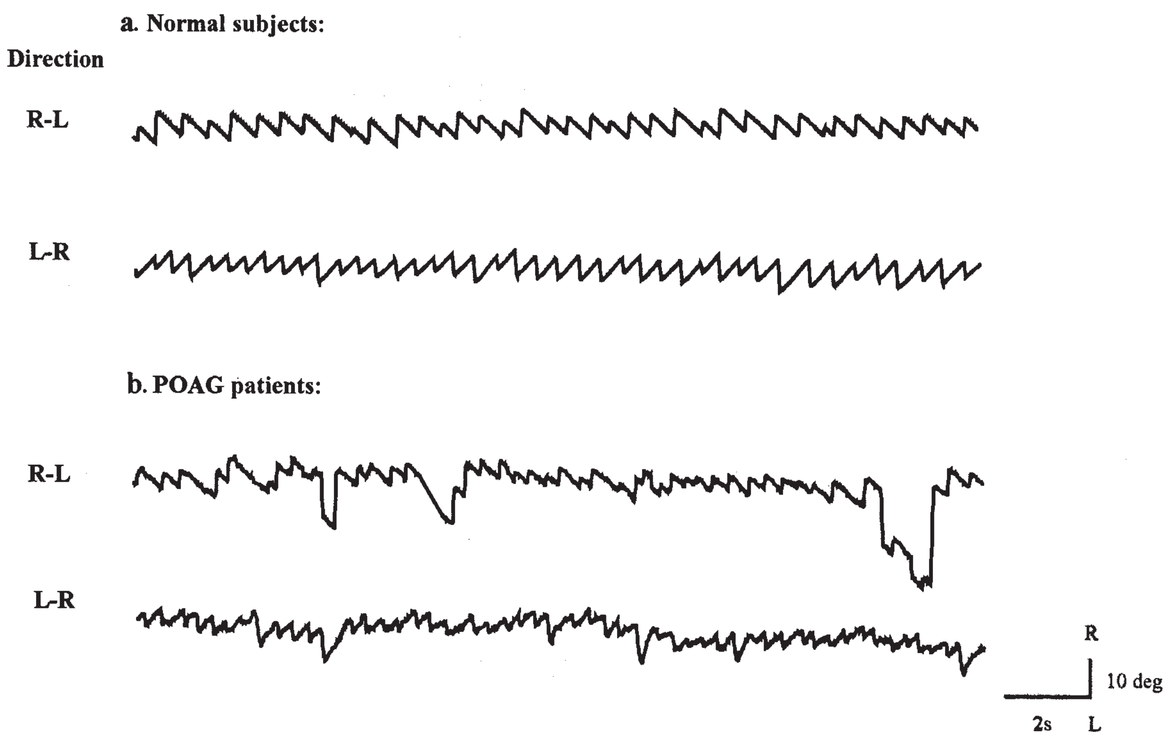

Figure 1. Samples of OKN evoked by the continuously moving gratings. Speed = 12°/s; L-R for the grating moving from left to right, R-L for right to left. (a) normal subjects, (b) POAG patients.

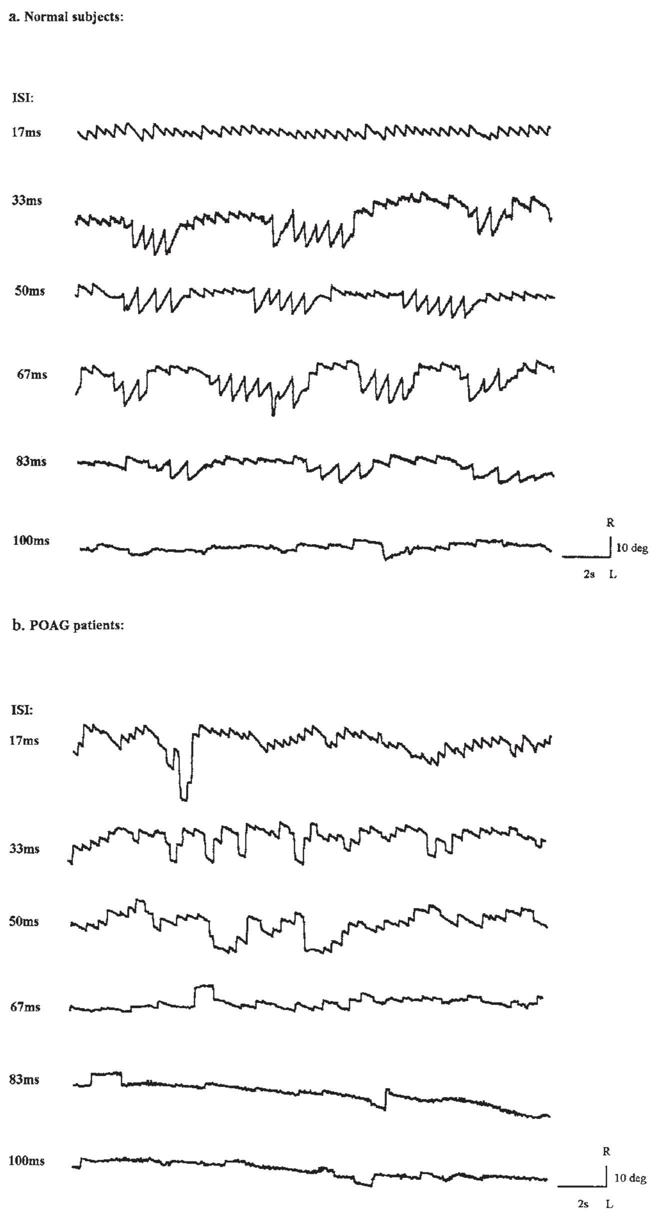

Figure 2. Samples of OKN elicited by the intermittent display of sinusoidal luminance gratings with $\pi/2$ phase shift for variant ISI duration. (a) from a normal subject (left eye), (b) from a POAG patient (left eye). The direction of the $\pi/2$ phase shift was from right to left. ISI duration is marked on the left column. A homogeneous field with a mean luminance of stimulus grating ($16\,cd/m^2$) was presented during ISI.

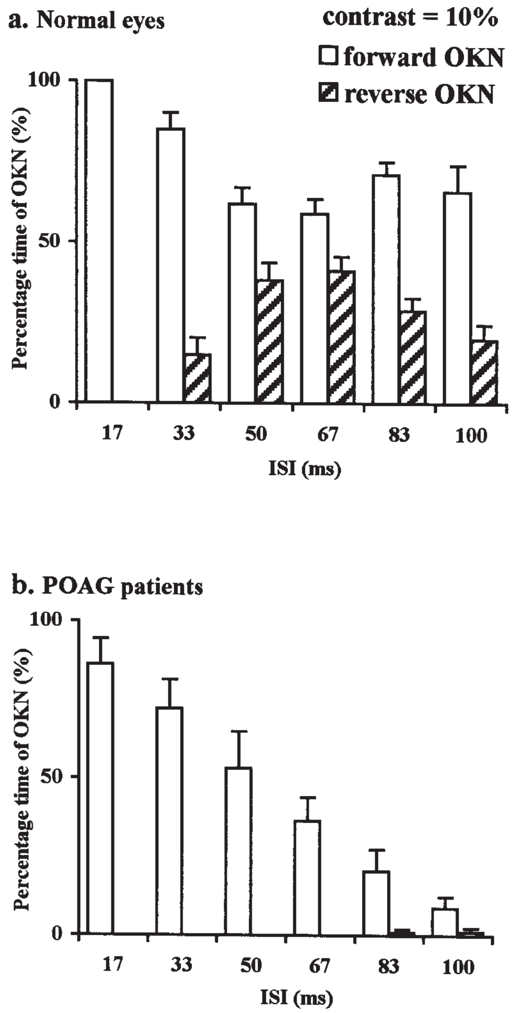

Figure 3. The percentage time of the OKN vs. ISI duration. The luminance contrast was fixed at 10%. Bars indicate one standard error. (a) Data from 14 normal eyes. The high percentage values of reverse OKN appeared at ISI duration of 50 and 67 ms. (b) Data from 11 glaucomatous eyes, with almost no reverse OKN evoked.

A plausible explanation for the occurrence of reverse OKN is related to the biphasic temporal impulse response in the visual pathway. We found that the present ISI range for the occurrence of reverse OKN is close to the time range of the negative lobe of biphasic temporal impulse response reported in previous investigations.[20–25] Previous studies reported that single-step moving stimuli presented with an interstimulus interval (two sequential frames separated by an interstimulus interval, ISI) could evoke a reverse motion perception, the direction of which was opposite to the actual shift of two frames.[28–30] This reversed motion perception has been appropriately attributed to the biphasic temporal impulse response, a positive lobe followed by a negative lobe (see Fig. 5a). Owing to the biphasic temporal impulse response, the counterphase effect resulted from the negative lobe of the first stimulus grating, combining with the inphase effect resulted from the positive lobe of the next $\pi/2$ phase-shift grating, could evoke the reverse motion perception. The present study extended the single-step stimuli to the repeated presentation, i.e., the intermittent display of sequential $\pi/2$ shift gratings. The normal subjects could perceive both reverse motion perception ($-3\pi/2$ phase-shift direction) and forward ($\pi/2$ phase-shift direction) motion perception (see arrows indicated in Fig. 5b). These would induce the alternation of motion perception and the corresponding alternat-

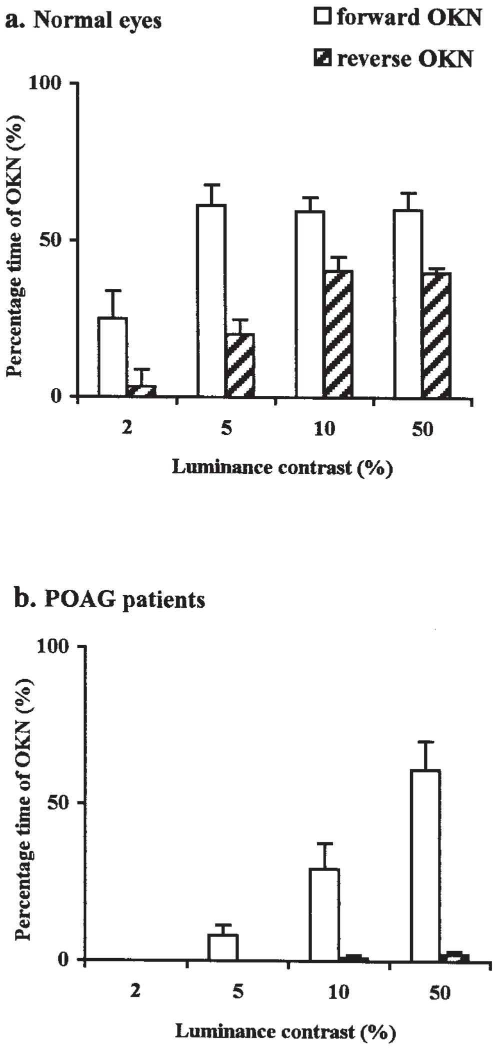

Figure 4. The percentage time of the OKN vs. luminance contrasts. (a) Data from normal eyes, (b) Data from glaucomatous eyes. Bars indicate one standard error. The ISI duration was fixed at the optimal value of 67 ms noted from the ISI experiments.

ing OKN. The slow phases of this OKN alternately tracked forward and reverse directions. This explanation is also supported by the fact that the slow phases of reverse OKN were faster than the forward OKN (see the samples of OKN in Fig. 2a), because the perceived velocity of the reverse movement would be three times higher than the forward movement according to the theoretical calculation. Moreover, the necessary ISI range found in the present experiments is consistent with the data of previous findings of the reverse motion perception induced by the single-step moving stimuli.[28–30] In our results, it should be noticed that the first slow phase of OKN after each OKN alternation usually was slow, with subsequent phases raising in speed. This could result from the rapid adaptation of OKN slow phases.[38,39]

As to the POAG patients, the lack of reverse OKN could not be attributed to that the glaucoma subjects were blind to high velocities, because they had no difficulty in tracking a fast forward moving grating. For example, the speed of forward OKN trace, labeled ISI = 17 ms in Figure 2b, was higher than the possible reverse speed labeled ISI from 67 to 100 ms. Therefore, the lack of reverse OKN in POAG might suggest that the negative lobe of the biphasic temporal impulse response severely diminished or even vanished. Correspondingly, compared with normal subjects, the decreasing percentage time of forward OKN in POAG patients suggested the positive lobe of the biphaisc temporal response might also be impaired. Numerous histopathological studies have indicated vulnerability of larger retinal ganglion cells and larger optic nerve fibers in human and experimental glaucoma.[1,2,3,40,41,42] And, data on M-type ganglion cells of macaque retina have revealed a biphasic temporal impulse response similar to psychophysical results on human subjects.[24,26,27] To summarize, the lack of reverse OKN in the present experiments is likely related to the defects of M cells in POAG patients.

One exception in our results was that reverse OKN appeared for one glaucomatous eye. This residual reverse OKN might be due to a lighter glaucomatous symptom of this eye (the C/D of this eye, 0.6, was the smallest one in our glaucomatous patients) However, to confirm this explanation, systematic experiments from massive samples of POGA with different C/D parameters will be required for future study.

The current findings are supported by previous psychophysical tests about the temporal frequency deficit in glaucomatous eyes. Tyler[7] reported that significant losses in the temporal frequency sensitivity near 35 Hz occurred in glaucoma. Later investigations reported the significant loss of temporal sensitivity occurred not only at the high frequencies, but also at the mid-frequencies.[8–10] Moreover, the deficiency of temporal contrast sensitivity at high frequency was also found under full visual field condition[11] and by visual evoked potential method.[43] In the present study, our OKN recordings suggest that for glaucomatous eyes, the temporal impulse response might degenerate from biphasic to monophasic due to a deficiency of the negative lobe. According to the Fourier transform, the monophasic impulse response corresponds to a low-pass temporal frequency function that contains the reduced higher temporal frequency components as compared to the biphasic response.

For the diagnosis of POAG, the frequency doubling (FD) illusion, in which a low spatial frequency sinusoidal grating is seen to be twice the original spatial frequency when the grating undergoes counterphase flicker at high temporal frequencies, has been employed as an effective and valuable approach to discriminate glaucoma from normal subjects.[13–18] Although all subjects in the present OKN experiments did not observe FD illusion, it is interesting to notice that: both "biphasic visual temporal impulse response" and "frequency doubling illusion" have been originally reported in flicker studies by the same author,[20,44] so that these two phenomena may be correlated to each other in the neurolog-

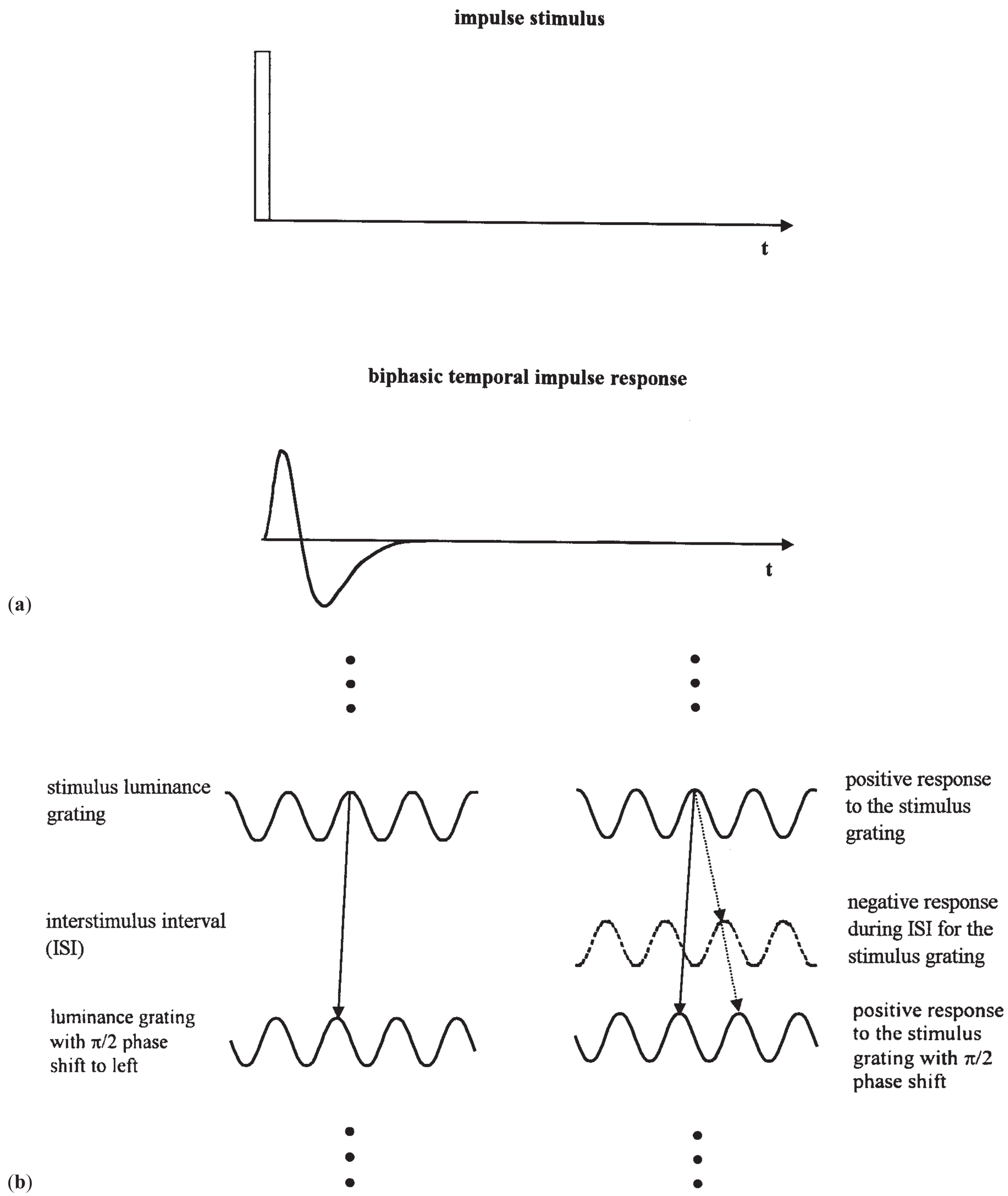

Figure 5. Schematic diagrams for the dual-directional alternating motion perception induced by biphsic temporal impulse response to the intermittent display of gratings with $\pi/2$ phase shift in normal subjects. (a) Schematic diagrams of the impulse stimulus (upper trace) and the biphasic temporal impulse response (lower trace), a positive lobe followed by a negative lobe; (b) Schematic diagrams for the induced dual-directional alternating motion perception: the left panel illustrated one segment of the stimuli; the direction of $\pi/2$ phase shift was sketched by solid arrow. The right panel shows corresponding temporal impulse responses. Obviously, these stimuli could elicit the motion perception alternating between forward (sketched by solid arrow) and reverse (sketched by dashed arrow).

ical mechanism. Further systematic experiments to investigate their correlation would be helpful for POAG diagnosis, however, it is beyond the scope of present paper.

In summary, the present results showed different OKN in normal subjects and POAG patients. We suggest this difference might relate to defects of temporal impulse response in glaucomatous eyes. Considering that explicit OKN deterioration in patients can be objectively measured, our findings may provide a potential capability for distinguishing glaucomatous eyes from normal controls.

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