The Pattern Evoked Electroretinogram: Origin, Characteristics and Clinical Usage

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Abstract

This paper consists of a literature review of the clinical observations of the pattern electroretinogram (pERG) and theories concerning its origin. Normative data are presented for subjects aged 20 to 29 years to document variations in pERG response characteristics as a function of selected stimulus parameters. Clinical cases of visual neural dysfunction are also presented to illustrate the usage of pERGs in the realm of electrodiagnostic testing. Emphasis is placed on new or complimentary information provided by these retinal potentials.

Résumé

Ce document consiste en une revue de la documentation relative aux observations cliniques des électrorétinogrammes de grille et aux théories sur leur origine. Il présente des données normatives sur des sujets de 20 à 29 ans afin de documenter les variations de réponse électrorétinographique en fonction de certains paramètres d'excitation. On y présente aussi des cas cliniques de dysfonction nerveuse visuelle pour illustrer l'emploi des ERG de grille dans le domaine électrodiagnostique. L'accent est porté sur l'information nouvelle complémentaire générée par ces potentiels rétiniens.

Introduction

The clinical electroretinogram (ERG) can be elicited in the human eye by a diffuse flash of light. It is now widely accepted that the flash ERG (fERG) originates in the outer and middle third of the sensory retina (Brunette, 1982, Norden, 1979): the outer retina containing the photoreceptors and the middle third consisting of bipolar, Mueller, horizontal, and amacrine cells. Each of these layers contribute to a separate component of the biphasic fERG; the electronegative a-wave originates in the receptors while the electropositive b-wave originates in the middle retinal layer.

Recently the ERG has also been investigated in response to the use of patterned visual stimuli such as checkerboards or bar gratings reversed in counterphase. Figure 1 illustrates the difference in stimuli used for flash and pattern ERGs. In comparison to the diffuse fERG, which is universally accepted as a luminance-evoked response, general agreement does not exist as to whether the pattern ERG (pERG) is exclusively a pattern-evoked response, a luminance-evoked response, or whether both components occur. Furthermore, there are some conflicting reports concerning the site of generation of the pERG in man, and the degree and nature of changes in the pERG in various ocular disorders and systemic diseases affecting vision. Some of the discrepancies in vision literature undoubtedly arise from the technical difficulties in recording the pERG which is a very low amplitude signal (0 to 4 microvolts) and the variety of test conditions used to elicit the retinal response.

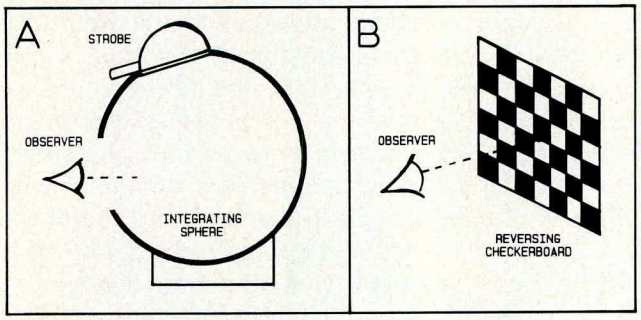

Fig. 1
Diagram illustrating the stimuli used to elicit the flash ERG (Plate A) and pattern ERG (Plate B). For the fERG, the observer receives a light flash delivered by a strobe directed into a light integrating sphere. This method of stimulation (Ganzfeld presentation) ensures a uniform distribution of light across the retina and a response from all portions of the retina. The pERG is elicited by a checkerboard target generated electronically on a television monitor. The black and white checks can be reversed in counterphase at a fixed rate, and check sizes changed to produce high to low spatial frequency stimulation.

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Nevertheless, based mainly on fairly extensive clinical observations of alterations in pERGs in ocular diseases of varying severity, but only one animal laboratory study, the current trend is to view the pERG as a reflection of ganglion cell activity.

This paper reviews some of the literature pertaining to the nature and origin of the pERG, and its clinical appearance in ocular disease. In addition, the recording methodology for the pERG, and clinical cases are presented to show its diagnostic utility in relation to other objective neurophysiological tests of visual function employed at the University of Waterloo, School of Optometry, Electrodiagnostic Clinic.

Pattern versus Luminance Responses

As early as 1973, Spekreijse et al (1973) proposed that the ERG in response to checkerboard pattern-reversal stimulation was the summed response of local luminance increases and decreases. This was later supported by Riemslag et al (1983) who also concluded that contrast specific components play no role in the generation of the pERG and suggested that it was due solely to local luminance distortions. In an earlier study, however, Korth (1983) had evaluated pattern- and luminance-evoked responses in the human ERG using pattern onset-offset (pattern appearance-disappearance) stimuli and determined that the pattern-onset wave exhibited spatial selectivity with a peak amplitude at 3 to 4 cycles/degree. Further studies by Korth & Rix (1984) indicated that the spatial selectivity occurred at a constant spatial frequency (maximum amplitude at 3.67 cycles/degree) but was more evident at low contrast.

Origin of Pattern Evoked ERG

Maffei & Fiorentini (1981) observed the pERG in a cat model before and after unilateral optic nerve section. Using sinusoidal gratings of varying spatial frequencies (.17 to 2.5 cycle/degree) reversed at 8 Hz, Maffei & Fiorentini demonstrated that 4 months after sectioning, no pERG could be elicited from the test eye at any spatial frequency. The control eye had pERG amplitudes similar to those obtained prior to the operation. For the test eye, the pERG responses became attenuated earlier at low spatial frequencies indicating that perhaps ganglion cells with larger receptive fields located more peripherally in the retina were impaired before those with smaller receptive fields, located in the central retina. Flash ERGs remained comparable in amplitude between the 2 eyes and comparable to that obtained prior to the optic nerve section. Histological analysis of the retinas indicated degeneration of the ganglion cell layer, more so in the periphery than in the centre of the retina.

This single laboratory study is frequently referenced as providing the strongest evidence that the pERG has its origin in the ganglion cell layer of the retina. However, the applicability of the results of this study to man has recently been questioned since the retina of the animal model used for experimentation (the domestic cat) differs both anatomically and physiologically from man (Zrenner et al, 1985). Further well-controlled studies using primate-like models are required to validate the current clinical impression concerning the nature and origin of the pERG in man.

Optic Nerve Disorders

ERGs in response to sinusoidal gratings of varying spatial frequency and fERGs have been examined in patients with unilateral retinal and optic nerve diseases (Fiorentini et al 1981, 1982). In all these patients, the fERG was normal whereas the pERG was absent or reduced in amplitude in the diseased eye. Patients examined included those with unilateral optic nerve atrophy, retrobulbar optic neuritis, temporary occlusion of the central retinal artery, monocular chronic glaucoma and unilateral section of the optic nerve. The observation that the pERG is altered in optic nerve disease led Fiorentini et al to conclude that the ERG in response to alternating gratings was correlated with the functional integrity of ganglion cells.

May et al (1982) compared the records of flash and pattern ERGs in patients with optic nerve dysfunction and noted that fERG amplitudes and latencies were normal whereas pERGs showed abnormalities. In the early stages of optic nerve disease, abnormalities in the pERG were seen when they were elicited by low spatial frequency sine-wave gratings and large check size stimuli. In more advanced optic nerve disorders, pERGs elicited by gratings of higher spatial frequencies or smaller check sizes were also affected. The observed relationship between spatial frequency requirement of the visual stimuli used to elicit the pERG and pERG alterations support the theory that the generators of pERGs are the ganglion cells which are known to have spatial requirements for optimal excitation (Davson, 1980).

Dawson et al (1982) recorded the pERG using a dot matrix phase alternating stimulus pattern from the eyes of one subject with a unilateral optic nerve section resulting from trauma. While no pattern ERG or Visually Evoked Response (VER) could be recorded from the lesioned eye, a normal flash ERG was elicited. Responses from the contralateral eye were normal for both flash and pattern evoked ERGs as well as VERs. These results led to the hypothesis that the ganglion cells and optic nerve are responsible for the ERG recorded in response to pattern stimuli.

In contrast to the above findings, Arden et al (1982) found that, in 12 patients, there was no reduction in the pERG during the acute stage of

unilateral optic neuritis although VER changes were evident and form vision was absent. As vision returned, 2 to 7 weeks after the attack, the pERG was larger in the affected eye suggesting a hypernormal phase due to hyperexcitation of the neurons at the point of degeneration. Still later, the pERG was reduced in the affected eye, an observation believed to be consistent with some retrograde degeneration of the optic nerve. The same researchers (Vaegen et al, 1982) also demonstrated that the pERG was reduced in conditions such as multiple sclerosis, trauma, and toxic optic neuritis.

In a study with results similar to those of Arden et al, Sherman (1982) reported that in 7 patients with long-standing optic nerve disease, pERGs were not grossly abnormal but VERs were extinguished. In a further study, Sherman & Richardson (1982) obtained relatively normal pERGs in both eyes to 14, 28 and 56 min. check sizes for 3 patients with unilateral optic nerve atrophy due to trauma. These results were interpreted as indicating a preganglionic source for pERGs. More recently, however, Celesia & Kaufman (1985) noted that in 7 eyes with diagnosed optic atrophy, pERGs were abnormal in 67% of cases when checkerboards with 15 min. checks were used to elicit the ERGs and 57% of cases when 31 min. checks were used, while fERGs were normal in all cases.

Multiple Sclerosis

Kirkham and Coupland (1983) examined the pERG in 28 patients with multiple sclerosis (MS) and did not find any significant differences in the pERG latency or amplitude when compared to subjects without MS. Bobak et al (1983) also found normal pERGs in 8 out of 10 patients with MS. On the other hand, Persson & Wanger (1984) reported significantly reduced pERG amplitudes in 50% of MS patients who had prolonged VER latencies. The reduction in pERG amplitude was significantly correlated with the magnitude of the delay in macular-cortical transmission. No significant difference from the normal group was noted in those patients who had normal VER latency measures. Additionally, no association was found between pERG amplitude and optic nerve appearance or history of optic neuritis. Persson & Wanger concluded that since an increased VER latency is indicative of optic nerve demyelination and the reduction in pERG amplitude is associated with prolonged VER latency, then pERGs probably reflect retinal ganglion cell activity.

In a recent study of 14 patients with MS, Celesia & Kaufman (1985) reported that pERGs were abnormal only in those who had pale optic discs or central field loss. MS patients with normal visual acuity had normal pERGs but delayed transient VERs. The discrepancy between the findings pertaining to the optic nerve head appearance and pERGs in this study and that of Persson & Wanger may be due to differences in the age of onset and duration of MS in the two test groups as well as the number of attacks of optic neuritis suffered by each patient.

Amblyopia

The pERG has also been studied in amblyopia. One study by Sokol & Nadler (1979) indicated that pERGs were more affected in amblyopia than fERGs. These findings provided the first electrophysiological evidence that amblyopia may have to be considered as a retinal phenomenon and not merely a manifestation of a cortical dysfunction. In another study, a significant reduction in waveform and amplitude was observed between normal and amblyopic eyes in patients who had no occlusion therapy or who had failed to improve with such therapy (Arden et al, 1980a). Further studies by Arden et al (1980b) and Arden & Wooding (1985) confirmed a significant reduction in pERG response from the amblyopic eye as compared to the normal eye and provided further support for the notion that amblyopia may be associated with changes in the peripheral retinal layers at the level of generation of the pERG. In their study of 62 amblyopic children, Arden & Wooding (1985) indicated that in most amblyopic children the pERG amplitude was reduced, although not absent. Reduction of the pERG associated with amblyopia was not related to the angle of deviation, poor fixation or improper optical correction. Additionally, occlusion therapy in young children reduced the pERG of the fellow eye but orthoptic training could increase the pERG. The difference in pERG amplitudes between the amblyopic and contralateral eye increased with decreasing check size (Vaegen et al, 1982). The onset and duration of visual deprivation have been shown to be positively related to the degree of disturbance of the pERG (Vaegen et al, 1982, Arden et al, 1982). This latter observation has led to the suggestion that the pERG is a direct measure of the function of cells in the inner retina, such as the amacrine or ganglion cells or the synaptic potentials feeding onto such cells.

Glaucoma

In 11 patients with unilateral glaucoma, no significant difference was observed in the amplitude of the fERG between glaucomatous and normal eyes, whereas a significant reduction in amplitude between the 2 eyes was found for the pERG. The oscillatory potentials in the flash ERG were equal in both eyes suggesting that their generators, likely the amacrine cells, are not affected in the glaucomatous process. The loss of pERG amplitude was significantly correlated with the visual field loss inferring impaired activity of the ganglion cells (Wanger & Persson, 1983a, Wanger & Persson, 1983b).

In a recent study of 28 eyes of glaucoma patients, Papst et al (1984) found normal pERG amplitudes in all glaucomatous eyes with normal optic nerve head appearance and visual field findings. Normal latencies but reduced amplitudes of the pERG were found in eyes with ophthalmoscopically detectable abnormalities in the optic nerve head and visual field defects. A functional impairment of the ganglion cell layer was tentatively identified as the cause of the reduced pattern ERG amplitude in glaucomatous eyes.

Ringens et al (1984) studied a group of 75 glaucoma patients and concluded that the pERG amplitude is reduced and the implicit time is significantly delayed. Bobak et al (1983) also reported the absence of a pERG in 3 out of 4 eyes with chronic glaucoma.

Thus, some studies point towards abnormal pERGs in patients with glaucoma while others report abnormal pERGs in glaucoma only when there are accompanying changes in the optic nerve head or measureable field changes. The difference in findings may be due to the degree and duration of glaucoma in the test groups as well as individual variations in ocular vascular perfusion pressures. The relationship of this latter factor to intraocular pressure and their combined influence on the function of retinal ganglion cells has not been examined systematically by pERGs.

Maculopathies

Support for the role of ganglion cells in the production of the pERG comes from Kirkham & Coupland (1981) who reported abnormal pERGs associated with cherry-red-spot-myoclonus syndrome. Although fERGs were normal, VERs were delayed, and pERGs were significantly reduced in amplitude. The absent pERG response was believed to reflect damage to the ganglion cells resulting from their storage of an abnormal metabolic product.

Arden et al (1984) reported reduced pERG amplitudes in 37 out of 40 patients with ocular disease restricted to the macular area. The average pERG amplitude was less than one-quarter of the normal value and was not correlated with fERG findings. A significant correlation did exist between the reduction in pERG amplitude and the reduction in visual acuity. The pERG therefore appeared to be a sensitive index of retinal abnormalities.

Celesia & Kaufman (1985) also reported abnormal or absent pERGs in 5 patients with maculopathies. Sherman (1982) found abnormal pERGs and VECPs to 14 and 28 min checks in patients with macular pathology.

Clinical Implications

Although a majority of researchers view the pERG as a pattern-evoked rather than a luminance-evoked response, vision literature contains conflicting reports as to the site of generation of the pattern ERG and the effect of various ocular disorders on the pERG response. Until this controversy is resolved and some of the factors affecting the pERG are better understood, the pERG should not be used in isolation as a procedure to arrive at a definitive differential diagnosis in the clinical environment.

Electrodes for ERG Recordings

There is a variety of electrode types available for recording the clinical ERG, in particular, the fERG. These devices consist of both corneal and non-corneal electrodes (Fig. 2-A) although recording from non-corneal sites (usually the lower lid margin) is often less than satisfactory due to variations in signal capture properties, attenuation of signal amplitude, and considerable electrical noise. Most corneal electrodes are not suitable for recording pERGs due to reduced optics resulting from the combination of the electrode and solutions used to protect the eye during testing. In addition, these electrodes require corneal anaesthesia, and are poorly tolerated by some patients, especially young children.

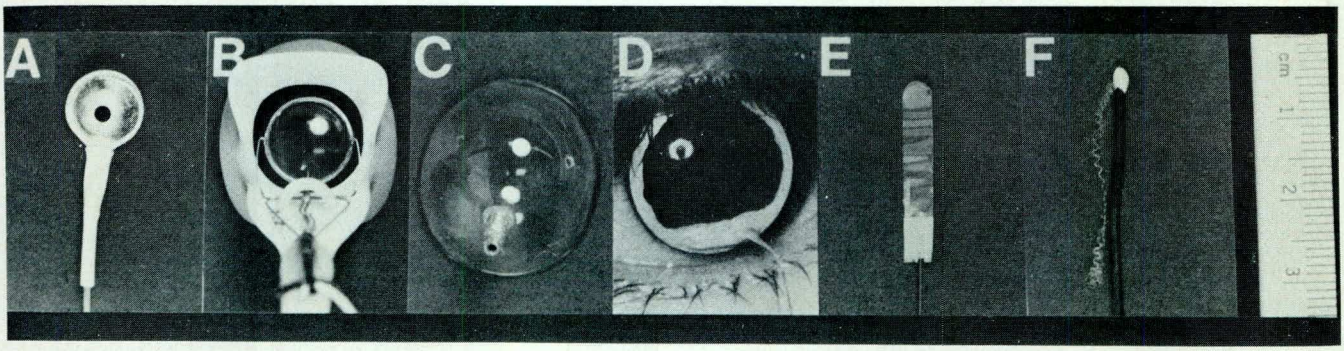

Fig. 2
A variety of electrodes used for recording the ERG, A: Surface cup electrode normally placed just below the lower lid margin. B: Burian-Allen electrode with lid speculum. C: Karpe electrode; a large haptic lens fitting under the upper and lower lids. D: A piggyback hard-soft contact lens electrode system. Electro-conductive silver paint on the rigid lens makes electrical contact with the cornea via the soft lens. (Figure adapted from Bloom & Sokol, 1977) E: Gold foil electrode. For use, the foil is shaped to vault the lid margin and touch the inferior corneo-scleral margin. F: DTL type fiber electrode. The scale on the right hand side applies to all frames but frame D.


LET'S CELEBRATE SOMETHING SPECIAL.

The Burian-Allen electrode (Fig. 2-B) is possibly the most widely used electrode for recording fERGs. It consists of a silver ring embedded in a plastic contact lens, which rests on the cornea, and a speculum that keeps the lids open (Riggs, 1977). A corneal anaesthetic, as well as a cushioning agent, typically methylcellulose, is required when the Burian-Allen electrode is used to record the fERG. Other types of electrodes commonly used for fERG recording include the Karpe and Henkes electrodes (Riggs, 1977) (Fig. 2-C).

Several researchers have designed new forms of electrodes suitable for recording the pERG. Bloom & Sokol (1977) introduced a corneal electrode system consisting of a silver ring painted on a plastic contact lens which sat atop a large soft contact lens (Fig. 2-D). In this piggyback system no corneal anaesthetics or other solutions are required. The optical characteristics of this electrode sandwich were reported to be excellent (Bloom & Sokol, 1977), and pERGs were successfully recorded.

Arden et al (1979) described the use of an ERG electrode made of gold foil and Mylar film (Fig. 2-E). This electrode was reported to be inexpensive, simple to fabricate and most importantly, non-irritating since the electrode hooked over the lower lid and made electrical contact with the cornea only at the inferior limbal area. Because this electrode did not interfere with the optics of the eye, pERGs could be recorded.

Dawson et al (1979) developed a corneal electrode (DTL electrode) consisting of a low mass conductive thread made of spun nylon fibres impregnated with metallic silver (Fig. 2-F). The thread is draped on the cornea or placed into the lower conjunctival sac and electrical contact with an averaging computer is made through the cornea-tear film-nylon thread interfaces. The DTL electrode is easily made in the laboratory from commercially available nylon fibre. Preliminary testing with the DTL electrode indicated excellent patient acceptance with no reports of corneal pain. Corneal anaesthesia is not usually required, nor are additional cushioning agents needed. Since the DTL electrode does not interfere with form vision, pERGs may be recorded.

Due to its ease of production, excellent patient acceptance, and non-interference with the optics of the eye, a DTL type electrode is the electrode of choice for recording pERGs in the Electrodiagnostic Clinic at the University of Waterloo, School of Optometry.

Contrast Dependent Electrodiagnostic Tests

The two most frequently utilized non-invasive electrophysiological tests of visual function that employ patterned visual stimuli are the Visually Evoked Response (VER) and the pattern dependent ERG. Both of these diagnostic procedures generally use checkerboard targets with checks of variable spatial frequency reversed in counterphase at pre-set rates. Although the response frequency of the retinal (pERG) and macular-cortical (VER) mechanisms parallel each other, as well as the checkerboard reversal rate, the amplitude and temporal features of salient components of the response differ significantly. Important differences also exist between the response amplitude-stimulus pattern size function for the pERGs and pattern VERs. To evaluate and compare the pERG and VER waveform morphology and their amplitude and time characteristics as a function of pattern size and reversal rate we recorded the pattern ERGs and VERs from each eye of 10 payed volunteers (6 males and 4 females) aged 20 to 29 years. All subjects had good ocular health, steady centered fixation and visual acuity of at least 20/20 (6/6) in each eye.

Pattern ERGs were recorded using fiber electrodes (Fig. 3-A) similar to those described by Dawson et al (1979). The fiber portion of the electrode was moistened with physiological saline, and then positioned in the lower conjunctival sac of the test eye (Fig. 3-B). The wire portion of the electrode cemented to the fiber was taped to the skin slightly below the lateral canthus, allowing the fiber to vault the lid margin. An adult size pre-gelled Ag/AgC1 electrode normally used for electrocardiograms was positioned about 1 cm temporal to the lateral canthus and served as a reference electrode. The circular plastic adhesive collar for the Ag/AgC1 electrode was cut tangentially to eliminate lid irritation once applied to the lateral canthus. (Neonatal/pediatric monitoring electrodes made by Ferris Manufacturing Corp. Illinois offer the advantage of a soft electrode that readily conforms to facial contours and has a more easily removeable collar for pediatric testing and for patients with sensitive skin.) A similar electrode placed on the inner wrist served as the electrical ground. Skin-

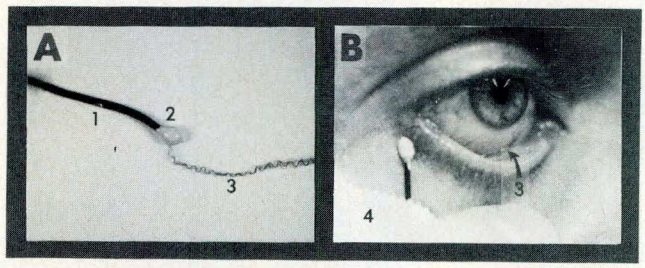

Fig. 3
A: Fiber electrode used to record pERGs. The key to the small numbers in plates A and B is as follows: 1) multi-stranded copper wire, 2) non-conductive epoxy covering the cold silver solder joint between nylon fibers and copper wire, 3) nylon thread composed of 6 to 7 silver impregnated nylon fibers, 4) surgical adhesive tape securing fiber electrode to temporal periorbital area.

B: Plate showing fiber electrode positioned in lower fornix. The lower lid is everted for illustration purposes. During testing, the lower lid covers the fiber portion of the electrode and holds the fiber in the lower cul de sac.

electrode impedance for the active electrode was in the order of 0.5 to 1.0 Kohms, and 0.5 to 2.0 Kohms for the reference and ground electrodes.

VERs were recorded using an active electrode placed approximately 2 cm above the inion with the reference electrode 6 cm higher along the mid-sagittal plane. The right ear served as the electrical ground.

The subject monocularly viewed a reversing checkerboard pattern on a Nicolet 1006 television monitor. The overall checkerboard field size for the 1 m observation distance was about 13 degrees by 17 degrees. A Spectra Pritchard photometer was used to measure the luminance of central and peripheral sectors of the checkerboard field. The space averaged luminance of the television screen was about 100 cd/sq m. Checkerboard check contrast was calculated to be about 87% by the following formula:

$$\text{contrast} = (L_{max} - L_{min}) / (L_{max} + L_{min}),$$

where Lmax was the measured luminance of a white check and Lmin was the measured luminance of a black check. Testing was performed for checks subtending 7, 14, 28, 56 and 112 min of arc at the corneal plane. All recordings were made with subjects wearing their habitual ophthalmic corrections. No cycloplegics or mydriatics were instilled into the observers' eyes.

Steady state pERGs and VERs were recorded for a checkerboard reversal rate of 7.5 Hz. An average of 100, 500 msec epochs constituted a single trial. Transient pERGs and VERs were recorded for a checkerboard reversal rate of 1.9 Hz. An average of 100, 200 msec epochs formed a single trial. Low and high bandpass input filters were set at 1 and 30 Hz, respectively.

The electrodiagnostic unit available to the investigators required that the testing sequence consist of sequential measurements of the steady state and transient pattern ERGs followed immediately by sequential recordings of the steady state and transient pattern VERs. The availability of a multi-channel averaging computer allowing independent specification of signal amplification for each channel would have made simultaneous recordings of VERs and ERGs possible, and significantly decreased the subject-investigator contact time.

ERGs and VERs were amplified (X10,000) on a Nicolet CA-1000 averager and stored on floppy diskettes for subsequent retrieval and analysis. Digitized data was down-loaded into a slave computer that had specially designed software for analysis and plotting of ERG and VER waveforms. The slave computer was programmed to search for and measure trough-to-peak amplitudes and display the averaged amplitude of salient waves in the evoked potentials.

Results

Group averaged steady state and transient ERG and VER amplitudes, as a function of checkerboard check size, are shown in Fig. 4-A and 4-B, respectively. Both steady state and transient VERs demonstrated spatial tuning properties with peak amplitudes occurring for a check size of 14 minutes of arc. The amplitudes of VERs decreased for check sizes below and above the selective maximal response tuned for 14 minute checks.

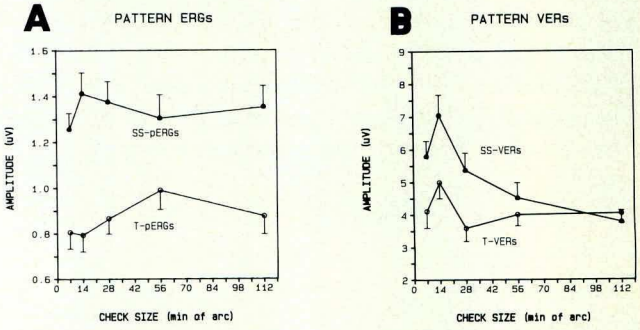

Fig. 4

A) Amplitude of the steady state pattern ERG (SS-pERG) and transient pattern ERG (T-pERG) as a function of checkerboard check size. For frames A and B each data point is the group averaged value for ERGs and VERs for 20 eyes. Vertical bars through the data points represent standard error of the mean (SEM) bars. For illustration purposes, only plus or minus SEM values are shown for each data point. The SS-pERG did not show strong spatial tuning, although there was a tendency to peak near 14 minutes of arc checks. T-pERGs showed a clear tuning for 56 minute checks.

B) Amplitude of the steady state pattern VER (SS-VER) and transient pattern VER (T-VER) as a function of checkerboard check size. Both SS-VERs and T-VERs showed clear spatial tuning for 14 minutes of arc checks.

Group averaged steady state pERGs demonstrated a trend for a peak in the response amplitude for 14 minutes of arc check sizes. This tendency for spatial frequency tuning at or close to 14 minutes of arc was also seen for a group analysis for right and left eyes. An analysis of the group averaged amplitudes of the q-wave (first major positive peak) in the transient pERG for each check size showed a strong tendency for the amplitude-check size function to peak at 56 minutes of arc. Thus, the transient pERG spatial tuning was for target sizes about four times as large as those for either the steady state pERGs and VERs or transient VERs.

The absolute amplitudes of the steady state and transient VERs and ERGs differed greatly. Group averages with standard error values are given in Table 1. On average, steady state VERs were approximately four times as large as steady state ERGs, while transient VERs were about five times larger than transient ERGs.

The implicit times (time from onset of a stimulus to the peak of the stimulus related response) of the P-1 and q waves of the transient pattern VER and ERG, respectively, varied with checkerboard check size.

Fig. 5 shows the implicit time of the P-1 and q waves as a function of check size. For the transient VER, the implicit time decreased with an increase in check size from 7 to 28 minutes of arc and then increased with a further increase in check size. The shortest implicit time was seen for the 28 minutes of arc checks. The biphasic implicit time-check size function for the transient VER was in sharp contrast to that seen for the transient pERG which showed a near linear trend. The implicit time of the q wave decreased as the checkerboard check size increased. In general, the implicit time of the P-1 component of the transient VER was much longer than the implicit time of the q wave in the transient ERG. The shortest time for P-1 (106 msec) was about twice as long as the shortest time for the q wave (54 msec).

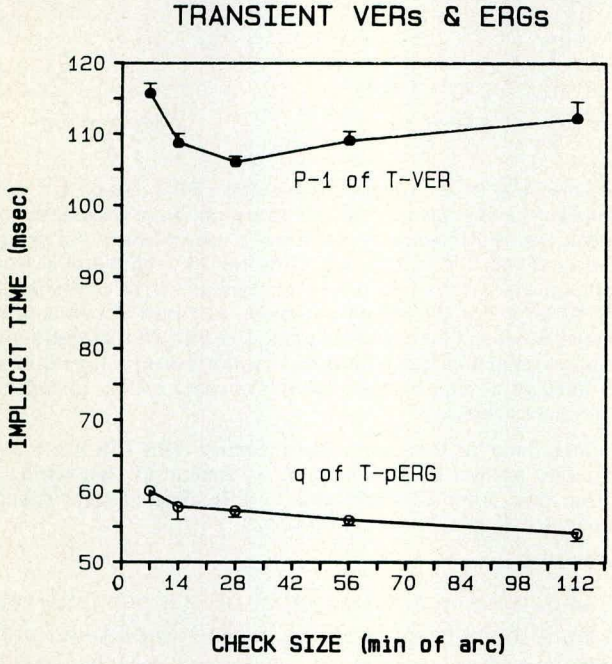

Fig. 5
The implicit time of the first major positive wave in the transient pattern VER (P-1 component) and transient pattern ERG ('q' wave component) as a function of checkerboard check size. The implicit time of P-1 decreased as check size was increased, reached a minimum value for 28 minutes of arc checks, and then increased with a further increase in check size. The implicit time of the 'q' wave varied monotonically with checksize, showing a progressive decrease with increased check size.

Sample recordings of steady state and transient pERGs and VERs for one subject are presented in Fig. 6. These records show the similarity of the waveforms elicited for each test condition and highlight the differences in amplitude and temporal aspects of retinal versus macular-cortical recordings.

Electrodiagnostic Evaluation of Visual Dysfunction

The function of the human visual system can be assessed objectively at various levels by the judicious selection and application of one or several electrodiagnostic procedures. Recently the pattern

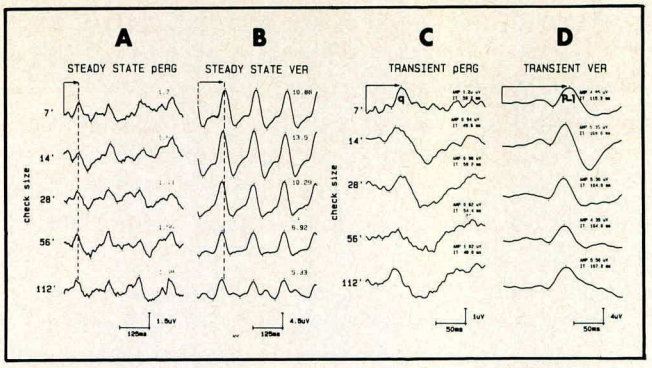

Fig. 6
Sample recordings for one subject for steady state pERGs (A), steady state VERs (B), transient pERGs (C), and transient pattern VERs (D). Each wave represents the average of 100 epochs. Note the similarity in the waveform for steady state recordings at the retinal level (A) and cortical level (B) but the very large difference in the amplitude of the response. The amplitude calibration scales at the bottom of each column of waves show that the VERs are several times larger than the ERGs. The horizontal arrows drawn above the first record in each column emphasize the difference in the time of occurrence of the first positive peak in ERG and VER samples within the steady state or transient recording mode. The longer implicit times for the VERs reflect the neural transmission time from the eyeball to the macular projection areas in the visual cortex. The small number beside each record for steady state pERGs or VERs is the computer determined average trough-to-peak amplitude of the first three consecutive positive waves. For transient recording conditions, the small numbers indicate the computer measured amplitude and implicit time of the 'q' and P-1 waves. The 'q' wave for the pERG and the P-1 wave in the VER are identified in bold print in the first record in columns C and D. The dots within each waveform identify the computer selected troughs and peaks for the 'q' and 'P-1' components.

Table 1 pERG and VER Amplitudes

	Pattern ERGs		VERs	
Check size (min of arc)	Steady State (uV)	Transient (uV)	Steady State (uV)	Transient (uV)
7	1.26 ± 0.07*	0.81 ± 0.07	5.79 ± 0.47	4.12 ± 0.52
14	1.41 ± 0.09	0.79 ± 0.07	7.05 ± 0.63	5.00 ± 0.49
28	1.38 ± 0.09	0.87 ± 0.07	5.37 ± 0.53	3.59 ± 0.40
56	1.31 ± 0.10	0.99 ± 0.09	4.51 ± 0.47	4.01 ± 0.35
112	1.38 ± 0.09	0.88 ± 0.08	3.77 ± 0.36	4.04 ±0.30

*wave amplitude ± standard error of the mean
N=20 eyes

ERG has been incorporated into the well-established range of neurophysiological tests used in the Electrodiagnostic Clinic at the University of Waterloo, School of Optometry. The scope and nature of the electrodiagnostic tests together with the specific and general levels in the visual system examined by these procedures is schematically illustrated in Fig. 7. The cases presented below will demonstrate the clinical application of these non-invasive tests towards the diagnosis of the nature and extent of visual dysfunction. Emphasis will be placed on any new or complimentary diagnostic information provided by transient or steady state pattern electroretinograms.

Case 1: Optic Neuritis

A 28 year old female, JM, with a history of retrobulbar optic neuritis and pars planitis in the left

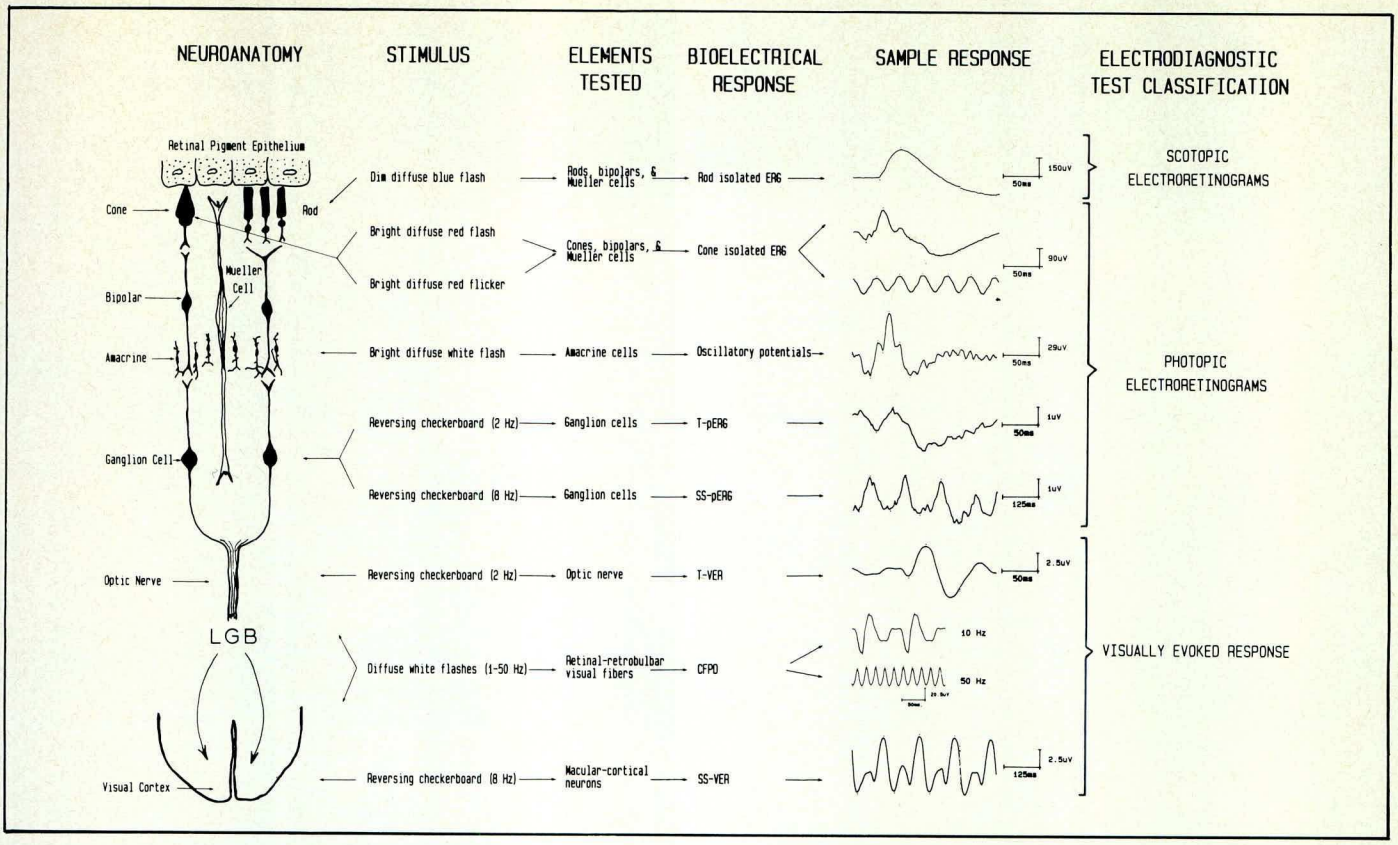

Fig. 7
Schematic representation of the test procedures used to clinically assess the functional integrity of various cellular elements within the retina and retrobulbar components of the visual system. Compare the amplitude-time characteristics for the sample waveforms provided for each test procedure. The pattern ERGs are much smaller than pattern or flash VERs. The key to some abbreviations used are as follows: T-pERG (transient pattern electroretinogram), SS-pERG (steady state pattern electroretinogram), T-VER (transient visually evoked response), CFPD (critical frequency of photic driving), SS-VER (steady state visually evoked response).

eye voiced complaints of some retrobulbar pain on movement of the eye at the time of testing. Aided visual acuities were OD, 20/20 (6/6), 0S, 20/30 -1 (6/9 -1).

An evaluation of gross cone function in each eye by photopic flash and flicker ERGs did not reveal any major dysfunction in either eye (see Fig. 8-A). The amplitudes of both flash and flicker ERGs were within normal limits, but the responses from the left eye were marginally smaller than those from the right eye. An assessment of the amacrine cell layer function by photopic oscillatory potentials did not disclose significant differences between the two eyes or deviation from normal limits, although the first oscillatory potential for the left eye was not well differentiated (see Fig. 8-B). Steady state pERGs were used to evaluate the ganglion cell layer function. The differential response to reversing checkerboards with graded check sizes revealed relative differences between the right and left eyes (see Fig. 8-C). Steady state pERGs for the right eye indicated spatial frequency tuning to 14 min checks while the left eye showed a progressive increase in response amplitude with increased check size. A significant reduction in the pERG amplitude and altered waveform for the left eye for 7 and 14 min checks inferred that the more centrally located ganglion cells with finer receptive fields were more affected than more peripheral ones which normally respond to larger check sizes. An evaluation of visual neurons within the macular-cortical tract by steady state VERs showed a significantly reduced response in the left eye for smaller check sizes (7, 14, and 28 min) (see Fig. 9-A). This indicated that the cause of the reduction in measured visual acuity for the left eye was an organic lesion. An examination of the optic nerve transmission property by transient VERs showed a significantly reduced amplitude for the left eye although implicit times were comparable for both eyes and within normal limits (see Fig. 9-B). This indicated a decreased number of responding fibers in the left eye, but no demyelination of residual visual fibers since the implicit time of P-1 was normal.

For this patient the combination of photopic ERGs and VERs localized the earliest site of the lesion to the ganglion cell layer in the left eye. This did not exclude lesions in retrobulbar visual pathways, but confirmed that the inflammatory process left sequelae within the innermost layer of the retina. The steady state pattern ERG and VER data were complimentary since very similar amplitude-check size functions were revealed within and between each eye.

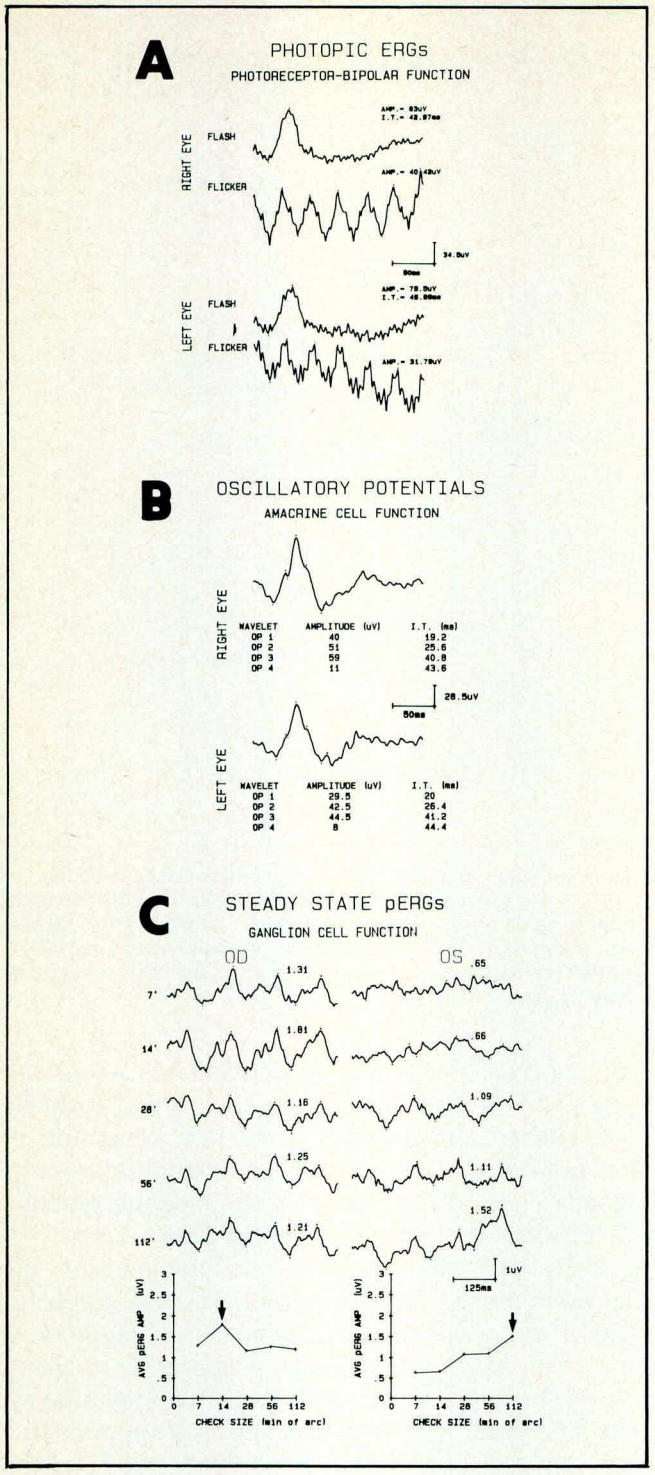

Fig. 8
Photopic ERGs (A), oscillatory potentials (B), and steady state pERGs (C) for a patient with a history of retrobulbar optic neuritis and pars planitis in the left eye. Photoreceptor and amacrine cell functions were within normal limits for both eyes. Pattern ERGs showed a loss of sensitivity to high spatial frequency stimuli in the affected eye. The small inverted arrows indicate the peak pERG response for each eye and emphasize the loss of ganglion cells responsive to fine detail in patterned stimuli.

Case 2: Multiple Sclerosis

KB, a 42 year old female, had a history of right optic neuritis and confirmed multiple sclerosis. Aided visual acuities were OD, 20/20 (6/6), OS, 20/15 -1 (6/4.5 -1).

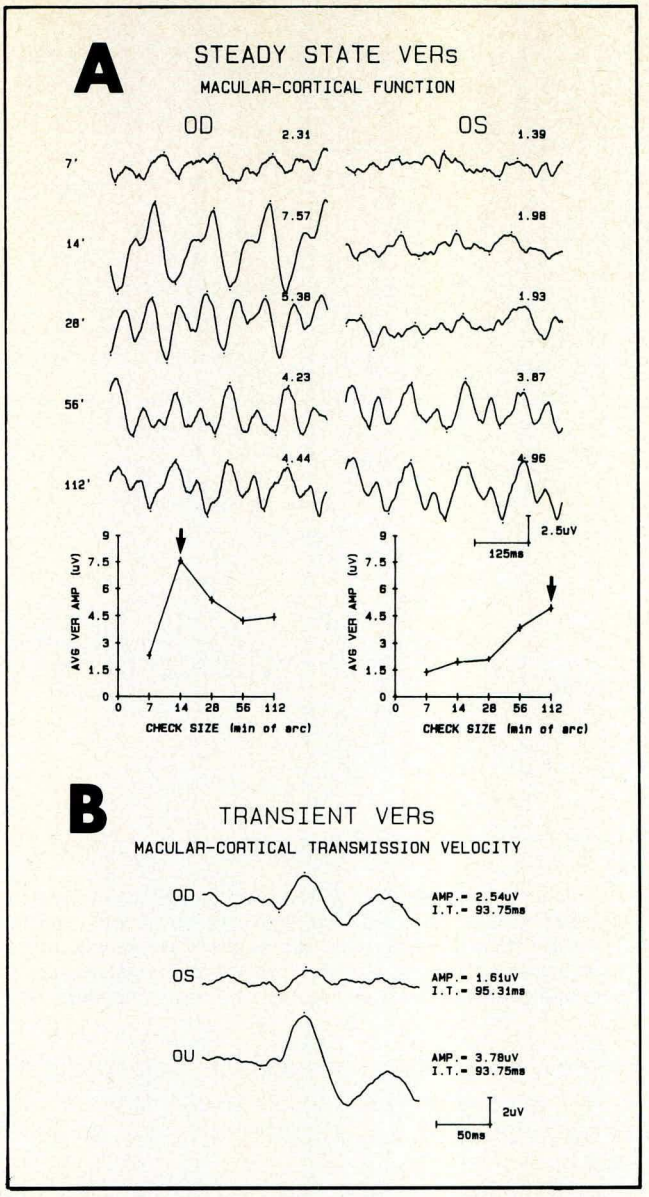

Fig. 9
Steady state and transient VERs for the same patient whose test results are shown in Figure 8. A clear reduction in the SS-VER waveform was seen in the left eye for 7 to 28 minutes of arc checks. The right eye showed a normal amplitude-check size function. The implicit time of P-1 in the transient VERs was equal and within normal limits for each eye. However, the amplitude of P-1 for the left eye was significantly reduced, indicating optic nerve damage.

Photopic flash and flicker ERGs were almost identical for the two eyes, and did not indicate any major cone dysfunction in either eye. Photopic oscillatory potentials were well formed and equal for the two eyes. Steady state pERGs revealed a similar relationship between wave amplitude and check size for the two eyes, with spatial frequency tuning to 56 min check size (Fig. 10-A). However, responses were attenuated for the right eye for all spatial frequencies inferring a reduction in the functional integrity of central and peripheral ganglion cells. Steady state VERs (Fig. 10-B) indicated normal functional integrity of macular-cortical pathways for both eyes but a considerably reduced response in the right eye for the 7 minutes of arc check size.

Transient VERs revealed a reduced amplitude for the right eye with a slightly prolonged transmission time (Fig. 10-C).

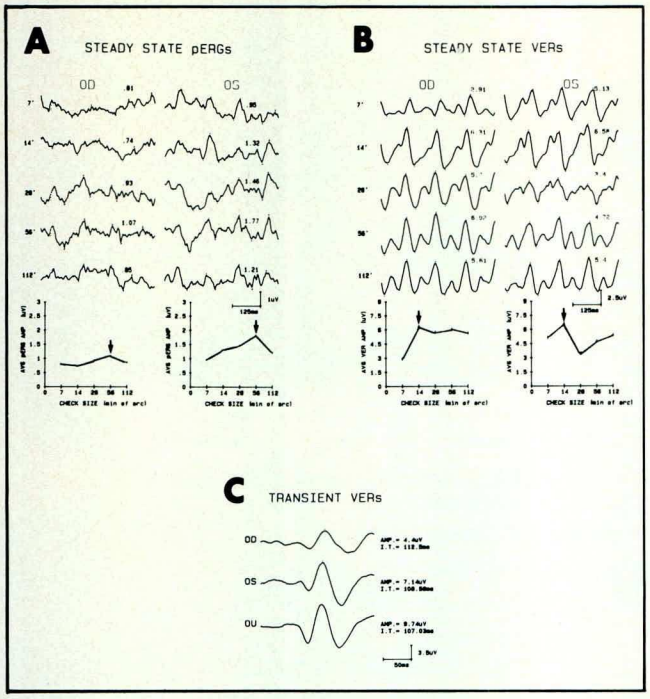

Fig. 10
Steady state pattern ERGs (A), steady state VERs (B), and transient pattern VERs for a 42 year old female with diagnosed multiple sclerosis and recurrent optic neuritis for the right eye. SS-pERGs showed spatial tuning for 56 minutes of arc checks (see inverted arrows) while the SS-VERs showed spatial tuning for 14 minutes of arc checks. The reduced responsivity to checks of all sizes for the pERGs from the right eye correlated with the patient's report of inferior vision for that eye even though she could attain 20/20 vision in both eyes. Transient VERs showed a slight delay in macular-cortical transmission time for the right eye as well as a reduced amplitude of the P-1 wave.

For this patient the electrodiagnostic test procedures implicated a lesion in the ganglion cell layer with some demyelination of the optic nerve for the right eye. These findings corroborated the patient's symptoms of inferior vision for her right eye despite a measurement of normal visual acuity.

Case 3: Glaucoma

A 70 year old male, PL, with a history of glaucoma in the right eye was assessed in the Electrodiagnostic Clinic. Prior to the therapy for glaucoma, the intraocular pressures were OD 32 mm Hg, OS 16 mm Hg. At the time of the electrodiagnostic assessment the pressures were OD 23 mm Hg, OS 17 mm Hg. Aided visual acuities were OD, 20/20 (6/6), OS, 20/25 +2 (6/7.5 +2). Superior visual fields were constricted in the right eye with some loss in the superior and inferior arcuate areas. The contrast sensitivity function, evaluated at the near point, indicated an overall depression for all spatial frequencies for the right eye.

Photopic flash and flicker ERGs were detectable but reduced in amplitude for the right eye. This finding was attributed to the inequality of pupil size (OD 2.5 mm, OS 6 mm) resulting from the use of miotics to lower the intraocular pressure in the right eye and/or a possible generalized dysfunction of the photoreceptors. Photopic oscillatory potentials did not reveal any significant differences between the two eyes. Steady state pERGs indicated spatial tuning for 28 min check size for the right eye and an increase in response amplitude with increased check size for the left eye (Fig. 11-A). A maximal response was seen for the 56 minutes of arc checks for the left eye. The differential response across spatial frequencies for the two eyes with reduced responses for higher spatial frequencies (small checks) in the left eye pointed towards a neural abnormality in the non-glaucomatous eye, probably due to non-pathological aging phenomena. The reduced pERG for the small checks likely reflects changes in ganglion cells tuned to higher spatial frequencies, and accounts for the reduction in visual acuity for that eye. Assuming an identical non-pathological selective deterioration of ganglion cells tuned for higher spatial frequencies to be present in the right glaucomatous eye, the larger response to 7 minutes of arc checks can be attributed to the optical effects of the miotic pupil which enhances retinal imagery by the associated increased depth of focus. The loss of sensitivity to lower spatial frequencies (larger checks) is consistent with the literature reports of earlier loss of more peripherally located ganglion cells in glaucoma which require larger targets for optimal excitation. Steady state VERs showed similar functional integrity of macular-cortical pathways for both eyes (Fig. 11-B). Transient VERs showed optic nerve

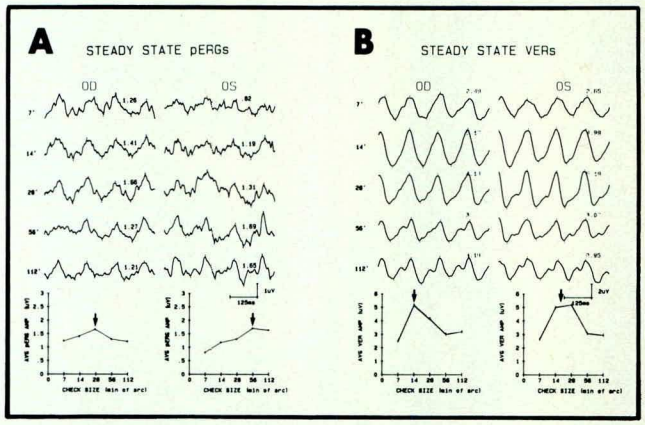

Fig. 11
Steady state pattern ERGs (A) and steady state VERs (B) for a 70 year old male with unilateral glaucoma in the right eye. VERs show similar amplitude-check size functions with maximal response amplitude centered at or close to 14 minutes of arc checks. SS-pERGs showed amplitude-check size functions that differed significantly for the two eyes. The small inverted arrows show response peaks for different check sizes for the two eyes. As well, a loss of sensitivity for lower spatial frequencies (larger checks) is seen in the glaucomatous eye. The greater response in the right eye for small checks may be due to enhanced retinal imagery resulting from the pupillary miosis caused by the pharmacological management of glaucoma.

transmission times to be prolonged bilaterally at a rate consistent for the advanced age of the patient.

In this patient loss of functional integrity was indicated at the photoreceptor and ganglion cell layer.

Case 4: Senile Macular Degeneration

WL, a 71 year old male patient, had reduced acuity in the left eye likely attributable to incipient senile macular degeneration. Aided visual acuities were OD, 20/20+1 (6/6 +1), OS, 20/25 (6/7.5).

Photopic flash and flicker ERGs indicated similar gross cone function for the two eyes with no significant deviation from the normal. Oscillatory potentials were unremarkable. Pattern ERGs (Fig. 12-A) exhibited spatial tuning to 28 min checks for both eyes, however response amplitudes were more reduced at higher and lower check sizes for the left eye. The reduced response at high spatial frequencies (small checks) was interpreted as a neural reflection of decreased potential for high resolution. Steady state VERs (Fig. 12-B) did not indicate a significant difference between the two eyes with respect to macular-cortical function. Optic nerve transmission time was typically and equally prolonged in both eyes for the patient's age.

In this case, the pERG was the only indicator of visual acuity deficits in the left eye.

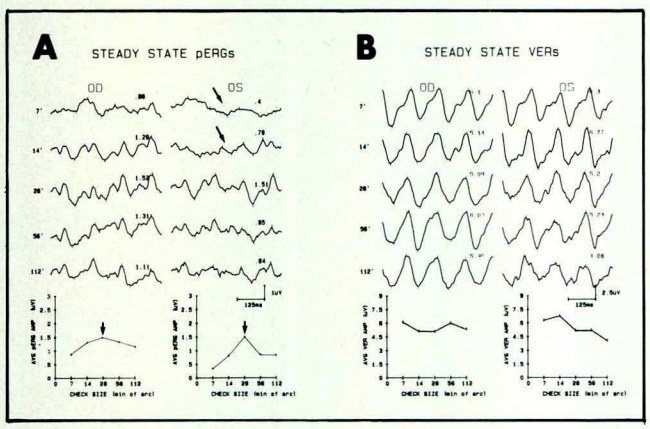

Fig. 12
Steady state pattern ERGs (A) and steady state VERs (B) for a 71 year old male with incipient senile macular degeneration in the left eye. VERs were unremarkable inasmuch as they showed similar intact macular-cortical pathways. On the other hand, while the response amplitude-check size function for the pattern ERGs peaked at 28 minutes of arc checks for both eyes, responses for high spatial frequencies (small checks) for the eye with presumed incipient macular degeneration were attenuated in comparison to the right eye. The small oblique arrows identify those records for the left eye where the waveform and signal strength were significantly reduced.

Discussion

The present investigation has shown that the two electrodiagnostic tests most commonly used to evaluate form vision, the pattern ERG and VER, can be differentially or similarly affected in ocular disease processes. Alterations in the pERG amplitude-check size function may be paralleled by similar changes in the VER (case 1), interocular differences in the overall level of the pERG sensitivity across the spatial frequency spectrum of check sizes may occur without a comparable alteration in the VER amplitude-check size function (case 2), and interocular differential loss of pERG sensitivity at specific spatial frequencies may not be accompanied by similar frequency dependent interocular differences in the VER amplitude-check size function (case 3 and 4). The fact that pERGs and VERs are similarly affected in optic nerve disease (case 1) suggests that they have a common generator, or alternatively, two distinct generators in close spatial proximity or in serial functional order. The apparent dissociation of pERGs and VERs, seen as alterations in the pERG amplitude-check size functions without changes in the same function for VERs, suggests that the pERG may be a more sensitive indicator of subtle neural dysfunction than the VERs. This may be explained on the basis of the most commonly accepted view concerning the origin of the pERGs; if pERGs reflect activity of retinal ganglion cells with representation in very large sectors of the visual field (Vaegan et al, 1982), then they may be more vulnerable to decay since disease processes affecting both central or peripheral vision would impinge on the pERG. On the other hand, pattern VERs may be less susceptible to visual neural disease than pERGs since they primarily reflect the functional integrity of neural links between retinal macular areas and their cortical projections. Thus an ocular disease such as glaucoma which clinically is diagnosed by its early preferential damage to arcuate fibers (Bjerrum's scotoma) may not be detected by the VER until extensive pressure related damage has occurred to the peripheral optic nerve fibers, or less severe damage has occurred to fibers corresponding to the macular areas.

The cases presented emphasize the value of performing both pERGs and VERs in order to identify subtle visual neural dysfunctions. For the patient with retrobulbar optic neuritis (case 1) the VERs readily identified the organic lesion causing the reduction in central vision. The pERGs were not essential for diagnostic purposes but did parallel VER results and helped to elucidate the full extent of neural damage. In the case of the patient with multiple sclerosis and right optic neuritis (case 2) the VERs detected functional loss for only high spatial frequency targets (7 min of arc checks) in the affected eye. The pERGs for that eye, however, showed a more generalized loss of sensitivity for all spatial frequencies tested. These results are reminiscent of those from contrast sensitivity testing where in spite of normal Snellen visual acuity measurements, a global decrease in contrast sensitivity is often seen for all spatial frequencies in

the presence of patient complaints of reduced visibility in the affected eye. Similarly, the detection of interocular differences in pERG amplitude-check size functions without significant differences in VER amplitude-check size functions emphasizes the necessity of employing multiple test procedures for clinical diagnostic purposes.

The discrepancies in ophthalmic literature pertaining to the effects of ocular and systemic disease on the pERG may be largely due to the restricted scope of stimuli used to evoke the retinal response. Most studies (Bobak et al, 1983, Persson & Wanger, 1984, Papst et al, 1984) have employed single check size checkerboards or bar gratings in their evaluation of retinal function. It is clear from the results of this study that testing with multiple check size checkerboards yielding a profile of the differential response across spatial frequencies (Trick & Trick, 1984) constitutes a more effective procedure for revealing neural deficits. The pERG amplitude-check size profile allows a broad spectrum interocular comparison of visual performance in cases of unilateral ocular pathology. The determination of distinctly different monocular response amplitude-stimulus size profiles or sensitivity levels for a patient is a diagnostic finding signalling the need for repeated or expanded investigation for incipient or previously undetected ocular disease. The pERG profile analysis also provides a viable method for monitoring longitudinal alterations in the physiology of ganglion cells where an assessment of interocular or intraocular changes can be made on a relative basis. Inter-trial variations in absolute pERG amplitudes due to variations in electrical resistances for the recording electrodes in situ can be ignored, thereby avoiding potential errors in diagnosis.

In summary, our examination of the relationship between pERG amplitudes and the spatial frequency of checkerboard checks in a group of subjects without ocular disease revealed a clear spatial frequency tuning for transient pERGs and a less distinct tuning for the steady state pERGs. Transient and steady state VERs showed a peak response for 14 minutes of arc checks. There were no significant interocular differences in any of these response amplitude-stimulus size functions. In contrast, subjects with diagnosed diseases showed significantly different pERG profiles. In all cases presented, the pERG duplicated VER findings or provided information not present in VER records. We conclude that the pERG is a useful clinical diagnostic procedure when used in conjunction with other well established electrophysiological tests. Care must be exercised in the use of pERGs for they can be difficult to record and show considerable variability in even normal subjects. Failure to record pERGs should not be considered diagnostic until repeated attempts with different electrodes and stimulus parameters have confirmed their extinction.

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