STUDIES ON THE LUMINANCE-RELATED CHARACTERISTICS OF THE TRANSIENT PATTERN REVERSAL ELECTRORETINOGRAM

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Doctor of Philosophy

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SUMMARY

The electroretinogram evoked by reversal pattern stimulation (rPERG) is known to contain both pattern contrast and luminance related components. The retinal mechanisms of the transient rPERGs subserving these functional characteristics are the main concern in the present studies. Considerable attention has been paid to the luminance-related characteristics of the response.

The transient PERGs were found to consist of two subsequent processes using low frequency attenuation analysis. The processes overlapped and the individual difference in the each process timings formed the major cause for the variations of the negative potential waveform of the transient rPERGs.

Attention has been paid to those having 'notch' type of variation. Under different contrast levels, the amplitudes of the positive and negative potentials were linearly increased with higher contrast level and the negative potential showed a higher sensitivity to contrast changes and higher contrast gain. Under lower contrast levels, the decreased amplitudes made the difference in the timing course of the positive and negative processes evident, interpreting the appearance of the notch in some cases. Visual adaptation conditions for recording the transient rPERG were discussed.

Another effort was to study the large variation of the transient rPERGs (especially the positive potential, P50) in the elderly whose distant and near visual acuity were normal. It was found that reduction of retinal illumination contributed mostly to the P50 amplitude loss and contrast loss mostly to the negative potential (N95) amplitude loss. Senile miosis was thought to have little effect on the reduction of the retinal illumination, while the changes in the optics of the eye was probably the major cause for it, which interpreted the larger individual variation of the P50 amplitude of the elderly PERGs. The studies by the aid of spherical dioptric lenses showed that convex defocus effected the transient rPERGs more effectively than the concave lenses, especially the N95 amplitude in the elderly. It was suggested that the disability of accommodation and the type and the degree of subjects' ametropia should be taken into consideration when the elderly rPERGs were analysed.

The thesis therefore has elaborated some theoretical mechanisms of the retinal detection of a pattern (receptive fields) and functional characteristics of the luminance-related response. The experiments data has provided some evidence supporting the assumption of the independent retinal origins of the two processes of the transient rPERGs.

KEY WORDS: pattern electroretinogram; transient reversal pattern; luminance-related response; defocus; near vision.

to my parents

DR. DA CUI AND DR. DAOJUN LU

&

my daughter

NAI

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CHAPTER 1.

THE ANATOMY AND ELECTROPHYSIOLOGY OF THE RETINA

1.1 RETINAL STRUCTURE

1.1.1 Introduction

The retina extends from the ora serrate anteriorly to the optic disc posteriorly. Around the disc and at the ora serrate the retina is mostly firmly attached to the pigment epithelium layer while elsewhere the attachment is looser (Miller, 1982). The most peripheral portions of the retina, particularly at 4-mm-wide zone in the temporal region, where the elements are smaller and more sparse (Salzmann, 1912), and oriented differently (Laties et al., 1968)), are devoid of function. The posterior pole (macula) of the eye measures 5.50 mm in diameter and subserves approximately 18 degrees 20 minutes of visual field and the highest visual acuity (Miller, 1982). The optic nerve head (its anterior surface is the clinically visible optic nerve disc), lies histologically nasal to the macula with a diameter of 1.5 to 2.0 mm (Straatsma et al., 1969) and forms the output of the retina. Human retina is organised in an inverted way that light must pass through all the retina laminae before it starts to stimulate the retina (Wirth et al., 1984).

The visual scene first comes to retina through pupil to form a retina image. The light flow begins with the photoreceptors where light energy is transduced into electrical activities. The electrical signals are processed through chemical and electrical synapses of the retinal circuitry and the light information is sent sent out of the retina by the innermost (distal) layer of the retina---the ganglion cell layer to higher visual cortex for further information integration (Miller, 1982). The light falling on the retina comes to three regions of the brainstem--the lateral geniculate nucleus of the thalamus, the midbrain, and the pretectum (Cotter, 1990) through optic nerve, optic chiasm and optic tract. The visual information (such as the scene form, colour, movement, orientation and depth) from these regions can be addressed in the primary visual cortex (striate cortex ,ie,Broadman area 17 or V1) and then, in turn, in a number of other higher visual areas in the cortex (areas V2, V3, V3a, V4 and V5 or MT) to form visual representation (Dow, 1990).

1.1.2 Macula

The portion which is a yellow colour when viewed with the ophthalmoscope is known as the macula lutea. The yellow colour is believed to be due to carotenoid, xanthophyll in ganglion cells as well as in the bipolars in this region (Wald, 1946). This region measures about 2.0 mm horizontally and 0.88 mm vertically.

Histologically, macula may be divided into several zones---(1) the foveola, being located 4.0 mm temporal and 0.8 mm inferior to the center of the optic disc, measuring 0.35 mm across and is devoid of accessory neural elements and blood vessels; (2) fovea, extending outward from the foveola for approximately 0.75 mm, measuring about half the thickness of peripheral retina; these two regions are comprised entirely of cones---the foveola contains 2500 closely packed cones and the whole fovea contains about 100,000 cones; (3) parafoveal surrounds the foveal region and has a width of about 0.5 mm, measuring about 2.5 mm in diameter. It is characterised by the largest accumulation of the nerve cells in the entire retina (Hogan et al., 1971); (4) peripheral region is the furthest extent of the macula, measuring 1.5 mm in width with its outer boundary being 2.75 mm from the foveola (Miller, 1982).

The retina macula is highly differentiated. The differentiation of the macula is not complete until 4 to 6 months after birth (Bach and Seefelder, 1914). The completion parallels the observations using contrast sensitivity (Dobson, 1976; Bank and Salapatek, 1978) and visual evoked potentials (Sokol, 1976 and 1978) that acuity improves to 20/20 by approximately 6 months of age.

1.1.3 Retinal Neurons

Classically, the retina maybe divided into ten layers as shown in Fig1.1. It is composed of three cellular layers interspersed by two synaptic layers. The perikarya of the cone (C) and rod (R) cells, make up the outer nuclear layer (ONL). Horizontal cells (H), bipolars (B), amacrines (A), and interplexiform (I) cell bodies form the inner nuclear layer (INL). And ganglion cell perikarya (G) constitute ganglion cell layer (GCL).

Photoreceptors

In man, photoreceptors terminals in the outer plexiform layer fall into two morphological categories, rod spherules and cone pedicles (Cohen, 1972). They synapse with bipolars in

(Vitreous Body)

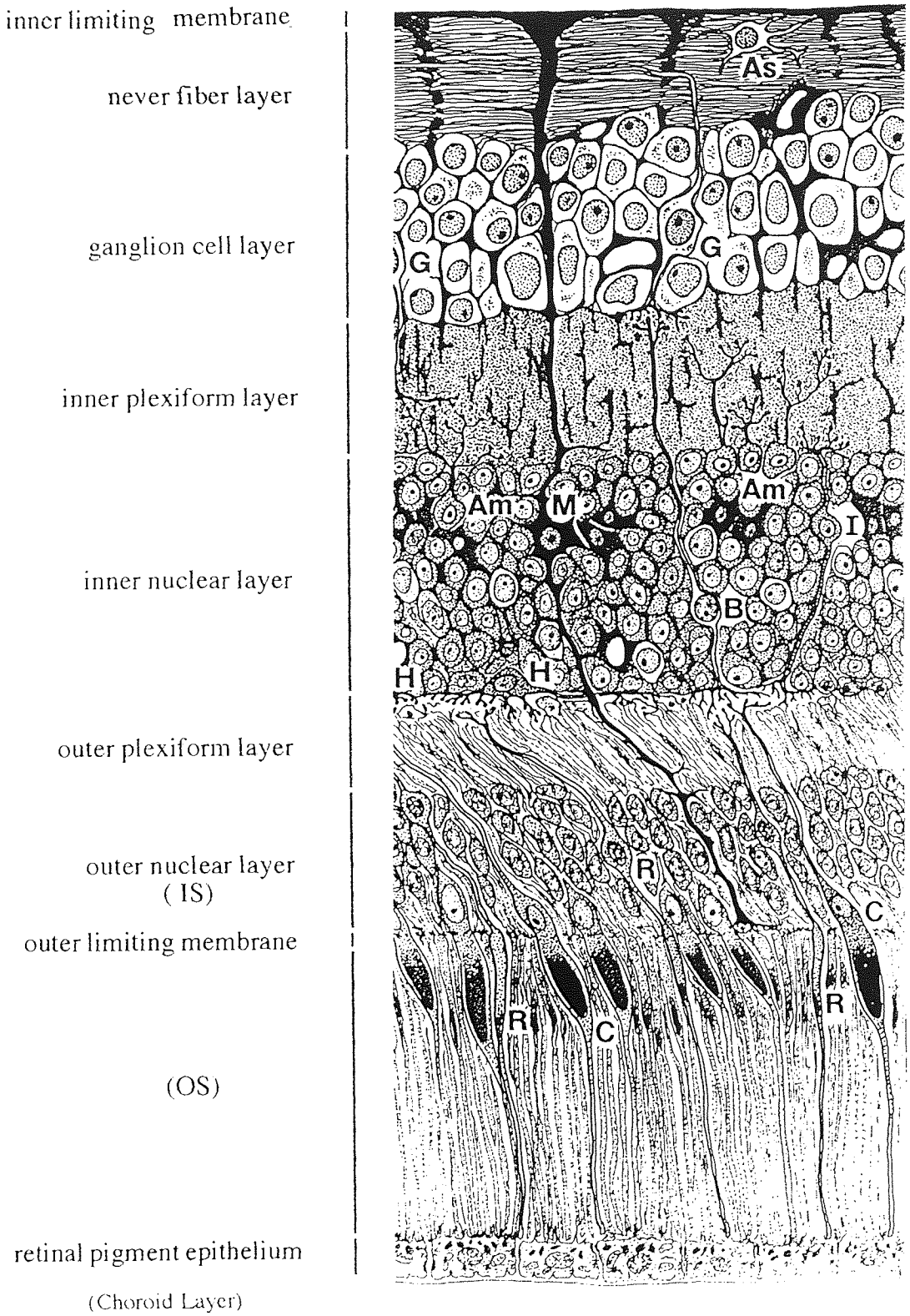

Fig 1.1 Summary diagram illustrating the transversal cellular organization of the human retina in the periphery of the central area. R: rods. C: cones. H: horizontal cells. B: bipolars. Am: amacrines. I: interplexiform cells. M: Müller's cells. G: ganglion cells. OS and IS: outer and inner sections of the photoreceptors. As: astrocytes (after Miller, 1982).

ribbon type (Dowling and Boycott, 1966).

Cones There are approximately 5 x 10^6 cones in the retina (Polyak, 1941). In the macula, cones outnumber rods, and in the fovea, the cone center segments become thinner and longer, and are oriented vertically with respect to the retina surface. In the periphery of the retina, cones are less numerous than rods and are boarder in shape. There are at least three different types of cones in primates and there are three or more different cone pigments (Miller, 1982). Colour vision and fine discrimination in light adaptation depend on cone vision (Slaughter, 1990).

Rods There are various estimates on the number of rods varying in human retina between a low of 75 x 10^6 and a high of 175 x 10^6 (Duke-Elder, 1932). At the fovea centralis there are no rods (Salzmann, 1912; Wyatt, 1988). Outside of this area rods become apparent, and within a very short distance they become many times more numerous than cones (Fig 1.2). Compared with the spectra of cones, which have maximum responses at wavelengths at 440-450nm for green, 525-540nm for blue colour, and 560-575nm for red, the spectrum of rods intermediate between blue and green, approximately 500nm (Fig 1.3) (Wald, 1964; Dartnall et al., 1983). The outer segments of the rods contain the photosensitive pigment, rhodopsin, which is bleached on exposure to light but reappears in the darkness, provided that the pigment epithelium is in contact with the rods. Rods are involved in low light vision and are primarily designed for the efficient capture, summation, and transmission of signals involving only a few quanta per rod per second (Slaughter, 1990).

Bipolar Cells

Bipolars lie predominantly in the middle zone of the inner nuclear layer. They constitute the second neuron in the direct path from the photoreceptors to the brain and are the principle relay neurons conveying visual afferent signals from the outer to the inner plexiform layer.

Cone bipolars (1) Each midget cone bipolar has a single synaptic connection with one cone cell, penetrating into an invagination of cone pedicles to form *Triad* (Fig 1.4a); A triad consists of two processes of horizontal cells, and a midget bipolar (Missotten, 1965; Stell, 1965; Dowling and Boycott, 1966; Cohen, 1981). Kolb (1970) reported that midget bipolar occurred in two types, the invaginating midget and also the flat midget, later making a superficial contact with the base of a single cone pedicle. A cone pedicle contains twenty five invaginating contacts and

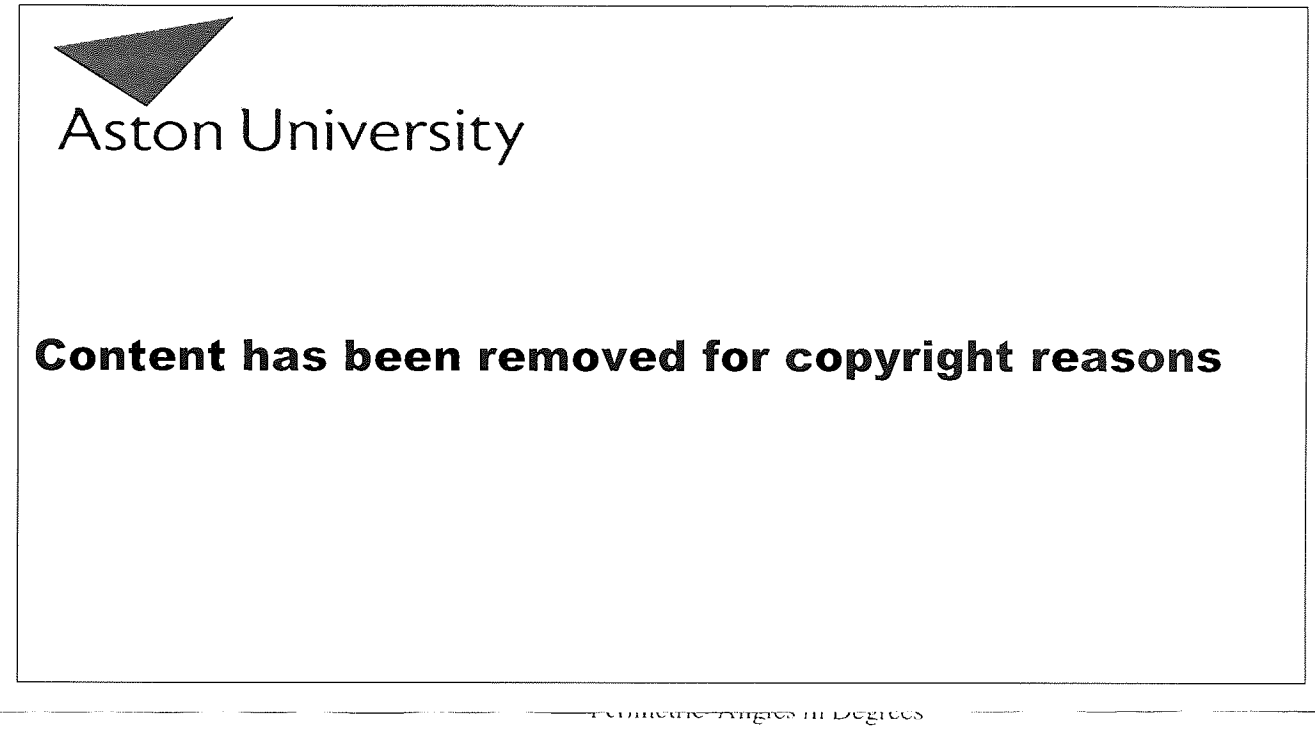

Fig 1.2 Distribution of rods and cones in human retina. Østerberg's values for corresponding perimetric angles are given. Distribution of rods and codes on nasal side in and near fovea, not given in this graph, would be approximately similar as distribution on the temporal side of the retina (from Pirenne, 1948).

Wavelength (nm)

Fig 1.3 Relative absorbance spectra of the four human photoreceptor pigments. (Curves according to Dartnall et al., 1983)

some forty eight superficial contacts. (2) the diffuse (flat) cone bipolar makes connection with some seven cones (Davson, 1990).

Rod bipolars Rod bipolars serve to collect message from rod, being connected to as many as fifty of these (Miller, 1982). Boycott and Dowling (1969) suggested that the relation between photoreceptors and bipolars can be of two types: in addition to the type shown in Fig 1.4a, bipolars can synapse with rod spherules (Fig 1.4b). The cytoplasm of rod spherules in the triads is invaginated and has synaptic connection with two processes of horizontal cells and of two processes of bipolars (Kolb,1970; Wyatt, 1988).

Bipolar cells synapse with amacrines and ganglion cells in the inner plexiform layer in a type called *Dyad* (Fig 1.4c), which consists of a bipolar, a ganglion cell dendrite and one or two amacrine cell processes. Frequently, amacrine cells in Dyad synapse back with bipolars to form a reciprocal connection (Dowling and Boycott, 1966).

Horizontal cells

They occur in the outer portion of the inner nuclear layer and serve a role in horizontal integration of the retina activity. The horizontal cells contact with other horizontal cells in gap junction across the retina that they act as a functional unit (Slaughter, 1990). The cells transmit signals from cone pedicles or rod spherules to bipolars or other horizontal cells (Dowling and Werblin, 1969; Dowling, 1988) and produce horizontal integration in the outer plexiform layer among photoreceptor-bipolar system. The dendrites processes in the triads made by horizontal cells are the base for the lateral process in the signal spreading (Davson, 1990).

Amacrine cells

They receive influence from bipolar cells and other amacrines, and they may transmit it to bipolars, ganglion cells and other amacrines in the inner plexiform layer. Amacrine cells represent the most diverse cells in the retina. They synapse either back onto the bipolar terminals (reciprocal synapses), for the local feedback or with an adjacent amacrine process (serial synapse) for the local interaction among the adjacent elements (Dubin, 1970). By their diverse circuitry, amacrine cells contribute mainly to information collection and also to lateral spread process, together with horizontal cells and ganglion cells.

Fig 1.4 The synaptic connections between photoreceptors and postsynaptic neurons, *Triads*, (a) and (b), and between bipolar cells and their postsynaptic neurons, *Dyad* (c). (according to Dowling and Boycott, 1966; Wyatt, 1988)

Inteplexiform cells

The interplexiform cell body lies adjacent to amacrine cells in the inner nuclear layers and send axons to both inner and outer plexiform layers. It receives input from bipolar and amacrine cells in the inner plexiform layer and synapses on all distal retinal neurons (Dowling and Ehinger, 1978). In the fish retina the interplexiform layer contains dopamine, which uncouples gap junctions between horizontal cells (Negishi and Drujan, 1979; Lasater and Dowling, 1985). This serves to shrink the receptive field of the horizontal cells and thereby reduce negative feedback to photoreceptors. Thus diffuse light stimuli produce a lager response in photoreceptors and bipolar cells than they would and the response-to-signal ratio is increased (Slaughter, 1990). Mangel and Dowling (1985) proposed that the interplexiform cell is involved in dark adaptation.

Ganglion cells

The innermost nuclear layer contains the cell bodies of approximately 1.2×10^6 ganglion cells (Potts et al., 1972). Ganglion cells are absent in the fovea over an area approximately equal in diameter to the capillary-free zone (foveola). The high concentration of ganglion cells at the posterior pole leads to a thick layer surrounding the fovea (Van Buren, 1963). The ganglion cells decrease at the optic disc, and are distributed sparsely in the retinal periphery (Miller, 1982).

The response of the ganglion cells are initiated by the response of many retinal photoreceptors and conveys relative changes in the level of illumination (DeMonasterio, 1978). The ganglion cells transmit the information to lateral geniculate nucleus and brain stem nuclei by varying the spikes rate. The spike frequency of ganglion cells is affected by the magnitude of excitatory and inhibitory potential changes in the presynaptic cells (bipolar and amacrine cells in the inner plexiform layer) (Dowling and Boycott, 1966; Boycott and Dowling, 1969).

1.1.4 Müller's cells

Müller's cells are the only glial cells in the retina. They extend vertically through the retina. Lessell and Kuwabara (1964) have showed that Müller's cells serve a vital metabolic role in the retina for they are a store facility of glycogen and some enzymes essential for the function of photoreceptors. In addition, the change of the extracellular potassium in Müller's cells is responsible for the development of retinal radial currents, which may be reflected in the changing

transretinal potentials (Miller, 1982).

1.1.5 Retinal Pigment Epithelium (RPE)

Pigment epithelium is derived from the outwall of the optic vesicle, forming the outermost layer of the retina lamina. Histologically, the layer is in continuity with photoreceptor outer segments. RPE plays an important role in the metabolism of the photoreceptors by regenerating the bleached photosensitive pigment and disposing metabolism products of the photoreceptors (Miller, 1982).

1.2 NEUROTRANSMITTERS

The neurotransmitter is the message carrier between chemical synapses. Normally, a cell at rest does not release neurotransmitter, though there are exceptions such as cholingergic neurons. When a neuron is depolarized, the neurotransmitters release. The amount of release is nonlinearly proportional to the membrane potential of the presynaptic cells (Slaughter, 1990).

Neurotransmitters can be divided into two types: excitatory and inhibitory types. Excitatory transmitters cause depolarization (due to the opening of a sodium channel or a calcium channel, or the closing of a potassium or a chloride channel) and inhibitory transmitters hyperpolarize the postsynaptic cell (Slaughter, 1990). The predominant neurotransmitters in the retina are the excitatory transmitters glutamate and acetylcholine and inhibitory transmitters gamma-aminobutyric-acid (GABA) and glycine (Massey and Redburn, 1987) (Fig 1.5).

The excited presynaptic neurons release neurotransmitters into the synaptic gaps, which are recognized by and bound with the receptors on the postsynaptic membrane. The sensitivities of some ionic channels on the postsynaptic membrane with voltage- or/and chemical- dependent properties change and the postsynaptic membrane is thus depolarized or hyperpolarized. When depolarization reaches to some extent (threshold), the excitation of the postsynaptic neurons is triggered and the signals are thus transferred to the second neurons.

Glutamate

Both photoreceptors and bipolar cells appear to use glutamate as their neurotransmitter

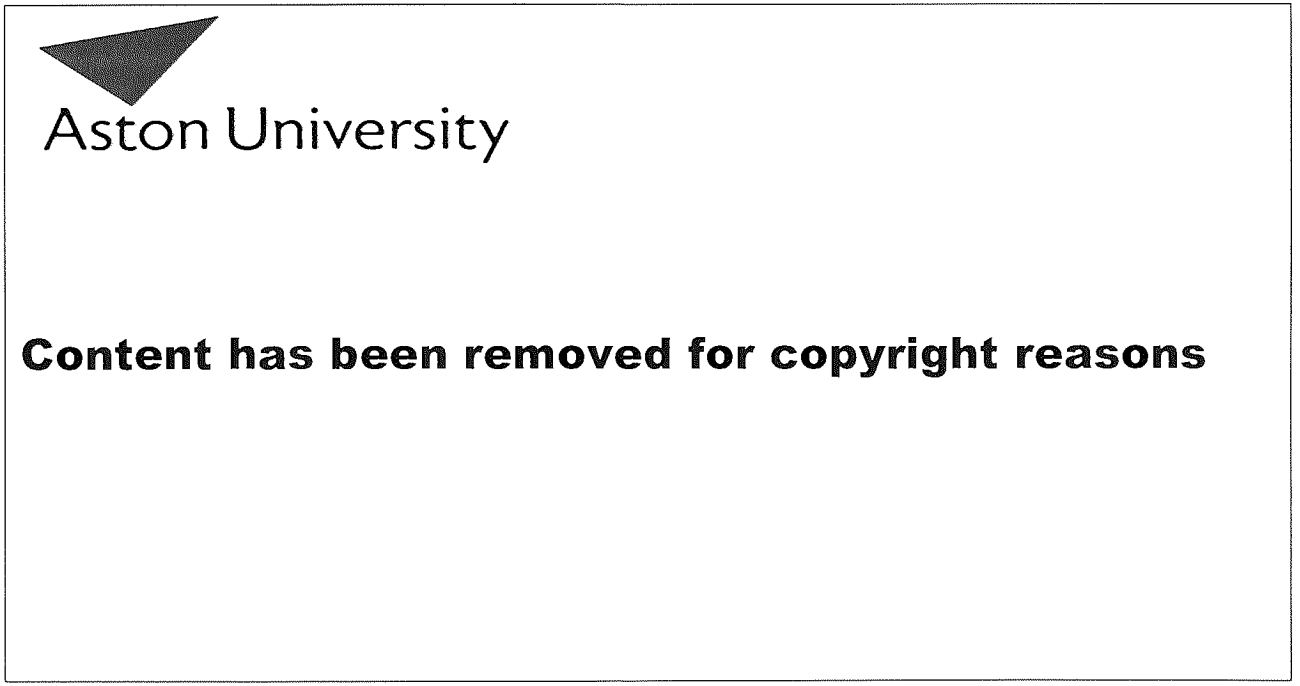

Fig 1.5 General circuit diagram for the vertebrate retina. (a) The primary visual or vertical pathways. Elements that are depolarized in darkness are shaded. Other cells are those depolarized by light. (b) The lateral pathways. In the OPL, horizontal cells provide negative feedback to photoreceptors. In the IPL, GABAergic and glycinergic amacrines form feedback loops with bipolars and presynapse to ganglion cells. (c) GABAergic and dopaminergic amacrines synapse on the interplexiform cells which synapse back to horizontal cells. (according to Redburn, 1988)

(Murakami et al., 1972, 1975; Slaughter and Miller, 1983a). Light causes hyperpolarization of photoreceptors, the rate of glutamate released from them is directly related to the degree of tonic, dark-induced depolarization of their terminals and inversely proportional to the amount of photopigment bleached (Redburn, 1988).

Glutamate has opposite effects on two classes of cone bipolar cells. It depolarizes OFF bipolars and hyperpolarizes ON bipolars. Thus OFF bipolars are driven in dark by direct glutamate depolarization, and ON bipolars are driven by disinhibition in the light (Redburn, 1988). Both ON and OFF bipolars probably release glutamate from their terminals and cause direct excitation of ganglion cells. Coleman et al. (1986) reported that the bipolars excite amacrines and ganglion cells by acting on kainate-type receptors.

In the retina, one type of cell may synapse on several postsynaptic neurons, this additional variable seems to be an important mechanism for information coding (Slaughter, 1990). Experiments indicate that there are three types of glutamate receptors and each class of second order neurons interprets the photoreceptor signal using a different receptor (Slaughter and Miller, 1981, 1983b, 1985a,b) and generate three different responses (Slaughter and Miller, 1985a,b).

Gamma-aminobutyric Acid (GABA)

GABA are inhibitory transmitters released by horizontal cells and amacrine cells. Horizontal cells are depolarized by glutamate and release GABA by Ca^2-dependent, stimulus-secretion mechanism. GABAergic horizontal cells are both pre- and postsynaptic to photoreceptor cells and provide inhibitory feedback loops that modulate the temporal properties of the photoreceptors response. Since horizontal cells are electrically coupled via gap junction, they have very broad receptive field. The gap-junction subserves another GABA-related function in the outer plexiform layer, namely, the establishment of center-surround characteristics of bipolar cells and hence retinal neurons (Redburn, 1988).

GABA is one of the three amacrine-released neurotransmitters. Glycinerergic and GABAergic dendritis make up almost two-thirds of all amacrines in the inner retina (Dick and Lowry, 1984), such that a primary role of amacrine cells is feedback and feedforward inhibition. Both of them can open chloride channels on the GABA/A receptor. The major effect in the opening of

chloride channels is not a voltage change but a decrease in cell resistance, resulting in the reduction of the light response (voltage) to excitatory input (current) according to Ohm's Law (voltage is the product of current and resistance). Activation of GABA/A receptor suppresses all light responses.

Another GABA receptor in the retina is termed GABA/B receptor (Bowery et al., 1980). Its activation closes calcium channels on bipolar cells (Maguire et al., 1989) and opens potassium channels on amacrine and ganglion cells (Slaughter and Bai, 1989), the later suppressing only sustained responses and thus transient signals predominate when the photoreceptors are stimulated. This implies that the GABA/B receptor can alter the response properties of retinal neurons and change the information of these cells.

Dopamine

Dopamine represents the major catecholamine transmitter found in retina in most species. It is released by interplexiform cells (Ehinger et al., 1969), which form loops with input from the inter plexiform layer and output primarily back to the outer plexiform layer. Dopamine activates the D1 receptors on horizontal cells and causes a decrease in the conductance of gap junctions among horizontal cells. The receptive field size of the horizontal cells is thus reduced, leading to a modification of the center-surround properties of other retina neurons (Redburn, 1988).

Glycine

The transmitter is released by amacrine cells and acts on other amacrines, bipolars, interplexiform and ganglion cells with reciprocal and serial synapses in the inner plexiform layer. Together with GABAergic amacrines, glycinergic amacrines play a role in feedback and feedward inhibition (Slaughter, 1990). They may be responsible for fast, transient inhibition, while GABA controls more sustained inhibition (Belgum et al., 1984; Slaughter and Bai, 1989). They thus provide inhibitory influence that establishes size, velocity, orientation, and the directionally selective responses in the ganglion cells.

As many as three glycinergic and five different GABAergic amacrines play an active role in establishing these complex characteristics in the ganglion cells. An additional subclass of glycinergic amacrine cell, named AII or A7, is thought to play a unique role in scotopic vision by providing a link between rod bipolar cells and ganglion cells. The A7 glycinergic cells

receives synaptic input from rods and in turn forms electronic gap junctions with other A7 cells and with cone bipolars. Thus it appears that scotopic visual information from rod photoreceptors reaches ganglion cells via cone bipolar terminals (Redburn, 1988).

\Serotonin (5-TH)

5-TH is also utilized as a transmitter by specific subclasses of amacrine cells. The functions of these cells are unclear. Redburn (1988) suggested that at lease one subclass displays a synaptic pattern similar to that of the glycinergic A7 cell and thus may provide a link in scotopic circuitry.

Acetylcholine (Ach)

Acetylcholine is also released by amacrine cells. Cholinergic amacrines are driven by glutamate input from bipolars and are inhibited by glycine and GABA. Ach provides excitatory input to ganglion cells through nicotine receptors and thus represents an exception from general inhibitory nature of most amacrines (Masland and Ames, 1976). The outer band of cholinergic amacrine terminals placed in the inner plexiform layer, along with bipolar terminals, and are involved in activity of OFF circuit. The innermost band of amacrines whose cell bodies are displaced to the ganglion cell layer, along with bipolar terminals within this sublamina, are involved in activity of the ON circuit (Massey and Redburn, 1985).

Others

Somatostatin, substance P, neuroactive peptide Y, enkephalin, vasoactive intestinal peptide, glucogon, cholecystokinin, thyrotropin-releasing hormone, etc. are the peptides whose antibodies show cross-reactivity in retina. Most neuropeptides appear to be localized within amacrine cells. Some are co-localised with a neurotransmitter. In general, peptides may provide slow-acting, long-term modulation of amacrine networks (Redburn, 1988).

1.3 VISUAL INFORMATION TRANSMISSION AND CODING

1.3.1 Light-Chemical-Electrical Procedure

The photoreceptors initiate the processes which mediate the perception of the visual world. They convert the light energy into neuronal potential changes, which triggers the transmission of visual information to the second and higher relay neurons.

The light intensities which human eye encounters range from about a hundred photons to more than 12 orders of magnitude above the absolute visual threshold. Rod vision operates over five orders of magnitude above the absolute dark threshold and cone vision overlaps with rod vision and takes over for the next six or seven orders of magnitude (Riggs, 1966). About 10% of light falling on the cornea reaches the photoreceptors. The rest is lost in transmission through the ocular media, the blood vessels, and the neural cells of the retina (Leibovic, 1990).

A human rod can absorb some 30% of the light to which it is exposed (Pirenne, 1962; Leibovic and Kurtz, 1975). When the light signals are transmitted, they are also amplified in the process more than 10^5 times. The 500nm photon energy of about 4×10^{-12} erg leads to the displacement of some 10^7 electronic charges through a potential drop of 30-40mV, an amplification of the order of 10^5 (Leibovic, 1990).

The chromophere is the basic chemical element in the photopigment. It is the same for both rods and cones, but the protein to which it is attached differs in rods and cones. It is these structural differences that give rise to the different absorption spectra (Leibovic, 1990). The rod pigment absorbs light maximally at 496 nm wavelength (Barlow, 1982). In human, three cones absorbs light maximally at wavelengths of 420-450nm (blue), 525-540 nm (green), and at 560-575 nm (red), respectively (Wald, 1964; Dartnall et al., 1983) (Fig 1.3).

In the dark, the inside of a rod or cone is of -40mV resting potential, which follows the Nernst formula:

$$Vm = \frac{RT}{zF} \ln \frac{[A]_e}{[A]_i}$$

where Vm is membrane potential, $[A]_e$ and $[A]_i$ are the external and internal ion concentrations, respectively, R is the gas constant, F is the Farady constant, T is the absolute temperature, and z is the ionic charge. The actual membrane potentials depend on also ion pumps, permeabilities, and concentrations given by the Goldman-Hodgkin-Katz equation.

$$Vm = \frac{RT}{F} \ln \frac{PNa[Na]e + Pk[K]e + PCl[Cl]i}{PNa[Na]i + Pk[K]i + PCl[Cl]e}$$

with Na, K, Cl being sodium, potassium, chloride and with P being ionic permeabilities. The membrane potential is kept steady by the Na^+-K^+ pumps on the membrane, pumping Na^+ out and K^+ into the cell (Leibovic, 1990).

The Na^+-K^+ pumps are thought to be the electrogenic structure to keep the resting potential of the receptors. Frank and Goldsmith (1967) used ouabain, an ATPase inhibitor, in the isolated retina of frog and found that it rapidly blocked the ERG. This finding is supported by the later report by Korenbrot and Cone (1972) that the permeability to Na^+ of the isolated rod outer segments was reduced by light. Brown and Pinto (1974) used choline to substitute Na^+ and found that shortly after the replacement the membrane hyperpolarized and the responses to light stimulus were abolished; after restoration of Na^+ to the medium, the membrane potential returned to its depolarised value and the responses to light returned.

After absorbing one quantum of visible light (between 400-800nm), the 11-cis-retinal, a chromophore in rhodopsin of rods, goes through a series of conformational changes (Yoshizawa, 1972). A millisecond (at metarhodopsin II stage) after absorbing light, a biochemical transduction cycle is triggered. The circle reduces the free cellular cGMP which results in the reduction of the function of the Na^+-K^+ pumps and thus closes light-sensitive channels (Na^+) (Nakatani and Yau, 1988b). Additionally the Na^+ permeability of the outer segment is reduced (Tomita, 1965; Toyoda et al., 1969). As a result, the photoreceptors' membrane is hyperpolarized (Bortoff and Norton, 1965; Baylor and Fuortes, 1970).

Unlike the fixed amplitude nerve impulse, the hyperpolarising membrane potentials increase with light intensity and at saturating intensities they develop a transient undershoot followed by a plateau (saturation). At the saturated phase, all the light sensitivity channels are closed and no additional response could be evoked (Baylor and Nunn, 1986).

The tips of the receptors were negative in relation to the synaptic region (Bortoff and Norton, 1977). Penn and Hagins (1969) and Hagins et al. (1970) placed electrodes at different depths alongside the rat rods and showed that electrode recorded a progressively positive potential when it moved from the tips to the rod synapses, whilst the light-induced voltage increased in parallel.

Moreover, the authors found that when the rod was partially illuminated, the photocurrent occurred in the outer segment and the unilluminated region acted as a sink of current, thus confirming that light reduce a standing dark current inward at the outer segment and outward along the remainder of each receptor cell.

The outer segment currents are essentially independent of voltage in the physiological rang (Bader et al., 1979; Baylor and Nunn, 1986). The authors found that between -80mV and -20mV, the current change within the outer segment of a rod cell showed a small slope, indicating that the outer segment conductance is fairly insensitive to voltage in the physiology range. It is the same case that occurred in the cones (Attwell et al., 1982).

Leibovic (1990) proposed that there is a process (probably voltage-sensitive mechanisms) occurring in the inner segments influenced by the transduction occurring in the outer segments and that membrane currents and potentials in the inner section thus modulate synaptic transmission to the second order neurons---horizontal cells and bipolars. There are various conductance in the inner segment (Fain and Lisman, 1981; Owen, 1987). Bader et al (1982) used voltage clamp recording in the salamanda rod and found that some ion channel (Cs^+) in the inner section was activated by hyperpolarization below -30mV in the outer segment.

The photoreceptors are excited in the dark and suppressed by light (Svaetichin, 1953; Tomita, 1963). When they are excited, they release glutamate, an excitatory neurotransmitter, at synapses with bipolar and horizontal cells (Murakami et al., 1972; Slaughter and Miller, 1981, 1983b). Wyatt (1988) suggested that there is no or less transmitter is released from photoreceptors when they are excited by light stimulus for the effect of light is equal to the effect of reducing transmitter.

1.3.2 Retina Organisation and Information Transmission

Synaptic organisation

In general, the relation between retina neurons is of the synaptic type. As in other neuronal tissues, there are two types of synapses, electrical and chemical. Electrical synapses are formed by gap junctions between cells (Slaughter, 1990). Their cell intercommunication is brought

about by so called electronic coupling (Raviola and Gilula, 1973). In retina they are common in photoreceptors (Kolb, 1977) and horizontal cells (Slaughter, 1990). Chemical synapses represent the predominant means of communication in retina neurons, involving the release of neurotransmitter substances from presynaptic cells.

Almost all synapses in the retina are confined to the two plexiform layers and in each of these layers, the processes of four cell types interact: in the outer plexiform layer, being among rods, cones, bipolars and horizontal cells; in the outer plexiform, being amacrines, bipolars, interplexiform cells and ganglion cells.

The synaptic contacts between cells are of two main types according to the pattern of presynaptic membrane, namely an invaginating synapse, when the dendritic process penetrates deep into the pedicle or spherule, and a flat contact, when the synapse occur more superficially. According to the types of the vesicles in the presynaptic cytoplasm, there are ribbon and conventional synaptic contacts. The chemical synaptic contacts in primate retina include : triads, dyads with reciprocal feedback and serial types (Miller, 1982; Davson, 1990).

Centripetal transmission

Vertical transmission According to the basic picture of a vertical retinal organisation, midget bipolars, connect only to a cone and diffuse bipolars makes synaptic relations with several photoreceptors. Similarly, the ganglion cells connect with either a single midget bipolar cell , or groups of bipolar cells. By this way, there are convergence and one-to-one connection in the vertical connection (Polyak, 1957) that retinal activity in the rods and cones is transmitted to the bipolar cells and thence to the ganglion cells and out of the eye into higher neuron centres---the lateral geniculate body, and so on. The ganglion cells may respond to light falling on a retinal point that is far further from each other that ganglion cells collect information from a wide area of rods and cones (convergence). In human, the average convergence from photoreceptors to a ganglion cell is of the order of 130:1 (Miller, 1982) !

Lateral spread Another picture of the retina organization is that in the inner plexiform layer, a single bipolar cell may activates many ganglion cells, so that the effect of a light stimulus may spread horizontally (divergence) as it moves vertically. The horizontal cells, amacrine cells and ganglion cells contribute to the lateral spread of input from the photoreceptors (Davson, 1990).

Centrifugal pathways

As a sensory organ that sends information about the outside world to the brain, the retina has a centripetal flow of information to accomplish this function. But there is also a reverse flow of information (Slaughter, 1990). Centrifugal connections from various brain regions have been demonstrated by anatomical (Zucker and Dowling, 1987; Schutte and Weiler, 1988; Uchiyama, et al., 1988) and electrophysiological techniques (Tornqvist et al., 1988; Yan et al., 1988).

In fish efferents from the olfactory bulb project to the retina and synapse on interplexiform cells, as well as other neurons. These efferents contain peptide neurontransmitters, LHRH and FMRFamide, which have the same effect on the fish retina as dopamine. When fish are exposed to odorants, the b-wave of the ERG is enhanced, indicating that the olfactory input can modify retinal response properties (Weiss and Meyer, 1988). But the functional importance of these connections in primate retina is still speculative.

1.3.3 Cellular Response and Interaction

The responses of retina neurons are measured in electrical terms. When a cell is depolarized (less negative charged inside the cell), it is termed excited. The excited cells can release neurotransmitters, which affect other neurons, so that depolarization means signal transmitting capability and hyperpolarization implies the diminishment of this capability (Slaughter, 1990).

Photoreceptors are depolarized and release glutamate at synapses with bipolar and horizontal cells in the dark (Svaetichin, 1953; Tomita, 1963; Murakami et al., 1972, 1975; Wu and Dowling, 1978; Slaughter and Miller, 1981, 1983b). The horizontal cells are depolarized in darkness and hyperpolarized in lightness as photoreceptors. Part of bipolars (OFF bipolars) follow the photoreceptors and are depolarized in the dark and excited by photoreceptors.

Another type of bipolars are suppressed by photoreceptor transmitter. This inverting synapse means that these cells are excited in the light (and therefore they are termed ON bipolars). The ON-OFF system is well conserved in all vertebrate retina (Werblin and Dowling, 1969--primate; Kaneko, 1970--fish; Dacheux and Raviola, 1986-rabbit; Muller et al., 1988---cat). The net result of these interactions in the distal retina is that light signals are divided into two pathways, a pathway acting when light is ON, carried by the ON bipolars, and a parallel pathway signalling when light is OFF (Werblin and Dowling, 1969; Kaneko, 1970). The OFF bipolars

synapse with the amacrine cells and the ganglion cells in the distal portion while the ON bipolars send processes to the proximal portion in the inner plexiform layer (Famiglietti and Kolb, 1976; Nelson et al., 1978), suggesting the anatomical segregation of ON and OFF signals. The ON-OFF system probably increase the dynamic range of neuronal signalling (Slaughter, 1990).

The amount and type of diversity of the incoming information formed by differing synaptic pathways can be reflected in the ultimate receptive field, the area where a cell responds to a spot light stimulus (Miller, 1982). Receptive field center and surround are in opponent arrangement and interact in response that the information carried by ganglion cells (including the colour-related center-surround opponents) reflect accurate picture processed in the retina, which will be discussed in Chapter 3.

1.4 ELECTRORETINOGRAM (ERG)

The transient light responses of retinal neurons are manifested in a field potential, termed the electroretinogram, ERG. ERG was the record of several events taking place very nearly simultaneously, so that the measured potential changes were the algebraic sum, at any instant, of these events (Granit's analysis). It is similar to the other field potentials, such as electrocardiogram or electroencephalogram, in the sense that each component consists of the summary activity of many cells of a given class which synchronised in response to light stimulus. Thus ERG offers an advantage that reveals electrical activity from certain classes of retinal cells. Electroretinography pertains to the study and the recording of this potential (Armington, 1990).

The earliest work to show ERG components is by Einthoven and Jolly (1908) who separated the retinal response to light into three components: (1) an early cornea-negative a-wave; (2) a cornea-positive b-wave; and (3) a slower, usually cornea-positive c-wave.

Granit analysed ERG into three fundamental processes and termed them as, PI, PII and PIII. The term "P" stands for process, for at that time the cellular origin was not known for any of the potentials (Brown, 1968). The components were then numbered in the order in which they

disappeared following the administration of ether anaesthesia.

In this finding, Granit found that the deflections of the cat ERG (rod retina) disappeared in three major steps. The c-wave disappeared first, then b-wave and off-response disappeared at about the same time, while the a-wave disappeared last (Granit, 1933). The author proposed that at high stimulus intensity, the c-wave resulted from PI. The b-wave is due to a peak of PII, which includes a very slow positive phase, the decay of which gives the negative off-reponse. The a-wave is then accounted for by the onset of PIII, a negative potential which is well maintained during the stimulus. After the negative off response, there is a small positive deflection, which is labelled the d-wave, and which is accounted for by the decay of PIII. At lower stimulus intensity, the cat ERG is shown to consist majorly of PII (Fig 1.6a).

Granit and Riddell (1934) analysed the light adapted ERG from the frog retina (cone retina). There is a prominent d-wave, which results from the decay of PIII, followed by the decay of PII. There is no distinct c-wave. In the dark adapted cone ERG that a small c-wave can be recorded (Fig 1.6b). The studies of the cone and rod retinas are the ways to know the components and origins of the human ERG. Human retina is mixed with cones and rods that human ERG contains all these components.

There are a few methods to localize the origins of the components in the gross ERG. One is the electrode depth studies to record the local ERG (Brown and Wiesel, 1961b; Brown et al., 1965). It has long been proposed that each component must be generated by a dipole that is radially oriented through the retina (Tomita et al., 1950), which can be indicated by the polarity inversion between a given component of the gross ERG and the same component local ERG (Brown, 1968). The time courses of these responses are different and they are generated in different retina areas (Brown and Wiesel, 1961a).

Another commonly used method is to clamp selectively the retinal circulation without affecting the choroidal circulation. Because the retinal circulation extends only to the outer margin of the inner nuclear layer, and terminates sharply at that level (Noell, 1954; Polyak, 1957), it is thought that the neurons in this layer are supported primarily by the retinal circulation while the photoreceptors in the fovea or pigment epithelium requires their metabolism from the choroidal circulation.

Fig 1.6 Analyses of the ERG components. *(a)*: illustrating the components (thin lines) of the rod ERG in the cat modelled by Granit (1933). The responses (thick lines) were evoked at stimulus intensities of 14 ml (upper graph) and 0.14 ml (lower graph). *(b)*: dark-adapted (upper graph) and light-adapted (lower graph) cone ERG in frog's eye, where thick lines represent ERG and thin lines represent components forming the response. (after Granit and Riddell, 1934)

1.4.1 a-wave

Granit (1933) proposed that PIII is from the photoreceptor cells on the base of the observation on the cat retina. PIII is the last component to be abolished by asphyxia brought about by occlusion of the retinal artery, and was highly resistant to ether.

Armington et al (1952) identified two components of the a-wave when recorded at the human cornea under dark adapted (scotopic) conditions. The a_p component had the spectral sensitivity of the cone system and was relatively unaffected by light adaptation while the a_s component had the spectral sensitivity of rod system and was depressed by light adaptation.

Noell (1954) found that occlusion of a monkey retinal artery impairs the b-wave much more that the a-wave. Brown and Watanabe (1962a, b) recorded successfully the receptor potential of the monkey retina extracellularly by clamping the retinal circulation that the potential had no contamination from b-wave. They found that a large a-wave in the central fovea of the monkey could be recorded, while in the periphery, the a-wave was much smaller and b-wave relatively larger. Since in the central fovea the photoreceptors are well developed while the ganglion cells are entirely absent and the inner nuclear layer is reduced to a few scattered cells (Brown et al., 1965), this study provides evidence that the photoreceptor layer is responsible for the a-wave.

It is now generally accepted that the a-wave of human ERG is generated by both rods and cones in the photoreceptor layer of the retina. Recently, Asi and Perlman (1992) proposed that a-wave reflects the photocurrent generated by light absorption in the outer segments of the photoreceptors, which results probably from the voltage-sensitive channels in the inner segments of the photoreceptors influenced by the transduction circle occurring in the outer segments (Leibovic, 1990).

1.4.2 b-wave

b-wave is the lager positive potential after a-wave. The cellular origin of the b-wave is less clear. Granit (1933) speculated that this component could not originate in the sensory cells but come from the second or third order neurons of the retina due to its high susceptibility to KCL, anaesthesia and asphyxia.

Henkes (1954) as well as Gouras and Carr (1965) showed that following central retinal artery occlusion in primates, cells in the inner nuclear layer are destroyed while photoreceptors remain intact. In such cases, the b-wave is eliminated while the a-wave is preserved, indicating the inner nuclear layer is probably responsible for the origin of the b-wave.

Hashimoto et al (1961) confirmed that responses similar in waveform to the b-wave were present when the tips of microelectrode were placed on the opposite sides of the inner nuclear layer. Brown and Wiesel (1961b) found that in the cat local ERG, the amplitude maxima for both the a-wave and c-waves were found close to the retina side of the pigment epithelium, while the amplitude maximum for the b-wave was about halfway through the retina, in the region of the inner nuclear layer. This amplitude maxima have been confirmed by electrode marking (Brown and Tasaki, 1961).

Kuffler and Nicholls (1966) and Miller and Dowling (1970) proposed that the b-wave potential probably relates with Müller cells which respond to the increase of potassium ion concentration within the extracellular space of the inner nuclear layer. Müller's cells have no synaptic relations with retinal neurons. They are radially orientated in the retina with terminals at the external and internal limiting membranes. It is assumed that the changes in extracellular K+caused by retinal activity modified the resting potential of the Müller's cells, a phenomenon which is well established in other parts of the central nervous system. Oakley and Green (1976) found two kinds of $[K^+]_o$ changes: a rapid rise in $[K^+]_o$ in the proximal retina, i.e., near the inner nuclear layer (amacrine and ganglion cells), and a small decrease in the outer plexiform layer near the photoreceptors, due to the hyperpolarization induced by light.

Subsequently, using pharmacological agents to separate components of ERG, Dick and Miller (1978) confirmed there is an increase of $[K^+]$ but they also identified a small increase in the distal retina which was probably derived from depolarized bipolars. The authors concluded that the later might well be responsible for the b-wave.

Newman and Odette (1984) reviewed the different explanations of the b-wave. Based on rises in $[K^+]_o$ near the inner and the outer plexiform layers respectively, and a decrease in the region of the photoreceptor inner segments, they set up a computer model with a postulated feature of a

high localized [K+]o permeability of the Müller's cell endfeet at the inner limiting membrane (Fig 1.7). This model can reproduce the local ERG with some accuracy, brisk feature of the b-wave being due to the relatively small influence on the Müller's cell of the proximal rise in [K+]o and thus on the transretinal potential.

Some authors concluded that the corneal positive response was generated by Müller cells when they are depolarized by the activity of the ON bipolars (Dick and Miller, 1978; Stockton and Slaughter, 1987; Niemeyer, 1994).

Müller's cells appear to function as potassium "electrodes" vertically across the retina. Some membrane regions with high permeability to [K+] are depolarized by the locally increased potassium. The result is that a radial current is developed within the Müller's cells due to [K+] flux (Wen and Oakley, 1990). Temporal and magnitude differences along the Müller's cells currents are reflected in the changing transretinal potentials, and therefore can be reflected in the initial and sustained portions of the b-wave (Miller, 1982).

1.4.3 c-wave

The c-wave is a slowly developing positive component; with strong stimuli, or after light adaptation, it tends to disappear. It accounts for the secondary rise in the positivity, PI and is prominent in dark-adapted state as shown in Fig 1.6a. When the retina was light adapted by repetitive stimulation, no c-wave could be detected (Brown et al., 1965).

The c-wave is absent in the pure cone-retina (Steinberg et al., 1970) (Fig 1.7). The c-waves vary considerably in different mammalian species. The positive c-wave, seen in the primates and the cat, is replaced by a long negative waveform in subspecies of dogs (Niemeyer, 1994).

Noell (1954) reported that using iodate to selectively destroy the pigment epithelium a reduced c-wave could be recorded and thus concluded that c-wave was generated by these cells. Also Yamashita (1959) and others could not record the c-wave from the isolated retina of cold blooded animals which give all of the other major components.

Steinberg et al (1970) compared the local ERG obtained with a microelectrode close to the

Fig 1.7 The origins of the ERG components. Left: Illustrating the radial orientation of the Muller's cells and the relation between $[k^+]o$ and radial current reflected in the b-wave (after Newman and Odette, 1984). Right: Showing the origin of the c-wave in the pigment epithelium. Negative responses are displayed downwards (after Steinberg et al.,1970).

retina with the changes in the intracellular potential of a pigment epithelium. As Fig 1.7 shows, the c-wave of the local ERG coincides with a peak in hyperpolarization of the pigment epithelium. This case indicates well the relation between the b-wave and its generator, the pigment epithelium. Subsequently, the authors (Steinberg et al., 1985) reported that the hyperpolarization of pigment epithelium could be induced by the decrease in [K+]o in the subretinal space.

Niemeyer (1994) referred that the c-wave recorded from the vitreous or from the cornea reflects the algebraic summation of two components that follow a similar time course but are opposite in polarity: retinal pigment epithelium hyperpolarization and the slow PIII component, which is a response of the distal part of Muller cells to the light-induced decrease in [K+]o occurring in the subretinal space.

1.4.4 d-wave

The d-wave is a phase of negativity that comes on immediately with the light stimulus and remains at constant level during the stimulus, falls abruptly when the light is switched off. It is a part of what Granit included in his PII, which gives rise not only to the b-wave but the sustained negativity during maintained stimulation. Cunningham and Miller (1980) compared the ERG, PNR (proximal negative response) and Muller cells response in the mudpuppy retina. They found that d-wave showed high sensitivity to glycine or taurine, suggesting mediation by hyperpolarization bipolars. Since glycine and taurine could also bloke the OFF-response recorded from Müller cells, suggesting the possibility that these cells as the origin of the d-wave as well as the b-wave.

1.4.5 Minor ERG Components

ERG has a multiphasic waveform that is shaped from the contributions of several underlying activities, any of which may be more or less prominent. Thus the stimulus characteristics, the state of the eye's adaptation, the species of the subject, and the recording conditions will all affected the result (Armington, 1988).

d.c. component

Granit's analysis of the cat ERG shows that at lower stimulus intensity PII tends to become

isolated, and the b-wave portion of PII becomes less prominent. Brown and Wiesel (1961a,b) demonstrated successively that when stimulus intensity was reduced sufficiently (less than 3.4 log units), the b-wave in the cat ERG could be abolished without abolishing the steady portion of PII. Since the remaining response had a time course similar to that of d.c. current pulse, it was termed the d.c. component. Thus, PII in Granit's analysis consists of the b-wave and the d.c. component.

Both b-wave and d.c. component are found to originate from the same retinal level , the inner nuclear layer but with different mechanisms (Brown and Wiesel, 1961b). Using gylocaine the b-wave could be abolished, without affecting the d.c. component , or c-wave, and the a-wave is secondarily enlarged (Brown, 1968). The author proposed that the d.c. component must be generated at earlier level of the retinal pathway than the b-wave .

Oscillatory potentials (OPs)

The wavelets were first described in the human retina by Cobb and Morton (1954). Later the potentials were found in many species and were termed "oscillatory potentials" (OPs) by Yonemura, et al (1963).

OPs are recordable in the scotopic, mesopic state and the light adapted range (Speros and Price, 1981; Karwoski and Karwoski, 1991; Wachtmeister, 1991). At high stimulus intensities rapid oscillations may be superimposed on the b-wave. Additionally, when an analogue filter with a frequency band 100-200 Hz is used, a series of rapid rhythm low amplitude potentials (OPs) superimposed on the b-wave can be recorded with all of the ERG components slower than 100Hz or faster than 200Hz selectively attenuated (Wachimeister, 1972; McCulloch et al., 1974).

Using the technique of electrode depth, Brown (1968) found that in the peripheral retina of cynomolgus the oscillations do not pass through an amplitude maximum where the a-wave or b-wave is maximum. Like b-wave, in the fovea, the OPs are recorded at smaller amplitude; they are abolished after clamping the retinal circulation. In the peripheral retina, the rather large oscillations begin on the rising phase of the b-wave and then diminish and disappear during the later part of the b-wave. The results exclude the possibility that the OPs are from either receptors or the inner nuclear layer but are dependent on the retinal circulation (Speros and

Price, 1981; Wachtmeister, 1987).

The retinal circulation nourishes the inner retinal layers (Miller, 1982) so that the amacrine cells in the inner retina, particularly those producing sustained responses at light onset, are the prime candidates for the generators of the OPs (eg,, Toyoda at al.,1973; Niemeyer, 1994). Other neurons such as bipolars and ganglion cells are proposed to contribute to the production of OPs due to their net-works with the amacrine cells (Asi and Perlman, 1992).

Rapid early receptor potential (ERP)

When the retina is stimulated with flash of light about 1 million times brighter than that required to elicit the ERG (Brown and Murakami, 1964a; Cone, 1964), a rapid early receptor potential (ERP) is detectable. It has biphasic in form (Brown and Murakami, 1964b). It consist of an initial cornea-positive phase, R1, that has associated with the conversion of lumirhodopsin to metarhodopsin I (Pak, 1965), and the later cornea-negative phase, R2, with the conversion of metarhodopsin I to metarhodopsin II (Cone, 1967) in the outer segment (Arden and Ikeda, 1966a). The latency of the first phase is extremely short and in the isolated toad retina it is about a few μsec and the total duration of the early RP is about 6msec (Brown, 1965). This type of recording has revealed the similarity to the early RP from human eye (Arden and Ikeda, 1966b) and from other mammals and lower vertebrates (Cone, 1964; Brown, 1965).

The first phase of the early RP can be isolated by abolishing the second phase using low temperature on excise albino rat eye (Pak and Cone, 1964) or by light adaptation (Brown, 1965). Brown (1968) proposed that the functional significance of the early RP is closely associated with very rapid events that occurs in the photopigment molecule after absorption of a light quantum.

In man, Goldstein and Berson (1970) found that 60 to 80 % of the total amplitude of the ERP is generated by cones and 20 to 40% by the rods. Carr and Siegel (1970) confirmed the cone dominance of the human ERP by showing that in the dark-adapted eye, the ERP action spectrum matched the human photopic luminosity curve with peak sensitivity near 555 nm (Miller, 1982).

Late receptor potential

When the b-wave and the falling phase of the d-wave are selectively abolished in monkey retina by clamping the retinal circulation, the remaining ERG response (which is the one that Granit designated PIII) rises quickly to a level that is well maintained during the stimulus and which decays in two phases after the stimulus terminates (Brown, 1968). The onset of this response corresponds to the a-wave of the normal local ERG (Brown et al., 1965). The rapid decay phase corresponds to rising phase of the d-wave. The response (PIII) in such a isolated status showed progressive decline in amplitude. Corresponding to the early receptor potential (Brown and Murakami, 1964a), Granit's PIII was designated the late receptor potential (LRP).

Brown et al (1965) recorded the late RP, isolated by clamping the retinal circulation, as a function of depth of tungsten microelectrode in the peripheral retina of the cynomolgus monkey and presented the evidence that the late RP is generated by the receptors. The results showed that the observed locations of the source and sink of extracellular current flow occurs in the peripheral penetration during the response (so that the generating cells must be oriented radially through the retina, and extend through the entire deeper half of the peripheral retina). The lager response and the source of current flow can be found in fovea but the sink is absent (for the axons in foveal receptors proceed from bodies turns laterally and course outward to the parafovea, where the cone pedicles synapse with second order neurons).

Arden and Brown (1965) observed the effect of the light intensity on the local ERG in the cat. They found that at the low light intensity (only about one log unit above the absolute dark adaptation human threshold), a late RP could be recordable. At higher intensities the rising phase of the late RP becomes the rise of the a-wave. Thus the late RP is detectable at lower intensity than required to detect other electrical responses. This result is in agreement with the evidence that the late RP is a receptor response.

Off Response

Following the rapid a-and b-waves, there is a period of negativity that continues during the remainder of the stimulus. When the stimulus terminates there is a simple negative deflection that constitutes the *off-response*. This is followed by the rising phase and peak of the c-wave (Brown, 1968).

Granit and Riddell (1934) analysed the frog retina (with numerous cones), and found that

there is a prominent d-wave, resulting from the decay of PIII, followed by the decay of PII and there is no distinct c-wave, but a relatively small c-wave was found in the frog's dark adapted ERG. In cone ERG the off-response is a d-wave, consisting of a rapid positive deflection followed by a slower negative fall to the baseline, and there is no detective c-wave (Brown, 1968).

1.4.6 Visual Adaptation and Cone / Rod ERG

Human retina, as that of many species (such as cynomolgus), is duplex (Gouras, 1970). It possesses a photopic or cone system that works at high levels of illumination and a scotopic or rod system that works at low. Thus the visual system works effectively over an enormous range of light intensities, about a hundred photons falling on the cornea at the absolute visual threshold to more than 12 orders of magnitude above that (Boynton and Whitten, 1970; Pepperberg, et al., 1978; Shapley and Enroth-Cugell, 1984; Leibovic et al., 1987a). Rod vision operates over five orders of magnitude above the absolute dark threshold, overlaped by cone vision for the next six or seven orders of magnitude (Riggs, 1966). These processes are completed by the photoreceptor adaptation. Leibovic (1990) defined the photoreceptor adaptation to be the change in functional state of the photreceptors as the operating range shifts in response to different levels of illumination and pigment bleaching.

Threshold The smallest detectable or threshold response when recording membrane potential (Leibovic et al., 1987a) from an adapted rod is the single photon response. In the presence of a background the threshold rises and a more intense flash is required to elicit a detectable response and onward its rising saturates, termed threshold elevation and response compression respectively. They are the consequences of adaptation in rods and cones (Leibovic, 1990). In rods, they are related with the bleach of the rhodopsin and its regeneration (Weinstein et al., 1967). Threshold elevation means that more photons are required to produce a measurable response to a flash; response compression suggests that fewer of the light-sensitive channels are open. When the background is turned off the threshold recovers again (Leibovic et al., 1987a).

Dark adaptation Dark adaptation is the process of adjusting to total darkness or to lower levels of illumination; light adaptation is the reverse. In darkness, the threshold drops rapidly in the first few minutes and then comes to a plateau. After a few more minutes, there is a second drop

in threshold followed by a lower plateau. About 45 minutes are required to reach the final absolute threshold. In general, the first drop is thought to represent an increase or recovery of photopic sensitivity in the dark and the second describes that of the scotopic sensitivity. The change of relative sensitivity in the dark adaptation is known as the Purkinje shift and the transition from the first drop to the second drop is known as the rod-cone break (Armington, 1988).

In the dark adaptation, the human ERG evoked by a single flash is called scotopic ERG. It records both faster cone and slower rod components. The pure cone ERG of the squirrel shows no distinct changes of form after dark adaptation (Arden and Tansley, 1955). In the rod retina (such as in the cat), dark adaptation may increase the amplitude of all the deflections (Brown, 1968).

Since the changes of the increment threshold versus adapation curve depend on the stimulus location on the retina and the spectral composition (Armington, 1988), the cone and rod systems can be stimulated separately according to their sensitivity spectra, and thus the cone and the rod ERGs can be recorded in the cone-rod mixed retina. Blue stimulus stimulates the scotopic system, if presented against a red adaptation, which is effective in reducing the sensitivity of the photopic system; orange yellow presented against a blue green background can stimulate the photopic system (Bartlett, 1965; Barlow, 1972; Rushton, 1981; Wyszechi and Stiles, 1982).

In the dark adaptation, spectral sensitivities in the first and second plateaus are found to be greatest near 555nm and 500nm, which matches respectively those of the characteristics of the photopic and scotopic (rhodopsin) (Armington, 1988) as shown in Fig 1.3. Thus above the rod-cone break, the response can be evoked by color stimuli and below it, colourless, proposed the temporal course of the adapation is controlled properly.

Light adaptation Light adapatation is measured by ploting the incremental threshold as dependent on the luminance of the background (Armington, 1988). At low levels, the background has no effect. As the background is raised the threshold rises, at first gradually and then more rapidly. At higher levels, there is a second plateau followed by a second rise. As in dark adapation, the twice increase of the threshold in the light adaptation is thought to be contributed by both rod and cone systems. When the eye is adapted to low levels, the rod

system is most sensitive, but at higher adaptation scotopic sensitivity drops below that of cones. The high background illumination is used to desensitize rods and isolate the cone ERG (Berson, et al., 1969), that the ERG in such cases tends to be like that of a predominantly cone eye, thus being called photopic ERG.

When a train of flashes or sinusoidally modulated light is projected onto a photoreceptor, the membrane potential is initially hyperpoloarized from the resting potential. Then the potential becomes into an oscillation, which faithfully follows the periodicity of the stimulus. As the stimulus frequency increases, the response amplitude decreases and tends to zero. At this point, it is called the "critical flicker fusion frequency" (CFF). In the presence of the background the CFF increases, and the cell responds to higher frequencies. Leibovic (1990) describes it as 'temporal adapation' of the photoreceptors.

When the flash frequency is increased up, flickering stimulus elicit an isolated cone response, for rods are unable to follow frequencies above a certain frequency. Hecht and Schaler (1936) reported the frequency for the rods to fail to follow is 15Hz. Armington (1988) proposed a flash flicker frequency of 20Hz for recording photopic response. The flicker ERG recorded at 30Hz is reasonably representing the cone response and now is oftenly used in clinical investigation. Apparently, the CFFs of the rods and cones are different.

1.5 ELECTROOCULARGRAM (EOG)

The human eye behaves as a dipole, oriented along its anterior-posterior axis with cornea positive with respect to the posterior pole. Between the cornea and the back of the eye, a difference in electrical potential from one to several millivolts exists (Dubois-Reymond, 1849), depending on the state of ambient retinal illumination. This resting potential is termed standing potential. Retinal luminantion causes an initial rapid fall in the standing potential over 60-75 secs (the 'fast oscillation') followed by a slow rise over 7-14 minutes (the 'light response' or 'slow oscillation') (Marmor and Zrenner, 1993).

Movement of the eye causes changes of potential in one electrode placed near the inner canthus relative to a second electrode placed near the outer canthus of the same eye, which can be

recorded as EOG (Berson and Goldstein, 1970b) for its capability to detect the spatial orientation of the current across the eye (Marmor and Zrenner, 1993). The clinical EOG measures the amplitude of the standing potential and light response (Berson and Goldstein, 1970b). Thus the EOG consists of at least two separate potentials, one that is is insensitive to light (standing potential, SP) and the other that is sensitive to light.

In EOG, the potential (SP) is measured indirectly, under conditions of dark adaptation after prior exposure to room illumination (Arden et al., 1962). In the darkness, it decreases slightly over a period of 8 or 9 minutes, at which time the lowest potential recorded in the dark-adapted state can be measured (dark-trough). After exposure to light, the potential gradually increases and reaches its peak in 10 to 15 minutes in human (light rise). The ISCEV proposes two standards for recording the EOG: (1) the ratio of light peak to dark trough (Arden ratio). The normal value for the Arden index is 180 and over in percentage unit (Arden et al., 1962); or (2) the ratio of light peak to a dark-adapted baseline. The ratio of light rise to standing potential is usually greater than 1: 9 in normal human subjects (Miller, 1982).

Light rise is thought to be the slow depolarization of the basal membrane of the retinal pigment epithelium (Griff and Steinberg, 1982; Linsenmeier and Steinberg, 1982). Dawis and Niemeyer (1986) proposed that dopamine is one of the candidates by the findings that it depresses the light peak and increases the SP in the perfused mammalian eye.

Microelectrode studies have located a large direct current (DC) component of the EOG just distal to the outer margin of the outer nuclear layer of the retina (Brown and Wiest, 1961). Since the SP is generated largely by the transepithelial potential across retinal pigment epithelium (Marmor and Lurie, 1979; Marmor and Zrenner, 1993), the pigmen epithelium is thought to contribute to the DC component, the SP in EOG.

Dawis and Niemeyer (1988) used pharmocological agents to observe their effects on the SP and light rise of the EOG and the gross ERG. The result showed that some monoamines (dopamine, nonepinephrine, melatonin, and serotonin) and dibutyryl cAMP could cause an increase in the SP, depress the light peak and increase the amplitude of the c-wave. Thus the authors concluded that it is the increase in conductance and depolarization of the basal membrane of the pigment epithlium caused by these factors which explains the

relationships among these three events. The correlation between the standing potential and the light rise of the EOG and the c-wave in the gross ERG has been studied by many other ways, such as repetitive stimulation with light on the primate retina (Gouras and Carr, 1964), central retina interruption in monkey (Gouras and Carr, 1965), azide injection in the cat eye (Linsenmeier and Steinberg, 1987) and discussed (Linsenmeier and Steinberg, 1983a; Steinberg, et al., 1985).

CHAPTER 2.

RETINA RECEPTIVE FIELDS AND PATTERN DETECTION

2.1 INTRODUCTION

The retinal ganglion cells carry the light information coded and processed through the retinal circuit in the sense that the graded potential in the 1.5×10^8 receptors are converged in the spikes of 1.0×10^6 ganglion cells. This convergent procedure induces the possibility that the spikes of the optic nerve represents the light information collected from a certain retinal area, ie, receptive fields. The concept of the receptive field was first introduced into visual studies by Hartline (1940). In his report on the activity of ganglion cell fibres in the eye of the bull-frog, Hartline wrote:" *A given optic nerve fibre responds to light only if a particular region of the retina receives illumination. This region is termed the receptive field of that fibre*" .

Since in the optic nerve, some fibers gave response when the light is switched on, others gave the discharge at cessation of illumination and some showed a short discharge or burst when the light is on/off, retina responds to *change* of light rather than the *incidence* of light alone. It implies that the light information has been processed and coded before coming to the retina receptive fields. This process is supposed to be completed within the complex retina circuit, including the retinal ganglion cells.

The information process within the retina is as complicated as the intricacy of the retinal structure itself. The studies by microelectrode techniques and some artificially interrupting methods (such as separately dyeing different neurons, perfusion with some pharmacological agents) in animals in vivo and in vitro have presented some content about the procedure. In human, the studies of the procedure is much more often through some electrophysiological methods by the aid of some visual stimuli, such as recording the retinal responses evoked by flashes and patterns. Since the properties of the receptive fields of the ganglion cells represent the existence and final accurate picture of the signals processing and coding in the retina and can be detected by some appropriate patterns, the study of the retinal receptive fields through corresponding patterns is a tool to probe for the mystery of the transmission and process of light through the complex retina circuit.

2.2 RECEPTIVE FIELDS

2.2.1 Central-Surround Phenomenon

In the pioneering studies by Hartline (1940), he proposed that the response of some retina area (receptive field) can be recorded by the discharges in a single optic nerve, based on the convergent anatomical connection between the ganglion cells and receptors. He found that with the stimulus intensity increase, the field where response could be evoked was enlarged and thus concluded that, in order to evoke a response in a single fibre, a more intense stimulus was needed; secondly, he found that some fibres responded when the light was on and others gave the discharge when the light was off.

Stephen Kuffler (1953) was the first person who recorded retina receptive fields with center-surround phenomenon. It was found that the cat's retina ganglion cells of the more peripheral part of the field gave the opposite type of response to that given by the centre. Thus, if the stimulus was at the *centre* of a receptive field the response increased (ON response), the response around the centre (*surround*) decreased (OFF response). And there was a mutual interaction (ON-OFF response) in the intermediate zone between the centre and the surround.

Following Kuffler's work, Granit (1955), Barlow et al (1957) and Baylor and Fettiplace (1975a,b) revealed the same patterned responses in the mammalian retinas. They found that the difference between the cood-blooded vertebrates and mammalian was that in mammalian retinas, the events occurred on the background activities. These observations have resulted in the conclusion that retinal ganglion cells respond more strongly to small spots of light confined to the field centre than large spots that stimulate both centre and surround areas.

Therefore the center-surround phenomenon occurred in the retinal ganglion cell receptive field, can be described as: when visual stimulus is within the centre field, the response is larger with the increase of the stimulus size. When the stimuli are larger than the centre size, the reduction of the response occurs due to the inhibitory effect from the surround area of the same receptive field. This opposite interaction between the centre and the surround of the receptive fields is termed as centre-surround antagonism. Thus the size and the properties of the receptive field centre and surround are important in discussing the center-surround systems and their mechanisms.

2.2.2 The Concepts of Centre-Surround System

Centre and Surround Rodieck and Stone (1965b) measured the centre and periphery of the cat ganglion cell receptive fields to small spots of light, using the summed spikes during the interval of summation. The sizes of the central areas varied from 0.4 to 4 degree. Beyond the centre, the strength of the surround response increased quickly to a maximum and then gradually decreased until no response could be recorded. With the increase of the spot size, the response transited from the pure ON response to the ON-OFF response and then OFF response if the centre of the ganglion cells was excited by light. The converse was the same for the those centre field excited by dim light (Rodieck and Stone, 1965a).

The sizes of the centre and surround fields were best demonstrated in cat lateral geniculate nucleus by Hammond (1972) who projected light annuli of increasing diameters on to a receptive field, and at the same time used a small spot projected on to the centre; if the discharges in the annulus were increased by the spot on the centre, the annulus was within the centre, otherwise, it was within the surround. As shown in Fig 2.1 where a discharge of 100 represents that due to the central spot alone, the centre of the field occurs about 2 degrees in diameter and surround extends beyond 9 degrees, with a maximal inhibitory action at about 3.5 degrees.

ON- and OFF-centre Cells The distinction was first presented by Kuffler's report (1953). According to his physiological observation, the ganglion cells were divided in to ON-centre and OFF-centre types. On the ON-centre cells, the cell discharge increased when the light was over their receptive field centres; OFF-centre cells were excited when the light over the centre was dimmed or extinguished. The anatomical report showed that the contacts between bipolar and ganglion cells made at different sublaminae of the inner plexiform layer by the ON- and OFF-cell layers could interpret the phenomena (Famiglitti and Kolb, 1976).

Peripheral Effects Ikeda and Wright (1972a, b) have shown that there is a region beyond the inhibitory surround of an ON-centre ganglion cell, which they describe as *disinhibitory*. When a spot of light is fallen onto the centre of an ON-centre ganglion cell the response reaches maximum and then decreased when the spot fall on the more peripheral part of the field , at about 2° to 2.5°, an OFF- response appeared, although the ON-response was larger. When the spot moved to more eccentric positions, the OFF-response disappeared and the ON- response increased; and this range (3°-5°) was termed as the disinhibitory zone.

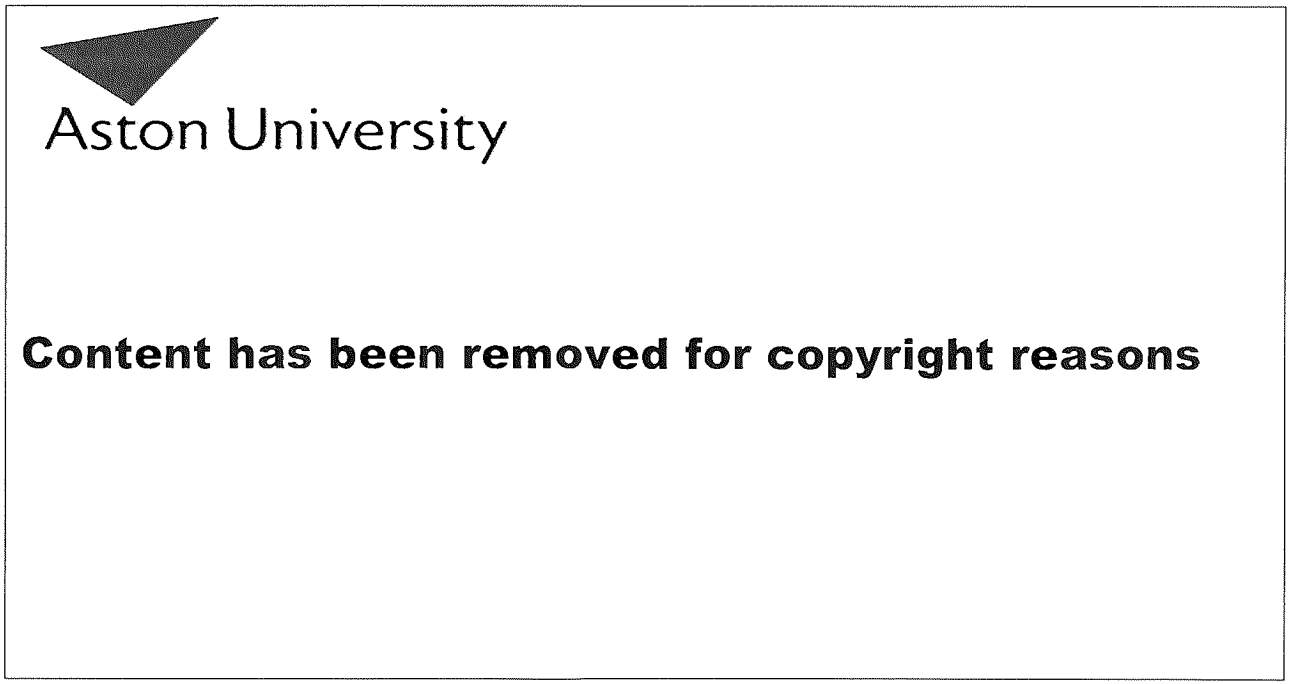

Fig 2. 1 Determination of the size of the receptive field. An annular stimulus is projected on the retina and the discharge and its effects on the discharge caused by a small centred spot are recorded. (after Hammond, 1972)

MacIlman (1964, 1966) found that, in cat retina, when the stimulus was far beyond the traditional limits of the receptive field surround, the response could be altered. Similar report in the cat retina was showed by Krüger and Fischer (1973a, b) that the regions as far away as 40° from the receptive field centre can exert a strong influence on the response to central stimulation, even when stimulation of these remote regions alone produced little or no response. This effect is termed as peripheral (shift-) effect by MacIlman.

2.2.3 Classifications of Ganglion Cells and Their Receptive Fields

Enroth-Cugell and Robson (1966) divided the cat retinal ganglion cells mediating foveal vision into two groups: X and Y cells, which respectively make up 45% and 5% of the total population (Stone, et al., 1979). The third type of ganglion cells is W-cells, first described and termed by Stone and Hoffmann (1972), which accounts for 50% the cells in the cat retina (Stone and Fukuda ,1974).

In the primate retina, according to the projection of retina ganglion cells at lateral geniculate nucleus (LGN), there are P and M cells. There are 1.2×10^6 of P cells and 0.15×10^6 of M cells; 80% of the retina ganglion cells are Pß cells and 10% are M cells (Perry et al., 1984a; Rodieck, 1988). Pß-cells are found to be X-like; 75% M cells are X-like and the rest 25% of M cells are Y-like if compared with the X/Y/W classes of the cat retina (Hicks et al., 1983; Derrington and Lennie, 1984; Kaplan and Shapley, 1986). The visual system of the macaque monkey has been shown to be very similar to the human visual system (DeValois et al., 1974).

Each region of the retina is subserved by a range of ganglion cells with different receptive field sizes. There is a large concentration of X cells in the fovea, where Y cells are distributed more equally through visual space. Similarly, the proportion of P cells to M cells is large in the fovea. M cells have larger receptive field centres than P cells in corresponding retina area (Kaplan, 1991). In average, the receptive field centre size of the neuronal population is smaller in the fovea and increases with eccentricity (Dow et al., 1984).

2.2.4 Central-Surround Organisation and Mechanisms

Originally the receptive field was thought to represent the dendritic field of a neuron alone according to Kuffler's findings. However, cells can response to stimuli outside their dendritic

fields (Kaneko,1973). Thus as for receptive field, the terminology of " receptive field centre" is used to describe direct effect within the dendritic area, whilst "receptive field surround" indirect effects from some neighbouring neurons. Essentially, the centre consists of the dendrite fields of the ganglion cells, which receive the input directly from the centre photoreceptors; the neighbouring cells, which mediate surround, are horizontal cells, assistant by amacrine cells (Davson, 1990).

Centre field

It was suggested by Brown and Major (1966) and Leicester and Stone (1967) that the size of the centre of a ganglion cell's receptive field was determined by the size of its dendritic tree, which would govern the number of bipolar cells that could make direct input into ganglion cell. Peichl and Wässle (1979) confirmed the good correlation between dendritic tree size and receptive field by flashing a small spot of light at different positions in the receptive field.

In a more recent study, Fukuda et al (1984) have characterised the receptive fields of more than 400 ganglion cells on the basis of X-, Y- and W- classifications, and examined the morphologies of some 21 recognised after horseradish peroxide injection. Receptive field centre sizes of these three types of cells by physiological measurement were characteristically different, being 0.2-1.0°, 0.6-2.4° and 0.8-3.7° respectively. Surprisingly, compared with the anatomical check, the X-cells revealed a greater centre field size than expected of their dendritic trees (probably due to some convergence through horizontal or amacrine cells); Y-cells seemed to have smaller field centres than their dendritic field.

Yet this paradoxical finding does not influence the good relation between the dendritic tree and the centre size. Linsenmeier et al (1982) found that the centre radius (r_C) of the receptive fields was two to three times larger for Y than for X cells at any eccentricity, consistently with the anatomical large dendritic fields of Y cells and the small fields of X cells. r_C increased with the retinal eccentricity, but r_S did not. The dependence of r_C and r_S on retinal eccentricity is rather different that the total strengths of centres and surrounds of a cell near the area centralis would be more balanced and sharply selective to the pattern size (Linsenmeier et al.,1982).

Gaussians models

Wagner et al (1963) suggested that the surround field, in fact, extended into the centre, so that the response to spot was really the algebraic of centre and 'surround' responses. Rodieck (1965) provided a quantitative model, Difference of Gaussians model (DOG model), for the receptive field centre and surround (Fig 2.2). It was assumed by Rodieck that the receptive field response is a linear combination of two distinct spatial mechanisms: a narrow, sensitive mechanism in the centre, and a large, overlapping and less sensitive mechanism for the antagonistic surround. Both mechanisms were assumed to have a circular Gaussian sensitivity distribution, with coincident centres. The response at any point in the receptive field would be just the arithmetic sum of the contributions from these two mechanisms. The central response is stronger but generated over a smaller spatial extent; the surround is opposite in polarity, smaller in amplitude, but encompasses a larger area.

The sensitivity S at a point r from the middle of the receptive field was given in this model by

$$S(r) = Kc.\ exp.\ [-(r/rc)^2] - Ks.\ exp.\ [-(r/rc)^2]$$

where Kc represents the sensitivity of the centre region in the middle of the receptive field; rc is the radius of the centre region. Ks and rs are the sensitivity and radius of the surround. The sensitivity declines to 1/e (approximately 0.37) of its maximal value at the characteristic radii, rc and rs . According to this model, the response of the cell at time t and distance r from the middle of its receptive field could be expressed as the sum of contributions from a spatial-temopral coupled centre and a surround:

$$R\ (r,t) = f_C\ (r) \cdot h_C\ (t) + g_S\ (r,t)$$

where f is a function of space, h is a function of time, and g is a function of both space and time.

The amended DOG models were proposed independently by Enroth-Cugell et al (1983) and Dawis et al (1984). The Dawis's new model considers the effect of the temporal frequency on the centre sensitivity to the spatial frequency of the stimuli and allows the 'displacement' of the mid-points of the centre and the surround regions. Thus, formally, a cell's response R as a

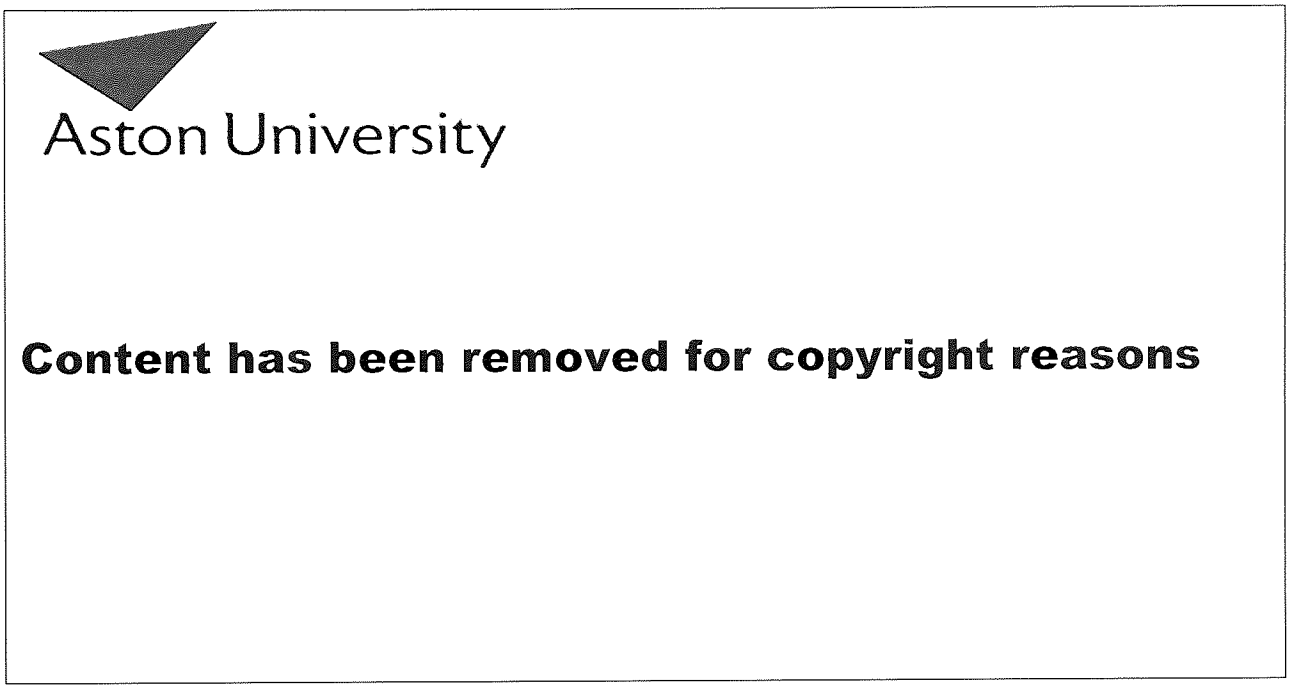

Fig 2. 2 Theoretical hypothesis of the center and surround mechanisms. (according to Rodieck and Stone, 1965b)

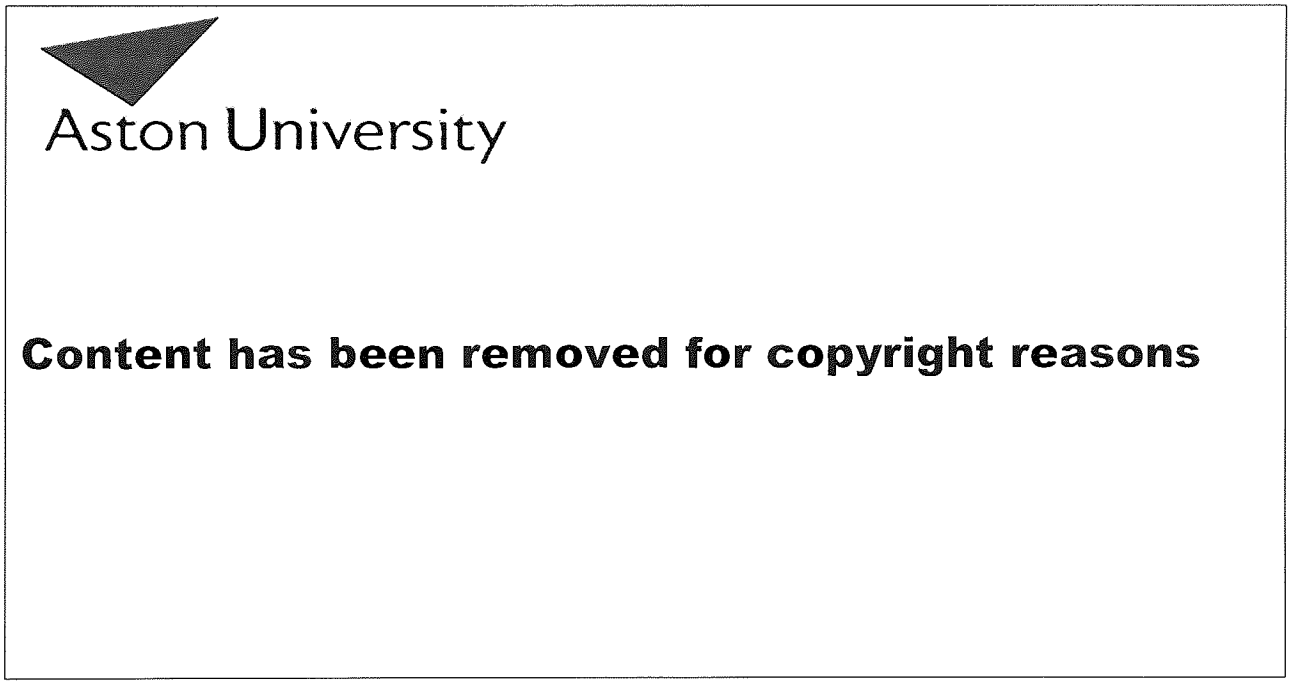

Fig 2. 3 Schematic 'wiring diagram' of the mud-puppy retina. R, receptor; H, horizontal cell; B, bipolar cell; A, amacrine cell; G, ganglion cell. Note that in this retina, the horizontal cell influences both receptor and bipolar cell, and the amacrine cell influences both bipolar cell and ganglion cell. (after Dowling and Werblin, 1969)

function of spatial frequency v at a given temporal frequency w can be represented as

$$Rw\,(2\pi v) = Kc\,(w)\cdot exp\,[\,-(\pi\cdot r_C\,(w)\cdot v)^2 + i\,(\,\pi/180)\cdot(\,\phi_C\,(w) - 360\cdot x_C\,(w)\cdot v)]$$
$$+\; Ks\,(w)\cdot exp\,[\,-(\pi\cdot r_S\,(w)\cdot v)^2 + i\,(\,\pi/180)\cdot(\,\phi_S\,(w) - 360\cdot x_S\,(w)\cdot v)]$$

where $Kc\,(w)$ is the strength of the centre's response, v is the spatial frequency in cpd, $r_C\,(w)$ is the radius of the centre region (in degrees), $\phi_C\,(w)$ is the temporal phase lag between the stimulus and the response (in degrees), and x_C (w) is the location of the peak of the centre region.

Enroth-Cugell et al. (1983) presented a similar model, but constrained the mid-points of the centre and surround regions to coincide. The quantitative difference between the old and new models are rather small. However, the models are only matched to the linear characters and thus restricted to X-cell rather than Y-cell (Kaplan, 1991), which will be discussed later in this chapter.

The 'wiring diagram' of *Necturus*

The pioneering study is that of Werblin and Dowling (1969) on the retina of the mudpuppy, *Necturus*. The synaptic structures and relations between retinal cells in *Necturus* are similar to those of primate retina but the relation between horizontal cells and receptors and bipolars appeared to be different. Yet the 'wiring diagram' of the *Necturus* retina offers a brief picture about the centre-surround structure and mechanisms (Fig 2.3). Between photoreceptors and bipolar, horizontal cells not only mix the response between rods and cones but also forms presynaptic relation with bipolar cells and thus contribute to vertical transmission. The reciprocal synapse of the amacrine cells provides the negative feedback responsible for the process (Maguire et al., 1989). The importance of such anatomical base is that the feedback allows activity in one receptor to influence activity in its neighbours. In a similar way, the amacrine cells not only link bipolars horizontally but also transmit input from bipolars to ganglion cells.

Cellular origins of the centre-surround System

Using intracellular recording by inserting microelectrode into different regions of the retina, the existence of the opponent responses typical of those described for ganglion cells were ascertained by Werblin and Dowling (1969). In the receptors, the striking feature is a graded

hyperpolarization. It was the same case happened in the horizontal cells, hyperpolarization, but with longer latency than that of the receptors. The difference was that there was a summed light effect over quite a wide field.

By the same way, the authors found similar slow potentials in the bipolars but a concentrically organised opponent response was recorded as well---if the centre hyperpolarises, the periphery causes depolarisation, and vice versa; the response in amacrine cells consists of one or two spikes superimposed on a transient depolarising potential; the intensity of the stimulus is represented in the variation of the the latency and number of spikes.

Thus, the centre-surround phenomenon of the receptive fields recorded in the ganglion cells starts from bipolar cells and formed with the assistance of the horizontal and amacrine cells owing to their presynaptic effects as well as the reciprocal feedback effect as shown in Fig 2.3.

Cellular interactions in the centre-surround system

Horizontal Cells

Horizontal cells processes widely in the outer plexiform layer. They exert their inhibitory effects in centre-surround mechanism either by feeding back onto the receptors (Baylor, et al., 1971) or by antagonising directly the bipolar cells (Dowling and Werblin, 1969), or both.

Horizontal-photoreceptor interaction

Baylor et al (1971) hyperpolarised a single horizontal cell by injection of current, and found that an impaled cone would exhibit depolarisation, indicating an inhibitory action, or negative feedback; similarly, the cone response evoked by light was depressed by hyperpolarization of the horizontal cells. When they recorded simultaneously the responses from both cells, they found that: when a small spot of light caused cone hyperpolarization, horizontal cell had no/little response, when the size of spot increased slightly (within 70μm), cone hyperpolarization enhanced alone; while when spot diameter was over 70μm, horizontal cells response increased and response in cones showed a depolarising deflection, confirming a depolarising feedback from horizontal cells on cones.

This horizontal cell-cone interaction extends over wide areas of the retina owing to the massive junctions between horizontal cells, which work as a syncytium through the electric couplings

(Yamada and Ishikawa, 1965; Kaneko, 1971; Fuortes et al., 1973). The larger size of the surround is due not only to the larger dendrite field of horizontal cells, but also to gap junctions between them (Slaughter, 1990). The size and amplitude of the surround can be reduced by uncoupling horizontal cells and this may be important during dark adaptation, since the elimination of the surround suppression allows effective summation over a large number of photoreceptors (Mangel and Dowling, 1985, 1987; Witkovsky et al., 1988).

Horizontal-bipolar cell interaction

The surround responses of the bipolars are provided by the horizontal cells (Dowling, 1990). Naka and Witkowsky (1972) showed that, using an extrinsic current (de- or hyper-polarisation) in a dogfish horizontal cell through an electrode, a slow potential developed in a bipolar cell at the same time and the response pattern depended on the type of polarising current passed through the horizontal cell. This could be associated with a discharge in a ganglion cell,

One horizontal cell can antagonise both ON- and OFF bipolars (Sakuranaga and Naka, 1985). This phenomenon has been shown by injecting hyperpolarising current into horizontal cells, which induces depolarising responses in centre-hyperpolarising (OFF) bipolars and hyperpolarising responses in centre-depolarising (ON) bipolars. Thus the authors concluded that the centre field of the bipolars reflects the direct input of receptors, whereas the antagonistic receptive field surround response reflects an horizontal output from receptors.

Amacrine Cells

Amacrine-ganglion cell interaction

The second type of centre-surround related cells is amacrine cells. In the IPL, amacrine cells interact with both bipolar terminals and ganglion cell dendrites (Dowling and Boycott, 1966). As shown in Fig 2.3, amacrine cells are postsynaptic to bipolar cells in the sublamina a of the IPL, making reciprocal synapses to these bipolars and in presynaptic to ganglion cells.

Cleland et al (1971, 1973) classified the amacrine cells in accordance with the duration of their responses, *sustained* and *transient*. When a moving bar passed, sustained units continued to respond when the stimulus over the centre field was on and off (ON and OFF responses) until the pattern was too fine to discriminate. There was only a brief transient increases of the discharge when the grid was jerked into motion on the transient unit (ON response). The result

indicates that the sustained type of cells respond to the spatial pattern of the stimuli, whereas the transient units represent the initial stage in development of a specific sensitivity to motion of an subject within the receptive field.

This classification has been accepted in some other reports. Amacrine cells respond to light in two ways: those with sustained response to light and those respond transiently to retinal illumination (Werblin and Dowling, 1969; Kaneko, 1971; Toyoda et al., 1973). Dowling (1990) suggested that ganglion cells receiving little input from amacrine cells and having response and receptive field properties similar to bipolars are of sustained response in centre-surround organisation and that those receiving more amacrine cell input showed more transient characteristics and often of more complex receptive field properties.

Another function related with the interaction between these two types of cells is the directional sensitivity. Barlow et al (1964) reported that, in rabbit, the ganglion cells with the typical centre-surround arrangement, showed the directional sensitivity in the sense that the maximal response occurred when a moving spot traversed a certain 'preferred' direction, while, in the opposite ('null' direction), there was no response at all to movement of the spot. The'null' direction resulted from inhibition and in this direction, very slow motion could evoke a response.

Barlow and Levick (1965) demonstrated that segments of a ganglion cell receptive field could act as separate units for directional selectivity and they proposed a model, using delayed inhibition, to explain the generation of these responses. They proposed that synaptic excitation and inhibition are arranged such that movement in one direction evokes excitation first, followed by inhibition. The time delay prevents the inhibition from suppressing the excitation and a vigorous response results. If movement in the opposite direction produces inhibition that coincides with excitation, the result can be a weak response.

The transient amacrine is thought to contribute to the direction selectivity in the similar way as the ganglion cells (Ariel and Daw, 1982b). DeVoe et al (1985) have found that directional selectivity in turtle retina is not restricted to ganglion cells but also found in amacrine cells and bipolar cells. The spectral properties of directional selectivity in the transient ganglion cells and amacrines are similar but distinctly different from those in bipolars, suggesting that directional selectivity in the distal and proximal retina is formed independently and that amacrine cells are

probably assistant to the ganglion cells in forming the directional selectivity.

Thus amacrine cells may (1) contribute to antagonistic surround mechanisms for the pattern discrimination and (2) may also impart more complex properties to the ganglion cell receptive fields, such as directional selectivity (Caldwell et al., 1978).

Transmitters in the centre-surround system

GABA in horizontal cells

Many horizontal cells release inhibitory GABA (Lam, 1978; Ayoub and Lam, 1985), and therefore they are responsible for production of the negative feedback control and thus centre-surround mechanism.

Dopamine in interplexiform cells

Dopamine is released by inteplexiform cells (Ehinger et al., 1969). Interplexiform cells receive all their input from the IPL and send most of their output on horizontal cells and bipolars in the OPL (Dowling and Ehinger, 1975). Dopamine effects the horizontal cells by (a) reducing the light responsiveness between the cells (Hedden and Dowling, 1978; Mangel and Dowling, 1985) and (b) uncoupling the electrical junction between the cells (Teranishi et al., 1983; Piccolino et al., 1984; Teranishi et al., 1984) through reducing electrical conductivity between the cells (Negishi and Drujan, 1979).

The effects of dopamine on horizontal cells are not mediated directly, for at physiological concentration it alters neither membrane potential nor membrane resistance (Lasater and Dowling, 1982), but is mediated by cyclic AMP (Van Buskirk and Dowling, 1981). Dopamine interacts with the receptors that are linked to the enzyme adenylate cyclase through a G protein. Activation of adenylate by the agent results in the conversion of ATP to cyclic AMP. Cyclic AMP, in turn, interacts with kinases that phosphorylate the glutamate channels or the gap junction channels; phosphorylation of the gap junction channels reduces conductance between the horizontal cells (Negishi and Drujan, 1979; Dowling, 1990). Thus it shrinks the receptive field size and lessens effectively the inhibitory influences of horizontal cells, which in turn, decreases negative feedback to the photoreceptors and then a decrease of bipolar and receptor cell surround responses (Hedden and Dowling, 1978). The result is that diffuse light stimuli produce a larger response in photoreceptors and bipolar cells than they would.

Furthermore, Mangel and Dowling (1985, 1987) found that after prolonged dark adaptation (100-120 ms), the receptive field profile of horizontal cells in the carp retina closely resemble those of horizontal cells from control retina exposed to dopamine and suggested that the release of dopamine plays a role in the darkness, and depresses the horizontal cell activity. Their and Alder (1984) used dopamine in cat retina and found that the agent could reduce the strength of the antagonistic surround in all cell types (X/Y and ON-/OFF- centre cells), as well as reduce the rate of the spontaneous discharge.

GABA , Glycine and Acetylcholine (Ach) in amacrine cells

GABA and glycine are the inhibitory transmitters released by amacrine cells which make up almost two-third of all the amacrine population (Dick and Lowery, 1984) and thus play key role in the centre-surround mechanisms. The excitatory transmitter (acetylcholine)-released amacrine cells make up the third major cell group. Fig 2.4 showed that the relation between the transmitters released by amacrine cells and the effect of these transmitters on the ganglion cells. The concrete role of amacrine contributing to the mechanism is not very clear, probably because of its massive subtypes (Kolb and Nelson, 1981) and the existence of the transmitters diversity (Slaughter, 1990).

GABA preferentially acts on the ON pathway while glycine acts on the OFF pathway (Ikeda and Sheardow, 1993). The studies on the cat ON-/OFF- centre ganglion cells showed that in the ON-center cells, the surround responses of the transient Y-cells, classified by Cleland et al. (1971, 73), can be blocked by bicuculline, a GABA antagonist and the size of the centre of the ON- centre Y-cells can be reduced by the agent (Kirby and Enroth, 1976), while the surround response of sustained ON-center X-cells can be blocked by strychnine (a glycine antagonist); in the OFF-center cells, the surrounds of both X and Y cells can be blocked by bicuculline, which increased the centre size of the Y cells (Kirby and Schweitzer-Tong, 1981; Saito, 1983). Thus it is assumed that glycinergic amacrines are related more with center-surround antagonism by affecting the sustained X cells alone; while the GABA-ergic amacrines are probably involved in the more complex properties of the receptive field by effecting more on the surrounds of Y cells. Therefore GABA appears to control transient inhibition, while glycine plays probably a role in sustained inhibition (Belgum et al., 1984; Slaughter and Bai, 1989).

Wyatt and Daw (1976) hypothesised that directional sensitivity in the ganglion cells relied on

Fig 2. 4 Suggested circuits and neurotransmitters involved in the center-surround mechanisms involved in from bipolars to ganglion cells. (after Ikeda and Sheardown, 1983)

inhibition. They infused the right internal maxillary artery of the rabbit, with picrotoxin, an GABA antagonist (with the right lingual, temporal and internal carotid arteries clamped). As a result, directionally sensitive ganglion cells became equally responsive to movement in both directions. Strychnine, the glycine antagonist, had no effect, although it did influence the response of edge detectors. Caldwell et al. (1978) showed also that directional sensitivity could be blocked by applying picrotoxin, thus implicating GABA as the inhibitory transmitter in the function. Since amacrine cells were known to contain GABA, the authors concluded that the inhibitory effects required for directionality were derived from amacrine rather than horizontal cells.

Both GABA and glycine can open chloride channels (Slaughter, 1990). The chlorine reversal potential values of amacrines and ganglion cells are close to the resting potential so that these channel changes do not hyperpolarise the cell too much. The major effect in these cases is resistance instead of voltage change. When large number of chlride channels are open, there is a large decrease in cell resistance. Thus it reduces the light response (voltage) to excitatory input (current) according to Ohm's law, as other classical inhibitory transmitters, and suppresses all light responses.

Additionally, GABA-B receptor (Bowery et al., 1980) can close calcium channels on bipolar cells (Maguire et al., 1989) and open potassium channels on amacrine and ganglion cells (Slaughter and Bai, 1989), which suppress only sustained responses and thus the transient response predominates in such cases. Thus GABA-B receptor in the amacrine cells can alter the response properties of retina neurons and change the information content of these cells. When GABA-B receptors are stimulated, the retinal neurons that show no directional selectivity under normal conditions become directional (Pan and Slaughter, 1988), which may represent a mechanism for selective attention (Slaughter, 1990) for a suppression of 'unattended' information (sustained) and an enhancement of 'attended' information (transient signals).

Acetylcholine (ACh) in amacrine cells

ACh-ase can be found in the retina (Nichols and Koella, 1968; Masland and Mills, 1979). Hayden et al (1980) showed that ACh synthesis was defined to amacrine cells, which included the 'displaced' amacrine cells with their somatoplasm in the ganglion cells layer. The cholinergic amacrines control the transient OFF- and ON- excitation (Masland et al., 1984 a;

Massey and Redburn, 1983) and are thought to be linked with directional selective ganglion cells (Ariel and Daw, 1982b).

Suppression of GABA inhibition is known to be able to eliminate directional selectivity, resulting in that ganglion cells respond to all directions of motion (Wyatt and Daw, 1976). In the rabbit, the cholinergic blockers have been shown to have a similar effect to the suppression of the GABA inhibition implying that the cholinergic amacrines may play also an important role in directional selectivity (Ariel and Dow, 1982b).

Light releases Ach in the retina, which can be blocked by the glutamate analogue, 2-amino-4-phosphonobutyric acid (APB), to block the ON-signals arising from depolarising bipolars (Massey and Redburn, 1983). Masland et al (1984a) labelled amacrines with ^{3}H-acetylcholine in the incubated retina and found that the blocking ON response by APB tended to confine release of transmitter to the dendrites of the displaced amacrine cells in the inner part of the plexiform layer. In reviewing earlier studies on the effects of cholinergic agents on responses of ganglion cells (Masland and Ames, 1976; Ariel and Daw, 1982), the authors concluded that a common feature of amacrines was the influence on motion sensitivity. They suggested that the detection of motion of a stimulus within the receptive field of the ganglion cell might be mediated by 'unit' of amacrine dendrites.

Massey and Neal (1979) and Cunningham and Neal (1983) showed that light evoked release of Ach was reduced by GABA; it reduced the resting release of Ach in the dark. The authors proposed that there was a tonic inhibiting action of GABA on the amacrines. It seems that the antagonistic effects of Ach and GABA are balanced well in functioning the directional selectivity that they work cooperatively to assist the ganglion cells in forming the directional sensitivity described by Arie and Daw (1982b).

2.3 PATTERN AND FOURIER ANALYSIS

2.3.1 Pattern

Pattern is defined as an arrangement of lines, shapes, colour, etc. As a vision stimulus, it may be any contour with these elements. The commonly used patterns are sinusoidal gratings and

checkerboards. A pattern is fully described by four parameters: mean luminance, contrast, spatial frequency and spatial phase.

The *mean luminance* (Lm) of a pattern is given by the summation of the maximum (Lmax) and the minimum (Lmin) luminance (amplitudes) divided by two, which is expressed as: Lm = (Lmin+Lmax) / 2, in the unit of candela per meter squared (cd/m^2) (Fig 2.5). *Rayleigh-Michelson contrast*, is the magnitude of luminance variation in the stimulus relative to the average luminance. It is defined as: Cm = (Lmax-Lmin) / (Lmax+Lmin) = (Lmax-Lmin) / 2Lmean, which can range from zero to 1.0 (Rayleigh 1889; Michelson, 1927). The spatial period of a pattern is the distance between successive peaks and the *spatial frequency* (F) is the reciprocal of this distance (1/T). F is described in cycles per degree (cpd). 1 cpd is that an object 1 cm wide viewed at a distance of 57cm subtends approximately 1° at the eye (Regan, 1990). The spatial frequency (F) of a bar, or band of a grating, can be calculated by the formula F =1/ (2w), where *w* is the width of a bar/ grating in degrees. The fundamental spatial frequency of a check pattern can be expressed as F = 1/ (2$\sqrt{2}$w), where w is the width of a single check in degrees (Camisa, et al., 1981; Bodis-Wollner et al., 1990). *Spatial phase* (Sp) defines the spatial position of the gratings in terms of spatial period. A change of 180° of spatial phase means that the grating is displaced bodily by half a cycle so that bright bars exactly replace dim bars and vice versa.

2.3.2 Fourier's Components of a Pattern

Schade (1956) first introduced sinewave gratings as stimuli into human vision. Campbell and Robson (1968) proposed that the visual systems have parallel spatial frequency channels owing to the receptive fields, which can be detected by corresponding spatial patterns (DeValois and DeValois, 1988; Wilson et al,1990). These findings attracted widespread attention on the use of Fourier analysis to human vision for system analysis, including the analysis of the signal input (i.e., visual stimulus) and signal output (such as ERG and VEP, etc). The basic principle of Fourier analysis is that any waveform (visual stimuli or response) that is infinitely repeated along the time axis at a frequency of F times per second can be described as the sum of a series of sinewaves (called a Fourier series) whose frequencies are FHz, 2 FHz, 3FHz, 4FHz, and so on (the FHz term is called the *fundamental* or *first harmonic components*, the 2F term is called the *second harmonic component*, and so on). In the Fourier analysis of spatial patterns or a response, two factors are related: the time and spatial frequency domains as shown in Fig 2.6.

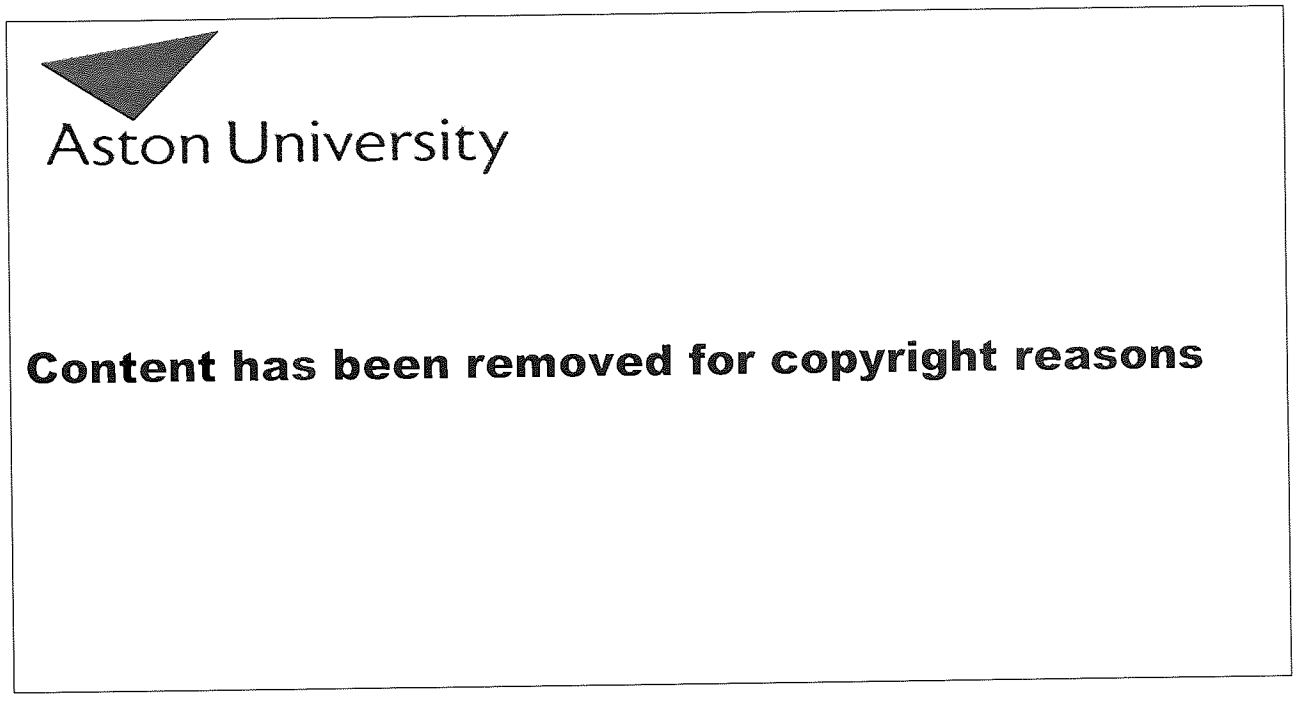

Fig 2. 5 Luminance profile of a pattern. (a) grating pattern; (b) reversal checked pattern; (c) on/offset checked pattern. Sp= spatial phase (90°); T=spatial period. (after Regan, 1990)

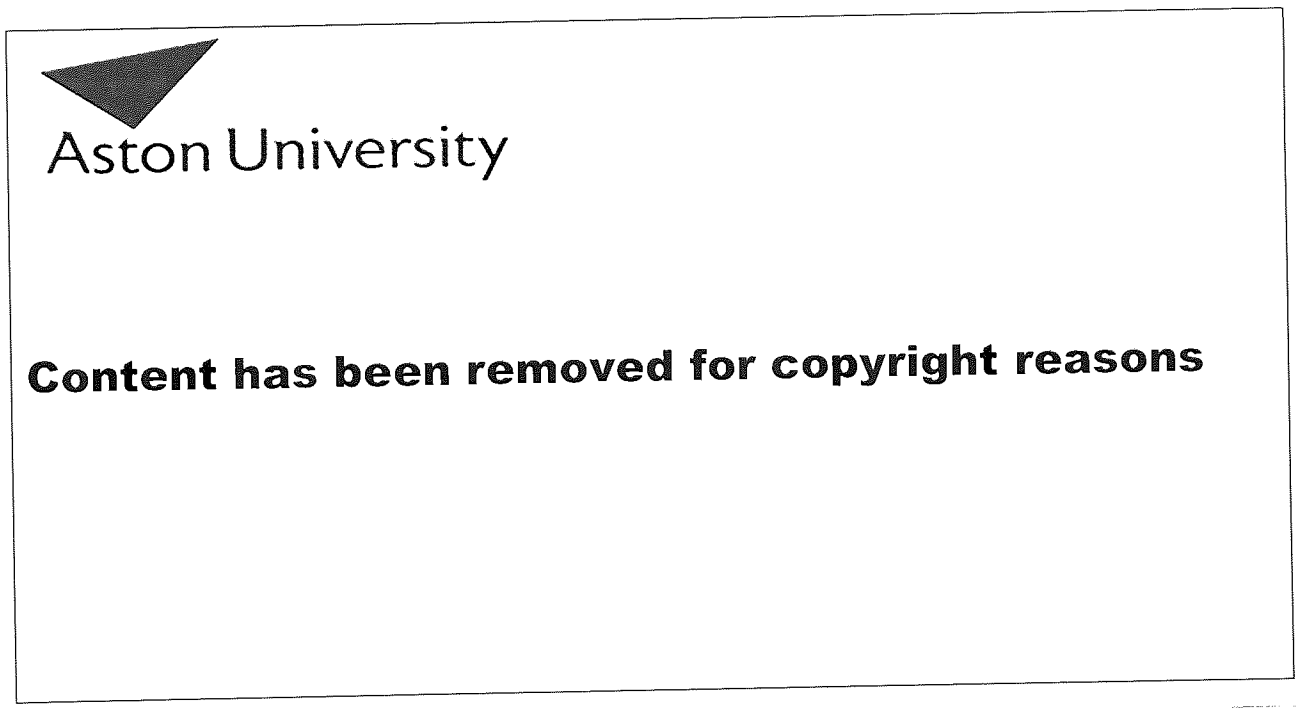

Fig 2. 6 Complementarity between the time domain and the temporal frequency domain for an infinitely-repeated waveform. Frequency spectrum is plotted as magnitude vs frequency (after Regan, 1990)

These two doctrines are mutually exclusive and related by the forward and the inverse Fourier transforms.

Spatial patterns can be described either as as a spatial frequency spectrum or a temporal variation of light intensity (radiance/power), which relates the use of a pattern with ERG and VEP recordings. The spatial frequency spectrum can be plotted as amplitude/power/magnitude vs. frequency. Amplitude can take positive or negative values. Magnitude is amplitude with negative values given a positive sign. Power is proportional to the square of amplitude (Regan, 1990).

Duffieux (1983) extended Fourier methods to the analysis of spatial distribution of light and showed that any physically realisable spatial pattern of light can be described as a sum of multiple sinusoidal components plus a constant term. A checkerboard could be decomposed into a series of discretely sinusoidal gratings of specific spatial frequencies and orientations whose contrast (amplitudes) show a regularly fixed sequence (Bodis-Wollner et al., 1990).

The fundamental spatial frequency components of a checkerboard (the largest black spots in Fig 2.7) are at an angle of 45° to the edges of the checks and, therefore, have a frequency of $(1/(2w/\sqrt{2})$ cpd where w is the side length in degrees of any given check. For a sine wave grating, all the power is in one spatial frequency and one orientation. When the edges of a checkerboard are aligned vertically and horizontally, all the power is concentrated in the oblique orientations (Camisa et al., 1981; Regan, 1990).

2.4 RETINAL PATTERN DETECTION

2.4.1 Contrast

Rayleigh-Michelson contrast is the basis for a pattern to evoke the response. When patterns with a certain contrast are repeated in either appearance-disappearance or counterphase reversal, the response is produced by the difference or the change of the luminance level and summed on the same stimulated area.

Contrast gain is used to describe the extent of the contrast sensitivity of a response to a

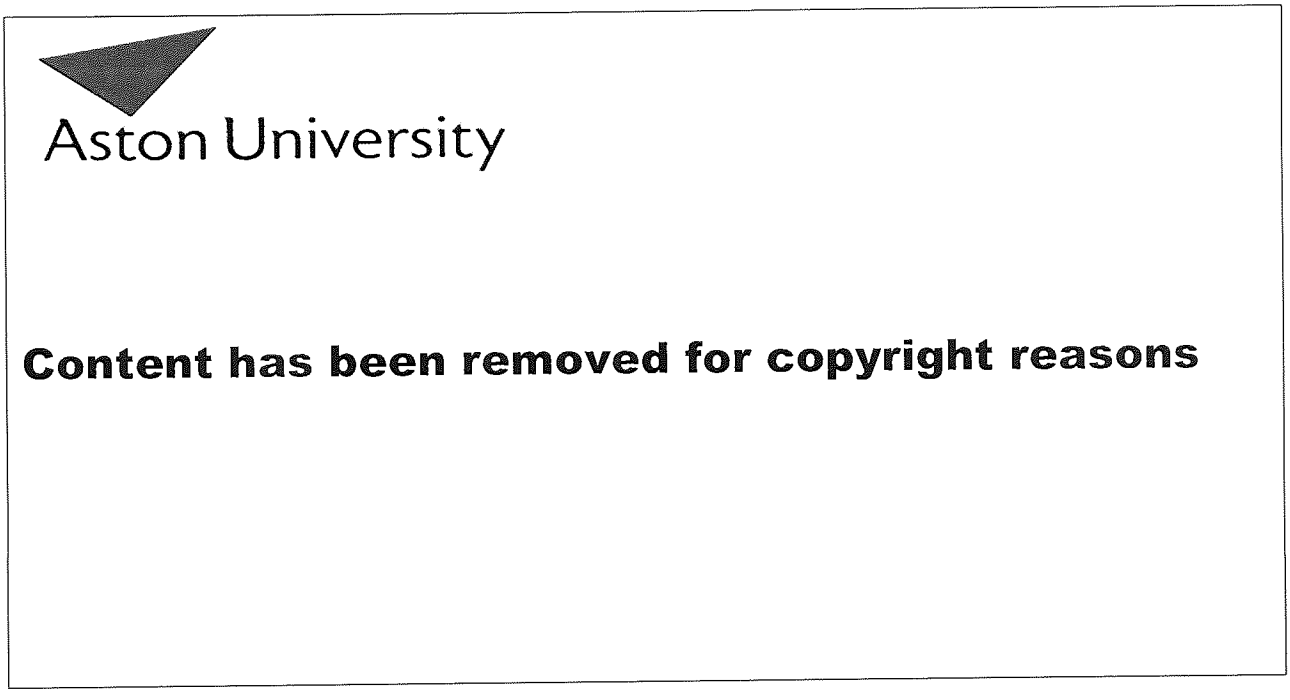

Fig 2. 7 Fourier spectrum analysis of an indefinitely-extended sinewave grating (A) and of a checkerboard (B). Those polar plots radially distant from the origin indicate the Fourier's spatial frequency distribution and the largest dots are the fundamental harmonic. For a checkerboard alligned vertically and horizontally, all the power is concentrated in the oblique direction and the second harmonics are displayed in the smaller dots. (From Camisa et al., 1981)

pattern. Its definition is neural response divided by stimulus contrast in the limit as contrast approaches zero, and will have units mV or impulses per second (Shapley and Enroth-Cugell, 1984).

The contrast gain is proportional to the area of a receptive field centre (which grows as the square of the radius) as well as peak sensitivities (Kaplan, 1991). Though the peak sensitivity of P cells is as high as, and sometimes higher than, that of M cells (Purpura et al., 1987), M cells are more sensitive to contrast than P cells, for the summation of their large receptive field centre size (De Monasterio and Gouras, 1975) offshoots the high sensitivity of P cells. Kaplan and Shapley (1986) confirmed in primate that in light adaptation the contrast difference between M and P cells was 8-10 times by recording S potentials in the lateral geniculate nucleus, which have been confirmed to originate from retina (Kaplan and Shapley, 1984).

Linearity and saturation Another property of the ganglion cells of the macaque retina is that the response of P cells increases linearly with contrast without saturation, whereas the M cells' response has higher contrast gain at lower contrast level and saturate above 10-15% (Kaplan and Shapley,1986).

2.4.2 Pattern Size (Spatial Frequency)

Due to the centre-surround mechanisms of the receptive field reflected on the retinal ganglion cells, the retina area can be selectively stimulated by appropriate pattern sizes (spatial frequencies). The centre cells around fovea are sharply selective to the spatial frequency and pattern element size needs to be larger to optimally stimulate peripheral neurons with increasing eccentricity.

Spatial contrast sensitivity is defined as the inverse of minimum contrast which is needed for an observer to detect a given spatial frequency. A normal contrast sensitivity function reveals an "inverted U". The spatial contrast sensitivity peaks to moderate spatial frequencies and is attenuated at lower and higher spatial frequencies. The maximum sensitivities for fovea (acuity or spatial resolution peak) lies around 5 cpd, and 2 cpd for parafovea, so the best stimuli for stimulating the fovea and parafovea are check sizes of 8 and 21 min of arc.

The size and sensitivity of the antagonistic surround region determine the low frequency

attenuation of the spatial frequency response, and thus shape the selectivity or tuning of the cell for the size of visual stimuli (Kaplan, 1991). The size of the centre region of the receptive field controls the high frequency cutoff of the cells. When a pattern is too fine (high spatial frequency) for the receptive field centre to resolve, the modulation (Lmax-Lmin) of a pattern is reduced as a function of spatial frequency, which is called *Modulation Transfer Function (MTF)* (Regan, 1990).

Spatial resolution The spatial resolution is defined as the finest pattern which eye can resolute, or evokes the response from a cell (Kaplan, 1991). The pattern image fallen on to the eye is first degraded by the optics of the eye (the lens, vitreous humor, geometrical optical aberrations and diffractions at the pupil) before it comes to the retina (Wässle, 1986). Thereafter, the image on the retina is sampled first by the photoreceptors. Cones control the upper limit to the spatial frequency band, since the resolution process here is limited. Each individual photoreceptor does not respond to light incident at point on the retina, but is collected over a small area roughly equal to the cross section of the cone's inner segments.

In cat, there is not a bipolar cell which contacts only one cone (Kolb, 1970), that the density of the bipolars is lower than that of the receptors. The spatial resolution is lost through the bipolars. Thus it is the receptive field centre of the ganglion cells, governed by the dendritic tree, that sets the lowest spatial resolution, or the spatial contrast sensitivity peak (acuity).

The spatial resolution relates with the density of the retinal neurons. Their relation can be calculated by the following formula (Snyder and Miller,1977):

$$\lambda = a\sqrt{3} = (2/D\sqrt{3})^{1/2}\sqrt{3}$$

where a is the intercell space and D is the density of the neurons. In cat, the cone peak density is 26,000 cells mm^2 (Steinberg et al., 1973), equal to the spatial resolution of 3-4 min of arc (Robson and Enroth-Cugell, 1978). In the fovea of the macaque monkey, the peak density of cones is 250,000 cells /mm^2, corresponding to 1 min of arc, which is roughly equal to that of human (Campbell and Green, 1965). In the cat central retina, the X ganglion cells, which give a peak density about 5500 cells/mm^2 (Hughes, 1975), are at 1: 6 related with the cones. The Y-

cells have a peak density of about 180 cells/mm2 (Wässle et al., 1981b) which would give 90 mm^2 ON-center and 90 mm^2 OFF-center. A X- cell can resolve 0.13 degrees (Cleland et al., 1979; Peichl and Wassle, 1979). Clearly, the retinal ganglion cells have higher spatial resolution and therefore subserve the lower limit of the spatial resolution.

Since smaller cells are more sensitive to small light spots than larger cells when the retina is light-adapted, it is assumed that the spatial resolution of P cells in primate retina is considerably higher than that of the M cells (Linsenmeier et al., 1982). But it has been found that there is little difference of the spatial resolution between M cells and P cells, regardless of retinal eccentricity (Crook, et al., 1988). Kaplan (1991) explained it as that the response amplitude is decided by the receptive centre size (the smaller the size is, the larger the amplitude is) and the contrast gain. That the M cells are four or nine times as sensitive to contrast as P cells makes up some for their spatial resolution.

2.4.3 Temporal Frequency

Fourier Frequency Domain--- Linearity and nonlinearity of the receptive fields

The first subdivision of retinal ganglion cells was that of Enroth-Cugell and Robson (1966), who used grating stimuli to characterise the responses of ganglion cells. They found that some cells, the X-cells, were linearly additive to give a combined centre-response and a combined surround response. The final response of a neuron would be determined by subtraction of the combined centre- and surround-responses.

Hochstein and Shapley (1976a, b) compared the cat retina responses evoked by drifting grating and contrast-reversing sinusoidal grating of increasing spatial frequencies. They found that with the increase of spatial frequency, Y cell stopped producing a modulated response before X cells at any given retinal eccentricity and the responses of both cells contained only the first harmonic components (*linearity*). Differently, when the contrast-reversing bars were used, Y cell could resolve the spatial frequency as high as X cells; in addition, Y cells kept on responding to each reversal of the gratings' contrast, and thus produced a typical frequency-doubled response; the second harmonic component (*non-linear*) was pronounced in Y cell while X cells had only nearly negligible second harmonics. The calculation of the rations of the second harmonics to the first ones (non-linear index) indicated that the index for Y cells was always over 1 while X

cells showed the value below one. The author concluded that Y cells contained nonlinear components in Fourier frequency domain, while the linear properties could be found in both X and Y cells. In primate, P cells are X-like for they have linear spatial summation. The average nonlinearity index is higher for the M cells than for P cells (Derrington and Lennie,1984).

This difference becomes important when one considers the temporal relationship between a visual stimulus and the response of the cell. In the Y cells there will be a distortion in frequency of the output, i.e.,Y cells responding to the gratings at twice the rate of stimulation (Enroth-Cugell and Robson, 1966).

Spatial-temporal separation

Derrington and Lennie (1982), Enroth-Cugell et al (1983) and Dawis et al (1984) have all shown that spatial transfer functions (the response amplitude functions of spatial frequency under different temporal frequencies) of the cat ganglion cells depend systematically on the temporal frequency that is used to measure them. Frishman et al (1987) have shown that temporal transfer functions (the response amplitude functions of temporal frequency under different spatial frequencies) depend on the spatial frequency which was used to obtain them. Therefore space and time are inextricately coupled in the receptive field response and the proper temporal frequency has to be considered when the pattern size was chosen in PERG. The mechanism of the spatial-temporal coupling is unclear. Enroth-Cugell et al (1983) reported that the interaction between centre and surround could produce the spatial-temporal coupling. Another mechanism for the space and time coupling is reported by Dawis et al (1984), which considers more the spatial-temporal coupling in the centre field.

Contrast-temporal frequency

Shapley and Victor (1979) discovered that the summation of centre and surround responses to temporally varying stimuli was nonlinear in both X and Y cells, and that the effect was stronger in Y than in X cells. The stimulation of periphery modified the response to centre simulation in ways that violate the principle of superposition. The authors attributed this nonlinearity to the action of a contrast gain control. When contrast increased, the optimal temporal frequency increased, and the phase of the response advanced.

2.4.4 Visual Adaptation

Under photopic conditions, the centre-surround balance is stable (Enroth-Cugell et al., 1977a). The ratio of the strengths of the centre and surround mechanisms of the average cat ganglion cells is kept approximately at 1.2 (Linsenmeier et al., 1982)

Barlow et al (1957) reported that as the mean luminance level dropped to scotopic levels, the surround response disappeared that the response be dominated by its centre mechanism. Opposite report by Enroth-Cugell and Lennie (1975) showed that the surround is maximally sensitive at the lowest luminance level, which was supported later in a report by Kaplan et al (1979). But the modulation of the relative strength of the centre-surround mechanisms can still be seen at very low scotopic levels.

The fact that, in the prolonged dark adaptation, the release of dopamine reduced the responsiveness of the cold-blooded vertebrate ganglion cell (Hedden and Dowling, 1978) confirmed the assumption: in the dark adaptation, the antagonistic surround of many ganglion cells are reduced in strength or even eliminated (Barlow et al., 1957). Furthermore, a reduction of relative effectiveness of the surround following dopamine application in the cat ganglion cells (Thier and Alder, 1984) was also a convincing evidence for the assumption.

An alternative proposal was presented by Sterling (1983). In this proposal, the change in the organisation of the receptive field is brought about by switching the signal flow from a mixed pathway to a pure rod pathway. In the mixed pathways, active at mesopic level, rod signals are communicated through gap junction to cones, and then to cone bipolars before coming to Y cells. At scotopic levels, the mixed cone-rod pathway is inactive, and signals flow from rods to rods bipolar cells and then through AII amacrines to ganglion cells. AII amacrine cells are electrically coupled to each other, which explains probably the diameter expansion of the receptive field centre.

Secondly, in the dark adaptation, the centre size of the receptive field expands (Kaplan, 1991). A doubling of the centre's radius in lateral geniculate nucleus (LGN) has been reported by Enroth-Cugell and Robson (1966) and Kaplan et al (1979). A small expansion was reported by Derrington and Lennie (1982). The expansion occurs as the light level goes from mid-scotopic to low scotopic vision and thus the change has no relation with the Purkinje shift from cone to rod vision (Barlow et al., 1957), which might complicate the explanation about the result if the

shift exists. Therefore, in a review by Kaplan (1991), the author concluded that the expansion of the centre size under dark adaptation had no relation with the switching from the mixed cone and rod pathways at the mesopic level to the pure rod pathway at scotopic levels (Sterling, 1983; Smith et al., 1986; Sterling et al., 1988). In general, this expansion is thought to have the same effect as the dilation of the pupil in the dark, allowing more light to collect and increase the sensitivity of the receptive field.

In the dark adaptation, Y cells continue to response at low light level, even at 0.001 cd/m^2 (Linsenmeier and Jakiela, 1979). Linenmeier and Jakiela concluded that both rods and cones contributed to the production of this local non-linearity and that such non-linearity was not related to the interaction between rods and cones. Purpura et al (1988) found the similar results in monkey retina that lowering mean luminance lowered the contrast gain of both M and P cells. Since M cells had substantially higher contrast gain at photopic levels (8-10 times higher), they could continue to function even at mesopic and scotopic levels (near or below 1troland). Whilst the P cells could no longer respond to patterned stimulus of moderate or low contrast at mean luminance level below 1troland as M cells could. Thus in order to elicit a response from some P cells under scotopic condition the full-field stimulation at very high contrast appeared to be needed.

It was found by Tootel (cited by Kaplan, 1991) that under scotopic condition (approximately 0.6 troland), only the cortical layer receiving magnocellular input (IVcϑ) accumulated the radioactive glucose analogue ^{14}C-2-deoxy-d-glucose (Sokoloff et al., 1977), suggesting that the cells in this layer continued to respond to visual stimulus, whereas the cells receiving input from the parvocellular layers (IVß) were relatively inactive. Thus under low luminance level it is the M-cells rather than P cells that subserve the pattern vision.

It is assumed that the reduction of surround strength and the centre size expansion occur probably only on the large ganglion cells (Y/M cells) and thus assist to increase the sensitivity to light stimulus in the dark. These observations provide some possibility to spare the P cells and stimulate the M cells alone under scotopic condition; while P cells can be exclusively stimulated by different light wavelengths under isoluminant condition, which has not been discussed in this review.

2.5 SUMMARY

The basic mechanisms responsible for the retinal ganglion cell receptive fields are centre-surround antagonisms formed at preganglionic and ganglionic stages. The centre size is up to the dendritic field of the ganglion cells, synapsed directly with bipolar cells, such that the centre-surround mechanisms are more determined by the activities of the 'surround' field, involving the effects from horizontal cells and amacrines cells based on their presynaptic effects and reciprocal effects subserved by the related transmitters.

Due to the diversities of the subclasses, synaptic connections and transmitters of the mechanism-related cells, the centre-surround mechanisms are so intricated that the mechanisms of the retina response evoked by a pattern can not be known well by this way alone. Additionally, the data of the receptive field properties obtained are mostly from the studies on some invertebrate and vertebrate animals, which are more or less different from those of the human retina. However, the mechanisms of the centre-surround antagonisms described have presented roughly the basic principles of retina's detecting the pattern stimuli due to the anatomical and functional similarity between human and animals and these principles are useful when a pattern evoked response is studied. In general, the sensitivity to luminance and wavelength, temporal frequency, spatial frequency of the receptive field have to be considered for a pattern, with a certain size, being reversed at a certain rate and under a certain luminance background, to evoke an ideal retinal response.

CHAPTER 3.

PATTERN ELECTRORETINOGRAPHY

SECTION I RECORDING TECHNIQUES OF THE PERGS

3.1 INTRODUCTION

The cornerstone in the development of the electroretinography (the method of studying electroretinogram) is the discovery of resting potential in the living tissues in the early nineteenth century by Du Bois-Reymond (1849). In his study on a frog eye, an electrical potential difference was found positive at the anterior external surface of the eye with respect to the back.

Holmgren (1865-1866) in Sweden first used light stimulation on the frog's eye and obtained the response. Without being aware of Holmgren's work, Dewar and M'Kendrick in Scotland (1873 a, b, c) recorded a corneal potential in the frog eye, being positive with respect to the posterior pole of the eye, in response to light. These results are the first electroretinogram (ERG), the transient resting potential changes in the retina in response to light.

The human ERG was pioneered by a work of Dewar early in 1877. Placing a ring of clay filled with saline on the frog eye, a deflection was recordable on a galvanometer whenever the eye was stimulated. Since then, the ERG techniques have been developed greatly in electrodes, stimulation and recording systems and analysing techniques over the past one century from the initial method of recording the action potential in the eye by a salt bridge between the eye and the recording circuit.

It was the introduction of the grating bars as a stimulus into the ERG recordings by Riggs and his associates (1966) and Johnson et al (1966) that made the electroretinograhy enter a new period. One of the major advantages of such stimuli is that it permits to localize the stimulus without influencing the total light flux. The pattern evoked retinal responses was labelled as pattern electroretinogram (PERG) by Dawson et al (1983).

Though the technique had been introduced into clinical investigation by Lawwill early in 1974, PERG received only limited attention at that time for clinical use until two events occurred. First one was the development of the recording electrodes---DTL fibres (Dawson et al., 1979) and gold foil electrode (Arden et al., 1979). These corneal electrodes, initially proposed for use in flash ERG can avoid the visual disturbances and are easily accepted by subjects. The second event was the discovery of specific elements of inner retinal layers, the retinal ganglion cells, involved in the ERG to pattern stimulation by Maffei and Fioretini (1981). The discovery makes layer-by-layer analyses by the PERG possible and enlarges the content of the PERG studies and thus the theoretical development of the retinal mechanisms of the ERG. The considerable interests in clinical use have made the PERG a practical tool for evaluating visual system functions in conjunction with the earlier accepted techniques, flash ERG and VEP.

3.2 PATTERN PRESENTATION

3.2.1 Pattern Stimuli

Patterns used in many physiological (Campbell and Green, 1965), clinical contrast sensitivity (Bodis-Wollner, 1972) and clinical VEP (Bodis-Wollner and Yahr, 1978) studies are sinusoidal grating patterns. The reasons for applying such stimuli are based on the interests in the question of whether the visual system may behave as a set of Fourier's analysers (Campbell and Robson, 1968; Blakemore and Campbell, 1969; Green et al., 1970b; May and Matteson, 1976). For clinical ERG, the commonly used patterns are checkerboards. Checkerboard may produce stronger response than sine- or square-wave gratings (Parker and Salzen, 1977) which has a practical advantage for obtaining an ideal PERG.

A checkerboard or pattern of identical element size may be presented to produce a response in one of the following three ways: (1) a flash presentation of the pattern (Spehlmann, 1965; Rietveld et al., 1967; Harter and White, 1970); (2) reversal of the pattern (Johnson et al., 1966; Spekrejse et al., 1966; Campbell and Maffei, 1970; Halliday and Michael, 1970); (3) appearance/disappearance (on/off set) of the pattern (Spekreijse et al., 1973b; Padmos et al., 1973; Kulikowski, 1977; Jeffreys, 1977). The technique of one flash presentation of a pattern was not advocated for clinical use because the response was found not to be different from a simple homogeneous flash stimulation and contamination by stray light is inherent in this

technique (Barber and Galloway,1974).

3.2.2 Reversal (Counterphase) Pattern

Riggs and his associates (1966) first introduced grating bars into the ERG recording. The stimulus introduced by Riggs has an advantage of avoiding stray light that falls outside the stimulus area so as to minimize scotopic response components. Subsequently checkerboard lined vertically and horizontally was introduced into the ERG recording (Van Der Tweel and Spekreijse, 1972). When two sets of checks are modulated equally and in counterphase the total amount of light on the eye remains constant. Technically, the intensities of two sets of elements can be modulated independently through two fluorescent tube light sources (Spekreijse, 1966; Van Der Tweel and Spekreijse, 1968) to keep the mean luminance constant and thus the interaction between the changes of spatial contrast and of luminance (Estevez and Remond, 1972; Spekreijse et al., 1973b) can be avoided but otherwise mean luminance will be changed whenever contrast of a pattern varies.

The use of alternating patterns is to produce a spatial contrast in the stimulus. On the retina imaged by such patterns, there is a local change of illumination each time the patterns reverse and this process provides a stimulus for the retina. The spatial contrast is obtained when both sets of checks have the same mean intensity. The 'bright' and 'dark' checks interchange rhythmically at twice the temporal modulation frequency. The response components which are even multiples of the stimulus frequency can be obtained regardless their contrast or luminance origins (Spekreijse et al., 1973a).

According to Fourier theory, a square wave or a checkerboard can be considered as the sum of a number of sine-wave components whose frequencies are odd multiples of the fundamental frequency. Thus a checkerboard which is a function of x having unit amplitude (peak-to-peak amplitude = 2) and period X can be considered as the sum of the infinite series

$$4/\pi \, [\, \sin(2\pi x/X) + 1/3 \sin 3(2\pi x/X) + 1/5 \sin 5(2\pi x/X) + \ldots)]$$

Thus the amplitude of the fundamental (first harmonic) components of a square wave grating of contrast m is $4m/\pi$, while the amplitudes of the third, fifth and higher harmonics are respectively $4m/3\pi$, $4m/5\pi$ and so on. The even harmonics all have zero amplitude (Campbell and Robson,

1968).

When two sets of elements of equal area (eg, checks) are modulated temporally exactly 180° out of phase, a pattern reversing at a rate (2F) twice as high as the modulation rate (F) of each individual check is produced. The response to each individual check may include linear components, ie, at the fundamental (F) of the modulation rate, and also non-linear components, ie, at the higher harmonics (2F, 3F, 4F,...). When two sets of checks in the same area are modulated temporally exactly 180 degree out of phase, the summed response on the same area contains only the second harmonic (2F) and higher order even harmonics (4F, 6F,...), since the fundamental and the odd higher harmonics are out of phase and hence cancel. Since the contrast reverses with twice the modulation rate, the contrast-related components of the PERG will also contains only even harmonics (2F, 4F, 6F). The over-all reversal response, therefore, will contains only second harmonic and higher even harmonics irrespective of their contrast or luminance origin (Riemslag et al., 1985).

3.2.3 On/Offset Pattern

Patterns appear and disappear by adjusting the intensities of two sets of checks in such a way that their mean luminance are equal during half the stimulus period. Patterns first appear from and then disappear into a blankfield of equal average luminance in each stimulus cycle, without change in total luminance (Spekreijse 1966; Spekreijse et al., 1973a; Lawwill, 1984). The ERG elicited by such a pattern can be seen at the beginning and the end of the stimulus.

When a pattern appears, the brighter parts produce on-response, while some off-response will be developed on the place where a pattern appears. When a pattern disappears, the previously bright parts will produce the off-response, while those regions dim during the pattern's appearance will be brightened and produce the on-response. In PERG, the onset (appearance) response is always larger than the offset (disappearance) response (Arden and Vaegan, 1983), which is contrary to the prediction by simple sum of spatial changes of luminance, probably due to lateral inhibition of the inner retina.

3.3 RECORDING TECHNIQUES

3.3.1 Gross Response Measure

Recording Electrodes

Theoretically, the maximum retinal response can be obtained between the outer and the inner surfaces of the retinal laminae. Practically, human ERG can be recorded with remote electrodes only. The signals may be conducted from their source through the globe to the recording electrode even though no electrode is placed close to the retina. The reference electrode is usually placed at the ipsilateral temple. The ideal position for an cornea electrode is direct cornea contact for good electric contact.

Wick electrode

The wick electrode reputedly made the ERG recording possible for the first time. It was a cotton tread electrode immersed with saline (Du Bois-Reymond, 1849). The simple salt bridge was built by the conductive wire between the cornea and a galvanometer. However, it is irritating to the eye; it moves whenever the eye blinks. and dries out over the extended recording procedure. It was impossible to record the ERG in human until 50 years later a design of electrode fitted into a pair of goggles was shown by Hartline (1925), which started the history of the human ERG. Since then, many attempts have been made to produce some comfortable and stable recording electrodes.

Contact lens

It was not until the design of contact lens with appropriate correction of refractive errors that the ERG recording was practically used for clinical purposes (Riggs ,1941). The use of the lens directly on the cornea affords uniquely a good condition for electrical contact and reduced the effects of eye movement. The discomfort by subject's wearing the lens can be overcome by superficial anaesthesia.

Many modified types of contact lens have been suggested, such as Karpe lens (1945), Henkes lens (1951) and Burian-Allen lens (Burian, 1953; Burian-Allen,1954) and multi-channel corneal electrode (Kawashima et al., 1990). In a recent report at the 33th ISCEV symposium, the modified design of multi-channel ERG corneal electrode was reported to be a safe and produce reliable results compared with Burian-Allen electrodes (Kimura and Kawashima, 1995). Burian-Allen electrodes have been confirmed to give the largest signal and lowest impedance but to be the least comfortable and to have the highest artifacts rate compared with other electrodes (McCulloch et al., 1995).

The inherent problems are (*a*) repeated instillation can result in a softening and desquamation of the cornea epitheliums (O' Conner Davis, 1976); (*b*) Air bubbles under the lens can reduce the electrical contact (Armington, 1974). Additionally, the use of contact lens requires that patients receive additional optical correction to counteract the blurring of the lens.

Though there were some innovative designs such as a soft contact lens (Dawson, 1974) which could be placed under the hard lens as a cushion or a conducting materials bearing contact lens (Bloom and Sokol, 1977; Honda et al., 1986), or as the fenetration technique (Armington, 1974), many attempts have been made for the electrodes which may record the corneal potential without direct corneal contact.

Skin electrode

One type of non-corneal electrodes is to attach the electrode to the lower eyelid or outer canthus of the eye. The use of such an electrode may reduce the response amplitude compared with contact lens but it is a useful recording electrode when corneal contact is contradicted, eg, in cases of corneal infection and surgery (Giltrow-Tyler et al., 1978; Sierpinski-Bart et al., 1978; Leguire and Rogers, 1985) or when subjects are difficult to cooperate such as in recording the ERG in children (Coupland and Janaky, 1989). The inevitable problem is that the responses are easily affected muscle artifacts.

Gold foil electrode

The initial design was a ring of gold placed on cornea (Ziv, 1961). The modified gold foil electrode was a thin strip of metal-coated plastic foil, or gold-coated mylar (GCM) electrode (Chase et al., 1976; Borda et al., 1978). The electrode is inserted into the sac between the eyeball and the lower fornix. The electrodes are suitable for the use in cases of cornea pathology (Arden et al., 1979). The eye movement or blink artifacts can be eliminated by hooking the gold foil electrode over the lower lid. Due to the change of electrode position in contact with eye, some reports have indicated its disadvantages of instability, considerable variations and fragility (Holopigian et al., 1988). Recently, Arden et al (1994) re-estimated the reliability of this electrode and recommended that the gold foil electrode still is a stable and reproducible technique suitable for repeated use.

DTL fibres

Another material with similar properties to gold foil electrode is the DTL fibres (Dawson, Trick and Litzkow, 1979). The fibres are extremely low mass and their conducting threads are composed of nylon monofilaments impregnated with silver. The contact between the tear film and the adjacent metal conductor provides massive conduction area.

There is no need of anaesthesia and the visual disturbance is the least so that the technique is well accepted by subjects. The slightly higher noise and lower amplitude from the use of the DTL fibres can be compensated by averaging devices (Riggs, 1986). Special care should be taken for the contamination by eye movement and some volume conducted potentials such as VEP (Peachey et al., 1983; Arden, 1986).

Some later modified designs have improved the use of the DTL technique in clinical investigations (Dawson et al., 1982; Thompson and Drasdo, 1987). The DTL fibre holder (Thompson and Drasdo, 1987) used the extensible properties of the Perisil sleeving to secure the fibre into the silver wire holder hook, which made the use of DTL fibres disposable.

HK-loop electrode

To adapt individual size and shape for subjects of any age, Hawlina and Konec(1992) designed a non-corneal HK-loop electrode for clinical use. The electrode consists of a thin wire forming a loop modelled to fit into the lower conjunctival sac. Electrical contact is made with the scleral conjunctive through an exposed portion of otherwise insulated wire. It is adaptable particularly to normal or abnormal anatomical configurations of the subject' eye and eyelid.

Compared to that obtained by skin and gold-foil electrodes, the flash ERG signals obtained with HK-loop electrode is thought to be clean and reproducible and approximately doubles the amplitude of that obtained by a skin electrode and about the same range as that obtained with a gold-foil electrode. The recorded PERGs are in the same amplitude range as recorded by gold foil electrode and GCM electrode. Hawlina (1992) showed that the amplitude of the PERG recorded with HK-loop electrode ranged from 3.6 to 6.2 μV, with a coefficient of variation of 18.4%. Additionally, It needs only a short insert time so it is convenient when recording ERG in those subjects who are difficult to cooperate.

Variability

Compared with VEP and flash ERG, the PERG variability is high. The PERG recorded by on/off-set pattern has larger variation than that evoked by reversal pattern. Here are some data about the variations of the PERG described by the averaged coefficients of variation (CV), which is equal to the standard deviation divided by the mean x 100 (Sokol et al., 1969):

Schuurman and Berninger (1984) showed an averaged CV of 20-35% for the pattern reversal ERG; Korth and Rix (1985) showed a 31% of CV for the positive component and 26% for the negative component of the pattern reversal ERG. Korth and Ilschner (1986) presented an average CV of 37% for the pattern onset response and 55% for the pattern offset response; In a report by Hess and his colleagues (1985), the averaged CVs for the PERG amplitude are as high as more than 100%! In summary, most of reports have showed a large interception variation between 15-50% of CV values.

Sources of the Variation

Unlike flash ERG with an amplitude of several hundreds microvolts, PERG is small, of the order of several microvolts. Any factors resulting in either the reduction of the amplitude or the increase of the artifacts may produce the low signal-to-noise ratio and thus influences the fidelity of the response. This influence occurs variably during the recording session and thus results in the intrasession and intersession variations of the PERG results. So far as it has been known, the factors related with the production of low signal-to-noise ratio are as followings: (1) recording electrodes (gold foil and DTL fibres); (2) the position of the reference electrode; (3) transient analysis; (4) artifacts from recording system; (5) subject.

Electrodes

Recording electrodes The variability in the amplitude of the PERG can occur if the recording electrode position changes. The DTL thread electrode may be swept down into the lower fornix and the gold foil electrode blinked into the lateral canthus. Thus in both cases, the recorded response can be reduced (Berninger and Arden, 1991).

The position of reference electrode In the early stage of the PERG studies, the position of the reference electrode was a problem in getting an ideal PERG. Interference from muscle, heart beat, electrocardiography, and contamination from thalamus and cortical potentials can be picked up and covers the small retinal response evoked by patterns if the reference electrode

was improperly placed.

The artifactual PERG, resulted from the conducted signals on the reference electrode, have been noted in some reports (Hobson et al., 1984; Leguire and Rogers, 1985; Berninger and Schuurmans, 1985; Arden et al., 1986). Arden and associates (1986) have suggested that the contamination is a complex function of the resistant network formed by tissues around the eye.

Transient Analysis

Steady state stimuli are delivered at a greater rate that the response to one stimulus has not died away before the next one is delivered. The greatest portion of the response potential derived from this process occurs at the negative potential (Berninger and Schuurmans, 1985), and thus if the fast Fourier's transform is available, the amplitude of the second harmonic response can be analysed directly. The advantage of this analysis is that mains interference is no problem but the price to be paid is that the loss of some (nonlinear) information that the response contains pattern specific response alone (Odom et al., 1982; Baker and Hess, 1984; Hess and Baker, 1984; Odom and Norcia, 1984).

Transient analysis is commonly used in clinical investigations for its advantage of including the whole information of the response, including linear and non-linear components (Regan, 1982). Transient stimulus follows each other at sufficiently long intervals that retina returns to its initial state before the next stimulus occurs. The evident disadvantage is that the analysis allows more artifacts to be collected during the session, resulting in larger noise than the steady-state analysis.

Subject

Eye movement The noise from subjects' eye movement may be 100 time as large as the PERG. Small blinks or eye movement, which maybe roughly five to ten times the amplitude of the PERG (Berninger and Arden, 1990), cannot be discriminated by the artifact rejection routines and thus may be included in averaging. Since eye movement usually follows the stimulation alternation (Johnson et al., 1966) when reversal patterns are used, the variation from eye movement maybe lead to the erroneous analysis on the optimistic results.

Fixation In studying an eye with poor visual acuity, it is not easy to ascertain how well it

fixates the pattern. The poor fixation often causes irregular eye movements which can result in a poor reproducibility of the response. Some reports have recommended that the good eye could maintain the fixation when the bad eye is recorded (Fiorentini et al.,1981; Bodis-Wollner et al., 1983; Holder, 1987). A report by Holder (1987) showed that there was no statistical difference between two eyes on the same subject, suggesting the practicality of the technique. However, in this way, volume conducted potentials can be registered over the affected eye and yield possibly an erroneously optimistic result.

Pupil Size No difference has been observed in the positive component of the pattern reversal ERG as the pupils are constricted (Holder and Huber, 1984; Berninger, 1986; Thompson and Drasdo, 1987a). By contrast, Berninger (1986) observed significant reduction for the negative potential and a highly significant increase in latency for both the positive and negative components on the small pupil.

Improvement of the Variability

The Position of the Reference Electrode

This technical issue has been solved in some recent reports. The commonly recognised position is on the ipsilateral temporal point (Berninger, 1986; Yanashima et al., 1986; Odom et al., 1987 ; Tan et al., 1989). The pickup of the cortical potentials was reported being less than 10% after a variety of different recording electrodes configurations were examined and compared (Hess and Baker, 1984). In a report by Berninger and Schuurmans (1985), the negative component was attenuated in amplitude if the ipsilateral temple is used as a reference. While the positive component was only slightly reduced (Berninger, 1986).

Odom et al (1987) examined the artifacts of reference electrode using the DTL fibres to record PERG. They compared the artifacts from ipsilateral outer canthus, contralateral eye, forehead, vertex and ear and found that the least artifacts were obtained when the reference electrode was placed at ipsilateral canthus. Unlike the reports for gold foil electrodes (Seiple and Siegel, 1983; Peachey et al., 1983; Berninger, 1985; Arden et al.,1986), there was no significantly significant evidence of an artifactual PERG at any reference site for the DTL fibres.

The second best position for the reference electrode was the contralateral eye (Odom et al., 1987). All the correlated noise between two eyes should be eliminated as a result of differential

amplifications (Fioretini et al., 1981). However, it has certain disadvantages for binocular stimulation is required in some patients who cannot maintain fixation with the diseased eye.

Recording System

Averaging techniques Since the baseline is never completely free of disturbance, the improvement of the signal/noise ratio (s/n ratio) is one of the technical problems in the ERG recordings. The averaging technique (Dawson, 1951; Barlow et al, 1957) is known to reduce the noise from the recording system. Armington et al (1961) firstly introduced an analogue system for averaging visual responses into the ERG recording. In a later report by Armingtom (1974), the digital averaging system was suggested to be more reliable and flexible. The s/n ratio can be improved by reducing the random noise in a way of being oppositely proportional to the square root of the number of averages (Armington, et al., 1961; Regan and Spekreijse, 1986). However the technique can only solve the large artifacts. The small artifacts are still the main factors influencing the obtainment of an ideal s/n ratio in practical ERG recording. In a report by Arden et al (1982), the authors advocated a proposed upper standard of the noise as o.25μV.

Holopigian et al (1988) replicated the PERG recording session made by Berninger and Schuurman (1985) and obtained two similar coefficients of variation (CVs): 34% for the positive component and 40% for the negative component. By changing the stimulus conditions such as reducing subject fatigue for improving fixation drift and possible ganglion cell adaptation (Odom and Norcia, 1984) could not improve the variability, while recording conditions were apparently related to the variability. For increasing signal-to noise ration two parameters were recommended by Holopigian and his associates: one is to reduce the acceptance band from ±0.8 volts to ±0.4 volts; the other was to decrease the sweeping time to 150ms in order to reduce the amount of direct current drift in the records. These manipulations could decrease the interception variability to an averaged CV of 17% for the positive component and 18% for the negative component. This improvement is particularly effective in reducing the interception variation for the positive component of the pattern reversal ERG.

The bandpass of the filtering is one of the factors to produce the noise and thus to effect the repeatability of the recording. Celesia (1985) recommended high band-pass filtering (1-250Hz) in the PERG recording. In a later report by Barter et al (1991), it was shown that the initial

negative potential was not identifiable under such a high bandpass. Instead, Bartel and his colleagues used the digital filtering (ie, 1-40 Hz) to calculate the coefficient of the repeatability (rather than the usually used CV values) and demonstrated that there was a slight increase in the group means for both amplitude and the implicit time of the positive potential. However, the digital filtering can not increase noticeably the PERG repeatability, or improve the variability, although the statistical calculation provides a measure to check the repeatability of the PERG recorded.

Power Measure (Fourier's Signal Power Spectra)

All quantifiable physically occurring signals may be assumed to meet the conditions for use of the Fourier transform (Bracewell, 1978; Gaskill, 1978). It has been known that there are different functional roles played by amplitude and power information in the central nervous system. Wasserman et al (1979) presented a theory that amplitude and integral (power) measures of single neuron activity yield different functional relationships to stimulus properties--amplitude being related to threshold detection while integration to suprathreshold discrimination. Power is an integral measure and a better indicator of neural unit activity for the use of suprathreshold stimuli than related field potential amplitude (Schmeisser and Dawson, 1980). Comparatively, amplitude measure has relatively poor signal-to noise ratios.

It can be determined using an algorithm for the calculation of the *fast Fourier transform* (FFT) When a FFT algorithm is employed to estimate the Fourier transform, a sufficiently long sample of the signal and some low pass filtering are required to avoid the introduction of well understood leakage from windowing (Bendat and Pierson, 1971; Hemming, 1977). Odom et al. (1982/83) found that the signals could be filtered well below the Nyquist criterion (i.e., one-half one's upper limit, which is only one quarter of the reversal rate).

Selection of the power at the second harmonic of the stimulus frequency as a response measure in reversal pattern evoked potentials is based on the theory that the reversal patterns elicit responses at twice the stimulus frequency at both retina (Riggs et al., 1964; Riggs, 1966; Johnson et al., 1966; Armington, 1968) and cortex (Spekreijse, 1966; Regan, 1972; Regan, 1981). There are some advantages in using the second harmonic power analysis in the PERG as such: (1) second harmonic power (in units of picowatt, or watt x 10^{-12}) is roughly analogous to the use of "near-ideal" notch filtering of the response with the centre frequency at the

harmonic; (2) there is usually a significant improvement in the signal-to-noise ratio (Gur and Zeevi, 1980; Dawson et al., 1982; Odom et al., 1982/3). In a conclusion by Odom et al. (1982/83), the authors suggested that more efficient detection of spatial tuning in the retina using power may be attributed to the improved signal-to-noise ration; (3) it does not selectively decrease the influence of local luminance responses since they also contain power at twice the stimulus frequency (Bendat and Pierson, 1971; Spekreijse et al., 1973a; Regan, 1981); (4) it minimises the effects of small imbalance or eye movement which follow the alternation (Riggs et al., 1966; Johnson et al., 1966; Armington, 1968); (5) the LSFA has been found greater when second harmonic power is used as the response measure (Odom et al., 1982/83). These advantages have indicated the desirability of the wider use of this response measure.

Other Techniques Holder (1987) reported that the measurement could be made in short bursts while patients could maintain fixation and refrain from blinking. A few seconds after the session starts, the recording is interrupted, and patients are instructed to blink and move their eyes, and then are asked to take up fixation, at which point recordings continue. By this interrupting technique, the PERG uncontaminated by baseline shift can be obtained. Weinstein et al (1988) and Ryan and Arden (1988) choose a 4Hz of reversal rate and increased the recording time from 115 to 250 ms for obtaining a complete response and the first part of the following response. Both positive peaks are supposed to be on the same baseline level, and the baseline shift was corrected by a soft programme.

3.3.2 Layer-by-layer Measure

Intracellular Recordings

There are some other methods to trace the PERG sources. In reviewing the origins of the flash ERG (see Chapter 1), some techniques for layer-by-layer component analyses have been mentioned such as using microelectrode to record intracellular responses (Brown, 1968; Miller and Dowling, 1970; Rodieck, 1973; Armington, 1974; Tomita and Yanagida, 1982). In such cases the recording electrode can work as stimuli at the same time. For example, in studying the retinal ganglion cells' receptive field, the stimuli composed of a small spot and an annulus can be used to study the activity properties of the receptive centre and surround fields, respectively (Hammond, 1972). There is limit for such techniques to be used in human, though recording PERG in the mammalian retina using penetrating electrodes (ie, electrode depth technique) have been reported (Sieving and Steinberg, 1985; Hess et al., 1986).

Transretinal Recordings--Current Source Density Analysis (CSDA)

Using penetrating electrode, the intraretinal current source density (the source and the sinks) of the ERG can be analysed. The basic principle is: ERG is produced by the currents that flow radially through the eye. The local current density decreases and increases when current enters and leaves a cell. When current flows through a lamina with the cells having similar current density changes, their resistances give rise to a voltage drop across the lamina according to Ohm's law. The current changes whenever the electrode enters or leaves each retinal laminae so that the difference in current between successive lamina gives the sites of source and sinks of the ERG. Though there are species differences in the retina structures, the results of the current source density analysis are very similar for cat and monkey (Bodis-Wollner et al., 1990). It is found that the pattern response generators are located more proximally and consist of a source-sink pair between the middle of the inner plexiform layer and the nerve fibre layer. The pair site is more proximal than the generators of the b-wave of the ERG in response to uniform field stimulation in monkey (Heynen and van Norren, 1985; Baker et al., 1989) and in cat (Sieving et al., 1984; Sieving and Steinberg, 1985).

According to Fourier's analysis, the responses to uniform-field luminance modulation should be of the first harmonic component with linear properties and the response to the pattern should be of the second harmonic content with nonlinear properties. This analysis principle has been used in the CSDA by Baker et al in monkey (1989). On the assumption that the fundamental and second harmonic components in the PERG should be reflected in the density profiles, they analysed the density profiles of the PERG and found that the fundamental component has a predominant source-sink pair in the distal retina, while the second harmonic component has a current source density profile with multiple sources-sinks more proximally.

The actual distribution of sources and sinks is complex and may be of species dependence. The lateral spread distribution of retinal neurons can be one of the factors for its complexity. In a report by Berninger and Arden (1991), authors suggested that several different components with similar temporal characteristics may be generated in overlapping lamina. The second harmonic component has been found depressed and accompanied by the total suppression of the PERG, after the optic nerve in the cat and the monkey is sectioned, while the fundamental component source-sink can remain unimpaired (Bodis-Wollner et al, 1990).

3.4 SPATIAL FREQUENCY TUNING OF THE PERG

3.4.1 Contrast Sensitivity

The reports from the basic psychophysical studies of the effect of pattern size on the incremental threshold of contrast detection have provided the early data for the spatial frequency tuning of visual system (Schade, 1956; Campbell and Green, 1965; Campbell and Robson, 1968; Kelly, 1977). Schade (1956) pioneered these works by showing the first evidence of contrast sensitivity function. In his study, grating bars were designed to have the luminance varying sinusoidally with distance perpendicular to the direction of the bars and their visibility was measured. It was found that the threshold level of contrast for detecting such patterns was a function of spatial frequency of the gratings and showed a clear minimum at a spatial frequency which varied with the mean luminance. The author interpreted the fall in sensitivity at higher spatial frequency as the optical blurring and the fall at lower spatial frequencies as the effect of the retinal lateral inhibition.

Based on this finding, Enroth-Cugell and Robson (1966) used the gratings of the kind Schade used and measured the contrast sensitivity function of the cat ganglion cells. The contrast required to evoke a certain fixed response under each spatial frequency of the gratings was determined by interpolation in both X and Y cells. The contrast sensitivity function was obtained by plotting the reciprocal of the contrast needed to evoke a modulation of the pulse density of amplitude 10/sec at the different spatial frequencies. At the same time, the subjective measurements were made by getting the threshold (of contrast) listening to the barely detectable discharges evoked under a fixed spatial frequency. The results showed that the contrast sensitivity of the X-cells was maximal at 0.5 cpd and fell off rapidly at higher spatial frequencies and more slowly at lower frequencies (Fig 3.1). There was no unique contrast sensitivity function for the Y-cells due to their nonlinear properties but the subjective measurements showed a similarity to the properties of the X-cells. The spatial frequency tuning properties in mammalians have also been reported by some later reports (Spekreijse et al., 1973b; Sokol and Jones, 1977).

The field potentials elicited from a system having lateral inhibitory effects have been termed

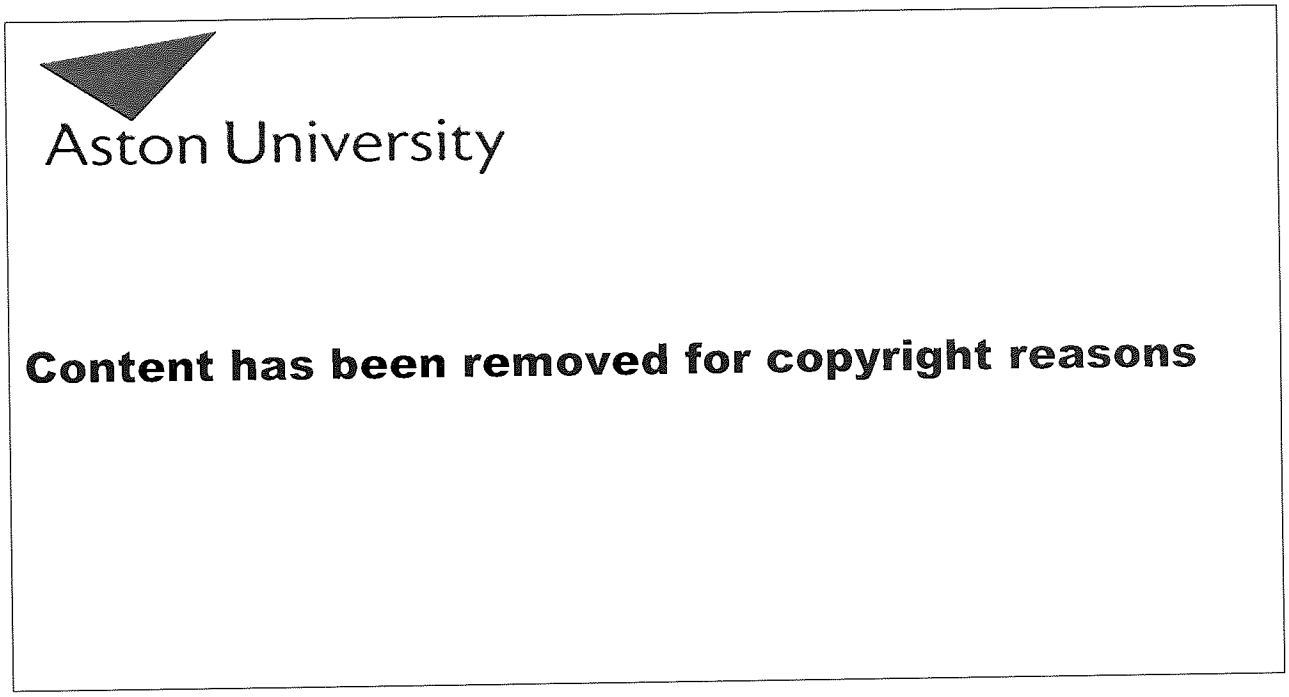

Fig 3.1 Objectively and Subjectively determined contrast sensitivity functions for an on X-cell. Objective measurements (filled circles) are based on the responses of the cell to sinusoidal gratings drifting at 4c/s. Response amplitude versus contrast curves were drawn for each spatial frequency and from these curves the contrast required to evoke a pulse density modulation of amplitude 10/sec was estimated. Reciprocals of these values are plotted against spatial frequency. Subjective measurements (continuous line): the reciprocals of the contrast required for a barely audible modulation of the cell's discharge are plotted as a function of spatial frequency. (after Enroth-Cugell and Robson, 1966)

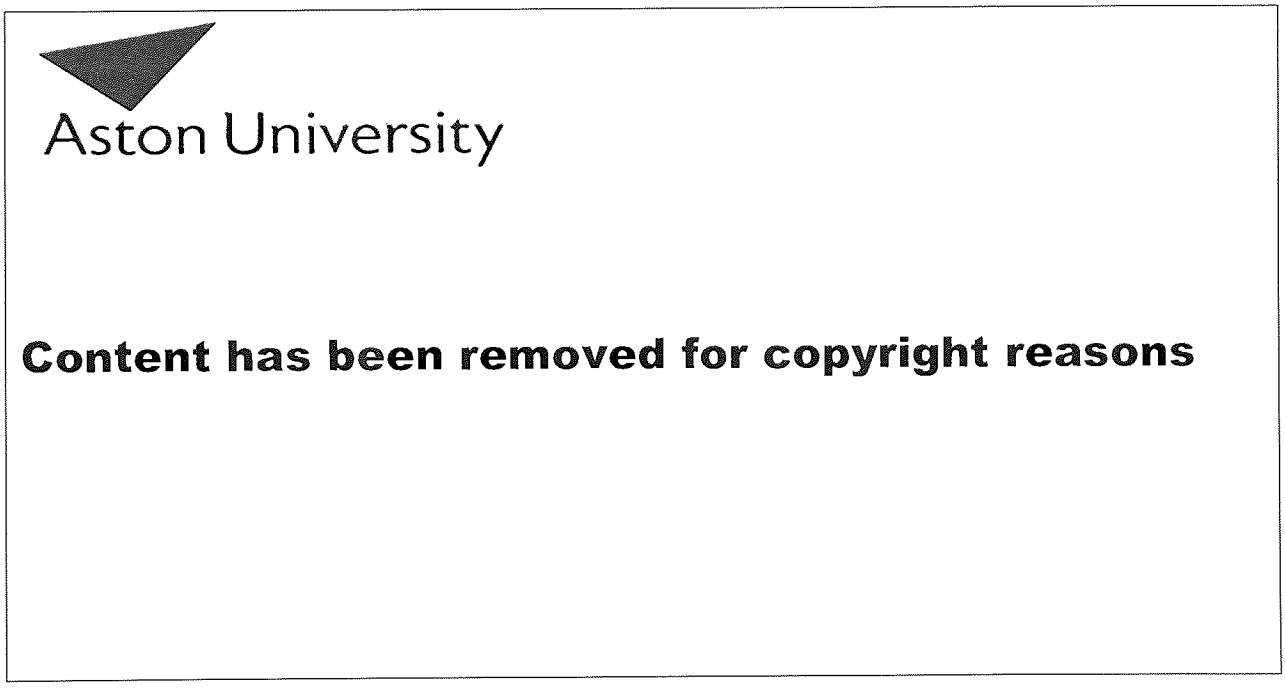

Fig 3.2 Percent second harmonic power (•) and amplitude (°) of the PERG as a function of spatial frequency. (after Odom et al., 1982/1983)

pattern contrast responses (Armington et al., 1971; Spekreijse et al., 1973b; Korth, 1981). A response reflecting such mechanisms should have a spatial frequency tuning and have, therefore, such response properties -----(1) there is an attenuation at higher spatial frequencies (HSFA); (2) at intermediate spatial frequency, a maximum response can be elicited; (3) there is an attenuation at the spatial frequencies lower than the maximum (LSFA) (Armington et al., 1971; Spekreijse et al., 1973b; Korth, 1981).

The first report showing a low spatial frequency attenuation and thus a spatial frequency tuning in human PERG was by Odom et al (1982/3) (Fig 3.2). They used the fast Fourier transform power and the field potential amplitude analyses for detecting particularly the LSFAs of the PERG and the PVEP. In these cases, the power analysis showed its advantages in its improving the signal-to-noise ratio; not selectively decreasing the influence of the luminance sensitive component in the PERG; and minimising the effects of small imbalance or eye movement which follow the alternation occurring at the stimulus rate (Riggs et al., 1966; Johnson et al., 1966; Armington, 1968). The spatial frequency tuning of the VEP elicited by low contrast sinusoidal grating was bimodal and there was a maximum response at a high spatial frequency, a lower spatial frequency attenuation and then with decreasing spatial frequency an increase in response. The spatial frequency selectivity of the PERG is broader and is concentrated at a spatial frequency approximately 1.88 octaves below the VEP peak at 2.22 cpd. The authors explained this sharpness in PVEP as the magnitude of the refinement of spatial detail accomplishment at cortex which was related probably to cortical magnification (Schmeisser and Dawson, 1980) while the broadness of the PERG as the effect of contrast or luminance.

3.4.2 Relation with Ganglion Cells

Experimental Data

Armington et al (1971) first reported the spatial sensitivity of the human PERG obtained with stripe and checkerboard patterns. It was found that the spatial sensitivity decreased monotonically with increasing spatial frequency whereas the visual evoked potentials showed a spatial selectivity which was pronounced at high spatial frequency, more prominently with the checkerboard than that with the stripe pattern.

Using alternating square-wave stripes and checkerboard patterns contrasted at 90% with a mean

luminance of 4.65 photopic log troland, Korth (1981) found that the amplitude of the positive wave obtained with two types of pattern showed a more or less monotonic decrease with increasing fineness of the pattern, thus confirming the results obtained by Armington et al (1971). The authors attributed the decrease in amplitude of the positive potential with increasing spatial frequency to retinal summation elements detecting local luminance changes whereas the optimum in response for certain spatial frequencies to lateral inhibitory action because of a centre-surround organisation.

A report by Maffei and Fioretini (1981/1982) was reputed as the first experimental evidence to demonstrate that the integrity of the ganglion cells is necessary for the generation of the pattern reversal ERG: the pattern ERG and the flash ERG in cat before and after unilateral transection of the optic nerve kept being recorded for 4 months; the PERG remained unaffected in the affected eye for a few days after the section, then progressively decreased in amplitude, and disappeared completely about 4 months after the section. The flash ERG remained unchanged during the whole process, and both flash and pattern ERGs remained constant in the unoperated fellow eye.

Hollander et al (1984) reported similar results in cat. Within 4 months after the section of the optic nerve, flash ERG kept normal while PERG decreased progressively. Maffei et al (1985) repeated the work in primate retina. Because of these observations the authors concluded that the PERG originated from the retinal structures different from those responsible for the flash ERG. They assumed that the PERG was closely related to the activity of the third retinal neuron, i.e., the retinal ganglion cells.

The morphological studies on animals showed that degeneration of ganglion cells invariably followed the serious injury to their axons after the rabbit optic nerve section and there were occasional normal ganglion cells 20 days after the section (James, 1933). Other histology reports supported it by similar experimental results (Arden et al., 1982; Dawson et al., 1982; Fioretini et al., 1982; May et al., 1982; Tobimastu et al., 1988/89).

Recently, a series of studies indicating the retinal ganglion cells' involvement in the PERG were reported by Drasdo and his colleagues (1987a). Applying the Fourier's analysis to the retinal image of a pattern, the authors differentiated the on/offset pattern ERG into two

responses: one was the pattern specific response (PSR) and the other was the retina illuminance response (RIR). Subsequently, they observed the PSR under three eccentric stimulus fields: a 0-5.1 degree angular radius for the central zone, 5.6 to 12.6 degree for the mid-peripheral zone and 12.3 to 26.3 degree for the peripheral zone (Drasdo et al., 1990). They found that (1) the PSRs in each zone showed that the response amplitudes increased linearly with increasing spatial frequency and a cut-off at higher spatial frequency, similarly to those reported by the earlier observations, and suggested it to be related to the receptive field center and dendritic field diameter (DeManasterio and Gouras, 1975; Perry et al., 1984; Schein and DeMonasterio, 1987). (2) the maximum response increased linearly with eccentric visual angles. Additionally, the authors calculated the volume of the layer thickness, averaged over all meridians, from the radial section of Van Buren (1963b) and compared with the corresponding data of the PSR. So (3) the comparison showed consistence of the eccentric maximum PSRs with the distribution of the ganglion cells while the retinal illuminance response corresponded to the distribution of the inner nuclear layer.

Clinical Studies

Sokol and Nadler (1979) demonstrated that the ERG evoked by checkerboard pattern was smaller in the amblyopic eye of the anisometropic and strabismic subjects than the normal fellow eye. Similarly to this finding, Arden et al. (1980) reported that the PERG decreased in the amblyopic eyes, for which they suggested that the PERG was related with the ganglion cells.

Galloway et al. (1986) demonstrated a progressive reduction of the PERG amplitude in a series of recordings made between 1 and 11 weeks after trauma to the optic nerve in one patient. This procedure is known to be consistent with the time of the retrograde degeneration of ganglion cells after damage to their axons (Duke-Elder and Scott, 1971).

Groneberg and Teping (1980) were among the first to provide clinical evidence for the suggestion that PERG originated from the inner retina. They examined a 55-year old patient who had suffered an injury that included a section of the optic nerve. PERGs were recorded some days after the accident and 3 months later. After three months no PERG was recordable, and the flash ERG was unchanged. The similar results were reported by Dawson et al (1982).

Fioretini et al. (1981/82) used sinusoidal vertical gratings of variable spatial frequency and

contrast to record PERG in the patients with retrobulbar optic neuritis (RBN). The stimulus conditions were as such : mean luminance was 20cd/m^2; the patterns were reversed at a rate of 8Hz, and contrast was kept at 30%. The observation showed that in the normal eye, the amplitude of the ERG was a function of the grating spatial frequency, with a maximum around 2 to 3 cpd and high-frequency cutoff at about 10cpd. In patients with RBN, a similar spatial frequency tuning appeared but with lower amplitude at each spatial frequency. The flash ERG was unaffected.

Following microdiathermy burns to the edge of the optic disc in monkey, ganglion cells degenerated over a period of 210 days when PERG amplitude was progressively decreased (Dawson et al., 1986). The pathological changes happened on the optic nerve due to the traumatic, degenerative or inflammatory reasons appears to be in the same way: the retrograde degeneration along the optic nerve towards the ganglion cells.

In addition, the proportional change of the amplitude of the PERG to the damage degree of the ganglion cells has been reported in other diseases, such as, on the patients with early chronic open angle glaucoma (Groneberg and Teping,1980; Fioretini et al., 1982; May et al., 1982); diabetes (Arden et al., 1986; Ryan and Arden, 1988) and arterial occlusions (Fioretini et al., 1981; Vomberg et al., 1984).

Holder (1987) recorded PERGs in 72 patients with diseases of the anterior visual pathways and demonstrated that the retinal or macular dysfunctions are mainly reflected in the changes of the positive potential (P50) while the negative potential, N95 component, of the PERG was selectively affected in 81% of patients with diagnosed optic nerve dysfunctions. The author recommended the intraocular N95 : P50 ratio to measure reflect the ganglion cells' function.

Mechanism Discussion

In their further studies on the properties of the cat retinal ganglion cells, Enroth-Cugell and Robson (1966) examined the contrast sensitivity of the X-cells to a simple contrast edge pattern. The results demonstrated that the magnitude of the response depended up to the position of the edge of the pattern, that the polarity of the response changed as the edge was moved from one side of the receptive field centre to the other and that when the edge was in the centre, there was virtually no response at all as shown in Fig 3.3. The contrast sensitivity of the cell for the edge

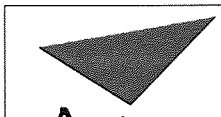

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Fig 3.3 Contrast sensitivity of an on-center X-cell for an edge pattern. This is the same cell shown in Fig 3.1. A vertical edge was alternately introduced and withdrawn at 1c/s while held stationary in different positions. For each position the minimum edge contrast which resulted in a just-audible change in the discharge frequency was determined. The reciprocals of these contrast values are plotted here. The open circles indicate responses of one polarity, the filled circles indicate responses of opposite polarity. Note the reversal of response polarity at the midpoint of the receptive field. The full line through the points is the edge contrast sensitivity of this cell calculated from its contrast sensitivity function for sinusoidal grating patterns. At the bottom is shown the line weighting function of the receptive field also calculated from the contrast sensitivity function. (after Enroth-Cugell and Robson, 1966)

pattern is shown as a function of the distance from the receptive filed centre. The sensitivity is least when the edge passes through the centre of the receptive field and greatest when it lays on either side of the centre. This property has not only shown the importance of a pattern edge in evoking response from the ganglion cells (thus the use of check or square-wave gratings should be more effective than a sinusoidal grating !), but also interpreted the fall in spatial sensitivity of ganglion cell at high spatial frequency, i.e., what will occur if the checksize is smaller than the finest receptive field centre size. The form of the contrast sensitivity function of a typical X-cell resembles that of the human vision (eg, Schade, 1956) in the sense that it has a rapid fall-off at high spatial frequency and a less rapid fall-off at spatial frequencies below some optimal value.

The contrast sensitivity function from centre vision in human has been shown to be determined partially by the dioptric mechanism of the eye and partially by neural mechanisms (Campbell and Green, 1965). The influence of the MFT of the eye on the high spatial frequency cutoff will be discussed later. The neural mechanisms involved in human contrast sensitivity is a little bit more complicated for they include not only the properties of the ganglion cell but also the higher visual pathway. This complexity has been demonstrated by (1) the psychophysical contrast sensitivity of central vision is broader than the individual ganglion cells (Kulikowski et al., 1966) and (2) the spatial frequency tuning in VEP elicited by pattern stimulus is sharper than that in PERG (Korth and Armington, 1976; Odom et al., 1982/83). However, the existence of the spatial frequency tuning among these records relates, convincingly, the function of ganglion cells to the spatial frequency cutoff of the field potentials, including PVEP and PERG.

3.5 LUMINANCE RELATED RESPONSE

3.5.1 Effects of Contrast and Luminance on PERG

Luminance related components

When Enroth-Cugell and Robson (1966) observed the influences of the mean luminance on the cat retinal ganglion cells' response, they had already noted that at low spatial frequency range, decreasing mean luminance induced a fall-off of the contrast sensitivity. This was interpreted by Barlow et al (1957) (Fig 3.4) as disappearance of the effect of the antagonistic surround at low light levels.

A similar property in PERG was reported first by by Odom et al (1982/83): a pattern with

Fig 3.4 Effects of mean luminance levels on contrast sensitivity function of cat on-center ganglion cells. Four mean luminances were used: 16 (empty circles), 0.5 (filled diamonds), 0.016 (filled circles), and 0.005 cd/mm^2 (empty triangles). Contrast sensitivity was the reciprocal of the contrast to produce a just audible modulation of the spike rate at the modulation frequency of the grating, 4Hz. Note the near identity of the spatial frequency responses at the two higher mean luminances, all across the spatial frequency spectrum. (from Enroth-Cugell and Robson, 1966).

a low mean luminance, 43 cd/m^2, or pattern contrast lower than 60% could induce a low spatial frequency attenuation, ie, LSFA. Such that the authors pointed out that the use of the high contrast or/ and high luminance was the reason for a loss of the LSFA reported in earlier studies (Armington et al., 1971; Gronberg, 1980; Korth, 1981; Trick and Wintermeyer, 1981).

Clearly, the PERG contains some response component sensitive to mean luminance/ contrast changes. Thus PERG contains, apparently, both pattern contrast and luminance related responses (or components) (Arden and Vaegan, 1983; Korth, 1983; Riemslag et al., 1985; Sherman, 1986; Spekreijse and Apkarian, 1986; Drasdo et al., 1987a,b), as does the VEP (Spekreijse, 1966; Spekreijse et al., 1973b; Spekreijse et al., 1977; Padmos et al., 1973; Kulikowski, 1977). The field potentials having no or little lateral inhibitory effects have been termed local luminance responses (LLR) (Armington et al., 1971; Spekreijse et al., 1973b; Padmos et al., 1973; Korth, 1981).

Effects of contrast/ mean luminance

According to Michaelson-contrast, mean luminance of a pattern is equal to the summation of maximum (Lmax) and the minimum (Lmin) luminance (amplitudes) divided by two; while contrast is given by the subtraction of Lmax and Lmin divided by two times of the mean luminance. Thus two factors are correlated. Arden and Vaegan (1983) demonstrated a method of keeping mean luminance stable when pattern contrast was varied by adjusting two sets of check generators. In general a change in pattern contrast will accordingly induce a change in mean luminance.

It was found there was an almost linear relationship between the amplitude of the human pattern reversal ERG (rPERG) and a wide range of contrast (Arden and Vaegan, 1983). In a later study by Korth et al (1985), PERG was found to be proportional to contrast levels (0.03-0.93) at any spatial frequencies without saturation. Similar results was demonstrated in PERG evoked by on/off-set stimulation (Korth and Rix ,1984; Thompson and Drasdo, 1989).

Korth and Rix (1988) found that the PERG were prolonged when a pattern with a given high spatial frequency was presented under different luminance and colour contrast levels. The authors interpreted that the contrast reduction resulted from the optical degradation was the reason for the delay, implying the contrast reduction as a direct factor for the effect. This

explanation was not supported by Thompson and Drasdo's finding (1989) that the latency had no relation to the contrast change while all the amplitudes showed a clear increase with the incremental contrast. Thus the effect of pattern contrast changes on the PERG latency seems much less clear than that on the PERG amplitude.

Korth et al (1985) showed that at higher contrast levels, the spatial selectivity of the PERG was reduced. The effect could be observed in both amplitude and peak latency-versus-intensity curves obtained with pattern reversal stimuli differing in light wavelengths. These properties were interpreted as reflecting a transition from rod to cone activity with increasing stimulus intensity (Korth and Armington, 1976).

Effect of Luminance

According to Armington (1973) luminance intensity is measured in a photometric unit, candles per square meter, millilambert, or foot-lamberts; the most convenient way of controlling luminance is by attenuating light with neutral density filters (grey filters) for they can attenuate all wavelengths to about the same extent. The amount of luminance intensity is defined as retinal illumination and expressed in unit of troland (viewing a surface whose luminance is 1 candle/m^2 through an pupil with an area of 1 mm^2.

Content and Spectral Sensitivities

In a study by Korth and Armington (1976), they noted that three potential deflections of the reversal pattern ERG evoked at low temporal frequency (ie, the transient rPERG) had different behaviours in content and spectral sensitivities. Under photopic conditions obtained by stimulation alternation (Johnson et al., 1966; Armington, 1967), (1) the PERG content changes with the increase in luminance (max. strength = 7800 photopic troland) in such a way that the late negative potential (below the baseline) appeared first at filter density 5.0 and then a positive potential at density 2.6. The initial negative potential showed up at the highest intensity (density 2.0); (2) the PERG was larger to short wavelength than to long ones. When the PERG was compared with the scotopic CIE function (CIE, 1951. cited in Wyszecki and Stiles, 1967), the intrusion of the photopic system into the positive potential was evidenced by the high spectral sensitivity at above 550nm. The authors concluded that the initial negative potential could provide a measure of the photopic function (Brown and Watanabe,1962; Dowling, 1970); at low

luminance level, the positive potential was scotopic and at higher luminance level mixed with photopic and scotopic; the late negative potential appeared to be scotopic.

Central and Peripheral Preponderance

At a high level of light adaptation with a retinal illumination of 3.3 log trolands, a preponderant photopic activity in both VEP and ERG could be produced (Korth and Armington,1976). Armington and Brigell (1981) adopted this parameter in their studies on PERG and used checkerboards with 90% contrast in a diametric stimulus ring ranged up to 21° of visual angle and 2° of ring thickness. The results showed that the positive potential (measured from the initial negative potential trough to the positive peak) is larger in the centre than in the peripheral area under high light adaptation. The authors interpreted it as being due to the cone receptors, which initiated the response at high level of lightness and were most concentrated in the centre of the visual field.

Earlier work conducted with the ERG under photopic conditions has indicated that its amplitude is proportional to the number of cone receptors stimulated (Armington, 1968). It seems that the initial negative and positive potentials, which are known to be luminance-related, are related with central field vision and of photopic properties. Unfortunately, the authors did not mention the observation on the negative potential. According to its scotopic properties and relation to retinal ganglion cells, it appears that negative potential is related more with peripheral vision.

Korth (1983) observed the the effect of luminance changes on the onset/offset PERG and found that if the peripheral retina was stimulated above cone threshold (Daitch and Green, 1969), the high cut-off of the contrast sensitivity occurred at a lower spatial frequency than when the central retinal was stimulated; with reduced retinal illumination, the contrast sensitivities with both central and peripheral areas were decreased and the peak of the function shifted towards lower spatial frequency (Campbell and Robson, 1966; Daitch and Green, 1969). The authors concluded that when a large visual field was used, the contribution of the peripheral ERG (Lawwill et al., 1977) would be expected. Additionally it is believed that the peripheral retina contributes more strongly to the ERG than to the VEP (Mollodot and Riggs, 1970).

Scotopic and Photopic Preponderance

Most of PERG studies was performed under light adaptation. Theoretically, under photopic

conditions, the retinal center-surround balance of the receptive field is stable (Enroth-Cugell et al., 1977a).

Barlow et al (1957) reported that as the mean luminance level dropped to scotopic levels, the surround response of retinal ganglion cells disappeared and that the response was dominated by its centre mechanism. Some reports showed an opposing phenomenon: the surround was maximally sensitive at the lowest luminance level (Enroth-Cugell and Lennie, 1975; Kaplan et al., 1979), but the modulation of the relative strength of the centre-surround mechanisms could be seen at very low scotopic levels.

The second proposal for interpretating the center-surround imbalance under dark a daptation was presented by Sterling (1983) based on the observation on cat. In this proposal, in the mixed pathways, active at mesopic level, rod signals were thought to communicate through gap junctions to cones, and then to cone bipolars before coming to Y cells; the change in the organisation of the receptive field was brought about by switching the signal flow from a mixed pathway to a pure rod pathway (the Purkinje shift).

In addition to central-surround imbalance, in the dark adaptation, the centre size of the receptive field expands (Kaplan, 1991). A doubling of the center's radius in lateral geniculate nucleus (LGN) has been reported by Enroth-Cugell and Robson (1966) and Kaplan et al (1979). A similar result, but, with smaller expansion, was reported by Derrington and Lennie (1982). The expansion occurs as the light level goes from mid-scotopic to low scotopic vision. The authors concluded that the expansion of the centre size under dark adaptation had no relation with the Purkinje shift (Barlow et al., 1957; Sterling, 1983; Smith et al., 1986; Sterling et al., 1988). This expansion has the same effect as the dilation of the pupil in the dark, allowing more light to collect and increase the sensitivity of the receptive field.

Purpura et al (1988) found some similar results in monkey retina: lowering the mean luminance lowered the contrast gain of both M and P cells. The authors interpreted that M cells have substantially higher contrast gain at photopic levels (8-10 times higher) so that they could continue to function even at mesopic and scotopic levels (near or below 1td); whilst the P cells could no longer respond to patterns of moderate or low contrast at mean luminance level below 1troland as the M cells can. At last, the authors concluded that under low luminance level

it was the M-cells rather than P cells that subserved the pattern vision.

Few had been report about the PERG studied under dark adaptation. The potential significance of dark adaptation after the cone-rod break in the studies of the PERG appears that under low luminance level, the scotopic component of the PERG should be highly sensitive. Transient analysis is undoubtedly advantageous for it permits the full development of the scotopic potentials (Armington et al., 1970). Though overlapping of the positive and negative potentials makes the analysis difficult, the distinct difference of the positive potential and the negative potential under visual adaptation appeared to have shed some light on the possibility of differentiating the response.

Stray light effect

When PERG was recorded under light adapted condition, stray light effect has to be considered. Brindley and Westheimer (1965) demonstrated that the stray light effect was suppressed when a large surround was illuminated to 10% of the mean (screen) luminance level. Arden and Vaegen (1983) proposed that a ten times surround referred by Brindley and Westheimer should be used for precaution. But such a large surround onto retina can reduce the effective contrast and thus reduced the response more than the pattern with a given contrast could. A recent report by Van Denberg and his colleagues showed that when a checkerboard with high mean luminance (200cd/mm^2) under same strength of surround, the loss of modulation depth (contrast) in a young healthy eye could be up to 16% and even more in old people.

When the incident light strikes a cone in an oblique direction, the effectivity of the light will be reduced (Le Grand, 1968) due to the Stiles-Crawford effect and thus the effect diminishes the effect of aberration (which includes diffraction, spherical aberration and chromatic aberration in human eye). The S-C effect can be neglected at small pupil size but has slight effect on aberration at larger pupil sizes (van Meeteren,1974), in a way of counterbalancing the MTF of the eye (Deeley and Drasdo, 1987).

Retinal origins?

Except some occasional question (Spekreijse et al., 1973a), most of the PERG investigators have accepted a theory that the PERG originates differently from the ERG elicited by the

unstructured light stimuli (Arden and Vaegan, 1965; Nelson et al., 1979; Diehl and Zrenner, 1980; Arden et al., 1980; Fioretini et al., 1981; May et al., 1982). These early theories were based on the observations that when the ganglion cells were injured, flash ERG was unaffected while pattern PERG was abnormal. The observations showed an evidence of flash ERG having no relation with the ganglion cell layer and, at the same time, left an unpresented question ----probably, pattern ERG did not represent necessarily the functions of the ganglion cells alone. More recent works have suggested the possible preganglion cell origin of the PERG luminance-related component (Korth,1983; Riemslag et al., 1985; Spekreijse and Apkarian, 1986).

A case for example is that in human optic atrophy a stimulus with high contrast and low spatial frequency could produce retina signals in the absence of ganglion cells whereas when the low contrast and high spatial frequency stimulus no response could be elicited (Dawson et al., 1982). Similar reports were reported from clinical investigations that PERG could be 'unaffected' even though the ganglion cells have been seriously impaired (Fioretini et al., 1982; Sherman, 1982; Harrison, 1987). In a report by Harrison (1987), thirty months after surgical transection nerve in the course of an operation for removal of an optic nerve glioma, a PERG could be still be recorded from the blind eye, and it was slightly reduced when small checks were used. These authors concluded that cells other than the ganglion cells produce the PERG and part of the response, maybe mainly the positive component, is elicited by these cells. Since the flash ERG originates from all the retinal layers but ganglion cell layer (Brown, 1968; Rodieck, 1973; Armington, 1974; Timita and Yanagida, 1982), the observation suggests that both flash ERG and the luminance-related component of the PERG might share some common retinal neurons, such as the inner nuclear layer (Drasdo et al., 1990), even though the mechanisms might be totally different.

The mechanism is still not clear. An example is that in the early period (15-20 days) of the optic nerve section, the PERG amplitude is reduced to lower spatial frequency patterns and the response to higher spatial frequency is not impaired until 3-4 months later (Maffei and Fioretini, 1982/83). The response changes to high spatial frequency follow the retrograde degeneration of the ganglion cells after their axons are damaged (Duke-Elder and Scott, 1977). So which retinal mechanisms subserve this initial reduced (but presented) PERG at low spatial frequency? It seems that the luminance-related component is affected first and remained unchanged during the progressive antidromic degeneration of the optic nerve.

3.5.2 Optical Degradation and Contrast

The contrast of a high spatial frequency bar grating (or checkerboard) can be greatly reduced in the retinal image due to the optical degradation (Charman, 1983). In other words, the actual contrast of a retina image is less than that of the external stimulus in such case. Schade (1965) report linked this phenomenon with optical factors to interpret his findings in testing the visibility of sinusoidally varied grating patterns. He found the threshold level of contrast was high in high spatial frequency and interpreted it as the joint effect of optical blurring and retinal summation.

This 'optical blurring' has now been attributed to the optics in the eye. The reduction of the contrast influences the PERG amplitude in such a way that in the modern PERG studies, the terms of describing the actual retinal luminance profiles, such as "retinal illumination" to represent the effective luminance profile of a pattern on the retina and the term "retinal luminance response" (RIR) (Drasdo et al., 1987a,b), is often used to stress the importance of the optic degradation.

Temporal Contrast Attenuation Function of a Pattern

By definition, the contrast of a spatially and temporally moving pattern has two elements: one is the spatial contrast(SC) and the second one is the temporal contrast (TC). Michelson contrast (1891), originally designed for sinusoidal gratings, has been used to express the spatial contrast of any repetitive stimuli (Westheimer, 1985), reflecting the luminance difference at different points in space at the same time. A similar formula was referred by De Lange (1958). The temporal contrast represents the contrast applied to the luminance difference at the same point (mean background) on the image at different times.

For reversal checkerboard stimulation, SC is equal to TC at each point of the pattern but it is not the same case for on/offset stimulation. TC is different for light and dark elements (Drasdo et al., 1987a). The temporal contrast varies at many different points on a spatially repetitive element of the pattern. The appearance of a black check from a mean background will induce three times of contrast change compared with the white check at 100% modulation depth (spatial contrast is equal to the difference of the luminance profiles between the maximum and the minimum), while at mean background the contrast is 50% modulation. The space-averaged temporal contrast can be used to reflect the effective illumination stimulation of an on/offset

pattern. The contrast varies as a function of check size (*space-averaged temporal contrast function)* and this function relating contrast attenuation to diminishing check size cane be represented by *the temporal contrast attenuation function* (Drasdo et al., 1987a). A reversal pattern has a higher optical attenuating factor than an on/off-set pattern.

Optical Transfer Function

Fig 3.5 illustrates how the lens of human eye reduces contrast as a function of spatial frequency. Supposing the modulation (ie, the Lmax-Lmin) is fixed at the highest possible value with Lmin = 0, the contrast decreases with the increase of the spatial frequency of a pattern or image. Such a phenomenon is called the Modulation Transfer Function of the optical system. The right plot is called the Phase Transfer Function (PTF), which can be neglected for the optic degradation (Drasdo et al., 1987b). The two functions together are called the Optical Transfer Function (OTF).

The terms are recommended by the International Commission for Optics in London in 1961 (cited by Regan, 1990) and were first suggested in analysing the visual system by Johnson (1970). The model for calculating the MFT of the eye has been suggested by Johnson (1973):

$$M = exp - (F/Fc)^{n}$$

where F is the spatial frequency, Fc is the frequency constant and n is the MTF index. Thus the MTF represents the contrast loss across the spatial contrast.

Defocus

Defocus is an artificial factor to produce the optical blurring of a pattern image. The actual effect is to reduce the contrast of a pattern. Its effect, therefore, is more likely related with the the MTF of the eye (Fig 3.6, top graph). When the defocus MTF is compared with the normal MFT, it is noted that as the defocus is increased, the high frequency drop of the MTF progressively occurred earlier. In other words, the fine detail perception disappears first. As the spatial frequency increases further to a certain value, the MTF falls to zero, then it crosses zero contrast and becomes negative at last (Hopkins, 1955).

Regan (1990) suggested that the defocus effect was related to the grating visibility and

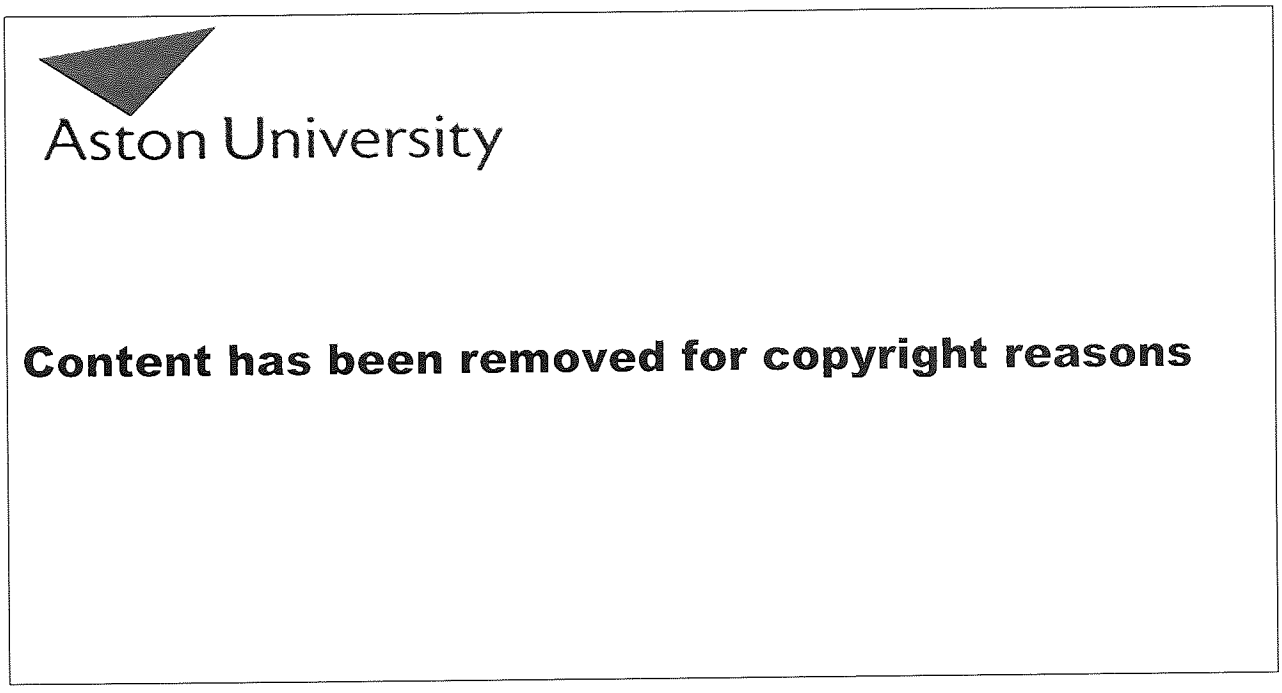


Fig 3. 5 Modulation transfer function for a real lens. Left: Modulation versus spatial frequency in the image plane where modulation is defined as (Lmax-Lmin). Right: The phase transfer function for the same lens. The variation of phase with spatial frequency is caused by lens aberrations. (after Regan, 1990)

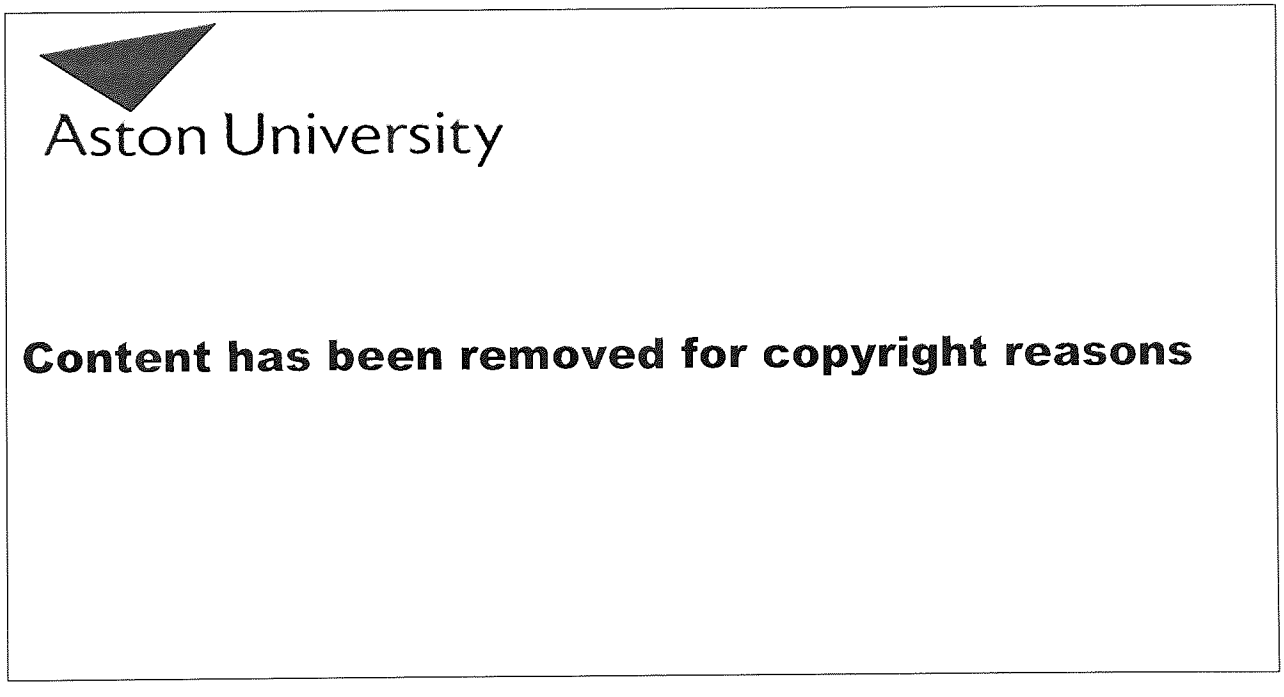


Fig 3.6 Contrast reversal, ripples and spurious resolution produced by real lenses. Top: Effect of defocus on the MTF of an aberration-free lens. Numbers indicate increasing defocus. (after Hopkins, 1955) Bottom: Effect of defocus on the MTF of an aberration-free lens (dashed line) and a lens with spherical aberration (continuous line). (by Regan, 1990)

resolution limit (due to the ganglion cell receptive field center size). The grating visibility reaches resolution limit when the MTF falls to zero. If a pattern beyond the resolution limit can be seen when the spatial frequency is increased at 'negative' contrast range, it is possible that the spatial pattern in the image can be not like the real object's image. Regan referred this imaging by a slightly defocus system beyond the resolution limit as *spurious resolution.* However when defocus is added up to a lens with spherical aberration rather than a diffraction-limited lens, the spurious resolution disappears and is replaced by *ripples* just above the zero contrast (Fig 3.6, bottom graph).

Defocus can influence both the low spatial frequency attenuation and the high spatial frequency attenuation of the PERG but with opposite effects and thus induce a large local luminance response. Odom et al (1983/2) observed that the power of the PERG in defocus conditions is a little increased at lower spatial frequencies but evidently decreased at high spatial frequencies. The result is consistent with the effect of defocus on the MTF, implying that defocus plays its role in the PERG in the same way as the MTF of the eye does.

3.5.3 Estimation of the Retinal Illumination

The actual contrast of a retinal image is less than that of the external stimulus owing to the process of optical degradation. When the optic transfer function of the eye and the image spectra of a pattern are known, it is possible to calculate quantitatively the actual retinal illumination profile of a pattern and the contrast of a pattern and then the retinal luminance response.

Spatial Frequency Spectrum of the Retinal Image

The first description of retinal illumination distribution was by Charman (1983). The theoretical principle is as such: every point (line) of source (pattern) is imaged as a patch of light which is distributed finitely and termed point spread function. A line of light produces a spatial frequency spectrum in Fourier's analysis and thus a series of lines an image spectrum. Since the effect of the optical degradation occurs in the spatial frequency in each line of light, the spatial frequencies are needed to multiple the optical transfer function of the eye. The pattern illumination distribution is given by the inverse Fourier's transform.

The two-dimensional Fourier transform of a checkerboard has been introduced by Kelly (1976) and can be expressed as following formula:

$$E(x, y) = Em + (8/\pi^2) \cdot \sum_{m,n=0}^{\infty} (-1)/(\beta m \beta n) \cdot [\cos \cdot [(\pi/L)(\beta m \cdot x + \beta n \cdot y)] + \cos \cdot [(\pi/L)(\beta m \cdot x - \beta n \cdot y)]$$

where Em is the mean luminance, L is side length of check with x and y axes parallelling to the edges and ßm = 2m +1.

The MTF suitable for the filtering of a two-dimension pattern can be expressed by this equation (Drasdo et al., 1987):

$$Amn = \exp[-\sqrt{(\beta m^2 + \beta n^2)^n}] / (2 \cdot Fc \cdot L)$$

where *Amn* is the amplitude attenuating factor for the *m,n* harmonic. The expression of $\cos \cdot [(\pi/L)(\beta m \cdot x + \beta n \cdot y)]$ describes the unidirectional harmonic components. Each component has a spatial *F* as expressed $Fmn = \exp[-\sqrt{(\beta m^2 + \beta n^2)^n}] / (2L)$.

The spectrum of each spatial frequency can be thus analysed until the 99th harmonic and then the retina luminance profile of a check or a square-wave grating is synthesized.

Due to the linear relationship of retinal illumination to contrast, the retinal illumination response can be calculated by multiplying the signal amplitude to the attenuation factor of temporal contrast function (Amn), in which temporal contrast is inversely related to spatial frequency. When a retinal luminance response is obtained in this way, the pattern specific response in the same PERG the same conditions can be subtracted by numerical techniques.

When a reversal checkerboard pattern is used, the retinal illumination response is smaller than that obtained with the on/offset pattern at the same spatial contrast because of its large attenuation of the temporal contrast at higher spatial frequency (Drasdo, 1981; Drasdo et al., 1987) and the calculation is more complicated due to its prominent second harmonics.

Optical Model

Another method of estimating retinal illumination is by optical measurement. The loss of

retinal modulation depth can be estimated on the basis of an optical model: optical point spread function for the human (Vos et al., 1976; 1983). The optical point spread function has been shown (Vos et al.,1976; 1983) to correctly describe the data of Campbell and Gubisch (1966) based on fundus reflectometry, supplemented by psychophysical data on intraocular light scattering. The method provides both the central peak of the point spread function and outskirt (stray light) over the full angular extent up to 100°. The straylight effect (S-C effect) can be used in both examining a localised source in flash ERRG and a pattern in PERG.

Van Denberg et al (1988) used this measure to obtain the local luminance model from the homogeneous ERG (focal ERG) and then subtracted this local luminance model from the PERG to obtain the pattern specific response. The conditions for comparability between two responses were given by these designs: (1) in order to let the two responses recorded have the same mean luminance with a same extent of loss of modulation, the homogeneous field and checkerboard response were recorded at 99% contrast and 200cd/mm^2); (2) in order to match the harmonic properties of a reversal pattern, only the even harmonics of the homogeneous ERG are analysed. The report has presented a technique to exclude the effect of the straylight effect on the PERG. It appears to be a good complementary method to the Fourier's spectral analysis of the retinal image of a pattern, which can estimate the loss of the retinal illumination from the MFT of the eye and a pattern.

SECTION III REVIEWS OF PERG COMPONENT DIFFERENTIATION

3.6 PATTERN PRESENTATION

3.6.1 On/Offset Patterns

A comparison between the results obtained with pattern reversal and on/off-set patterns has been made in the initial stage of the studies on the pattern evoked field potentials (Estevez and Spekreijse, 1974; Kulikowski, 1974, 1977; Jeffrey, 1977). These studies showed that the on/off-set pattern was more efficient tool in separating (pattern) contrast- from luminance-evoked responses/ component. Kulikowski (1974, 1977) first showed the possibility of the differentiation using on/offset stimuli: when small visual patterns were used, the onset response was dominated by contrast components, whereas the offset response represented a

predominant luminance-related response.

It is known that the on-response in PERG is produced by the bright checks superimposed on the dim ones and is equivalent to the pattern offset response, which is produced when black checks disappear. The stimulated area where black checks disappear and are replaced by bright ones receives thus many-fold of light increase compared with the on-response (equivalent to the pattern onset response and is produced in the other way around to the offset response) and should be larger. However, it has been found that the pattern onset/appearance response is larger than the pattern offset/disappearance response and thought as an effect of the lateral inhibition subserved by a center-surround organisation (Arden and Vaegan, 1983).

Korth (1983) noted that the pattern onset response was typical of a spatial frequency tuning while the pattern offset response was not. When the onset response amplitude function of spatial frequency, obtained in human PERG, with the contrast sensitivity of the cat ganglion cells elicited by sinusoidal and square-wave stripe patterns (Enroth-Cugell and Robson, 1966), it was noted that the properties of the onset response resembled closely those of the cat retinal X-cells: (1) the maximal onset amplitude occurred at a spatial frequency where the maximum maximum contrast sensitivity was obtained; and (2) the onset response amplitude did not change when spatial frequency decreased below 0.8 cpd, being analogous to the psychophysical contrast threshold (Campbell and Robson, 1966). Apparently, the onset response is subserved by the central-surround antagonisms. In conclusion, both Korth (1983) and Arden and Vaegan (1983) had a same suggestion: the onset response was not a simple linear summation of luminance changes but could be elicited either by the interaction in response to the changes in luminance. Yet, in a later study, Korth and Rix (1984) demonstrated that the spatial sensitivity could occur at both onset and offset responses also, if a low contrast pattern was used.

In a more recent report by Drasdo et al (1987b), the pattern onset ERG has been demonstrated a composite of luminance- and pattern-related responses quantitatively. The response was observed using those patterns with high contrast (75%), high luminance (250cd/mm^2) and low background luminance (25cd/mm^2). The relative proportion of each component varied according to the spatial frequency of the stimulating pattern. Assumed that luminance-related component was spatially insensitive and depended only upon the temporal contrast of the

stimulation, the authors subtracted the retinal illuminance response from the PERG using Fourier's analysis. The retinal illuminance response at any spatial frequency was estimated from that of the lowest spatial frequency by employing the response amplitude: contrast function.

3.6.2 Reversal Patterns

For the rPERG, luminance and contrast components can not be distinguished as easily as for the on/offset PERG. The reasons for the difficulty are (*a*) the fundamental components and the higher order odd harmonics can be cancelled when patterns reverse, such that the stimulus power will be greatly reduced before they stimulate the retina, resulting in a smaller response; (*b*) a reversal pattern's frequency spectra are rich due to its multiple higher harmonic components; (*c*) compared with on/offset pattern, retinal illumination response is more easily effected by the use of reversal patterns (Drasdo et al., 1987a,b); (*d*) both contrast- and luminance-related responses are produced simultaneously whenever the patterns reverse, with twice the modulation rate of the stimulation frequency. Yet, some efforts have been made using indirect methods, such as changing luminance level and spatial frequency, and local ERG.

Changing luminance level

Schuurmans and Berninger (1984) reported that the negative response of the rPERG could be recorded almost without a preceding positive deflection when it was recorded with a field size of 9° and mean luminance of 20cd/mm^2. On the other hand, using a same field size but a much higher mean luminance (120cd/mm^2), a PERG with a predominant positive component could be obtained (Spekrejse et al.,1973).

With a low temporal reversal rate, Berninger and Schuurmans (1985) demonstrated successfully that the positive response in rPERG was a luminance related response while the negative response was (pattern) contrast related response. The conclusion was based on the observation that a spatial frequency tuning could be observed on the negative response across temporal frequency while the positive component was 'only tuned' for the checks between 25 and 50 min of arc, thus showing a saturation at low spatial frequency (over 50 min of arc).

Changing Spatial Frequency

Another example for the rPERG components to be differentiated was reported by Tobimastu et al. (1988/89). By changing spatial frequency from 0.1 to 2.2 cpd in ten steps, the rPERGs were investigated in cat and human using the checks with high luminance (78.7cd/mm^2) and low contrast (55%), subtended 22 degrees of visual angle. The results showed peak amplitudes around 0.6-0.75 cpd (corresponding 71-56 min of arc) and 0.3 cpd (ie, 2.4°). Five months after the optic section in the cat, the responses to checks smaller than 0.3 cpd were absent, while those to larger than 0.3 cpd persisted. The histology exam displayed an almost complete absence of the ganglion cell.

The authors concluded that PERG was a mixture of contrast and luminance responses: at checks higher than 0.5 cpd (smaller than 1.4°), which was the spatial frequency of two peaks' separation, the tuning was due to 'contrast response' generated by the ganglion cells and at spatial frequency below 0.5 cpd 'luminance response' became predominant, generated by some preganglionic retinal cells. The investigation on patients matched the findings obtained in the cat: the PERG could be evoked only at large checks (31min rather than 15') in those patients with optic atrophy.

Focal ERG

In a recent report, van Denberg et al (1988) showed a differentiation of the rPERG using an optical technique. First the loss of retinal modulation depth due to stray light effect was estimated using the optical point spread function (Vos et al., 1976; 1983); then the effective retinal illuminance response was obtained from local ERG evoked by the effective retinal modulation (only including the second harmonic components in order to match the nonlinear properties of the pattern reversal ERG). Finally, the contrast related component was obtained by subtracting the effective retinal illuminance response from the rPERG obtained under a similar stimulation background.

The response elicited by reversal pattern at spatial frequency between 30' and 100' showed of the same order. The pattern contrast response was recognisable only to the checksize smaller than 120' and thus over 120' the response was thought a pure luminance response. while between 8-120 min, the luminance can account at best for half of the response.

Matched to the report by the Thompson and Drasdo (1987a), this report demonstrated

quantitatively the composition of the luminance- and the contrast-related components in the PERG using reversal pattern stimulation. And the analysis of the two response curves showed a similarity to the model suggested by Thompson and Drasdo.

3.7 SIGNAL ANALYSIS IN RPERG COMPONENT DIFFERENTIATION

3.7.1 Forward and Inverse Fourier Transforms

It is known that all quantifiable physically occurring signals may be assumed to meet the conditions for use of the Fourier transform (Bracewell, 1978; Gaskill, 1978). The transforms used in physical and engineering signal analysis were introduced by Regan (1982) to analyse some physiological responses. The basic assumption is that: (a) in spatial-temporal vision, a typical input signal is either a temporal variation of light intensity---a time series --- or a spatial variation of radiance, ie, spatial frequency spectrum, or combined both; (b) It is the same case occurred in the output signals, such that the same analysis procedure can be used. The only difference is that the signal-to-noise enhancement in analysing a physiological response, such as time-domain averaging or frequency-domain averaging may be necessarily considered (Regan, 1989).

The two major methods of describing and analysing a time series are in the time domain and the temporal frequency domain. These two doctrines are related by the forward and the inverse Fourier transforms. Two descriptions are alternative for modulations of the same data. A description that is intermediate between these two extremes can be defined as time-varying spectrum.

By definition the transformation from the time domain to the frequency domain is based on the forward Fourier transform. The transformation from the frequency domain back to time domain is based on the inverse Fourier transform. This Fourier transform pair is defined by Regan as

$$G(f) = \int_{-\infty}^{+\infty} g(t)\, e^{-j2\pi}\, dt \quad \text{(forward transform)}$$

$$g(t) = \int_{-\infty}^{+\infty} G(f)\, e^{j2\pi}\, dt \quad \text{(inverse transform)}$$

where g(t) is the time domain representation of the signal g and G(f) is the frequency-domain

representation of the same signal.

3.7.2 Transient and Steady-state Analysis

A transient response is, apparently, the one that is repeated once, implying that the relevant brain/retina mechanisms are in their resting states before each successive stimulus, and returns to their resting state before the next stimulus. Correspondingly, the steady-state response is defined as the response whose discrete frequency components remain constant in amplitude and phase over an infinitely/finitely long time period.

According to Regan (1989), a time series can be completely described in terms of frequency, and vice versa, since two descriptions are equivalent. The relationship between time and frequency can be described by a fundamental physical law, the so-called 'uncertainty relation' $\Delta f/\Delta T \geq 1$ by Gabor (1946): it expresses that a short duration event necessarily over a wide range in the frequency domain, and an event existing only over a narrow band of frequencies necessarily extends over a substantial duration in the time domain. For a steady-state analysis, the use of frequency domain or description in terms of its constitution frequency component; while for a transient response, it seems more natural to choose time domain analysis for each defined peak, probably because it can precisely represent the content of information in the time domain, while in its frequency domain, there is equal energy at all frequencies.

The terms steady-state and transient were first referred in PERG by Baker and Hess (1984). It was noted that the response could be recorded at two peaks when temporal rates were at 1-2Hz and 8-10 Hz. The response was composed of a fast diphasic component and a slow monophasic response. The authors termed the fast response with peak at 8-Hz as steady-state PERG and the slow response with a peak at 1-2Hz as the transient PERG. In the monkey, as in man, the response is largest at 8Hz, and has a secondary peak at 1-2Hz (Hess et al., 1986).

At higher repetition rate, only a few of harmonic components fall within the response's passband so that the steady-state response waveform is simpler than that at low repetition (Regan, 1970). The advantage is that it can produce a better signal-to-noise ratio than the transient analysis. The major advantage of the transient analysis is that it allows to collect the nonlinear components of the response. The drawback is that successive responses clearly overlap that in a sense that some peak latency measure may lose some meaning. Such that the

use of techniques depends upon which of the techniques is efficient in a particular situation.

3.7.3 The Properties of Reversal PERG (rPERG)

When two sets of elements of equal area (eg, checks) are modulated temporally exactly 180° out of phase, the summed response on the same area contains only the second harmonic (2F) and higher order even harmonics (4F, 6F,...)(Campbell and Robson, 1968; Spekreijse et al., 1973a, b). Since the patterns reverse with twice the modulation rate, the contrast-related components of the PERG will also contains only even harmonics (2F, 4F, 6F). The over-all reversal response, therefore, will contains only second harmonic and higher even harmonics (Riemslag et al., 1985).

It is known that the retinal ganglion cells subserve the contrast related component in the rPERG. Thus the properties of the rPERG was based on the linearity and nonlinearity of the receptive fields of the retinal ganglion cells. The first main subdivision was made by Enroth-Cugell and Robson (1966) on the cat retinal ganglion cells. The authors used grating stimuli to characterise the response recorded and found that some cells, the X-cells, were linearly additive to give a combined center-response and a combined surround response; while in Y-cells there is a distortion in frequency of the output, ie, Y cells responding to the gratings at twice the stimulation rate.

Hochstein and Shapley (1976a, b) compared the responses obtained with the drifting grating and contrast-reversing sinusoidal grating of increasing spatial frequencies in the cat retina. They found that with the increase of spatial frequency, Y cells stopped producing a modulated response before X cells at any given retinal eccentricity and the responses of both cells contained only the first harmonic components (linearity). Differently, when the contrast-reversing bars were used, Y-cells produced a typical frequency-doubled response, ie, the second harmonic (non-linear) component while X cells had only the nearly negligible second harmonic, represented by a higher nonlinear index for Y cells than for X-cells. The author concluded that Y cells contain nonlinear components in Fourier frequency domain, while the linear properties could be found in both X and Y cells. In primate, P cells are X-like for they have linear spatial summation (Derrington and Lennie,1984).

It is known that the PERG's energy is concentrated mainly on the harmonic components

second to the stimulation rate and the flash ERG's energy is concentrated on the fundamental component (linear) (Bass and Haker, 1984). Furthermore, with a reversal pattern stimulation, the second and higher order harmonic components could be shared by both contrast and luminance related components as described. Thus the contrast related component are of linear and nonlinear properties and reflected in the second and higher even order harmonic components. It appears that luminance related component contains, at least, some linear component, considering the properties of the flash ERG.

3.7.4 Power Spectral Density

In statistical analysis the power spectral density is used for random data to describe the general frequency composition of the data in terms of the spectral density of its mean square value (Bendat and Pearson, 1971,1986). It is particularly good when the analysis is performed under fast Fourier transform (FFT) due to its properties in frequency domain (Odom et al., 1982/3).

An important property of the power special density function lies in its relationship to the autocorrelation function, specially for stationary data, since these two functions are related by a Fourier's transform. The autocorrelation and power spectral density functions furnish similar information in the time and frequency domain, respectively. For stationary data , the later technically supplies no new information over the autocorrelation since the two are Fourier transform pairs. In general, power spectral density analysis was based on the second harmonic of the stimulus frequency. Selection of the power at the second harmonic of the stimulus frequency as a response measure in reversal pattern evoked potentials is based on the theory that the reversal patterns elicit responses at twice the stimulus frequency at both retina (Riggs et al., 1964, 1966; Johnson et al., 1966; Armington, 1968) and cortex (Spekreijse, 1966; Regan, 1972; Regan, 1981).

There are some advantages in using the second harmonic power analysis in the PERG: (1) it can produce a significant improvement in the signal-to-noise ratio (Gur and Zeevi, 1980; Dawson et al., 1982; Odom et al., 1982/3). In a conclusion by Odom et al (1982/83), the authors suggested that more efficient detection of spatial tuning in the retina using power may be attributed to the improved signal-to-noise ration; (2) it contains power at twice the stimulus frequency (Bendat and Pierson, 1971; Spekreijse et al., 1973a; Regan, 1981), thus not influencing the local luminance responses; (4) it minimises the effects of small

imbalance or eye movement which follow the alternation (Riggs et al., 1966; Johnson et al., 1966; Armington, 1968).

3. 8 PURPOSES OF THE PRESENT STUDIES

The theory that the PERG is related with the retinal ganglion cell layer has been generally accepted in experimental researches and clinical investigations. The studies on the spatial frequency tuning have fulfilled the content of the PERG mechanisms and provided some convincing evidences in the theoretical development.

The presence of the retinal luminance-related response in the PERG had been noted at the same time when the pattern specific response was studied. The response is typical of being related with retinal local luminance increase and thus has some properties entirely independent of the pattern specific response, though the two responses coexist in the same PERG. Most investigators agree that the positive and negative potentials of the PERG evoked by slow reversal patterns (transient rPERG) represent, respectively, the luminance-related / retinal illumination component and pattern specific component of the response. The co-presence of these two components (or responses) in the same response process makes the selective stimulation of a component difficult, due to the overlapping of the components. For example, when a pattern with a high frequency is used, the pattern specific component will be well developed but this pattern could produce some optical degradation which can result in contrast reduction and thus effect both the components and thus P50 and N95. So it is questioned that how much each stimulus protocol effects each component and how the effects are reflected in the corresponding changes in the recordable components, separately (ie, P50 and N95)?

In the present studies, the focus will be on the properties of the transient PERGs, especially those of non-spatial selectivity. The interrupting factors such as defocus, changes in contrast/mean luminance levels and visual adaptation will be used on the normal youth and elderly in order to study the causes of normal variations and conditions of a pattern selectively evoking one or two components of the response accordingly in the experimental conditions; and the combined observations of ERG and VEP evoked by flash and pattern stimulation will be made on some diseases (such as ischaemic optic neuropathy and retina ischaemia) based on the observations on the normals.

CHAPTER 4.

ANALYSES OF THE VARIATIONS OF THE TRANSIENT PERG WAVEFORMS

Introduction

Unlike flash ERG with an amplitude of several tens (photopic) or hundreds (scotopic) microvolts, PERG is small, of the order of several microvolts. Thus accurate obtainment and assessment of the biological signals is the main concern in recording the PERG, provided that the noise from non-biological sources has been removed. The averaged coefficients of the variation (CV) in the PERG amplitudes were reported to vary between 15% and 50% (eg, Schuurman and Berninger, 1984; Hess et al.,1985; Korth and Rix; 1985; Korth and Ilschner, 1986). Our investigations showed that the averaged CV of the transient rPERG was 23% for positive potential and 10% for the negative potential.

We noticed that the variability of the PERG evoked by low reversal patterns, the transient rPERG, could be represented either as variations in amplitude, as has been known, or in waveform; the later variations were mainly reflected in the negative potential. In estimating the repeatability of the PERG, Bartel and his colleagues (1991) found that the positive potential amplitude had an averaged coefficient of repeatability (CR) of 2.0μV, maximally; while the negative potential amplitude showed a poor repeatability with a much higher averaged CR, up to 4μV! It was assummed that the low CV values for the negative potential (eg, Korth and Rix, 1985; our observations) resulted possibly from the averaging process, since the differences from trial to trial have been covered, thus resulting in an optimistic low intersession variability. These results suggested that the variation of the waveform and the amplitude of the negative potentials are probably correlated between each other within a record.

Furthermore, in an estimate of the averaged CVs for the latencies of the transient rPERG, we found that the CVs of both positive and negative potentials were much lower for the response peak latencies than those of the response amplitudes, being varied only between 2% to 5%. Since each component in a response is independent of others (Regan, 1989), we assumed that such waveform as well as amplitude variations were related to the implicit times and durations of the successive response components.

The amplitude of the negative potential of the transient rPERG has been known for its clinical values in estimating the functions of the inner retinal layer (especially, the ganglion cells) by many reports. However large variability remains a vexing problem to tackle for every PERG investigator. In this study, we first estimated the recording system we used. Secondly we used the theory of low frequency attenuation (Regan, 1989) to decompose the response into several independent 'components' and analysed the timing course relationships among these 'components'. It was expected that the study could present some theoretical analysis of variations of the transient rPERG, especially of their waveforms, and thus the reliability of the PERG records.

SECTION I SIGNAL PROCESS BEFORE AND AFTER SESSION

Estimation of the Recording System

The factors resulting in the response waveform variations could be of multiple sources, such as stimulator and recording systems, subjects' status during recording, stimulus parameter protocols, etc. In a recent report, Holopigian et al. (1988) investigated the effects of stimulus and recording conditions on the PERG variability, and demonstrated that the recording conditions were apparently more related to the PERG variability than the stimulus conditions. Thus it is important for an observer to know the recording system s/he is using, ie, to what extent it would possibly effect the s/n ratio. In this part of study, we examined the recording system we used for the PERG recording and and demonstrated a necessity of processing the PERG records after the session.

For the present studies, the PERG data were obtained using the Nicolet Pathfinder II system. The factors possibly effecting output signals during recording were as followings: placement of the DTL fibres, sweep time/sampling rate, artifact rejection range, filtering settings, amplifier sensitivity and averaging times.

Recording Electrodes

The inputs from two electrodes are amplified by a differential amplifier due to its ability to reject 'common-mode'(common to the two input leads) noise signals (Geddes and Baker, 1968). "Common mode rejection ratio"specifies an amplifier's optimal ability to discriminate between the signals in antiphase and inphase at the two inputs. High common-mode rejection is essential

for in most of the situations common-mode mains interference is much larger than the response signals, particularly in the case of recording PERG.

In practice, the maximum obtainable ratio can be limited by the imbalance of the electrode impedances. The impedances (of the recording and the reference electrodes) to ground (Z_1 and $Z_2\Omega$, respectively) of the amplifier will, in general, be different. Supposing that the amplifier's input impedance is Zin Ω, the maximum obtainable rejection ratio is 2 Zin : $|Z_1-Z_2|$ (Regan, 1989). Thus there is a requirement for the recording electrode---the lower its resistance is, the better.

The recording electrodes used in the present studies were DTL fibres. The signals are known to be conducted by direct corneal contact with the fibre's metal (ie, silver impregnated within multiple nylon monofilaments). In the Nicolet Pathfinder II, the minimum detectable impedance (to ground) difference between both electrodes is 5kΩ. The resistance of the DTL fibres (supposed to be Z1) has a measure less than 0.1kΩ. Apparently the $|Z_1-Z_2|$ value depends on the extent of the noise conducted from reference electrode (Z_2), which might not be detected if it is below 5 kΩ. Providing Zin = 10MΩ, the maximum obtainable ratio will be 10,000 when $|Z_1-Z_2|$ is 2kΩ, but when (Z_1-Z_2) is 4kΩ, the ratio will be down to 5000! The solution for this problem is to choose a nearby position with least contamination and low tissue (volume conductor) resistance. The ipsilateral temporal (of the recording electrode) is known to collect the least contamination (<10%) from other biological sources (eg, Hess and Baker, 1984) and thus chosen for placing the reference electrode throughout the studies.

Secondly, it was found that the PERG amplitude was proportionally related with the corneal contact conditions of the DTL fibres (Fig 4.1a). Additionally, the fibres' tension, place or depth within the lower fornix and thickness of the tearing film were also factors effecting the signal size although the maximum corneal contact had been made. Under satisfactory corneal contact, the amplitudes among repetition could be of up to 20% difference. The results have suggested that caution should be taken in using the DTL fibres.

Artifact Rejection & Amplifier sensitivity

Another method to attain a high common-mode rejection ratio is to carefully adjust the amplifier's common-mode rejection to optimal. Holopigian and his associates (1988)

Fig 4.1 Comparison of the transient rPERGs records under different recording conditions in the Nicolet Pathfinder II recording system *a*: the rPERGs with different corneal contact areas; *b*: the rPERGs with the amplifier sensitivities of 200±50μV and 100± 50μV; *c*: comparison of the rPERGs baselines recorded with timebases of 200ms and 500ms; *d*: the rPERGs recorded with filtering settings of 0.5-250Hz and 0.5-100Hz.

demonstrated that reducing the acceptance band from ±0.8 volts to ±0.4 volts and the sweep time down to 150ms could decrease the intrasession variability (expressed in coefficients of variation) from 36% to 17% for the positive potential and from 40% to 18% for the negative potential in the transient rPERG. To match the averaged PERG amplitude approximations we obtained, we chose ±50μV as the artifact rejection range. The artifact reject system would operate if a signal is over 96% of the full scale deflection, ie, 90%±50μV, with proper amplifier sensitivity. The amplifier sensitivity was set at 100μV/±50 μV. The relation of amplifier sensitivity to the eye movement artifact was examined by Thompson (1987). It was found that the amplifier sensitivity set at 100μV/±50 μV in the Nicolet Pathfinder II could record a minimum eye movement artifact for the on/offset PERG. We compared the transient rPERGs recorded at the sensitivities of 100 μV/±50 μV, and of 200 μV/±50 μV, and found that the optimal amplifier sensitivity for obtaining a comparatively stable baseline was 100μV/±50 μV (Fig 4.1b) and therefore it was used throughout the studies.

Sweep Time & Sampling Rate

The minimum sweep window, or timebase, used for recording PERG was 150 ms (in some cases we used 250ms). The stimulus triggered the sweep at a rate of 1-2Hz such that the sampling rate was 1000/150 Hz or 500/150 Hz. It meets the requirement for the sampling rate of 2.5 to 4 times the maximum input frequency recommended by Regan (1989), thus satisfying (*a*) the Nyquist criterion, ie, the minimum rate required for sampling (usually twice the response input frequency), plus (*b*) the requirement for the transition band of the anti-liasing frequency. Therefore the input frequencies above the sampling rate ('spurious low frequency components') were impossibly present in the sampled signals due to such an 'anti-aliasing' filtering function. Another advantage for such a small timebase in recording PERG is that the small window timebase can limit the amount of direct current drift in the records compared with large window (Holopigian et al., 1988). Fig 4.1c displays the difference of the record baselines recorded with small (200ms) and large (500ms) windows on the same subject.

Filtering settings

The analogue filtering band for the present studies was set at 0.5-100Hz. Initially it was set at 0.1-250Hz. The wide filtering immediately brought about problem of large noise, thus making the measurement difficult (Fig 4.1d upper record). Since the major power of the response waveform was completed at 35Hz using Fourier's analysis, the recording bandpass

was accordingly set at 0.5-100Hz (33th ISCEV Standard), 3dB frequency cutoff and 12dB for each octave. It is demonstrated that the record with a bandpass of 0.5-100Hz (Fig 4.1d lower record) was significantly better than that with a broader bandpass.

Averaging times

The superimposition technique was invented more than a century ago by Galton (Pearson, 1914-1930). One of his aims was to identify common features in murder's face. Dawson (1947a,b) first used the superimposition technique for s/n enhancement in somatosensory evoked potentials in myoclonic epilepsy. The basic theory of the signal-averaging which developed on the base of superimposition (Dawson, 1951) is that: averaging N samples of a waveform improves the s/n ratio by a factor $\sqrt{N}$, providing that the following requirements are satisfied: (1) the waveform to be averaged is the sum of two independent waveforms, namely, the signal waveform and the noise waveform; (2) the signal waveform is produced by a process that is stationary from trial to trial, and its variance is negligible; (3) the noise waveform is produced by a stationary random process; (4) the N samples of noise are uncorrelated from trial to trial (Regan, 1989).

Assume that the ith poststimulus response is $f_i(t)$ and comprises the sum of a response component $s_i(t)$ and noise $n_i(t)$; and that the average of poststimulus records is $Z_N(t)$, then

$$Z_N(t) = (1/N) \sum_{i=1}^{n} f_i(t)$$

where $f_i(t) = s_i(t) + f_i(t) = s(t) + f_i(t)$, given the signal is identical in each poststimulus sample. The effect of averaging can be assessed by considering the variance $\partial^2(t)$ of the average $Z_N(t)$ in relation to that of the noise, so that

$$\partial^2_z(t) = \{ [(1/N) \sum_{i+1}^{n} n_i(t)]^2 \} = (1/N^2) N\partial^2_n(t) = \partial^2_n(t)/N$$

Thus, averaging of N responses leads to a $\sqrt{N}$-times improvement in noise variance (Armington, et al., 1961; Regan and Spekreijse, 1986). However, such a theoretical approximation for the signal-to-noise improvement is impossible to approach, for the signal records from trial to trial cannot be kept identical. Secondly, the technique can only solve the large artifacts. For PERG, small artifacts are still the main factors influencing the s/n ratio in practical recording.

Finally, excessive numbers of averaging make the recording session longer which might be intolerable to subject. Thus the averaging technique is not the only way of improving the s/n ratio. For present studies, 150 accepted responses were averaged for both clinical and research purposes.

Stimulators

It was found that the use of the stimulators was one of the important sources for the production of the noise in the PERG records. Fig 4.1 displays the difference recorded with different stimulators under the same recording system: Fig 4.1a and c are recorded with an optical projecting stimulator (OPS) and Fig 4.b and d with the Venus screen stimulator (CSS). It could be seen that the OPS produced little noise and thus was thought an ideal stimulator if the stimulus parameters for the experimental requirements could be met. The CSS provided an advantage of modulating stimulus protocols by programmes but also could produce a large noise, usually with a frequency band of 120-150Hz. The influence could be reduced when distance between the screen and subjects became larger, indicating an interference from subjects, such that long distance was recommended for the computer stimulator.

Data Smoothing After Session

Amplifier, nonbiological and biological noise may combine to produce a poor s/n ratio of a physiological response. Data smoothing utilised in physics and engineering sciences was first introduced by Blackman (1965). In addition to the averaging operations (Rosner et al., 1954; Clark, 1958) and filtering settings (analogue filtering) (Whipple, 1964; Donchin and Lindsley, 1969), digital filtering has been introduced as a technique to smooth the biological data (Dawson and Doddington, 1973; Wastell, 1979).

In general, analogue filtering can eliminate high frequency noise from the response data and yields a much more'clear' wave, but, depending upon the bandpass of the filter (Desmedt et al., 1974), it can also introduce phase errors, thus distorting the final waveform and increasing the latency. A typical active filter can create a 180 deg phase shift at the cutoff frequency. It is significant when significant energy is in the phase shifted frequency components. In order to afford accurate quantification of amplitude and time relationships of signals, Dawson and Doddington (1973) provided a solution to this problem: to use a family of interference filters with zero phase shift.

The basic theory for producing a 'digital response' is that: the resultant of a set of sinewave signals of the same frequency and various phase angles is a sine wave of the same frequency. By averaging a set of sine wave signals unshifted in phase or time with a set of positive shifted sine waves and a symmetric set of negatively shifted sine waves, one can obtain an output which is in phase with the unshifted input signal and is attenuated in amplitude compared to the output obtained by averaging the same three sets of signals if each set were unshifted. If equal numbers of shifted and unshifted signals are averaged together, complete cancellation of signal components will occur at frequencies for which the time shift used is equivalent to 180° + N (360°), where N = 0, 1, 2, 3. It was termed as interference filtering by Dawson and Doddington due to the similarity with filtering procedures in optics. The filtering can be up to 4th or higher orders. For the second order interference filtering the operation is

$$Sout\ (t_C + 3\beta_2) = (1S(t+0) + 2S(t+\beta_2) + 3S(t+2\beta_2) + 4S(t+3\beta_2) + 3S(t+4\beta_2) + 2S(t+5\beta_2) + 1S(t+6\beta_2))/16.$$

where t_C is time with reference to the first point in the computer output. β_2 is the time shift and $\beta_2 = \beta/2$. The magnitude of the second transfer function (signal out/signal in) is given by

$$TF2(\beta/p) = [\,1 + \cos\pi(\beta/p) + \cos 2\pi(\beta/p) + \cos 2\pi(\beta/p)]/4$$

where p is the period of frequency cutoff, fc. For example, for a 3dB fc = 49Hz, β_2 = period of fc/12.20 = 20.4/12.20=1.67ms; ß = 2ß = 3.34ms; ß/p = 3.34/20=0.164. Then TF2= 0.9999. It means that there is an amplification factor of approximately 1 and the digital filtering with a bandpass of 0.5-49Hz at 3dB frequency cutoff nearly does not effect the output signal amplitude and can avoid phase shift, as well.

This techniques have been widely used in filtering VEP waveform (Dawson and Doddington , 1973; Chatfield 1975). In a report by Dawson and Doddington (1973), using analogue filtering could create 19.4ms signal peak delay (shift) compared with using the interference filtering with the same frequency cutoff (3dB). They recommended using the second order filter after averaging process to remove the possible phase shift. Since the second order process allows passing of frequencies at points in the spectrum 4 times the first minimum of the transfer function, it is possible to further improve signal/noise by the use of analogue filtering.

Digital filtering in time domain is performed by a computer on the digital time series (digitised response), or averaged response (Abe and Iwata, 1976). In the Nicolet Pathfinder II recording system, it is possible to do digital filtering, ie, interference filtering, at the second order. We compared the results with and without digital filtering (Fig 4.2). The results indicate the necessity of digitally filtering for the PERG records, especially when a computer screen is used as stimulator. Since the process produced little phase shift (maximum value we obtained was 3ms), the digital filtering (0.5-49Hz) was used as a routine to smooth the PERG records after the session throughout the studies.

SECTION II ANALYSES OF THE TRANSIENT RPERG COMPONENTS

Effects of Lowpass, Highpass and Bandpass Filtering

In order to interpret the effects of low-pass, high-pass and bandpass filtering on sharp versus broad VEP waveforms, Regan (1989) experimented on a short (20ms) and a long (200ms) positive pulses with a 50ms interval between the pulses, which could reproduce with a filter bandpass set at DC-250 Hz.

The effect of high-frequency attenuation, or low-pass, is that: sharp corner of the pulses can be rounded by a slight change of lowpass caused by a 3-dB point from 250 Hz to 100Hz. The corners become more round as the extent of the high-frequency attenuation is progressively increased. The short pulse is more severely distorted by high-frequency attenuation than the long pulse. The lowpass down to 15Hz can reduce the peak amplitude of the short pulse and round the corner of long pulse, but the peak amplitude of the long pulse (200ms or 5Hz) is little reduced (Fig 4.3a).

Introduction of a slight low-frequency attenuation, ie, high-pass, causes appreciable distortion of the long pulse. The distortion consists of a sag along the duration of the pulse and a transient negative excursion at its termination. These two effects grow progressively as the severity of the low-frequency attenuation progresses. With severe low frequency attenuation, the long pulse no longer resembles a positive rectangle but only the onset and the offset are signalled; during the middle of the pulse, there is virtually no output at all (Fig 4.3b). Bandpass can produce the effects of both low- and high-passes (Fig 4.3c).

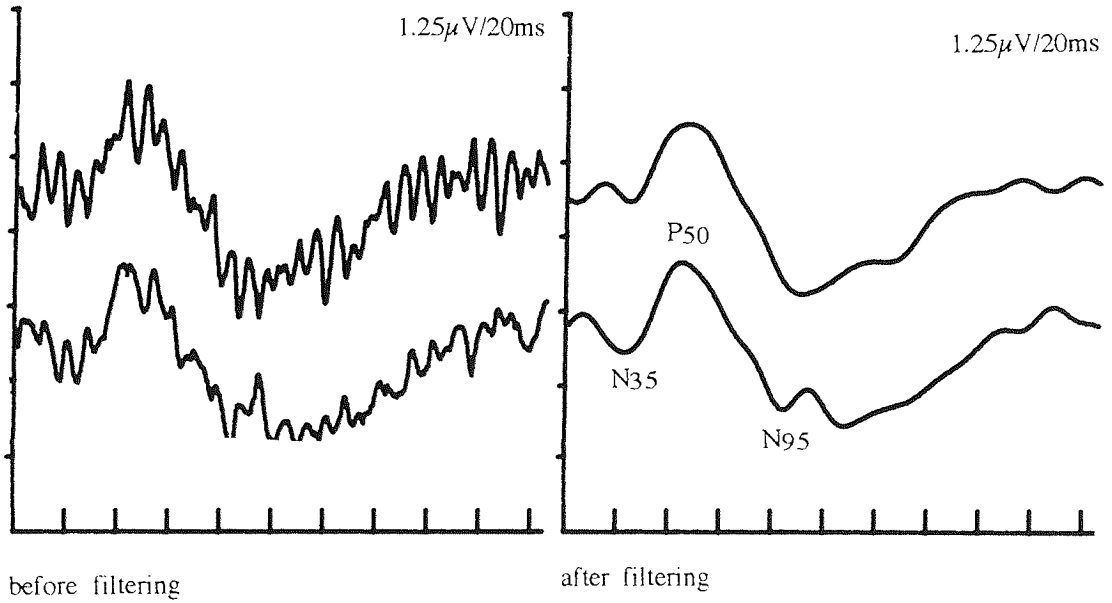


Fig 4.2 The transient (2Hz) reversal pattern ERG records with and without digital filtering after the session. The records were obtained with black and white checkerboards, sized 56 min of arc, in subject ST (25 yrs). The bandpass was set at 0.5-100Hz before the recording. After digital filtering (0.5-49Hz), the records became clean and the response peaks and deflections were recognisable and measurable (5th, May, 1995).

Fig 4.3 Effects of high frequency attenuation (left column), low frequency attenuation (middle column) and their combined effects (right column) on a short and a long pulses. (after Regan, 1989)

Regan noticed that when VEP was recorded with a bandpass of 0.6-100Hz, it consisted of a negative-positive (107ms)-negative waveform and a slow positive peaking at 240ms. Changing highpass in a 3dB point to 60Hz (0.6-60Hz) could attenuate the high-frequency noise and produce a clear looking VEP, but a drawback was that the double peak was removed. At the same time, increasing the severity of high-frequency attenuation further (0.6-30Hz), an appreciable delay could be also be created. Low frequency attenuation could distort the VEP waveform. When bandpass changed from 0.6-60 to 5-60Hz, large positive peak was strongly attenuated, where the immediately following negative peak was much enhanced. The main effect of too severe low frequency attenuation was to change VEP waveform, to distort the relative amplitudes of different components and to create some spurious peaks. Regan interpreted that changing the lower 3-dB point from 0.6 to 5Hz reduces the amplifier's ability to sustain a DC level, which is necessary for the stimulator to reproduce such asymmetry.

Decomposition of the Transient rPERG Components

Low-frequency attenuation is known to cause an appreciable waveform distortion which warns the filtering users of being cautious when choosing a bandpass to process the data waveform. However, two points in Regan's filtering theory attracted our attention: (1) low frequency attenuation has little effect on latency; (2) no matter how severely it effects the waveforms of the long pulse or VEP, there are always an onset and an offset potential shifts which can be signalled. Such potential shifts appear at the time the undistorted waveforms start and terminate, ie, the timing course of each single process within the whole response is not effected during the procedure so that presumably they can mark the implicit times and durations of the response components.

Like the transient VEP, the processes within the transient rPERG are overlapped between each other. According to Fourier's analysis, any wave could be taken as a frequency function along the time. It was predicted that 'distorting' the response waveform artificially without effecting the timing course of each process would make it possible to know the constitutions of a response. Therefore, we used low frequency attenuation to analyse the transient rPERG and observed its effects on the waveform of the transient rPERG. The results presented us such information as shown in Fig 4.4.

The highpass started at 0.5Hz and was increased at a step of 5Hz. It was illustrated that the

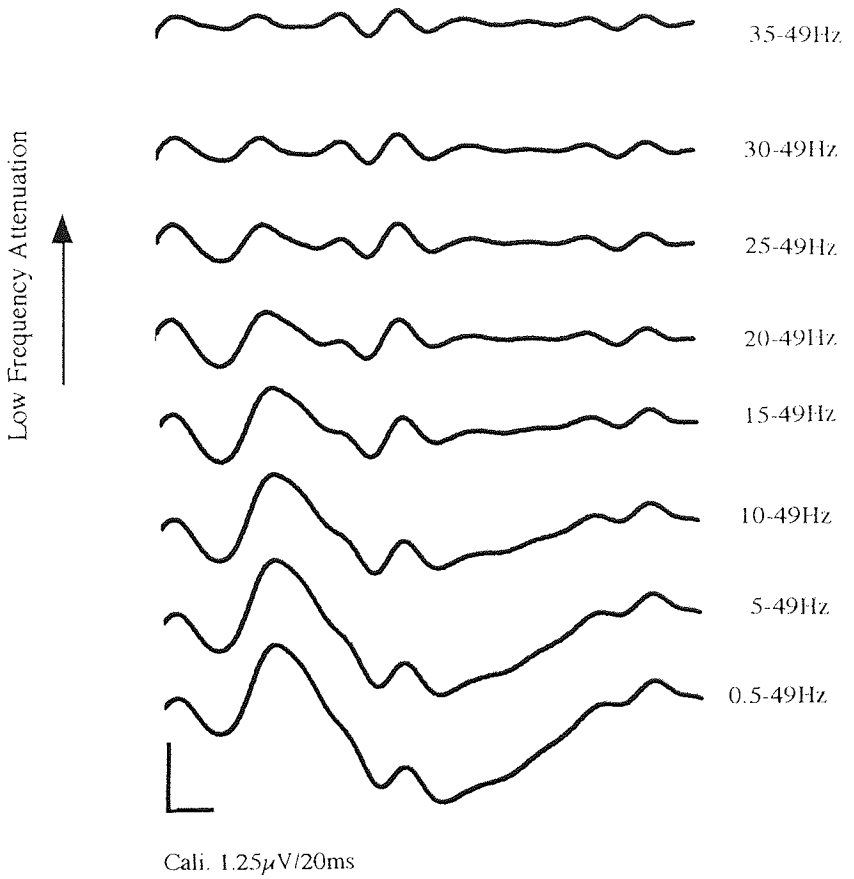


Fig 4.4 Effects of low-frequency attenuation on the transient rPERG recorded in subject ST. The . analysis was based on the record which had been digitally filtered with a bandpass of 0.5-49Hz. The results illustrated that with the increase of highpass, the response amplitudes were reduced and distorted progressively, but the peak latency of each visualised potential was unchanged during the process. The unclear notch in the middle of the negative deflection at bandpass 0.5-49Hz became progressively clear and kept unchanged at 60ms as other peak latencies did. (May, 1995).

response amplitude decreased progressively during the procedures. At the severe low-frequency attenuation, positive or negative deflections were almost unrecordable, while no clear spurious peaks were created, as the highpass did in VEP. It was found that, when the waveforms were changed, the peak latencies were little effected: N_{35} varied between 25ms and 30ms; P50 and N95 were kept at, respectively, 45ms and 85ms.

Interestingly the possible oscillatory notch in the middle of the negative potential obtained at the usual bandpass (0.5-49Hz) became progressively clear at the highpass lower than 30Hz and kept this latency at all the bandpasses (66ms at 0.5-49Hz and 65ms at 35-49Hz)! It was assumed that the peaks P_{50} and N_{95} probably mark the peaks of two major processes in the transient rPERG. These results imply that the filtered waveform after this notch point is probably another process peaked at N95 trough while the left part belonged to the preceding process. Furthermore, the averaged duration of the process peaked at P_{50} was calculated 40ms (25Hz) and it appeared that the filtered process had a timing course lasting about 40ms.

According to Hess and Baker (1984), a transient rPERG consists of two components: a diphasic fast wave with a duration of 100ms and a slow wave, which produces a visualised slope baseline between two responses (fast waves) evoked by 1Hz reversal patterns. Since such a baseline could be also elicited by eye movement, it is difficult to differentiate the sources of the slope baseline as shown in Fig 4.4. At bandpass 15-49Hz, the baseline returned to the 'zero' level, it is assumed that the slow wave mentioned by Hess and Baker has been filtered.

To date there has little been a report about the waveform analysis of the transient rPERG using signal analysis. A theoretical signal analysis technique in analysing the transient VEP waveform was introduced by Regan (1989). It is a multivariate analysis technique called principle component analysis (PCA) which can be directly used for peak or area analysis. The analysis is especially advantageous for dealing with the overlapping waveform. A basic assumption is that the observed evoked potential waveform is the linear sum of the activities of a number of neuronal generators whose currents are conducted to the recording electrode by volume conduction. An averaged waveform is expressed as a series of voltages at many (N) successive points in time. PCA represents this series of voltages as a linear combination of a new set of variable called principle components (PCs), thus,

$$Vij = w_{i1} PC_{1j} + w_{i2} PC_{2j} + \ldots\ldots + w_{im} PC_{mj} \quad (i=1, N; j=1,7)$$

where there are M components; Vij is the voltage at time j in waveform number i; PC_{1j}, PC_{2j},... PC_{mj} are PC 'loadings' representing the contributions of each PC to the voltage at each time point; and w_{i1}, w_{i2}, ...w_{im} are PC 'scores' representing the contributions of each PC to each of the averaged response waveform. The PCs are statistically independent of each other and each successive PC accounts for a maximal proportion of the original variance that remains unrelated with preceding PCs (Donchin and Heffley, 1978). In PCA, one component is considered as a single dimension, although its existence is manifest at many time points on the averaged response waveform. Four or eight dimensions are sufficient to account for 80% of evoked potentials and thus have been used to describe the visual or auditory evoked potentials (Donchin, 1969; John et al., 1964; Suter, 1970; Wood and McCarthy, 1984). It seems that the PCA can be used for the analysis on the transient rPERG.

However, the procedure involves massive mathematical procedures, eg, the N components is typically preferred between 250 to 1000. Furthermore, it should be stressed that the analyses can be met only approximately and a serious drawback is that there is, in practice, no unique linear expansion for a set of waveforms. According to Ruchkin (1986 cited by Regan, 1989), PCA-Varimax is not the only way of dealing with component overlapping. Thus caution should be taken whenever a mathematical method is used in the concrete data and more practical and comprehensive anaysis techniques are needed.

SECTION III VARIATIONS OF THE PERG WAVEFORMS

Introduction

With the present experimental conditions, we noticed that the variability of the transient rPERG could be represented as variations of the response amplitude or/and the response waveform; the waveform variations occurred mainly at the part from the first positive potential peak to the subsequent negative potential trough. Unlike the amplitude variations, the waveform variations could not be simply represented by the averaged coefficients of variation. It was assumed that some waveform analysis would tackle the problem.

According to the PCA theory, every single response component is independent of others. The response potential can be described as Vij, the voltage at time j in waveform number i, so that the timing course relationships between the successive processes or components are decisive in producing the waveform at some time points. Supposing that the transient rPERG contains such processes (ie, PC_{1j}, PC_{2j},...PC_{Mj}), the negative potential waveform or shape depends up to how the process with a peak at N95 overlaps with the preceding process peaked at P_{50}. In other words, one can describe the shape of the negative potential as summed contributions of each individual process at certain timing process. Based on this assumption, in this study, we (1) studied the waveform variations in a small population; (2) estimated and compared the effects of the decomposition using low frequency attenuation for each type of waveform; and (3) analysed the timing course relationships between different processes and thus the possible constitution of different type response waveform. The reasons producing the waveform variations of the transient rPERG were discussed.

Materials and Methods

Subjects were healthy people with corrected normal vision (6/6 and over). All the data were collected from 30 eyes, 15 of each in one of the two groups according to age: one aged at 30-35 years and the other at 60-70 years. The subjects were instructed to be in normally illuminated environment for a few minutes before experiments and requested to fixate a central screen dot during the recording.

The recordings were done on the Nicolet Pathfinder II system. The recording electrodes were DTL fibres. The recording device is illustrated in Fig 4.5. The bandpass 0.5-100Hz was chosen before experiment. The amplifier sensitivity was set at $100\mu V \pm 50\mu V$. The screen timebase was controlled at 200ms and samplings was averaged with 150 accepted responses. The session was repeated once with satisfying. The signals were amplified in a gain of 10^6 - 10^2, according to the s/n ratio. When the observations were finished, the data were transferred to a magnetic media for after-processing. After each session, the data were processed in two steps (1) digital filtering with a bandpass of 0.5-49Hz was done as a routine for all the data to remove the noise; and then (2) every typical waveform (in this study, we analysed three types of divisions) was processed by the low frequency attenuation: the waveforms were filtered with increasing highpass (in a step of 5Hz until 40Hz), thus producing some distorted waveforms with some potential 'shifts', which were proposed to mark the peak latencies in the unprocessed data.

Fig 4.5 Illustration of the diagram recording the pattern ERG. The DTL fibres (Dawson, Trick and Litzkow, 1979) are placed in the lower fornices of the eye as recording electrodes and fixated by the DTL fibre holder (Thompson and Drasdo, 1987). Ipsilateral tempora (Hess and Baker, 1984) are chosen for placing the reference electrodes for a binocular recording (Vision Sciences Department, Aston University).

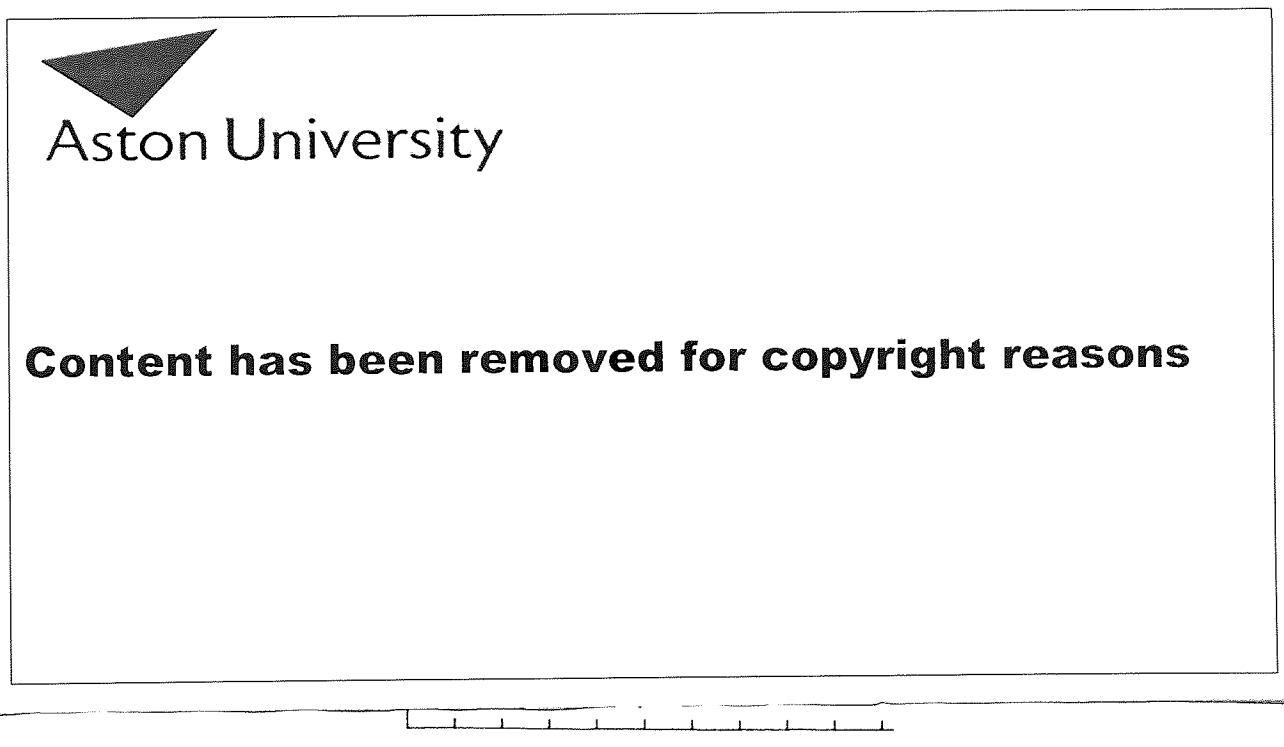


Fig 4.6 Transient rPERG records. Types I, II, and III of the rPERG waveform are displayed in graphs *a, b, c*. The lower graph in each type of waveform was recorded with a bandpass of 0.5-100Hz. The upper graphs corresponding to each type of wave was digitally filtered after the process. Note that the variations of the response waveform are reflected mainly in the negative potentials.

The stimuli were black and white checkerboards, of 56 min of arc and reversed at a rate of 1Hz by an optical projection stimulator and the Venus computer screen stimulator. The visual field subtended an area of 14° x 14°. The mean screen luminance was set at 60 cd/m^2. The contrast was 80% and examined for each checksize (for calibration). The responses were measured according to peak analysis.

Results

Waveforms of the transient rPERG

In general, the records we obtained were divided into three types, according to the waveform variations of the negative potentials, as shown in Fig 4.6. The first type of record showed no difference from the records we saw in most of the transient rPERG reports, being typical of negative-positive-negative pattern. In the second type record, there was a possible step change in the middle of the negative potential, like as a junction of two potential deflections, similarly to the record in Fig 4.4. Such a junction (we termed it as 'notch') was more clear after digital filtering (the upper graph of the record pair). The third type record presented us an unusual transient rPERG waveform: there was a clear notch with an afterward step in the middle of the negative potential. It was noted that most of the transient rPERG records (80%), recorded in both age groups, had waveform variations in the negative potentials (ie, type II and III).

We used the term 'N' to describe the appearance of such a notch in graphs. It should be stressed that the term 'N' does not imply that it could be taken as an equivalent to N_{35}, P_{50} and N_{95}, since the biological reasons for producing such waveform variations are yet unclear. Secondly, according to van Rotterdam (1970), a wave or a deflection, termed as 'component' in the principle component analysis (PCA), in a response does not necessarily have a physiological significance although it can be subtracted by the PCA. Thus a 'component' used in waveform analysis is slightly different from the response component, since 'N' used to describe visualised notch, or a 'component', could be, or be not, a response component and might have, or have not, biological significance.

Indeed, the biological presence of the notch obtained in type II and III records was very questionable, not only because it has never beeb reported, but also as it is easily taken as some fluctuation resulting from artifacts. In order to exclude the possibility of an artificial

phenomenon, we did two things: (1) to record the response with central and eccentric fixation to ensure that it follows the major response; (2) to record the response with different stimulators on the same subject for excluding the possible effect of the electromagnetic interference from the computer stimulator screen.

The results in Fig 4.7 demonstrated that when eccentric fixation (left 10°) was used, the response was reduced as expected (Hess and Baker, 1984a); the notch was noted in the middle of the negative potential in both central and eccentric fixation status. The stimulus protocols used in computer screen stimulator (CSS) and optical projection stimulator (OPS) were compared. It was found the notch was recordable with both stimulators. The Venus computer stimulator (CSS) was known to have a high frequency interference as shown in Fig 4.1b,d. The use of the Venus stimulator influenced the amplitude of the response (probably because the Venus system could produce a lower contrast, 60%, while the OPS produced a contrast of 80% in this study), but it apparently did not effect the appearance of the notch. So that the effect of the high frequency interference produced by CSS was thus excluded.

Decomposition of the Response Waveform Components

Furthermore, we chose three typical responses, represented respectively, as type I, II and III records and then processed them using low frequency attenuation (Fig 4.8). Assuming that each single process in the response could be marked by some potential shifts (on- and off-sets) after such a process, the timing course relationships among the processes of each record was analysed and comparison was done between these three records. The changes in type II record (Fig 4.8b) was quite similar to the case we described in Fig 4.4. The possible notch became clear at 10Hz lowpass, with a timing relation to the stimulus of 62ms. This relation was kept unchanged up to bandpass 40-49Hz. The potential shifts representing the latencies of N_{35}, P_{50} and N_{95} peaks were constant during the procedures, although the amplitudes were progressively reduced. The negative potential of type I record did not show prominent change , when its amplitude was progressively reduced, until highpass came to 20Hz (Fig 4.8a). At this bandpass (20-49Hz), and onwards, the timing relation of the response with the stimulation was kept at 60ms until the narrowest band was used. Similarly, the potential shifts making the peak latencies of N_{35}, P_{50} and N_{95} in type III record were unchanged throughout the procedures (Fig 4.8c).

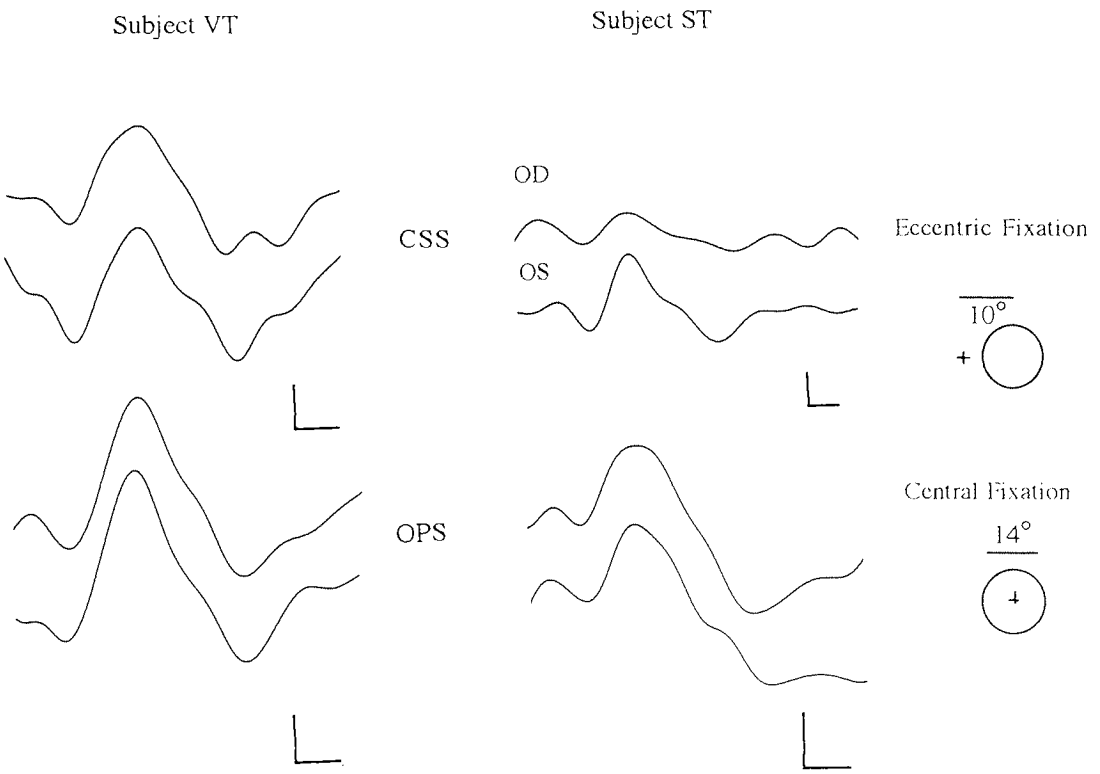


Fig 4.7 Comparison of the transient rPERGs recorded by (1) differenct stimulators and (2) with central and eccentric fixation. Note: CSS--computer screen stimulator; OPS--optical projection stimulator. Cali: 0.93μV/20ms.

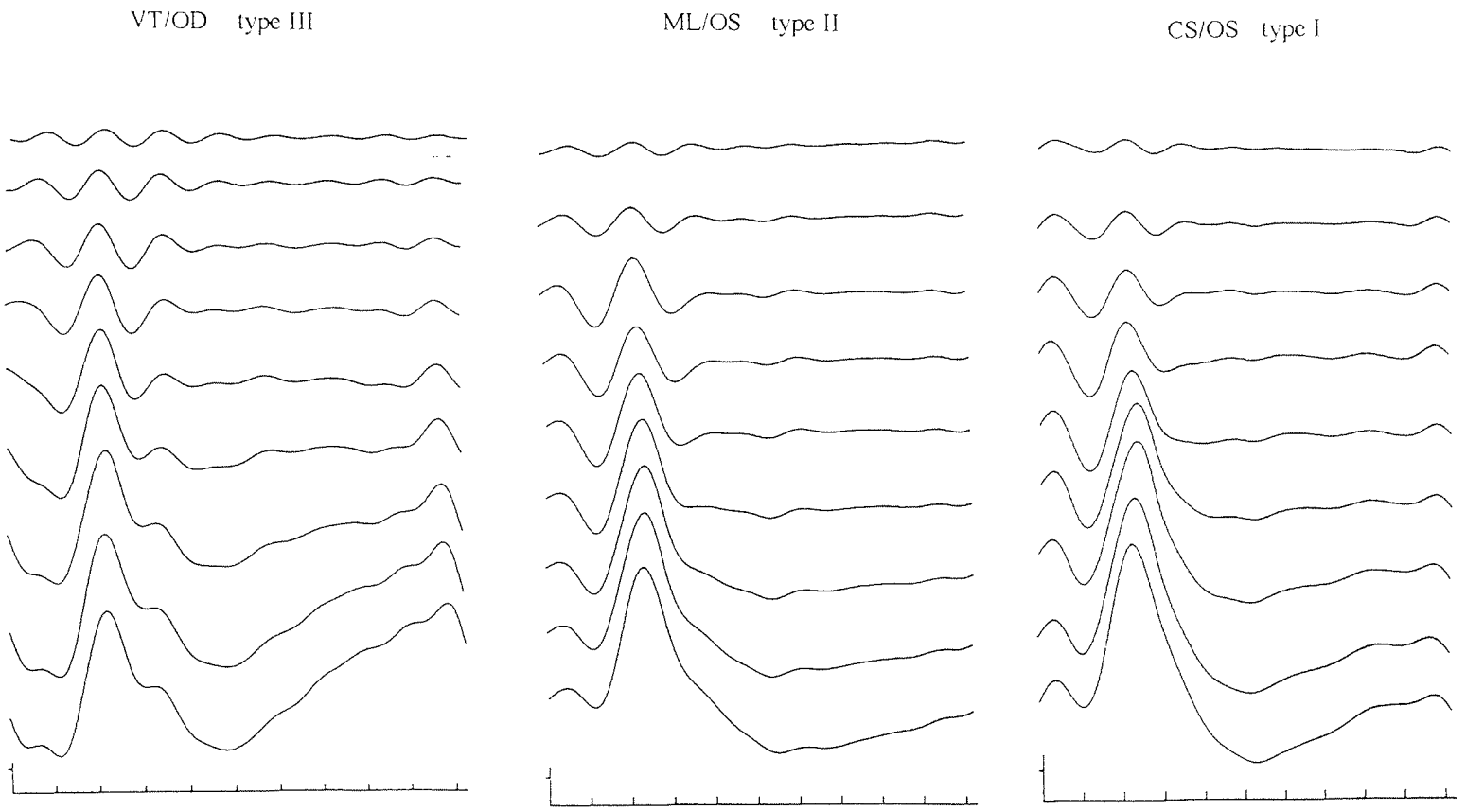


Fig 4.8 The waveform analyses of three types of the transient rPERG records using low frequency attenutation shown in Fig 4.4. (Cal = 0.62μV/20ms)

Discussion

Similar transient rPERG waveforms have been found in some reports (Dawson et al., 1982; Papst et al., 1984b; Holder, 1987; Bartel et al., 1991) (Fig 4.9). The recording conditions and stimulus parameter protocols used in these reports and ours were compared. It was found that the stimulus parameter protocols and recording conditions were highly different. among the laboratories, thus it is difficult to correlate the waveform variations directly to these factors in this study.

Since the transient rPERG consists of, multiple processes or components (supposed to be of two processes and more), the waveform variations reflect partially its constitution. The waveforms in type II and III records naturally lead us to think of a possibility that there is a 'response component', representing some physiological activities in them; a small deflection of one polarity can ride on the top of a large deflection of opposite polarity, such that the indication of the small deflection's presence may be only a shoulder on the rising or falling slope of some large deflection (Regan, 1989). Our analyses have shown a population presence of such a notch, or waveform variations, in the transient rPERG. Efforts have been made to exclude the possible influence of non-biological interference. The result analyses convinced us that the waveform variations reflected by the notch in the middle of the negative potential of the transient rPERG occur probably for some biological reasons. Similar result has been reported by Regan (1982) in the transient on/offset VEP. In the falling slope of the appearance response, two subdeflections similar to the type III record in our observation can be clearly seen and kept the constant latency when the waveform was changed with contrast variation.

However, interpretation is difficult. In practice, the repeatability of the waveform was as poor as the response amplitude. The conventional averaging process could probably cover the variations in both amplitude and waveform, which may occur from trial to trial. Thus the reasons producing these variations are probably of multiple sources. It is assumed that these two variations were correlated with each other. It is known that the transient response, either VEP or ERG, can be defined as a series of voltage functions versus time and each component itself is an independent function of time. Thus we prefer to believe that such waveform variations are, at least partially, due to the relationships among these multiple single process (voltage) functions versus time. Based on such an assumption, we hypothesised that the transient rPERG waveform is the temporal and spatial summation of different response

a b

Fig 4.9 Transient rPERG records from other reports. a: report by Dawson, et al. (1982); b: report by Papst et al (1984b); c: report by Holder (1987); d: report by Bartel et al. (1991).

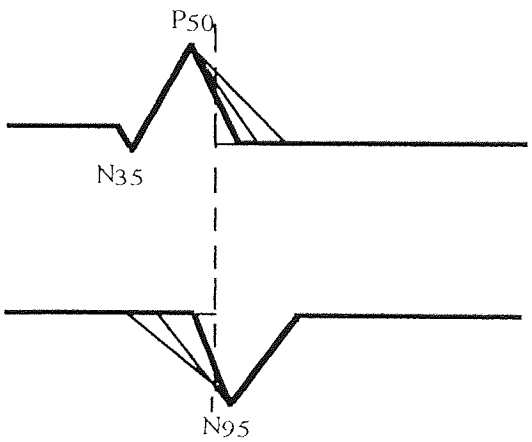


Fig 4.10 Hypothesis of the transient rPERG constitution. Dot lines indicate the assumed time when two components summed spatially with zero potential, ie, at baseline. The slopes of the falling potential in the first wave and the downward potential in the second wave are assumed to be varied (thin lines) and thus probably related to the visualised waveforms of the transient rPERG.

components as shown in Fig 4.10. The actual extent of overlapping probably depends upon the the implicit times and the durations of the response processes or components, therefore resulting in the visible waveforms as described. The present studies have visualised the possible relationships between the processes or components in the response. Similar consideration has been mentioned by some reports: Hull and Drasdo (1990) noted that identifying the starting point of the negative potential could be made only by the cases of advanced pathology of the inner retinal component; similar results were found in a report by Papst et al. (1984). Hull and Drasdo interpreted that '*the negative component must start fairly close to the peak of the positive component to produce the typical sharp decline*'. But as any signal analysis, the present analysis technique has its limit and certainly some drawbacks. More comprehensive analyses are expected by combining different analysis techniques.

Summary

In the present studies, attention was paid on the waveform variations of the transient pattern ERG. The efforts were made in order to find the causes of the waveform variations recorded in the present experimental conditions. The non-biological and biological noise was differentiated to estimate the reliability of the variation, which is divided into three types. By the low frequency attenuation analysis, the transient rPERGs were decomposed into two subsequent major processes, one being peaked at P50 and the other at N95. Therefore, the waveform variations we obtained were taken as the spatial and temporal summation of the two processes. The biological cause for these waveforms is still unclear.

CHAPTER 5.

EFFECTS OF VISUAL ADAPTATION, CONTRAST AND LUMINANCE ON THE TRANSIENT RPERG

Introduction

It is known that human's ability to perceive the details of a visual scene is determined by the relative size and contrast of the detail present. This is particularly clear when the scene is an extended pattern whose luminance is modulated at a fixed mean level. The mean-to-peak amplitude of a pattern divided by the mean (Regan, 1990), namely, the Rayleigh-Michelson contrast, is essential for a pattern to evoke a response. When patterns with such a contrast are repeated in a way of either appearance-disappearance or counterphase reversal, the response is produced by the difference or the change of the luminance level between the neighbouring patterns. Such that contrast and mean screen luminance are correlates of each other and are two important elements of a pattern in studying PERG.

An electrical response with a spatial selectivity, or spatial frequency tuning, can be taken as a typical pattern-specific response (eg, Padoms, et al., 1973; Spekreijse et al., 1973b; Korth, 1981). Since the onset response is tuned to certain spatial frequencies (pattern sizes) and the offset response has not such a spatial selectivity (Korth, 1983; Korth and Rix, 1984; Korth et al., 1985), the on/offset pattern stimulation has its unique advantage in separating a contrast related response from a luminance related response of a PERG by some reports (Korth, 1983; Drasdo et al., 1987a,b); and some experiments have demonstrated that contrast and luminance (light intensity) effected the pattern and the luminance related responses of the on/offset PERG differently (Korth and Rix, 1984; Thompson and Drasdo, 1989). The spatial selectivity has also been found in a response elicited by reversal patterns, namely rPERG (Korth, 1981; Fioretini et al., 1981; Vaegan et al., 1982; Odom et al., 1982/83; Hess and Baker, 1984). Some experiments showed that such a property was typically reflected in the negative potential of the rPERG, which, therefore, was representative of a pattern related component of the rPERG; the positive response was deduced to be a luminance related response due to its absence of the spatial selectivity (Schurrman and Berninger, 1984; Berninger and Schurrman, 1985; Tomimastu et al., 1988/89).

Some reports showed that contrast of a pattern effected linearly the amplitudes of both reversal PERG and on/offset PERG (Arden and Vaegan, 1983; Hess and Baker, 1984; Korth et al., 1985---reversal pattern; Korth and Rix, 1984; Thompson and Drasdo, 1989---on/offset pattern); and effected the onset response in a different way from it did on the onset response when the luminance was considered. The mean luminance was found effected the onset response's spatial selectivity, according to the contrast of the pattern and effected the offset response amplitude simply in a monotonic linear fashion (Korth, 1984). This result suggested that the luminance has different effects on the pattern specific and luminance-related responses.

In a report by Korth and Armington (1976), luminance level was demonstrated to change the content of the transient rPERG and the authors interpreted as resulted from the different sensitivities of its photopic and scotopic components to luminance. A similar result was reported by Schurrman and Berninger (1984). This difference suggested that the mechanisms of a pattern's contrast and luminance effecting the reversal PERG was not entirely the same as in the case of the on/offset PERG. One of the important reasons was probably that the division between the pattern specific and pattern non-specific (luminance-related) responses was unclear in the rPERG, especially in the case of the transient analysis, since the positive and the negative potentials lap over each other. In this study, efforts were made to differentiate the effects of contrast and luminance on the different component of the transient reversal PERG. The relevant mechanisms were discussed.

Methods

The PERGs were obtained by pattern stimulation with changing luminance between neighbouring checkerboards, ie, reversal pattern contrast. The contrast was described by the Rayleigh-Michelson contrast (Rayleigh 1889; Michelson, 1927), representing the magnitude of luminance variation in the stimulus relative to the average (mean luminance), and expressed by the equation

$$Cm = (Lmax-Lmin) / (Lmax+Lmin) = (Lmax-Lmin) / 2Lmean,$$

where *Lmax* is the luminance, or light intensity, of the bright check and *Lmin* represents that of the black check. The mean luminance is equal to the summation of the luminance measures of both black and white checks divided by 2.

The mean luminance at each contrast level was measured under light and dark environments and plotted as the mean luminance functions of contrast (Fig 5.1). The light environment was the usual room lighting. Each measure was the average of three trials. It could be seen that mean luminance was changed across the contrast range in the two surrounds, which was prominent at high contrast levels; and the mean luminance at each contrast level was lower in the dark environment than the one obtained under the room light.

The recording electrodes used in both experiments were the DTL fibres and binocular records were made in all the experiments. The bandpass 0.5-100Hz was used during the recording and the digitally filtered results were displayed throughout the present studies.

Results

Fig 5.2 gives the examples of the PERG records obtained at 2Hz of reversal rate (ie, the transient rPERG), and shows the methods measuring the response amplitudes and latencies in the present studies. In the preceding chapter, we described three types of the transient rPERG records obtained with our experimental conditions. Type II records describe those responses having a unclear notch in the middle of the negative potential and type III records describe the responses showing a clear notch and an afterward step in the negative potential. It was noted that there was a fixed timing relation between this notch and stimulation onset. Such that the appearance of this notch was assummed to be normal waveform variations and taken as a part of the response. We termed it 'N' and its latency and amplitude were measured as the other peaks N_{35}, P_{50} and N_{95}. The measurement of the deflection between 'N' and N_{95} was a little difficult since the waveforms in this part was variable among subjects, especially in type III records. Its amplitude relation with contrast (or luminance) was induced by subtracting the 'N' amplitude from the negative potential, ie, N_{95}. This measuring method was used in all the experiments and only those types II and III were used in the present studies.

Experiment I

In this experiment, the rPERGs were recorded under light and dark environments. The eyes were dark adapted for 20 minutes in order to obtain dark-adapted PERGs. After After the observation, the same procedures were repeated under light adaptation. Black and white checkerboards were used as stimuli, with a visual angle of 56 min of arc (visual angle, ϕ, was expressed by $tan(\phi/2) = w/2d$, where the w is the check width and d is the viewing distance).

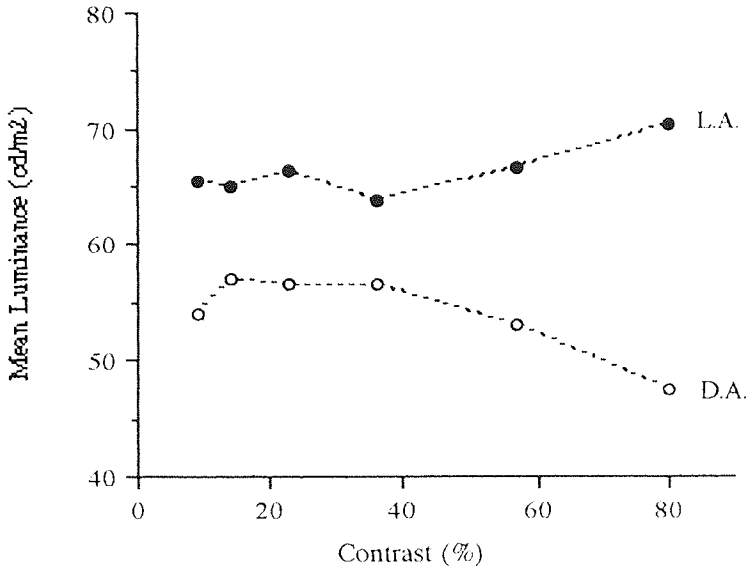


Fig 5.1 Mean luminance changes under different contrast levels. The upper curve was obtained under the room light; the lower one was obtained under darkness.

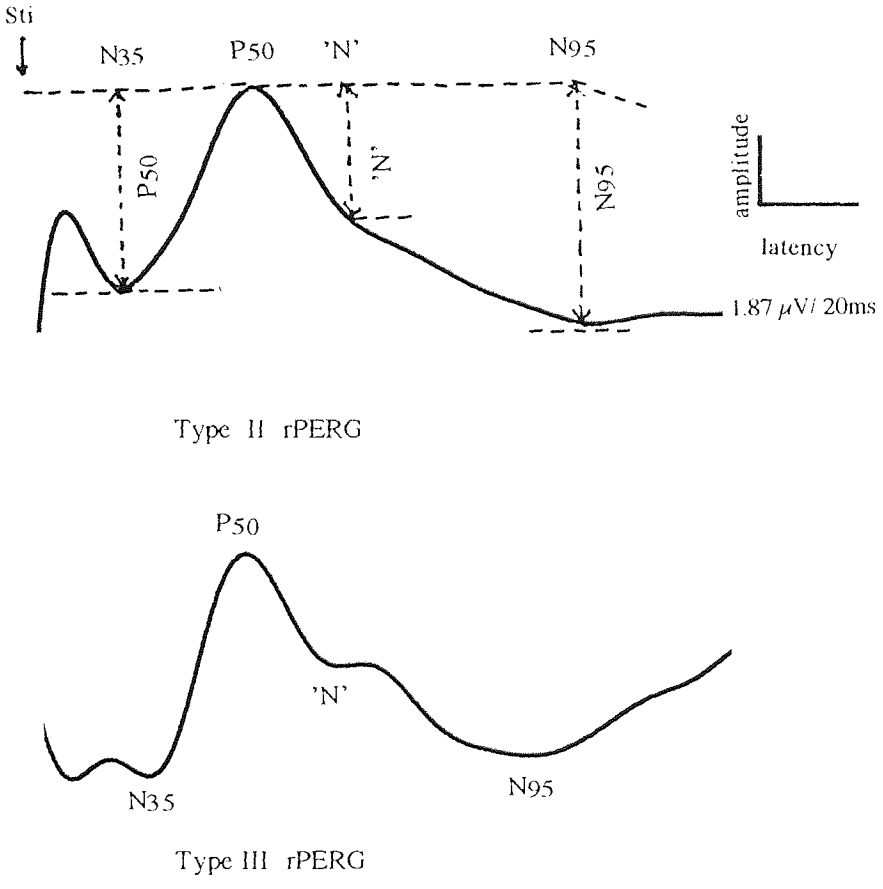


Fig 5.2 The diagrams illustrating the waveforms of the transient rPERG and their amplitude and latency measurement according to Regan's definition for the peak analysis. (Regan, 1989)

The stimuli were presented by the Venus computer screen. The screen contrast between white and black checks was set at 80%. At this contrast level, the mean luminance was 47.5 cd/m^2 under the darkness and 70.3 cd/m^2 under the room light.

The latencies of all the rPERG potentials showed a slight delay under dark adaptation (Fig 5.3, top). There was a clear increase of the 'N' amplitude (measured from the peak P_{50} to the visible notch, ie, 'N', in the middle of the negative potential), accompanied by a decrease of the N_{95} amplitude (Fig 5.3, bottom), which was measured from the peak P_{50} to the trough N_{95}. The P50 amplitude showed no changes under these two light conditions. The experiment displayed the result that slight luminance level change due to surround effected mainly the amplitude of N95, especially the later part of this potential.

Experiment II

Contrast was varied in six levels in this experiment, 90%, 57%, 36%, 23%, 14% and 9% and described in logarithmic units. Luminance and contrast were examined using a LS-110 Minolta Luminance Meter. Except that the highest contrast level was 80% rather than 90% as designed, all the contrast measures were consistent with the values the Venus programmed. The screen mean luminance was varied between 47-57 cd/m^2 across the contrast variation. The reversal rate was controlled at 1Hz by the Venus computer screen stimulator. The checks were viewed at a distance of 74cm with a visual angle of 56 min of arc, and a subtended visual field of 14° x 14°. The subjects were aged 30-35 years and effects of contrast variation were observed on 12 healthy eyes with corrected vision under dark adaptation.

Latency

When contrast was varied, the latencies of N_{35} and N_{95} were not effected. The latencies of P_{50} and 'N' were prolonged across the contrast variation range and their prolongation showed statistical significance ($p<0.05$). The lower contrast pattern stimulation seemed to delay the evokation of the first process peaking at P50 of the rPERG, but did not effect the subsequent process (Fig 5.4, left).

Amplitude

The averaged amplitudes of three PERG potentials were plotted as functions of contrast and

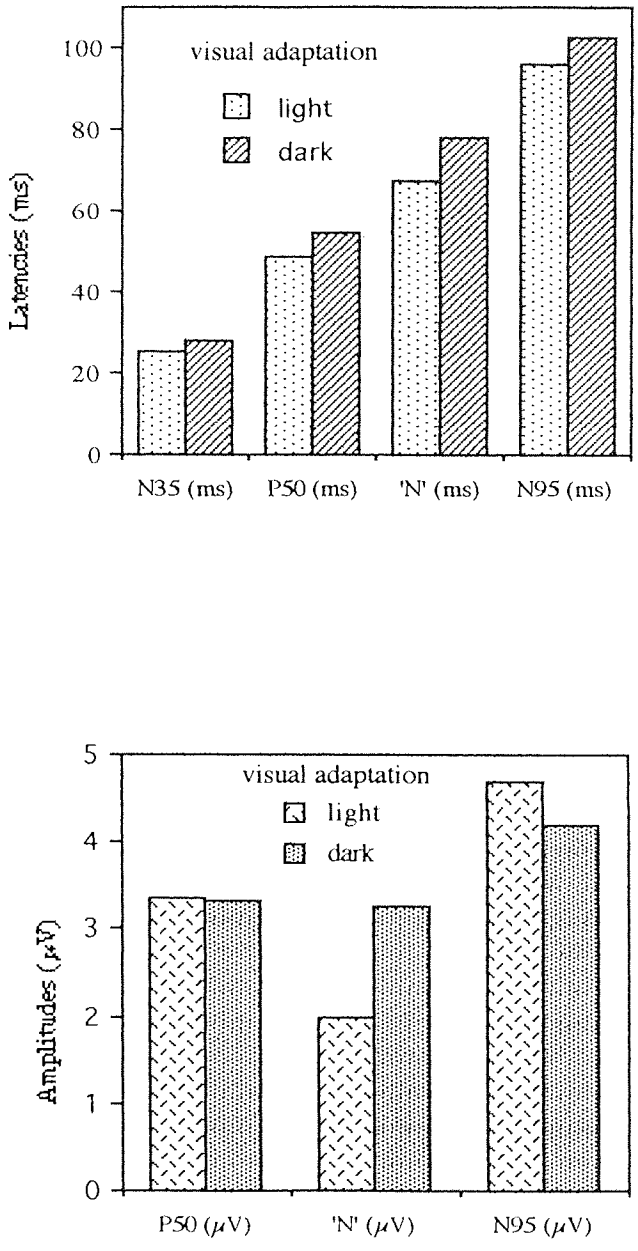


Fig 5.3 Comparison of the latencies (upper graph) and amplitudes (lower graph) of the transient rPERG recorded under light (light histograms) and dark adaptation (dark histograms).

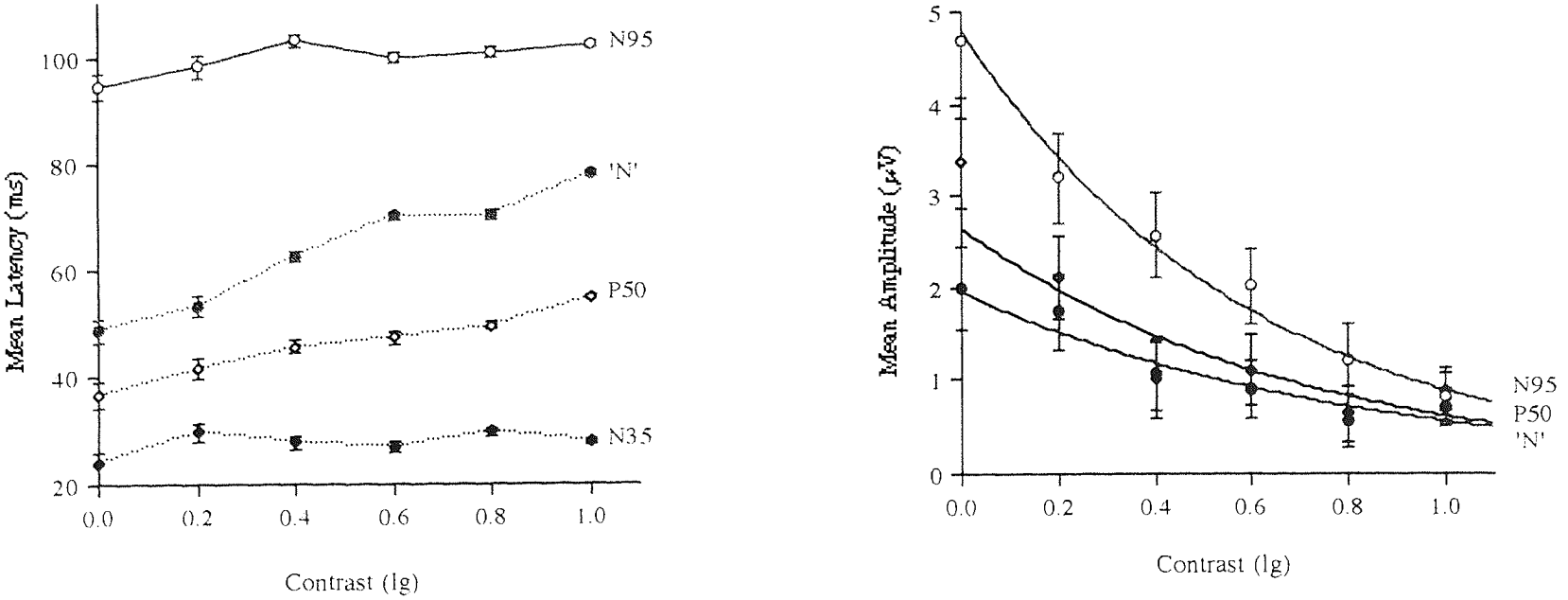


Fig 5.4 The group averaged latency (left) and amplitude (right) changes of the transient rPERG across the contrast range 80% (0.0) -9% (1.0) (n=12).

order to compare the data reported by the other reports (eg, Korth and Rix, 1984). When contrast was varied, amplitude changes of P_{50}, 'N' and N_{95} showed some similarity: the amplitudes were increased linearly across the contrast range; the higher the contrast was, the larger the amplitude was obtained. The linear regression equations for these changes were:

Y (P_{50}) = 0.19509 + 3.6071e-2x, R^2= 0.911, P<0.05
Y ('N') = 0.40284 + 2.0625e -2x, R^2= 0.961, P<0.05
Y (N_{95}) = 0.56397 +5.0713e-2x, R^2= 0.977, P<0.01

When the these results were compared with those obtained by on/offset stimulation, their properties of N_{95} were found to be highly close to that of the onset response, while those of the P_{50} and 'N' to the properties of offset response of the on/offset PERG: the onset response showed a higher sensitivity to contrast variation than the offset response; the N_{95} amplitude showed a higher sensitivity to contrast variation than P_{50} as well as 'N'; the effects in both cases were prominent at high contrast levels.

The records obtained from an individual and a group were displayed in Fig 5.5. With the decrease of the contrast, the subdeflections devided by the notch came to clear while the amplitudes were reduced. At the lowest contrast level, the peaks of P50 and N95 were recognisable but the whole response was devided into two parts.

Experiment III

In order to examine the possible simultaneous effect of mean luminance produced by contrast variation on the rPERG, we used the neutral digital filters (negative films, which reduce the incident energy through absorption) to control the luminance levels and observed the effect of luminance changes on the response. The neutral density filters are calibrated in units of density according to the relation $D = \log_{10}(1/T)$, where T is the fraction of the incident light transmitted through the filter and D is its density value (Fig 5.6, left) (Armington, 1974).

Checks were presented by an optical projection stimulator. The pattern's parameters were the same as those used in experiment II. The results were obtained under usual room lighting on four subjects who were the subjects in the second experiment. Mean luminance level was varied at six levels, being varied between 80cd/m^2 and 826cd/m^2. The records were started from the

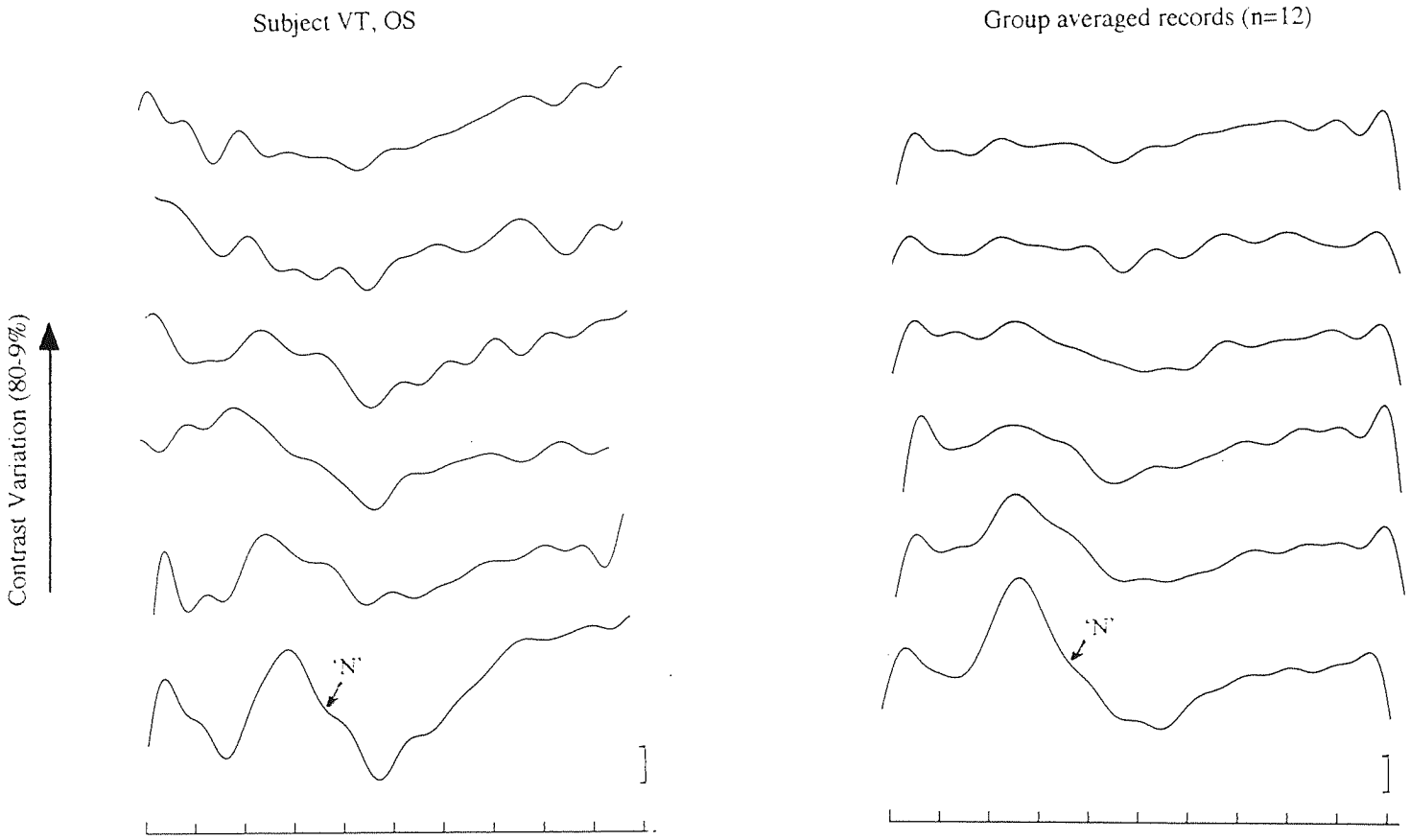


Fig 5.5 Individual (left graph) and group averaged (right) records of the transient rPERG to contrast variation (Cali.= 2 μV/20ms).

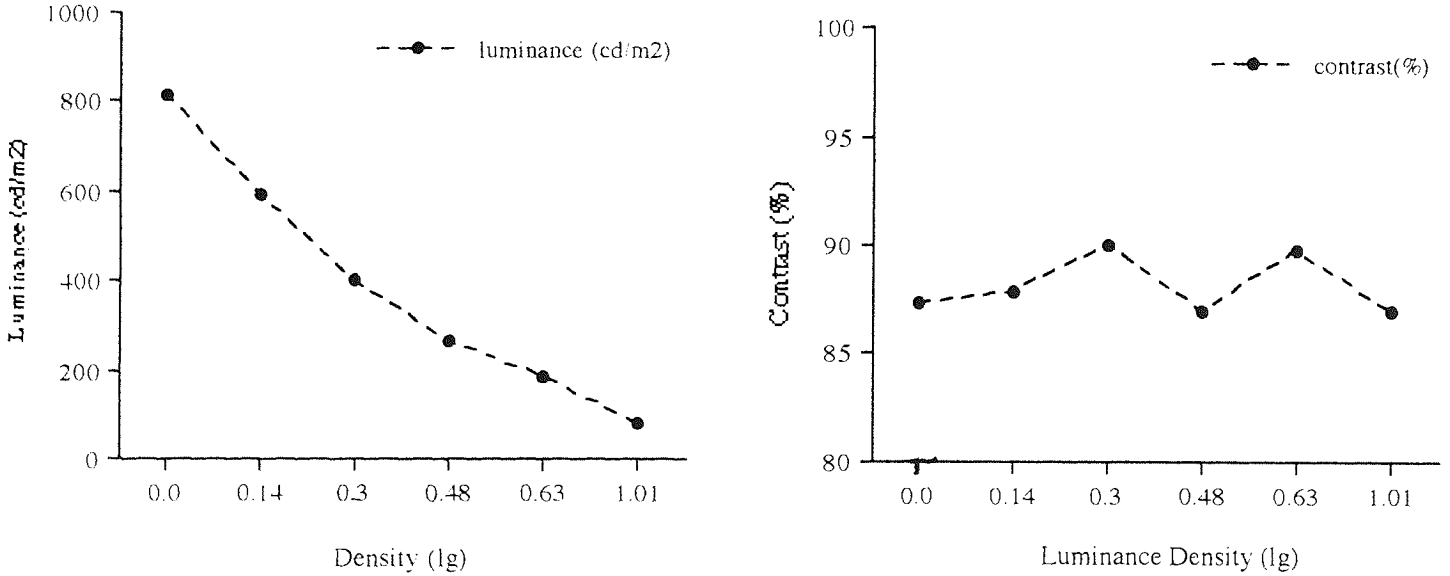


Fig 5.6 Diagrams showing the luminance variation and subsequent contrast changes expressed in logarithmic units. Luminance was varied between 80-826 cd/m^2 (top graph). The contrast changes across the luminance range was less than 5 % (bottom graph).

lowest luminance level, 80 cd/m^2 to minimize the interactions between successive stimulation presentations. The contrast changes across the luminance range was examined and found to vary between 85-90% so that its effect could be neglected (Fig 5.6, bottom). The response changes evoked by changes in mean luminance level were thus taken as the results entirely from the luminance effects their own.

Amplitude

The amplitude changes produced by luminance variation were quite consistent with those obtained by contrast variation (Fig 5.7 right): the lower the luminance level was, the smaller amplitudes were obtained. The effects of luminance level on the response amplitudes indicated that the effect of contrast variation on the response amplitude shown in Fig 5.6 might be mixed with the effect of luminance change, but it was comparatively weak and negligible, since the luminance drop in this case was only 10cd/m^2. And mean luminance had a similar effects as contrast on the rPERG when it was varied within a large range.

Latency

The influence of the luminance on the rPERG latencies was nearly negligible (Fig 5.7, left graph). Across the luminance range 80-826 cd/m^2, there was a slight latency delay (about 5ms) for all the components with no statistical msignificance ($p>0.01$). Thus it appeared that the latencies of PERG components were comparatively insensitive to low luminance. It was deduced that the delay of P_{50} and 'N'latency by lower contrast wa produced by contrast variation its own rather than by 'contamination' from luminance changes.

Experiment IV

Contrast gain is used to describe the extent of the contrast sensitivity of a response to a pattern (Shapley and Enroth-Cugell, 1984). Contrast gains in this experiment were obtained by the following procedures: (1) the first step was to calculate the amplitude increase percentage by subtracting the lowest averaged amplitude R_0 (at contrast level 9%) from the averaged amplitude at a certain contrast level (Rx) divided by the lowest amplitude (R_0),ie,

$$R = (Rx - Ro) / Ro$$

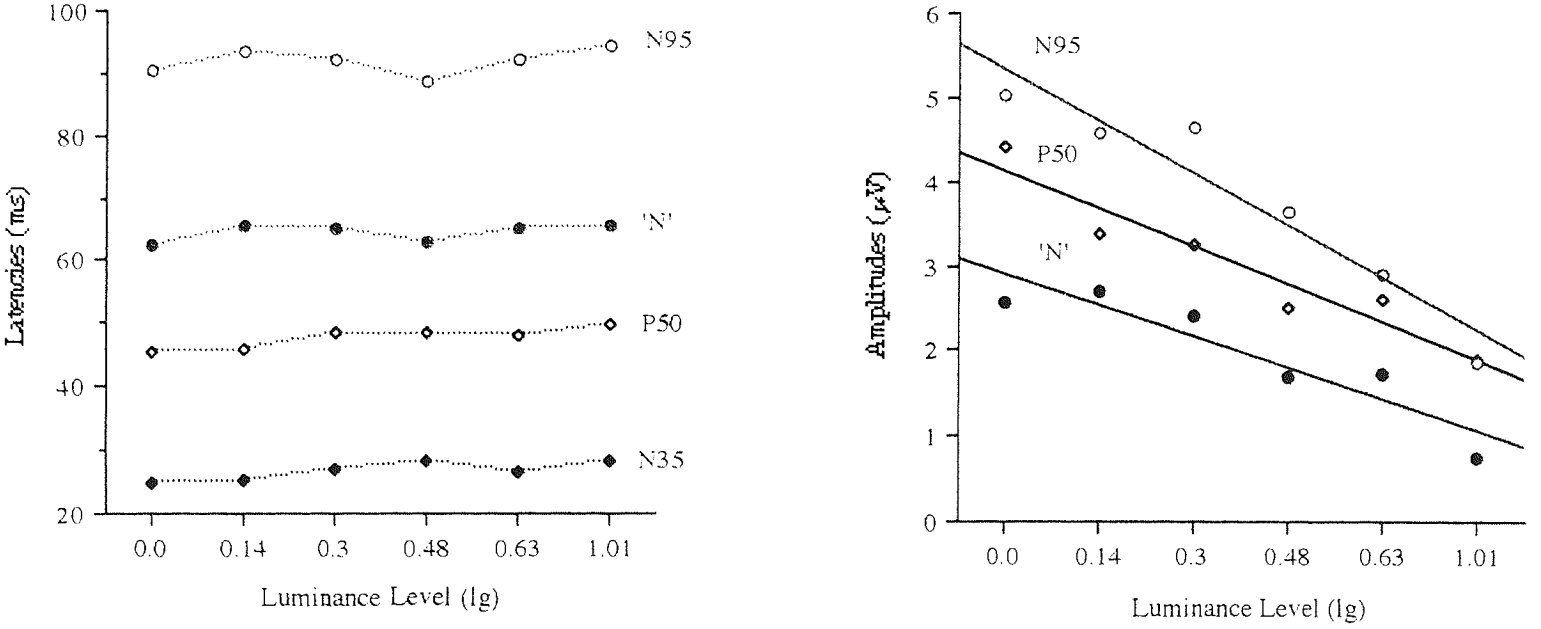


Fig 5.7 Latency (left) and amplitude (right) changes across the luminance range 80-826cd/m^2. The data were recorded under light adaptation from 4 subjects (n=8), who were the subjects for the records shown in Fig 5.4.

Such a calculation excluded the difference between the absolute averaged amplitudes but showed the extent of the amplitude change for all the components at each corresponding contrast level; and thus the comparison could be made on a uniform background.

(2) the second step was to use the Michaelis-Menton equation provided by Kaplan and Shapley (1986) for obtaining the contrast gain curve of each component. The equation has been used to describe the contrast gain of a physiological response such as the S-potentials in the lateral geniculate nuclear in the macaque monkey (Kaplan and Shapley, 1984), and can be expressed as the following

$$R(c) = Rm \cdot [c/(c+b)],$$

where Rm is the maximum response, c is contrast and b is the contrast which elicits half of the maximum increase percentage of the response amplitude, obtained in step (1).

The result analyses were displayed in Fig 5.8. The contrast gains of P_{50} and 'N' were nearly identical, while the N_{95} showed a higher contrast gain. The difference of contrast gains between N_{95} and P_{50} as well as 'N' was evident at high contrast levels (maximally 1.8 times higher for N_{95} than those of P_{50} and 'N'). Secondly, the gain curve of N_{95} showed a steep slope at low contrast level, implying a high contrast sensitivity of the N_{95} across a lager contrast range.

Discussion

PERG Under Dark Adaptation

The earliest suggestion for recording an ERG by intense flashes of light against a relatively weak surround light was by Granit (1933) for obtaining a large response. However in recording PERG, a large surround can not only result in a stray light effect but also produce a loss of contrast modulation (van Denberg et al., 1988). Brindley and Westheimer (1965) advocated 10% of mean luminance for the surround used in recording ERG, since at this condition the stray light could be well suppressed. Arden and Vaegan (1983) suggested 10 times of the criterion advocated by Brindley and Westheimer (1965), ie, a surround equal to the mean luminance. It is known that with normal pupil size, the scattered light can be neglected (van Meeteren, 1974). Furthermore in a report by Baker and Hess (1984), effects of the scattered

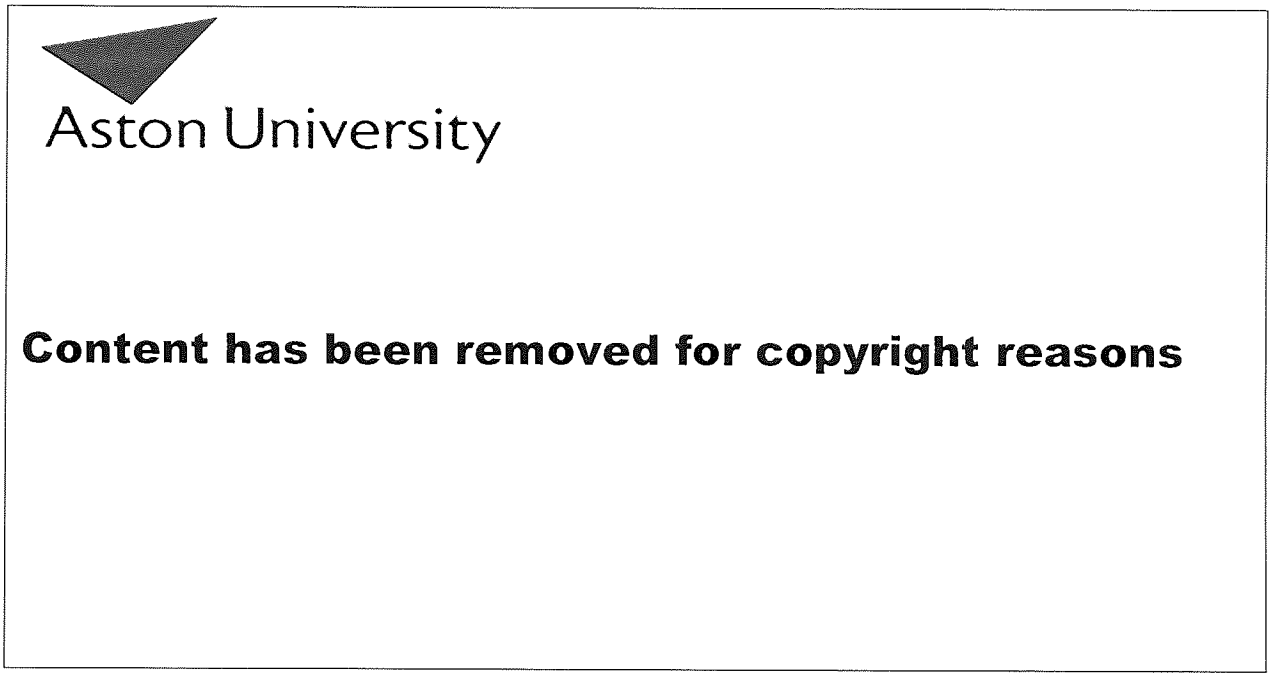


Fig 5.8 Comparison of contrast gains of the P50, 'N' and N95 amplitudes using the Michaelis-Menton equation (Kaplan and Shapley, 1986). Note that the contrast gain curves of P50 and 'N' were nearly identical and N95 showed a high sensitivity to low contrast and a large contrast gain at high contrast level.

light were much greater for a flash ERG than for a PERG, prominently reflected in the fundamental harmonic response. The authors concluded that the second harmonic response to contrast reversal (as well as flashes) was not prominently sensitive to the surround luminance. Thus the scattered light effect on PERG seems to be negligible. Yet in a report by van Denberg et al (1988), a matched surround (200cd/m^2) could produce a 16% contrast modulation loss, which could reduce the effective retinal illumination. It appeared that an appropriate surround still is a consideration when a PERG is recorded.

Since the N_{95} amplitude is representative of the spatial selectivity due to the center-surround organisation, the N_{95} amplitude reduction was assumed to result from the imbalance of the central-surround antagonism at darkness (Barlow et al., 1957; Enroth-Cugell and Lennie, 1975; Kaplan et al., 1979).

It is known that under dark adaptation (before the cone-rod break) both fast cone response and slow rod response can be recorded, thus mixed scotopic-photopic activity of the PERG was assumed to be obtainable and the scotopic component be well developed in the darkness (Arden and Tansley, 1955; Brown, 1968). P50 of the transient rPERG has been demonstrated to be typical of both photopic and scotopic properties while the later negative potential (rather than the whole negative potential) was of scotopic properties (Korth and Armington, 1976). The reduced N95 amplitude in dark adaptation in our observation indicated that the scotopic component did not developed well under a mean luminance of 47.5 cd/m^2 as it did under 70.5 cd/m^2 and was more sensitively effected by the dark surround. The results suggested a complexity of the N95 potential of the transient rPERG than the onset response of the on/offset PERG in reflecting the characteristics of the pattern specific response of the pattern ERG.

When the 'N' amplitude was subtracted from the N_{95}, it was found that the mostly effected part of the transient rPERG by dark surround illumination was the deflection between 'N' and N_{95}, suggesting that it was possibly the reduction in this part that was responsible for the N_{95} amplitude reduction. Since the lower part of the N95 was reported to related to the center-surround mechanisms by some clinical observation, it was thus deduced that this part of the negative potential played the role in the important function of the spatial frequency tunning and thus in the pattern specific response of the transient rPERG.

Linear relation with contrast

It was reported that there was an almost linear relationship between the amplitude of the human pattern reversal ERG (rPERG) and a wide range of contrast (Arden and Vaegan, 1983; Hess and Baker, 1984). In a later study by Korth et al (1985), the PERG was found to be proportional to contrast levels (0.03-0.93) at any spatial frequencies without saturation. Such a linear relation to contrast variation was also demonstrated in the PERG evoked by the on/offset pattern stimulation (Riemslag et al., 1983; Korth and Rix, 1984; Thompson and Drasdo, 1989). Our results were consistent with these reports.

However, when the experimental conditions used in these rPERG reports were compared, it was found that these results were obtained by a single factor---contrast its own by controlling contrast without mean luminance change. In the present studies, contrast change inevitably produced a slight change of the mean luminance. Thus the effects of both contrast and luminance should be taken into account when such a linear relation was described, since both contrast and luminance decrease could result in a linear reduction of amplitudes.

By definition, the contrast related components are those with show spatial frequency selectivity. In differentiating the pattern contrast and luminance related components, the term 'luminance related component' could easily result in an understanding that contrast related response has no relation to luminance. A noticeable fact in the present studies was that contrast related components were more sensitive to contrast and mean luminance than the luminance related components.

This phenomenon was also noted in the on/offset PERG. Korth (1983) demonstrated that when the luminance level was raised up from 457 photopic troland to 50119 photopic troland, the onset (contrast related) response amplitude was increased prominently compared with the changes in the offset response amplitude, especially at higher contrast level. In a report by Odom et al (1982/83), the pattern related response, ie, spatial frequency tuning (particularly the low spatial frequency attenuation, LSFA), was found almost unrecordable when the luminance was dropped from 86 cd/m^2 to 43 cd/m^2, indicating a high sensitivity of the pattern related response to low mean luminance. The consistent behaviours between N_{95} amplitude of the transient rPERG in our observation and onset (luminance related) response amplitudes in such a

case suggested the functional similarity between these two elements. Since N_{95} included a part (ie, 'N' amplitude) functionally similar to P_{50}, it was assumed that it was the subdeflection between the peaks 'N' and N95 which subserves such a property similar to the onset response. The functional differentiation of subdeflections of the negative potential has been confirmed using photopic and scotopic luminance intensities (Korth and Armington, 1976). Combined with the present studies, it was assumed that the pattern specific response of the transient rPERG is subserved by this subdeflection rather than the whole negative potential.

Another interesting finding in this study was that under different contrast levels, the latencies/ the timing courses of the P_{50} and 'N' peaks were changed proportionally, while the N_{35} and N_{95} latencies kept constant. It is known that the negative potential in the transient PERG is mixed with the successive subcomponents, triggered probably by different retinal mechanisms. The shorter latencies of P_{50} and 'N' under high contrast are probably the reason for the visualised smooth negative potential in most of the PERG records described in the other studies. A similar phenomenon was noted in a report by Regan (1989), where the transient pattern VEP was recorded. At contrast level 80%, the negative potential of the onset response showed a smooth deflection. But when the contrast dropped down to 40%, a similar notch described in the present report appeared. Regan described the potentials divided by such a notch as 'subdeflections'. When the contrast was at 10%, the waveform was highly likely to be the type III records described in Fig 5.2. There was no evidence to indicate that the negative potential in the transient PVEP was contrast related, but the components overlapping in both cases are dealt with equally in the transient analysis (Regan, 1986). Clearly, low contrast stimulation can differentiate such overlapped components.

Summary

The present observations demonstrated a functional property of the transient rPERG by contrast (as well as mean luminance) variation. It was found that the negative potential was more sensitive than the positive potential. This high contrast sensitivity by electrophysiological studies was more likely functioned by the later part of the negative potential (rather than the whole negative potential) and was probably related with the central-surround mechanisms involved by retinal ganglion cells according to the observations under dark environment.

CHAPTER 6.

STUDIES OF THE AGE-RELATED PERGS

SECTION I AGE-RELATED PERGS

Introduction

It is known that human PERG may well reflect the functional status of all retinal layers except photoreceptors (Armington and Brigell, 1981; Korth, 1983; Celesia and Kaufman, 1985), especially the ganglion cell layer (eg, Holder, 1987; Tobimastu et al., 1988/89) and has been used to diagnose the ocular diseases. Clinical observations demonstrated that the PERGs to be a sensitive diagnostic tests compared with some clinical examinations such as visual field loss in the chronic open-angle glaucoma (Quigley et al., 1982/83) and can test the abnormality before the visual performance is disturbed. However, in the elderly, the normal variation is often overlapped by natural pathological changes from one's aging process, depending upon the individual difference. Thus the reasonable interpretation for the normal and abnormal PERG in the elderly is effected. Thus improving the sensitivity of the PERGs in the elderly is one of the issues in using the rPERG for the clinical purposes.

Natural senescence of the retina occurs after age 40 so that a decrease in visual function with age occurs in normal individuals (Lakowski, 1984). It includes (1) clouding of the lens, (2) senile miosis, or and (3) a diminution in neuronal elements in the retina (Balazsi et al., 1984; Hull and Drasdo, 1990). There is evidence of aging changes affecting the cornea (Freeman et al., 1980; Johnson et al., 1982), but some studies have also shown that such changes do not appreciably affect the eye optics (Balazsi et al., 1984). In contrast aging of the crystalline lens reduces the amount of light that reaches the retina (Weale, 1982a). Since the crystalline lens acts as a filter, changes with senescence can reduce the retinal illumination beginning at the fortieth (Lerman and Borkman, 1976; Weale, 1982 a,b; Lerman, 1983) and produce a contrast fall of a pattern or a fine object (Hull and Drasdo, 1989). Weale (1982a) suggested that the increased threshold luminance reported in aging is related to flurogen accumulating in the lens.

Pupillary changes occur as an adult grows older (Weale, 1963; Loewenfeld, 1979; Sekuler, 1982; Sekuler and Owsley, 1983). The small pupil in the elderly is called 'senile miosis' by

Campbell and Green (1965) and is considered to be the cause of the decreased visual resolution when the pupil diameter drops below 3mm. The pupillary diameter decreases linearly from age 20 to age 60 (Loewenfeld, 1979). Sokol et al. (1981) reported that one's pupil decreased from an average of 5mm at age 20 to 3.5 mm at 80 years of age. Since the amount of light incident on retina is known to be proportional to the area of the pupil, clearly, the effectiveness of a pattern stimulation can be reduced when a pattern evoked response is recorded in older people due to senile miosis and lens opacification.

Thirdly, there is evidence of loss of retinal neurons (receptor or conductor elements) in aging (Gartner and Henkind, 1981). Weale (1975, 1982a,b) suggested that loss of visual acuity after age 40 was due to a 0.3 % neuron atrophy per annum and a 2.5% loss per decade (Hall et al., 1975) randomly throughout the visual system. The diminution of the retinal ganglion cells due to aging can be determined by nerve fibre count of the optic nerve. Balazer et al (1984) found that age had a significant effect on the axon count and time to fixation was also significant using a correction for age. The authors induced such a formula for the axon count based on their observations: the number of axons = 1647990 - 5637 x (age in years) - 13251 x (time to fixation in hours). The data suggested that a 70-year-old optic nerve might be expected to contain 1.25 million fibres. The aging may, therefore, account for a loss of approximately 400,000 fibres during a 70-year life span (24% of the original count !). Furthermore the retinal cells that remain in the retina show alternation with age (Marshall et al., 1979; Marmor, 1982). In the retinal ganglion cells, from 40 to 90, increased deposit of lipofucsin and argyrophilic granules in the cell body, loss of dendrites, and tortuosity in dendrites (Vrabec, 1965) will probably contribute to the functional deterioration. The PERGs are known to detect the functional status of the retina ganglion cell layer by its negative potential amplitude. Some studies have shown that PERG could monitor the progress of the optic verve fibre or the retinal ganglion cells since the PERG amplitude reduction is proportional to the extent of the optic nerve damage (eg, Galloway et al., 1986). Therefore it is expected that the effect of the senile retinal damage can be reflected in the PERGs of the normal elderly.

It is questionable that how much these factors effect the elderly PERG and how differently these senile changes work. Thus it is expected that such 'abnormalities' in normal old people could be found by comparing the PERGs in old people with those recorded in young group. Secondly, the retinal neuronal changes with aging may occur in the whole visual

pathway as a part of the changes in the central nervous system (CNS). There is a report to demonstrate a 35% loss of small neurons and a 50% loss of larger neurons in the CNS throughout one's life span (Henderson et al., 1980). Simultaneously recording PERG and PVEP under same stimulation conditions will be expected to show at which stage of the visual system aging changes exist and exert their effects.

Methods

Monocular PERGs and PVEPs were simultaneously recorded from 12 normal subjects, ten of their eyes were those at age 25-30 and rest of them were those at 65-75 years of age. The PVEPs were recorded from 12 eyes of the older individuals who were the volunteers for the observation on the PERGs. All the subjects had binocular vision 6/6 or better and wore spectacles when necessary. For the elderly group, both reading and distant vision acuity were examined and only those with 6/6 or better examined through two tests were chosen for the present observations. The general medical history and ocular status of each prospective subject were investigated according to the records in the hospital s/he was registered at, thus all the participants were those without cataracts, disorders of the ocular optic and systematic diseases. All the testing were done with subject's natural pupils.

The stimuli were produced by an optic projecting stimulator with a contrast level of 80% and mean luminance 60 cd/m^2 and triggered in a rate of 2Hz (4 reverses per cycle). The visual field subtended 14° x 14° and viewing distance was kept at 67.5 cm. Three check sizes were used: 28', 56' and 112' in recording both PERG and PVEP.

The PERG signals were recorded by DTL electrodes placed at the cornea, referred to the ipsilateral outer canthus. The forehead acted as ground. The PVEPs were recorded with two Ag-AgCl electrodes placed on the occipital scalp. The recording electrodes were referred to C3 (for O1) and C4 (for O2). Midfront point, Fz (20% apart from the central point, C, of the saggital measures) in the international 10/20 system provided a reference place for recording the PVEPs.

Amplitude was measured from the initial negative potential (downward deflection) peak, N35, to the positive peak (P50) for the positive potential and from the P50 peak to the subsequent negative trough (N95) for the negative potential in the PERGs; from the first negative peak

(upward deflection) to the positive trough for N75-P100 in the PVEPs. The ratio of the negative potential to the positive potential of the PERGs was described as the 'ratio N95 : P50' (Holder, 1987).

Latency was measured from the stimulus onset to the response peaks for P50 and N95 of the PERGs and for N75 and P100 of the PVEPs. Retinal-cortical time (RCT) was defined as the difference in millisecond between the latency of VEP waves and the PERGs (Celesia et al., 1987). Unlike the term 'b-wave' used by Celesia et al. (1987) to describe the positive peak in the PERGs, we used P50 instead: RCT (P50-N75) was latency difference between P50 of the PERG and N75 of the PVEP; RCT (P50-P100) = P100 (PVEP) - P50 (PERG) (ms).

Results and Analyses

I Age-related PERGs

Latency

The latencies of the PERGs to three checksizes 28', 56' and 112' were measured in a group at age 30-35 (n =10) and a group aged at 65-75 years (n =12) (Fig 6.1). In older group, P50 showed a larger latency average to large checks (56' and 112') and latencies of N95 were prolonged in response to small checks 28', if compared with the corresponding measures in younger group. These increases were statistically significant ($P< 0.01$). It is known that P50 is representative of luminance related response, N95 of pattern specific response. The predominant effects of P50 latency at large checks and of N95 latency at small checks in the elderly suggested that both sub-responses were affected and confirmed the characteristics of these two response components.

The relation between contrast as weel as luminance and rPERG has been discussed in the previous studies (chapter 5) based on the observation on the young people: the latency of P50 was prolonged when contrast levels were decreased, while luminance showed no effects on the PERG latencies. The latency changes of N95 in these two cases were negligibly changed. The causes for the prolongation of the PERG latencies in the elderly were therefore investigated in this study.

Based on the basic optic changes in the elderly eyes, the retinal luminance and contrast loss were taken as the main reasons for the difference of the rPERG between young and old people. The

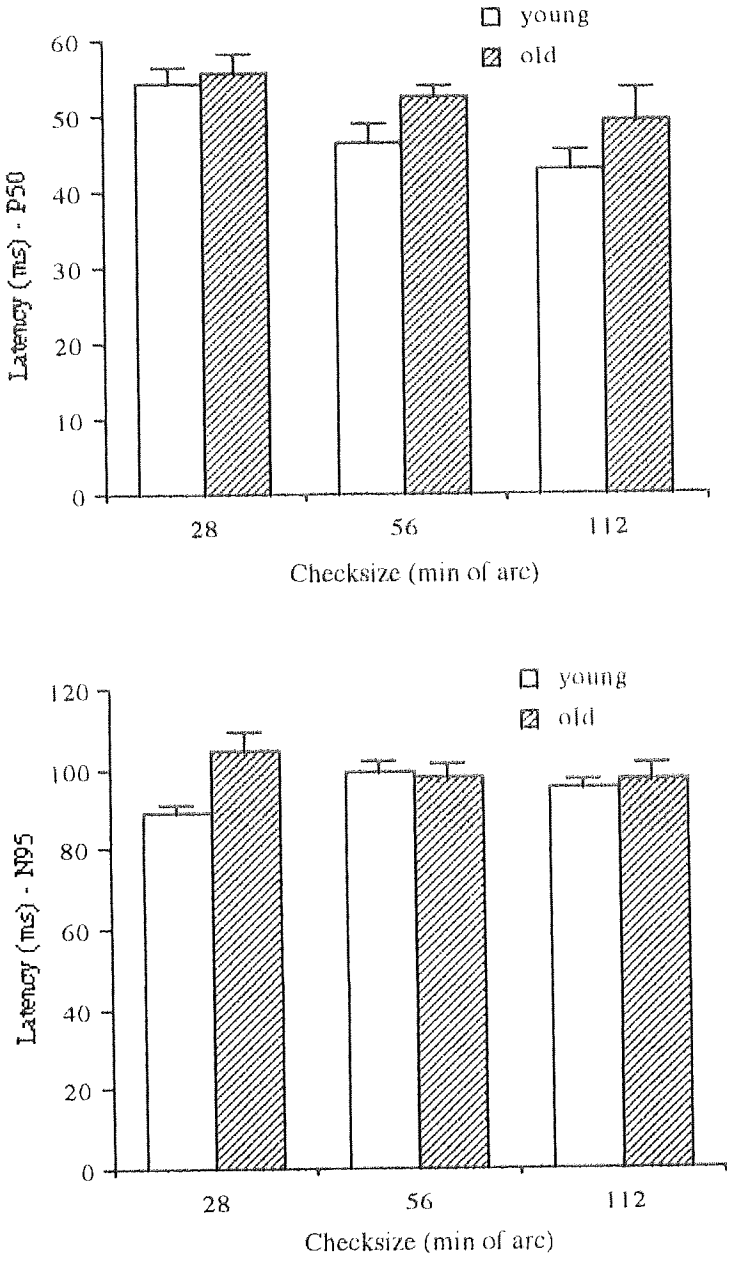


Fig 6.1 Analyses of age-related changes of the PERG latencies. The prolongation was significant ($P < 0.01$) for the P50 latency in response to checks 56' and 112' and for the N95 latency to checks 28', compared with the averages in the young group.

technique was used in a report by Trick (1987) to analyse age-related PERGs in the elderly. The author used the PERG values at 0.6 log unit of decreased retinal luminance obtained in young people to match the response in the elderly, based on the assumption that RRI was the only reason for the PERG changes in the elderly. The knowledge provided by Sokol et al. (1981) that retinal luminance reduction resulting from senile miosis, through one's 20-80 years life span, can be up to 0.3 lg unit. Considering that (1) the reduction of the retinal illumination result from both senile miosis and ocular lens opacification (so more than 0.3 log unit) and (2) the causes for the PERG changes in the elderly were possibly from both the RRI and contrast loss (so less than 0.6 log unit), 0.4 log unit was taken as retinal illuminance loss due to aging.

Firstly, we observed the effects of the RRI on the PERGs in four young eyes by neutral density filters changed in steps of 0.2 log unit. The maximum luminance was 60 cd/m^2. The P50 latency at 0.4 log unit of the original luminance level was found to be 48.4 ms and 3.2ms longer. Therefore there was a 7% retinal illumination loss to interpret the prolonged P50.

Secondly, according to the data provided by van Den Berg and Boltjes (1988), we found, for checks of 56', retinal modulation at age 70 relative to the one at 25 years was 65%:78% = 83% (from the graph of the calculated retinal modulation depth function of checksize), such that a 17% of contrast loss (CL) was obtained. Therefore the expected latency of P50 without RRI and CL = the actual value of the P50 latency obtained in the present older subjects ÷ (1 + RRI + CL). The calculation showed a value of 42.20 ms. This value was close to the value obtained in the present young people, in whom the averaged P50 latency was 42.9 ms. Based on the data provided by Holder (1987) that the retinal ganglion cell dysfunctions caused no changes in latency of PERG and our calculation, the effect of age-related ganglion cells or other neurons was neglected.

There was a 7.2 ms of increase resulted from CL. Again, we compared the results obtained by the previous studies in young people on whom the effects on the PERGs of contrast decrease were observed. At contrast level 57% (ie, 23% contrast loss from the maximum 80%), there was a 5.0 ms prolongation for the latency of P50 and the value was almost close to what was obtained in the elderly rPERG. The comparison showed that contrast loss had a large proportion in the age-related increase of the P50 latency. It appeared that the changes in contrast at these levels changed the PERG latencies in the young people did also effect the P50 latency in the

elderly, indicating a change of age-related sensitivities to contrast. Since the N95 latencies in young people had no relation to the RRI and the contrast loss, the causes for the prolonged N95 latency were not estimated.

Amplitude

Amplitudes of both P50 and N95 in the old group were significantly decreased in response to three checksizes and the ratios of N95: P50 were otherwise increased significantly, suggesting a prominent effect of aging on amplitude of P50 (Fig 6.2). Similar results were reported by Hull and Drasdo (1990) and suggested by the authors that contrast falling as a result of media change was the major cause, since the N95 amplitude was diminished less than the P50 (Weinstein et al., 1988). Under our experimental conditions, we noted that amplitude of N95 was, reversely, more sensitive to contrast changes than that of P50. It was therefore assummed that the presdominant loss of P50 amplitude in the elderly does not result from contrast loss its own. Thus it was questionable whether RRI, CL and the functional deterioration of the retinal neurons (we termed DRN), especially the retinal ganglion cells effected these two potential sizes differently during aging. By the same way used in analysing latency of P50, we compared their effects on the PERGs amplitudes to checks 56' by the following steps:

(1) Supposing that the amplitude removing effects of these three factors was A, then the amplitude without these factors (A) = actual measures obtained in the older individuals (Ao) ÷ (1-RRI - CL - DRN). Again, based on the data obtained from the young people, a RRI for P50 was 26% and CL = 17%; for amplitude of N95, RRI = 8% and CL = 17%. These figures provided an estimate that RRI effected P50 amplitude more than CL could and RRI was more effective in influencing P50 than N95. The analysis , more or less, interpreted the increase in the ratios of N95:P50. Thus there were two induced values: A1 was the amplitudes without RRI and A1 = Ao + RRI x A and A2 represented the amplitudes without RRI and CL, A2 = Ao + (RRI+CL) x A. A2 for P50 was close to the measures in young group. Combing the analyses on latency of P50, the neuronal factors appeared to be of little importance.

(2) Estimation of the DRN and the total amplitude loss According to Weale (1975, 1982 a,b), there is a 2.5% neuronal loss per decade occurring randomly through the visual system after 40 years of age (Hall et al., 1975) contributing to the loss of visual acuity. Supposing that a gross

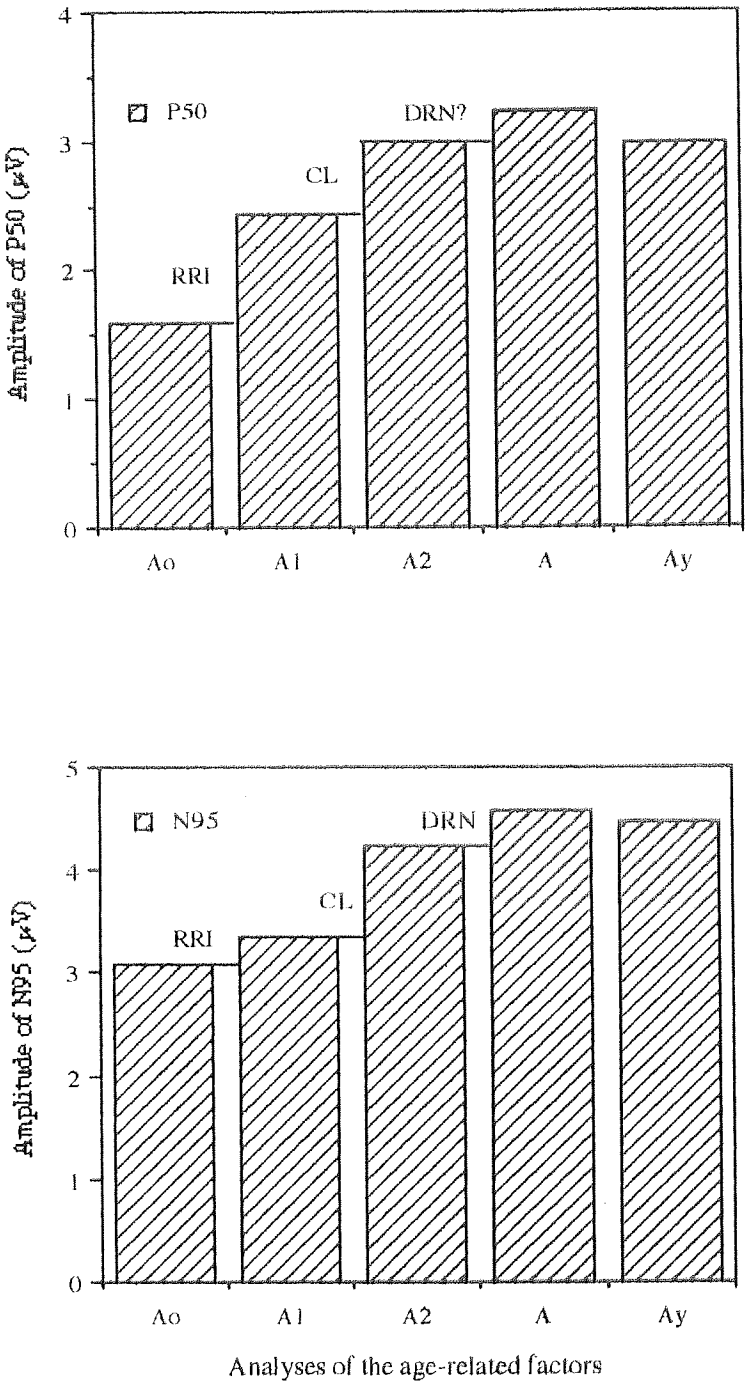


Fig 6.3 Effects of the age-related changes in ocular optics and the retinal neurons on the PERG amplitudes. Ao were the averaged measures obtained in the older individuals; A1 were the estimates without RRI; A2 represented the estimates without RRI (reduction of the retinal illumination) and CL (contrast loss); A were the predicted values of the PERGs for the older subjects after excluding RRI, CL and neuronal factors (DRN). The close levels between A and those measures (Ay) obtained in younger group (aged 30-35) displayed a comarability of the present analyses, especially for amplitudes of N95.

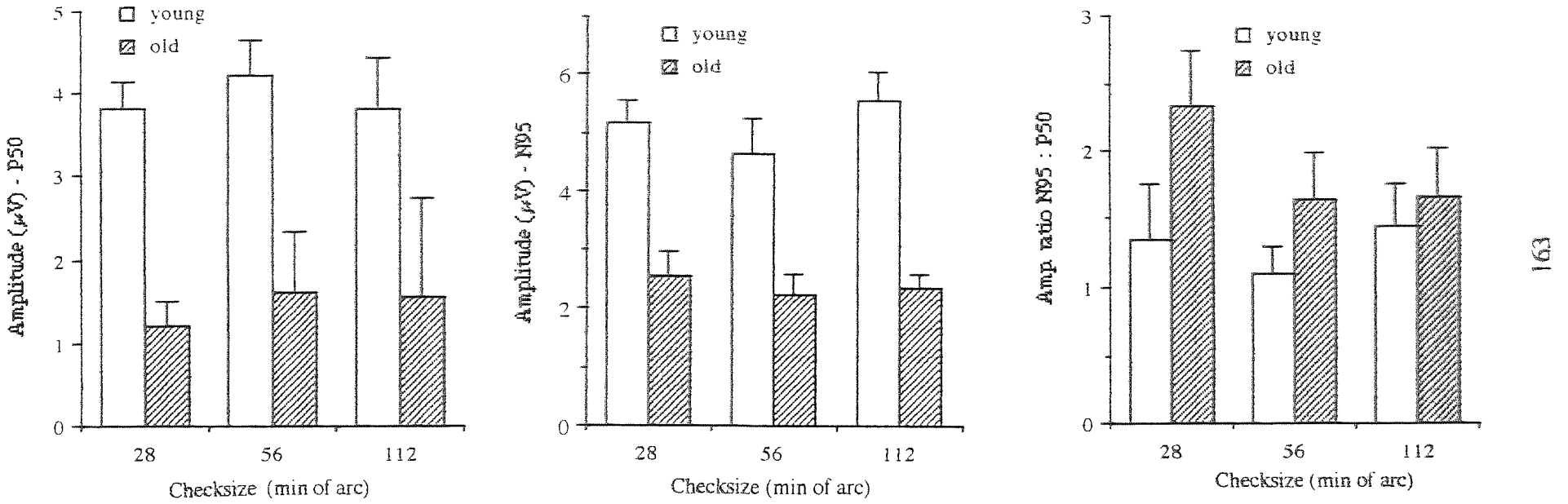


Fig 6.2 Analyses of the age-related changes in the PERGs. The amplitudes of both P50 and N95 were significantly decreased in the old group (at 65-75 years of age). The ratios N95:P50 were prominently increased, especially the one in response to checks 28', indicating a larger age-related reduction of P50 than that of N95.

estimate of 7.5% (for 70 years of age) obtained by the data could contribute to the loss of the PERG amplitudes in the same way, the data was used in the present calculation as the value of the functional deterioration by the retinal neurons, DRN. So that for P50, A = Ao ÷ 0.495 and for N95, A = Ao ÷ 0.675. Since the Ao values have been known: P50 = 1.60 μV and N95 = 3.10 μV, then A (P50) = 3.23 μV and A (N95) = 4.59 μV. The estimate for N95 (4.48 μV) were close to the corresponding averages obtained in the young people (Fig 6.3).

It is known that the axon loss count of the retinal ganglion cell during a 70-year life span is 400,000 and there therefore is an approximately 24% retinal ganglion loss according to the data provided by Balazer et al (1984). So what is the relation of this loss with the N95 amplitude loss? Supposing alternatively that this percentage contributed to the N95 amplitude loss proportionally, we calculated the A (N95) and obtained a value of 6.08 μV! Clearly it was an overestimated value for detecting the contribution of the retinal ganglion cells to the N95 amplitude loss. Since the calculated values by the first alternative, ie, DRN being 7.5%, were close to the measures in the young people, it was suggested that not all the age-related loss of retinal ganglion cells contributed to the age-related N95 amplitude loss. In general, RRI contributed mostly to the P50 amplitude loss and CL contributed mostly to the N95 amplitude loss. The analysis results were highly insistent with our previous observations that N95 had a higher contrast sensitivity to contrast loss than P50.

II PERG and PVEP in the elderly

The PERGs and the PVEPs were measured in 12 normal eyes of those subjects at age 65-75 years. The results are shown in Table 1 and Table 2.

Table 1 Averaged Transient PERG (mean ± SD, n =12)

Check size	Latency (ms)		Amplitude (μV)		
	P50	N95	P50	N95	N95/P50
28'	55.63 ± 2.55	104.48 ± 4.62	1.20 ± 0.30	2.53 ±0.42	2.32 ± 0.42
56'	52.36 ± 1.72	97.71 ± 3.59	1.60 ± 0.75	2.24 ± 0.34	1.64 ± 0.34
112'	49.41 ± 4.02	97.35 ± 4.09	1.56 ± 1.17	2.34 ± 0.24	1.65 ± 0.36
	$p < 0.05$	$p < 0.01$	$p > 0.01$	$p > 0.01$	$p < 0.01$

Table 2 Averaged Transient PVEP (mean ± SD)

Check size	Latency (ms)				Amplitude (μV)
	N75	P100	P50-N75	P50-P100	N75-P100
28'	79.71 ± 1.40	113.63 ± 4.39	26.9 ± 2.55	57.6 ± 2.01	6.85 ± 1.25 (LH)
	80.75 ± 2.29	111.23 ± 3.80			6.12 ± 2.42 (RH)
56'	81.97 ± 3.90	115.67 ± 3.15	31.6 ± 4.53	65.5 ± 4.05	7.34 ± 1.28
	79.12 ± 3.55	113.89 ± 2.66			7.36 ± 1.70
112'	83.29 ± 3.18	116.81 ± 4.11	31.9 ± 3.77	66.1 ± 3.75	7.86 ± 1.32
	82.39 ± 3.81	113.55 ± 3.18			7.51 ± 1.53
	$p > 0.01$	$p > 0.01$	$p < 0.05$	$p < 0.001$	$p > 0.01$

It can be seen that the latencies of P50 and N95 to 28' checks were significantly longer than those to the larger checks. The amplitude of P50 showed a slight larger amplitude in response to checks 56' and 112' and the N95 amplitude was slightly larger to checks 28'. But such changes were not statistically significant. The calculation of the ratio N95: P50 showed that they were significantly increased in response to 28' checks, suggesting a high sensitivity of N95 amplitude and low sensitivity of P50 amplitude to small checks. The comparison was shown in Fig 6.2 (right columns).

The latencies and amplitude of N75 and P100 of the PVEPs showed no difference to three checks. The RCT (P50-N75) and The RCT (P50-P100) to checks of 28'was significantly shorter than those to larger checks (56' and 112'). Since the latencies of N75 and P100 showed no relation to the sizes of these checks while the P50 latencies of the PERG were significantly longer to small checks 28' than to those larger ones, thus the shortening of the RCTs indicated that the changes occurred at retinal level rather than after the retina, such as visual pathway, or cortical level.

Discussion

Age-related Latency Changes in the rPERG Latency

It is known that a PERG to large checks is preferentially attributed to the retinal illumination

response component (RIR) and the response to small checks has a large proportion of pattern specific component (PSR) (Drasdo et al., 1989). Among the checks we used, checks 28' were taken as being capable of mostly reflecting the PSR, checks 112' as the RIR and the response to checks 56' as a mixture of both. The prolongation of the latencies to all the checksizes indicated that some age-related changes effected both RIR (in P50) and PSR (in N95). Furthermore the analyses showed that contrast loss effected the latency of P50 more effectively than the reduction of retinal illumination did.

Combined effects of RRI, CL and DRN.

Some reports have shown that the amplitude of the positive component of the pattern reversal ERG decreases with increasing age and the peak latency increases (Celesia et al., 1987; Trick, 1987; Hull and Drasdo, 1989) and also the reduction of both positive and negative components has been reported (eg, Hull and Drasdo, 1989). There was some argument as to whether the decline in amplitude in the PERG was due purely to optical factors (Celesia et al., 1987) or whether loss of ganglion cell function is the major cause (Korth et al., 1989); and some reports indicated that the change of positive component of the PERG was attributed by both factors (Trick and Trick, 1985; Trick et al., 1986).

Our analyses showed a combined effect of these factors. It is suggested that the reduction of the retinal illumination (RRI) is the main cause for the age-related P50 amplitude loss and the contrast loss (CL) contributed mostly to the N95 amplitude loss.

Similar analysis techniques have been reported by Hull and Drasdo (1989) for contrast loss and by Trick (1987) for reduction in the retinal illumination. Leipert and Gottlob (1988) reported that enhancing the luminance from 3cd/m^2 up to 60 cd/m^2 diminished significantly the implicit times and increased the amplitudes of various components. PQ (ie, P50) amplitude was increased monotonically up to 60 cd/m^2 while QR (N95) amplitude was maximal at 30 cd/m^2, implying that the P50 amplitude was more sensitive to changes in the retinal illumination than the N95 amplitude. They also demonstrated that when accommodation and refractive errors were corrected, 50% of mean luminance reduction caused a loss of P50 amplitude of more than 20%.

Does the RRI result from senile miosis or/and optic media opaque?

Trick (1985) reported an amplitude reduction of only 5% when miotics was used in recording the PERGs. If a 40% reduction of the amplitude was produced by using miotics, a retinal illumination reduction up to 1.2 log unit was needed (It appearred possible for a subject to have a pupil diameter of 1mm due to senile miosis). Similarly Holder and Huber (1984) reported that PERG amplitudes were not effected by pupil size even when the pupil size was reduced to less than 2 mm by miotics.

All these observations were done with miotics. The miotics could produce visual acuity attenuation, due to accommodation changes and luminance reduction, due to miosis. Leipert and Gottlob (1988) reported that when pupil size was controlled by an aperture its own after the use of tropicamide (to dilate pupil size) and after the correction of blurring by lenses, decrease of the aperture diameter (≤ 3-4 mm) could significantly increase the implicit times of N35, P50 and N95 of the PERGs and when the diameter was at 2 mm or less, the P50 and N95 amplitudes were significantly decreased. These results were similar to those obtained when luminance was decreased. The authors concluded that the PERG changes due to pupil size were based on variation of luminance, consistently with the theory that the direct effect of miosis to to reduce the retinal luminance (Hoffman et al., 1978). it appeared that senile miosis resulting in a RRI was not sufficient to interpret the large reduction of the P50 as well as the N95 amplitudes. Supposing that a 70-year-old person had a pupil size of 3.5 mm (Sokol et al., 1981), this size seemed sufficient to effect latency rather than amplitude. Thus the age-related reduction of the from the RRI was more to be likely related to other factors such as the changes in the lens transparency rather than the senile miosis.

Loss of the retinal neuron function.

Trick (1987) demonstrated that the PERG amplitude (ie, P50) was significantly greater for younger than the elderly observers. The author interpreted that such a PERG reduction (of the positive potential) was due to the loss of ganglion cells (Vrabec, 1965) and optic nerve axons (Balazsi et al., 1984) in the elderly. However, later studies showed that the negative potential was more related to the retinal ganglion cells than was the positive component (Holder, 1987; Ryan and Arden, 1988). Since the author did not report measures of the negative potential, such interpretation was not comparable.

We observed P50 and N95 amplitudes to three checks and compared the results obtained in young and old groups. It was found that P50 amplitude loss due to aging was restricted to lager checks (56' and 112'), while N95 amplitude loss to the smallest checks (28'). Trick et al (1986) also demonstrated that the reduction of the positive component in old people was greatest at low spatial frequencies (0.5-1 cpd). Again, in a report by Trick (1987), the most significant age-related difference in PERG amplitude (P50) was obtained when large checks were used. Decrement of spatial resolution as a result of normal aging has been reported (Anderson and Palmore, 1970; Seluker et al., 1980). Clearly, the luminance-related response of the rPERGs was evidently effected by aging.

The analyses demonstrated that neuronal factors acted more effectivly on the N95 than on the P50. We assumed that there was some loss of the inner retinal layer with increasing age, possibly the retinal ganglion cells; and that these inner retinal cells were probably those with the central-surround mechanisms, based on the analyses in the present studies and the previous observations of contrast gains of the response under dark adaptation. Yet, the analyses can not exclude surely the loss of non-ganglion cells which possibly subserve the luminance-related positive component of the PERG and play a role in the RRI.

Aging in the visual pathway

Retinocortical time expresses the interpeak interval between the P50 and either the N70 or the P100 peak and reflects the events occurring outside the retina somewhere along the optic nerve, visual pathways and visual cortex. Our observations on the RCTs in the old people showed that two RCTs to small checks (28') were shorter than those to checks 56' and 112'. Since the latencies of N75 and P100 showed no clear changes to the different checksizes, the results suggested that the P50 latency prolongation might have occurred in retinal level. Since at the retinal level, both the pattern specific response and the luminance-related response were effected as reported in the previous studies, non-difference in the sensibility in response to different checksizes at cortical level suggested that mechanisms of aging related effects on these two responses were different between the retina and cortex level. Celesia et al (1987) studied the effects of aging on PVEP and found that age-related changes did not occur with response evoked by 31' checks but 15' checks, implying that aging effects the efficiency of detecting small patterns by visual spatial frequency channels. These observations have provided supporting evidence to our assumption.

SECTION II EFFECTS OF DEFOCUS ON RVA AND PERGS IN THE ELDERLY

Introduction

In recording PERGs, the quality of the retinal image is the basic necessity. It is particularly noticeable in the elderly, in whom aging changes in the optics of the eye can prominently reduce the effectiveness of a pattern image on the retina.

According to Campbell and Green (1965), 'there are two main factors which limit the perception of the fine detail---quality of the optics of the eye forming the image on the retina and the ability of the retina (coupled to the brain) to resolve the details of that image'. The authors indicated that focus and pupil size are two basic elements related to the optics of the eye. When Leipert and Gottlob (1988) studied the effects of miotics on the PERGs, they found that when accommodation loss and refractive errors were corrected, changes in pupil size effected mostly the latencies and showed little effect on the amplitudes of the response. Our observations demonstrated that major changes of the elderly PERGs were amplitude reduction rather than its latency prolongation. Some other studies showed similar results that pupil size was linearly related to the P50 latency of the PERGs (Tobimastu et al., 1986; Celesia et al.,1987). We therefore assumed that effects of senile miosis on the PERGs are relatively less prominent and changes in the focussing ability of the eye are the main causes for the changes of the optics of the eye related to the elderly PERGs, which was the main concern for the present studies.

Age-related Loss of Visual Acuity Mostly used clinical examination on the optics of the eye is visual acuity, which refers to the ability of the eye to see the shapes of objects (Pitts, 1982), and can be expressed as Snellen fraction, d/D (Donders, 1864), where the distance that a letter or an object subtends in 5 min of arc is taken as the numerator (D) and the distance that the letter can be seen distinctly as the denominator (d). The earliest effort to relate changes in visual acuity to age was reported by Donders (1864). Later, Collins and Britten (1924), Geldard and Crockett (1930), Ferree et al (1934), Chapanis (1950), Burg (1966), Weymouth (1960) and Richards (1966, 1972) reported visual acuity reduction with age. Pitts (1982) analysed the data from these eight authors by calculating a weighted mean acuity for each age category and demonstrated that visual acuity showed a slight improvement in younger ages up to twenty to thirty years old, remained rather constant to 40-50 years of age, and then steadily declined to the age of 80.

As the eye ages, there is a reduction usually in distant vision and a concomitant but larger decrease in visual acuity at near ranges (Hofstter, 1965; Carter, 1982). The incapability of one's accommodation to sustain clear vision at near working distance is called presbyopia (Pitts, 1982). It begins at an earlier age in female than in males, probably due to the late start of the menopause and geographical reasons (Lebensohn, 1966; Weale, 1963, 1982).

The factors causing the loss of visual acuity in the elderly have been reported of multiple sources: (1) changes in light sensitivity due to senile miosis and media changes (Lerman and Borkman, 1976; Weale,1982 a and b; Lerman, 1983); (2) reduction in brightness contrast (Pitts, 1982; van DenBerg and Boltjes, 1988); (3) a disability glare increase causing greater scattering of light due to intraocular media changes (Wolf, 1960; Fisher and Christie, 1965). Among these factors, the foremost is the fact that refractive errors due to the loss of the accommodation contribute immeasurably to the loss of contrast sensitivity.

The eye accommodating for a better focus enables the eye to differentiate contour sharpness of an object (Carter, 1982) and allows clear vision over a certain range of distances, involving the alteration of ocular refracting power through changes in crystalline lens curvature. Contraction of the cilliary muscle permits the lens to become increasingly convex in near vision by relaxing tension on the zonular fibres. It is generally acknowledged that the age-related reduction in accommodation amplitude is due almost entirely to lenticular factors, where the lens fails to increase in convexity as the zonulae relax during cilliary muscle contraction. According to Hamasaki et al (1956), the average value of the true accommodation amplitude declines steadily from some early age until it reaches zero between the age of 50 and 52. Hofstter (1944, 1950) referred Duane's and Donders' date to a common spectacle plane location and derived a formula to describe how accommodative amplitude varies with age linearly: $D = 18.5 - 0.3\ A$, where D is the amplitude of accommodation in diopters and A is age in years.

Loss of contrast sensitivity in the elderly results in that older observers required higher illuminance than did young ones and that the increase in acuity with increase in illuminance was greater for the old eyes than for the young eyes (Ferree et al.,1934). Guth (1957) used visibility to determine the illuminance required to maintain equal visibility for observers from 17 to 65 year and found that twice the level of illuminance was needed for the 60-65-year age group. Weale (1961b) calculated the light sensitivity loss from miosis and media changes

and indicated the need for an increase in illuminance by a factor of 0.3 to compensate for aging process when the 60-year-old eye was compared with the 20-year-old eye. Later studies showed that a much more higher factor was needed for the compensation. Blackwell and Blackwell (1971) suggested that an increase in contrast by a factor of 3.03 was required to maintain the visual performance of the 60-year-old eye compared with that of the 20-year-old eye for maintaining a 70% modulation! Pitts (1982) also indicated that an increase of 2-3 times in illumination was required to maintain vision when the older person was compared with the young person.

Ogle (1962a and b) and Cole (1974) have demonstrated that ametropia could reduce contrast sensitivity: a 1.0 diopter defocus requires a two or three times increase in illuminance to be seen at the same level and a 2 .0 diopter of defocus requires a 5-6 times increase in illuminance to be seen. It was, therefore, presumed that age-related changes in the optics of the eye could be seen by using defocussing lenses.

Optical Point-spread Function (PSF). One of the systematic tests for detecting the quality of the retinal image is the optical point-spread function (PSF). The retinal image is the product of the whole PSF of the eye (the retina light distribution resulting from a point source of light) (van DenBerg and Boltjes, 1988). The function has a sharp central peak, based on the measurement of the line spread function (Campbell and Gubish, 1966), and declines monotonically towards the extreme periphery, based on glare experiments (Holladay, 1927; Stiles and Crawford, 1937). The 1° - 100° PSF was constructed by Vos et al (1976) and used by Vos (1983) in those incooperate inter-individual differences such as increased straylight at older age. It can derive a complete retinal image of any visual stimulus and define the overall optical quality of the eye.

$$PSF(\phi) = c.\,10^{6} \cdot e^{-(\phi/\phi c)2} + [c.\,10/(\phi + \phi_C)^3] + [p.\,10/(\phi + \phi_p)^2].$$

ϕ is angular distance in degrees. Parameters c, ϕ_c and p, ϕ_p control the individual shape of the PSF. From the point of the PSF, visual acuity is determined by the width of the central peak of the function and not sensitive to light changes outside of approximately 1 degree of visual angle. At the outside of the edge of this function, straylight (the light outside 1° of the visual

angle is called straylight) causes considerable loss of contrast (van Den Berg, 1986). By quantitative measurement, van Den Berg concluded that straylight could be increased considerably, more or less, independently of visual acuity. The strength of straylight can be much greater in older eyes. It was assumed such straylight would be reflected in the elderly PERGs, with normal or abnormal vision.

Present Experimental Design Defocus by spherical lenses can mimic the reduction of the focusing ability occurring in aging or resulted from other reasons and diminish the contrast sharpness of an object or checkerboard patterns (van Lith, 1977). Thus visual acuity and retinal evoked responses presumbly could reflect the changes of the optics of the eye in the elderly. Secondly, when straylight is increased up to six-fold in young people, visual acuity (size and shape of the central peak) can be kept unchanged (Van Denberg, 1986) such that large straylight resulting from aging can probably be only reflected in the elderly PERG response while visual acuity is otherwise normal. Since aging changes have large individual differences, comparison of the effects of defocus on visual acuity and the PERGs would be necessary in order to know the contribution of the age-related changes in the optics of the eye to the quality of the retinal image in the elderly.

Methods and Results

Experiment I---Defocus and Near Vision

All the tests were done on those subjects who were 65-75 years (n = 8). Subjects with cataracts, retinal pathology, macular degeneration, chronic open angle glaucoma, systematic and other ocular disorders were excluded as participants (those subjects who had cataract but experienced surgery were accepted to join the observations). The ratio of male to female was 7:1.

Every subject wore spectacles. The distant vision was measured with Snellen chart. Near vision was measured using topographic measuring chart (Sachsenweger, 1987). The viewing distance was designed as 67.5 cm. Only those subjects with vision acuity of 6/9-6/6 (including distant and near vision) were chosen to be observers.

Spherical concave and convex lenses were used to produce defocussing effect. The observations were done whenever each pair of ±0.25 D lenses were added up to the original ones. Near vision was measured according to subject's response, ie, the smallest letters which s/he could

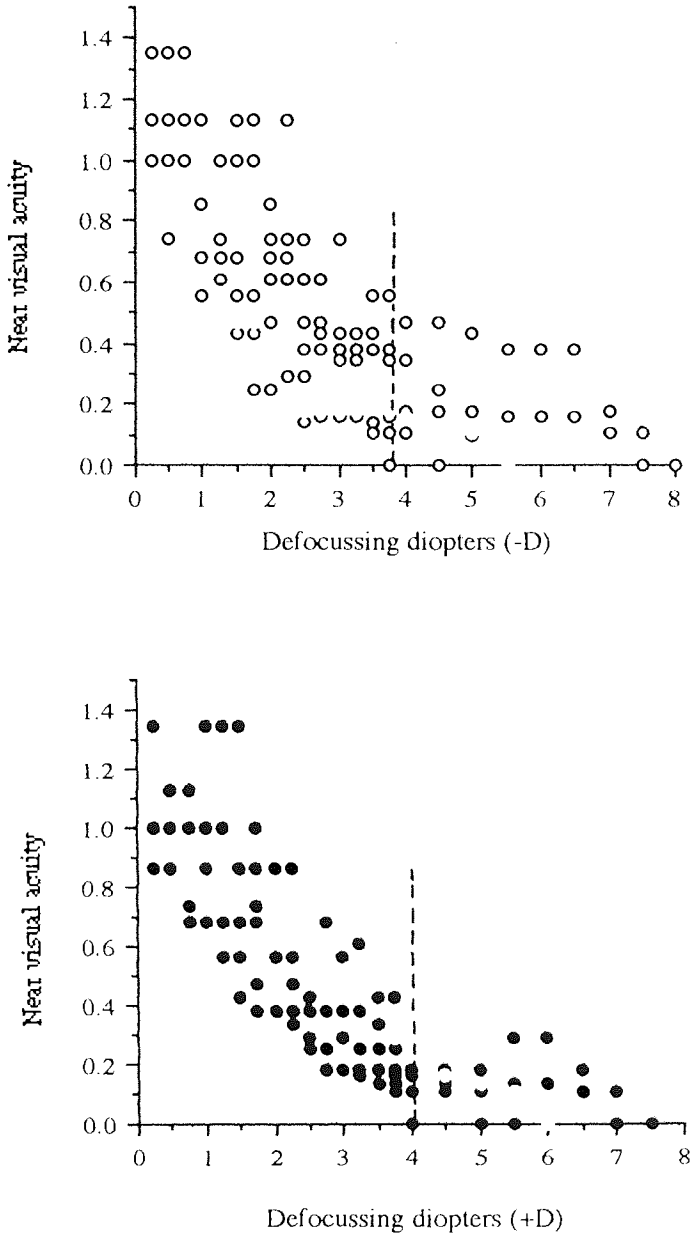


Fig 6.4 Relation between defocussing diopters and near visual acuity in the male elderly (aged at 65-75 years, n=8). *Top*: near visual acuity function of concave defocussing diopters. *Bottom*: near visual acuity function of convex defocussing diopters. *Note*: absent dots and impaired dots at each pair of diopters resulted from superimposition. Dot lines indicated the dioptric degrees where subjects could not resolve the largest letters on the vision chart.

just resolve to read at the viewing distance (67.5 cm) was taken as near vision. Then visual acuity was transformed into the value at the standard viewing distance for near vision (30cm) and expressed in Snellen decimal unit. The results were plotted as near vision functions of convex and concave diopters and displayed in Fig 6.4. Effects of defocus showed large inter-individual variations, being more clear when spherical concave lenses were used.

When the effects of defocus by concave and convex lenses were averaged among the individuals, the curves of the vision functions versus concave and convex diopters showed no clear difference (Fig 6.5). At -1.50 - -1.75D, the averages showed a fluctuation, which has been reported by Campbell and Green (1965) in observing the contrast sensitivity of the optics of the human eye. The diopters producing the functuation was coincidentally the upper limit for dioptric lenses to maintain the visual acuity at 1.0 in the elderly.

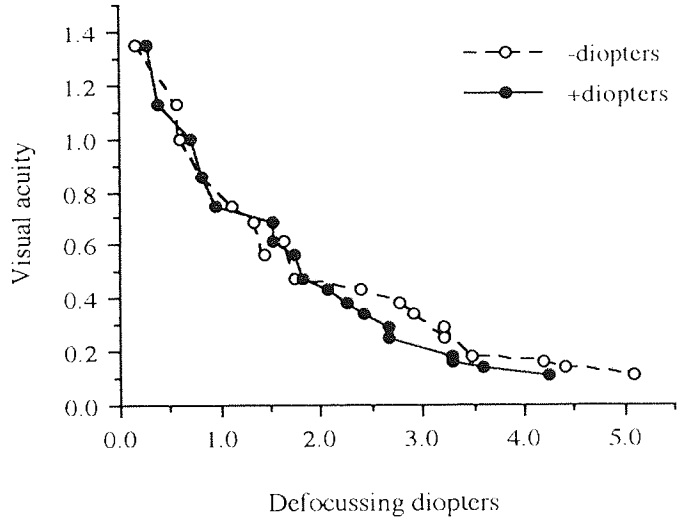


Fig 6.5 Averaged near vision functions of defocussing diopters.
Note: -D: concave lenses; +D: convex lenses.

When concave defocussing lenses were used, vision started to decrease at a power of -0.5D and more; within the range of -0.5D - -4.0D, near vision was decreased in a linear fashion; to produce vision of 1.0, dioptric lenses varying from -0.25D to -1.75D were needed; the lenses varying from -4.0 to -6.75D could result in a blurring vision. Similar phenomena occurred when convex lenses were used, where the defocussing band for maintaining normal vision and individual difference were larger.

Experiment II

In order to estimate the effects of refractive errors and of age-related straylight on the PERGs in the elderly, the PERGs were observed under different dioptric lenses and compared between young (n=8) and old groups (n=8). The procedures for recording the PERG were the same as have been described in Section I. Checksize was 56 min of arc.

It was found that, with two types of dioptric lenses, the PERGs in young people were decreased and the P50 reduction was more evident than did the N95 amplitude (Fig 6.6a and b). The latency showed no apparent changes. The PERGs amplitudes were found to be proportionally related to the degrees of the diopters. The observations showed no evident effect on the PERG latencies of defocus.

Under defocussing condition, the PERGs were more difficult to record than did in the young people and the variations of the response among individuals were larger than among young people. The largest diopters for an obtainable record was smaller than the ones in the young people and the PERGs could not be recorded at dioptric lenses larger than ±4.0D in 5/8 cases, while in young people, at a power of 5.0D, the PERGs were obtainable in most subjects and 0.3-0.5 of its original amplitudes could be obtained. When the PERGs under same degree of diopters were compared between young and old, it was found that the convex lenses effected prominently the N95 amplitude in the elderly (Fig 6.7) while concave lenses effected both N95 and P50 amplitudes as did in the young people (Fig 6.8).

Discussion

Based on the theory that defocussing lenses can mimic the phenomena of refractive errors, the loss of focusing ability in the elderly were estimated from the results in the experiment I. Since all the subjects' near vision had been corrected to 6/6 and more before the observations, which was equivalent to 1 degree of visual angle, the acuity changes were taken as resulting from refractive errors by the lenses and could be used to induce the relation between the existing refractive errors and near vision. It could be seen that for the normal elderly to maintain the visual acuity of 6/6 and better at near distance, the refractive conditions could be different among individuals and were allowed to have the 'errors' varying within a range of ±0.25 - ±1.75D without disturbing the normality of vision. This refractive error range reflected, more or less, the extent of the individual differences of the optics of the eye in the normal elderly.

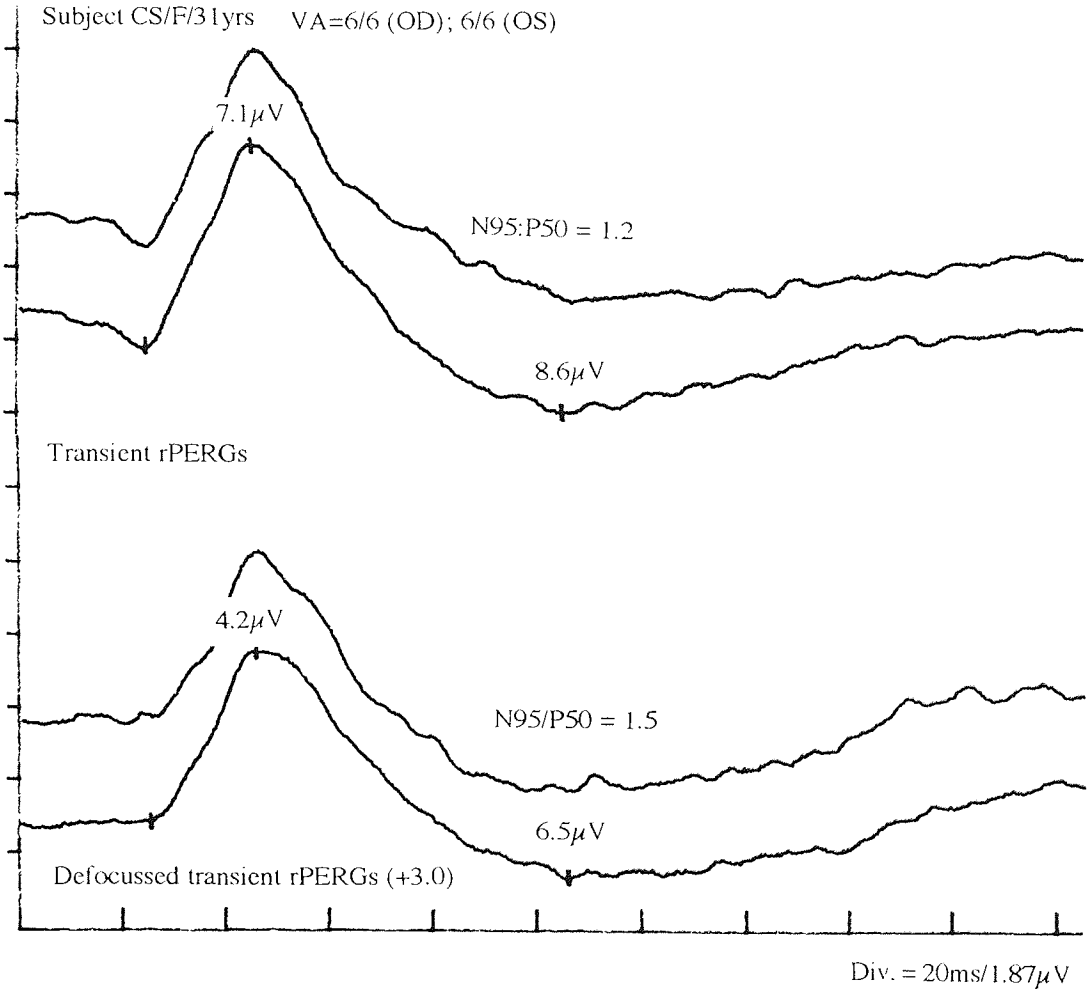


Fig 6.6a Normal and plus defocussed PERGs in a young subject.

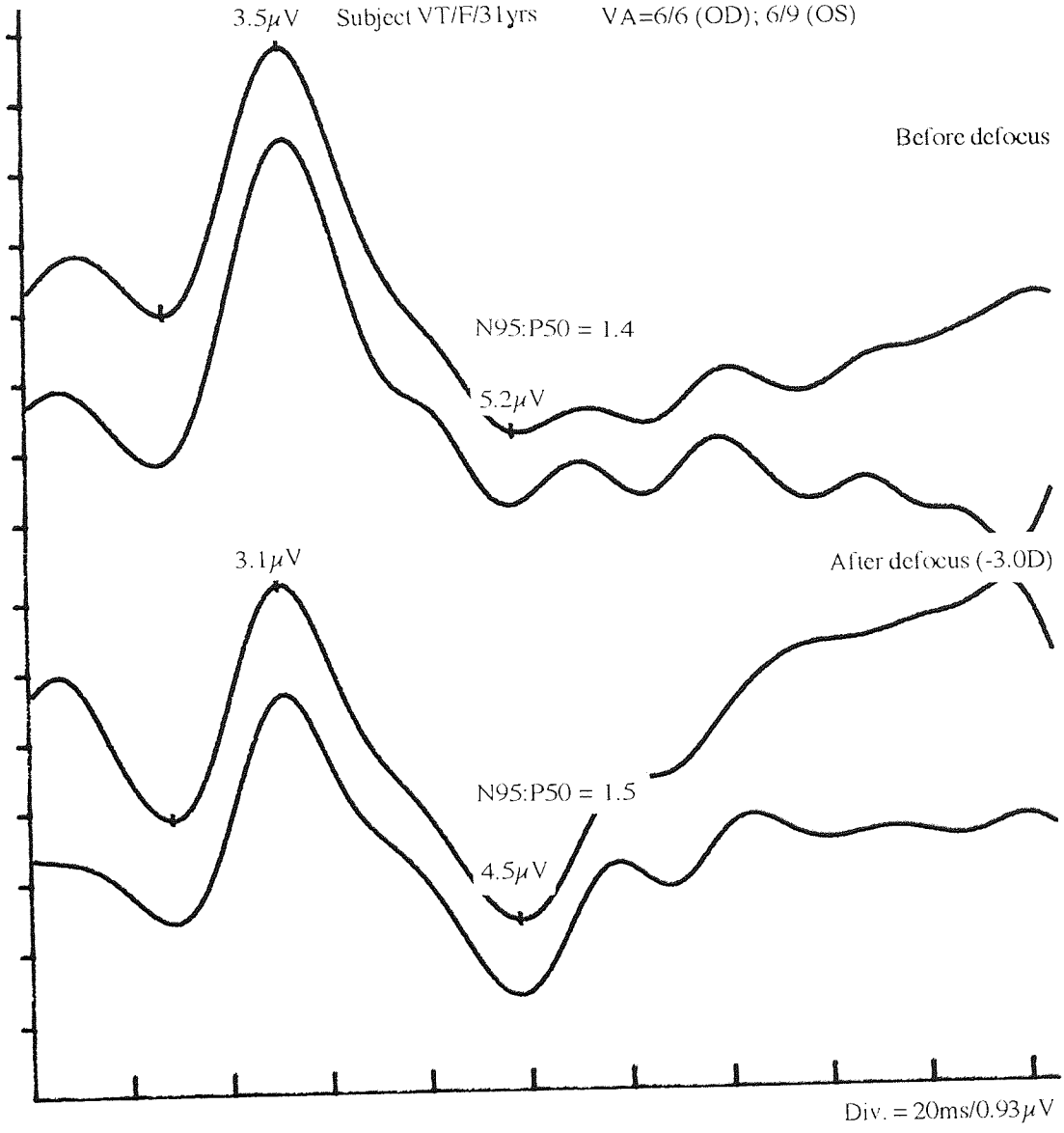


Fig 6.6b Normal and minus defocussed PERGs in a young subject.

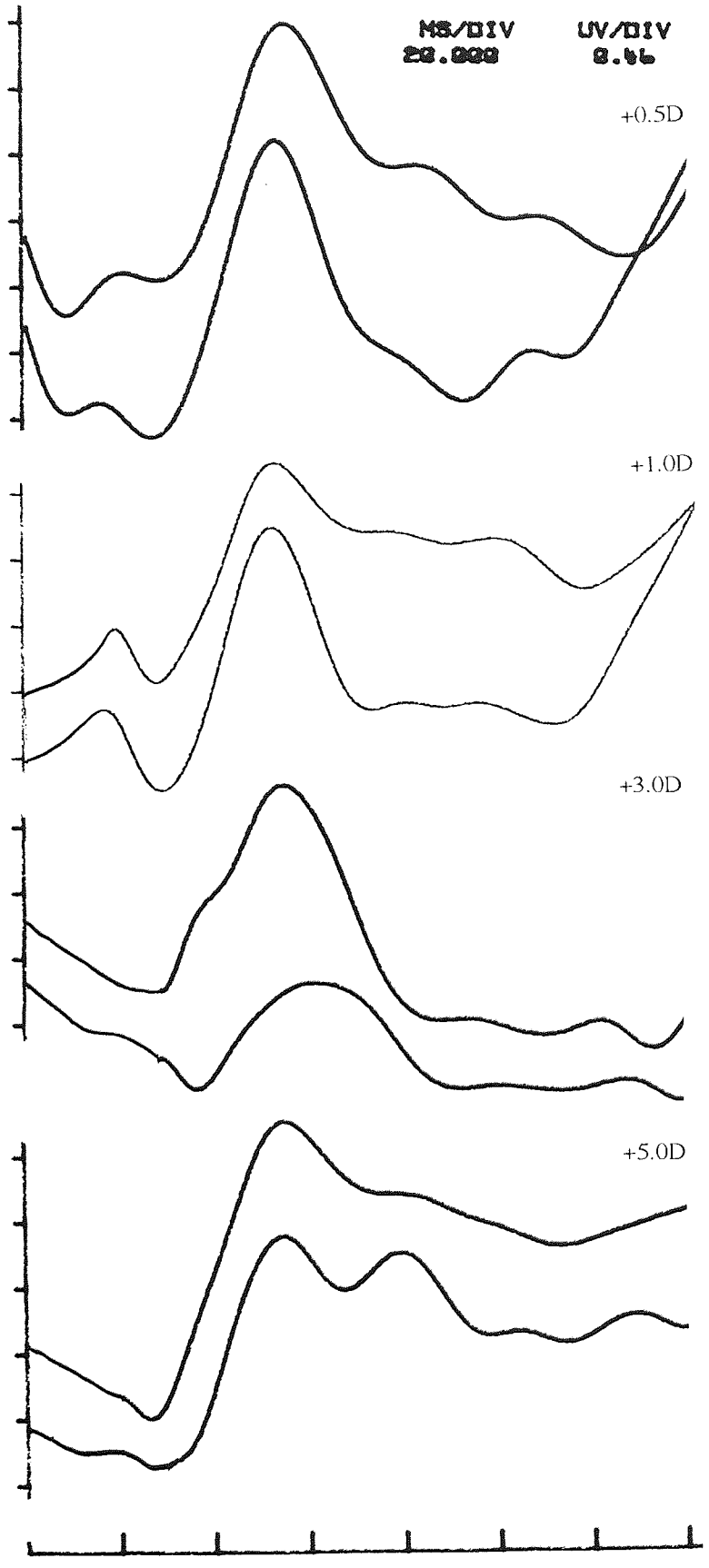


Fig 6.7 The defocussed (+D) transient rPERGs in the elderly (Subject EE/M/65yrs. RVA = 6/6).

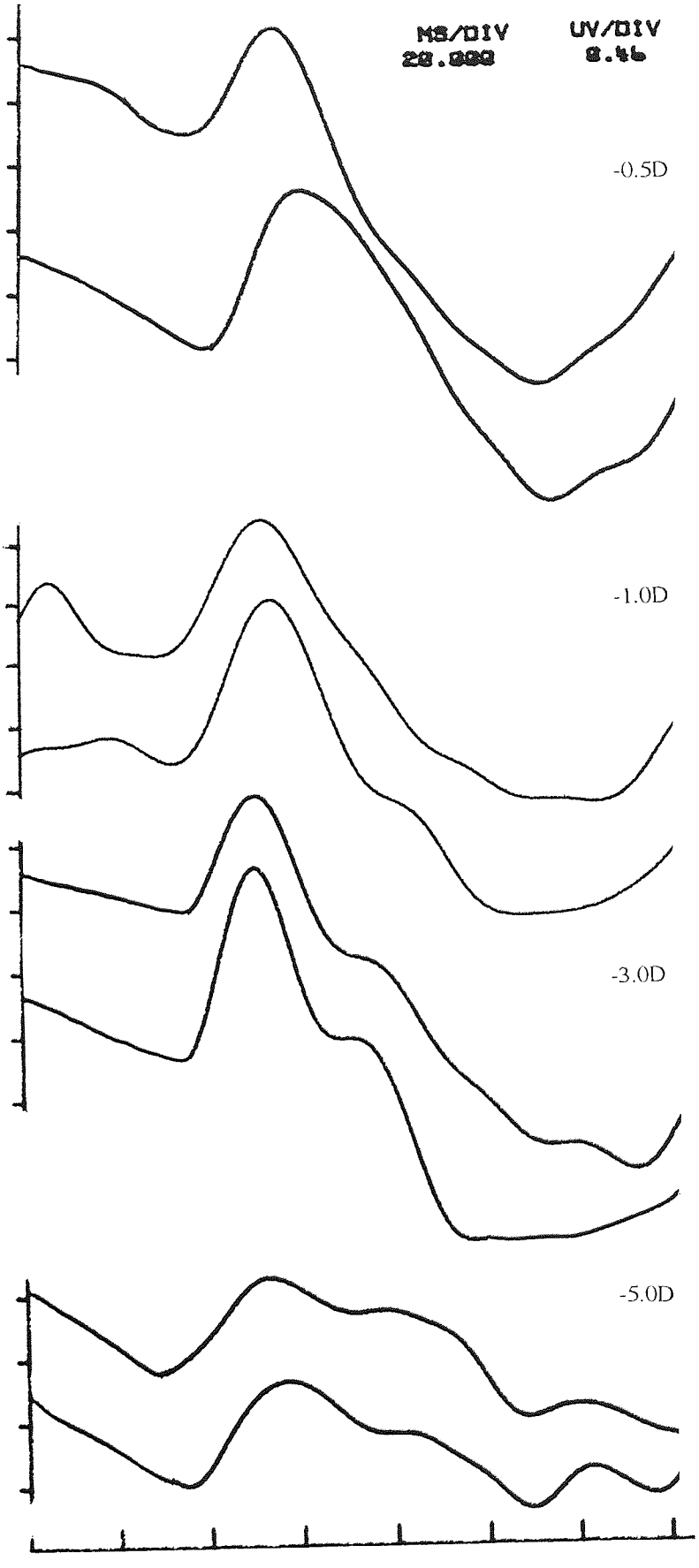


Fig 6.8 The defocussed (-D) transient rPERGs in the elderly (Subject EE/M/65yrs. RVA = 6/6).

The previous observations on the elderly in the age of 65-75 years showed that the standard variation of the PERG amplitude could be as large as ± 0.75 μV plus a mean value of 1.6 μV for P50 amplitude at 56' checks, with a 46.8 % deviation coefficients of variation (CV). With the same size of patterns and under the same stimulation condition, the standard deviation of the P50 amplitude in the young was 0.31 μV, being 8.6% deviated from the mean value 2.97 μV. Comparatively the CVs of the N95 amplitudes for the elderly were close to those in the young. Such large variations of the P50 amplitude was related probably to individual difference in refractive erorrs (or large and individually-varied straylight). The results suggested that the age-related changes in the peripheral optics of the eye should be paid more attention, especially the type of ametropia when the elderly PERGs were analysed.

Effect of defocus on the PERGs in the young have been reported. Millodot and Riggs (1970) and Odom et al (1982-83) observed that the PERG amplitude decreased with the degree of refractive errors. Chelva and van Lith (1982) reported reduced PERG amplitudes by blurring the pattern contours with defocus. Arden et al (1982) found a 0.5 defocus to be the minimum degree of blurring necessary to cause a significant PERG reduction when the accommodation of the eye was paralysed or when the refraction was artificially varied with lenses. Leipert and Gottlob (1988) demonstrated that insertion of spherical plus lenses from a power of 2.0D led to a significant decrease of both P50 and N95 amplitudes, which was caused by the refractive failure of accommodation. Inserting +1.0D decreased the initial P50 amplitude to 0.65, while the N95 amplitude was at 0.85 of its initial value. Similar property was found in our observations, suggesting the different sensitivities of the P50 and N95 amplitudes to refractive errors of accommodation. It is unclear about the reasons that the N95 amplitude was more sensitive to convex defocussing lenses in the elderly. The results showed a difference in the sensitivities of the N95 amplitude to the type of refractive errors in the elderly.

Summary

Aging was found to effect the rPERG amplitudes more effectively than its latencies. The factors producing these effects were analysed in the present studies. The retinal luminance reduction resulted from optic changes contributed mostly to the P50 amplitude loss, and the contrast loss as well as the retinal neuronal deterioration were demonstrated to related with the N95 amplitude loss. The pattern specific and luminance-related responses of the rPERG were found

to be affected equally by aging but in the post-retinal levels, only the spatial frequency channels were selectively effected.

The refractive errors due to aging were suspected to be the main causes for the large variations of the elderly PERG. In normal condition, the errors were allowed between ±0.25 - ± 1.65D for maintaining normal vision, which was presumed the reason for the large variation of the P50 amplitude in the elderly, implying that the illuminance-related response of the rPERG in the elderly was prominently effected. The effects of defocus were demonstrated to be different in the youth and the elderly. P50 was more sensitive to defocus than N95, when both convex and concave diopters were used in the youth and concave diopters in the elderly. The convex lenses showed their solely effect in the elderly that the N95 amplitude was more sensitively affected than the P50.

CHAPTER 7.

ELECTROPHYSIOLOGICAL STUDIES ON PATIENTS WITH ANTERIOR ISCHAEMIC OPTIC NEUROPATHY (AION) AND RETINAL ISCHAEMIA (RI)

Introduction

AION

The term ' ischaemic optic neuropathy' was first introduced by Miller and Smith in 1966 to describe ' a relative acute loss of visual function, usually with one eye involved in each episode, occurring in individuals at least in the fifth decade of life with little or no return of lost function; in addition, the fundus appearance is considered typical when sector or general pallid disc swelling is present at the onset of the visual systems (Dan et al., 1975).

The basic pathological changes of the anterior ION is that the occlusion of the posterior central arteries (PCAs) produces the infarction of the optic head as well as the retrolaminar part of the optic nerve (Hayreh, 1969). The determining factor for the production of AION is the level of the perfusion pressure in the PCAs as compared to the intraocular pressure. There are many causes for the fall in perfusion pressure in the PCAs such as local vascular causes, resulted from *atherosclerosis* and *temporal arteritis*, etc; and systemic causes due to *arterial hypertension*; and elevation in intraocular pressure as *chronic simple glaucoma* and *drusen in the optic nerve head.* The retinal circulation during the whole process is normal except in the case resulted from temporal arteritis (Foulds, 1969). Clinically, the AION caused by temporal arteritis is termed the arteritic AION and that caused by other reasons the non-arteritic AION.

Clinical presentation of patients with ION is reflected in patient's visual acuity, visual field defects, ophthalmoloscope exam and medical symptoms, depending on the etiology. The patients visit clinicians with sudden loss of visual function and present a typical optic head when examined. Since the diease occurs suddenly and develop progressively, the early electrodiagnositic tests combined with examinations could effectively assist clinicians for differentiating treatment from other diseases with similar symptoms.

Retinal Ischamia

As the AION, retinal ischamia (RI) is a term to describe the pathological status in the retina rather than a diagnosis on a disease. The retinal ischamia describe a condition in which blood supply is inadequate to supply the metabolic needs of the retina. Different from the optic neuropathy resulted from the infarction of the PCAs in the AION, the vascular involvement in the RI is dependent upon two vascular sources: one is choroidal circulation arising from cilliary arteries and retinal circulation from the ophthalmic artery. Due to the anatomical distribution of the arteries and their branches, the RI could be divided into several patterns. The commonly patterns are retinal veinous occlusion (RVO), retinal artery occlusion (RAO) and retinopathy.

The RVO, is mostly caused by *arteriosclerosis*, *hypertension* and diabetes mellitus (Gutman, 1983). For the RAO, most of cases are central retinal artery occlusion (57%) and branch retinal artery occlusion (38%) (Brown and Shields, 1979), caused by atheomatous disease or emboli, hypertension and advanced arteriosclerosis. *Temporal arteritis* is rare in developing into the CRAO, but well over 90% of BRAO involves the disease (Brown et al., 1981).

Though the symptoms leading patients to see the clinicians are various, the clinical techniques are effective method to diagnose the disease as well as its type. Yet, the etiology between the AION and RI is so similar that differentiating diagnosis on patients with the AION from those with RI is necessary in some cases, especially when the patients are over 50 years old with a bad vision in one eye and have a history of some of these diseases as arteriosclerosis and temporal arteritis.

In the present studies, there were 5 cases which were suspected as the AION and 3 cases as the RI. They were referred to the Clinical Neurophysiology Unit at the Aston University of Birmingham for the tests. The attention was paid on the characteristics of these cases and efforts were made to find some typical features in the electrophysiological responses as well as their values in ascertaining the clinical diagnosis on these two diseases.

Visual Stimuli and Routine Tests

The following teats were conducted in the present observations on the patients: flash ERG, pattern ERG; flash VEP and pattern VEP.

Flash stimulator was the photostimulator (Grass instruments) with a xenon flash lamp for full field stimulation. Patients wore the matte goggles for even light distribution and eye protection and sat in front of the stimulator comfortably. The flash stimulation for recording the flash ERG was of three types: scotopic, photopic and flicker stimulation and the recordings were obtained binocularly. The same instruments were used for recording monocularly the flash VEP.

The scotopic ERG was obtained by single flash stimulation after patients were dark adapted for 10 minutes. The photopic stimulation was presented by 10 times of flashes emitted at 1Hz under the light room environment for recording the photopic ERG. The flickers were presented by the same stimulator as used for the other two flash ERG tests. The flicking flashes were set at a rate of 30 Hz and presented 10 times for the superimposition under room light. The intensity for the flash ERGs was set at Intensity 8. Flash VEP was recorded at Intensity 4 and obtained by 50 times of satisfying results.

The pattern stimulator was an optical projecting stimulator designed by the Clinical Neurophysiology Unit. The checks were white and black patterns and reversed at 1-2Hz for producing a luminance difference between white and black checks. In some occasional cases, 6Hz was used for getting the response. Pattern contrast was kept at 80% with a mean luminance level of 60 cd/m^2. The stimulation field was 14° x 14°, subtending at three sizes, 28' , 56' and 112' as the routine pattern stimuli. The pattern sets were used for recording both binocular PERG and monocular PVEP. The record was the average of 50 times of responses for PVEP and of 150 times for PERG.

The ERGs were recorded by DTL placed at the cornea, referred to the ipsilateral outer canthus. The VEPs were recorded with two Ag-AgCl electrodes placed on the occipital scalp. The recording electrodes were referred to C3 (for O1) and C4 (for O2). Fz in the 10/20 system provided a reference place for the records. The forehead acted as the ground. The records were made on the Nicolet Pathfinder II system. The bandpass was set at 0.5 -100Hz for recording the responses and 0.5 - 49Hz for the digital filtering after the session, if necessary.

Normal Measures

Table 1 Flash ERGs (mean ±SD, n=12)

		a-wave (ms)	b-wave (ms)	a-b wave (μV)
photopic ERGs	OD	19.3±1.61 (22.5)	30.6±1.78 (34.2)	39.1±4.93 (30.5)*
	IOD	2.9±1.27 (5.4)	1.5±0.46 (2.4)	8.3±2.12 (12.5)
flicker ERGs	OD	20.7±1.93 (24.0)	31.3±0.83 (30.0)	35.3±9.23 (16.8)*
	IOD	3.8±0.70 (5.2)	0.8±0.20 (1.2)	5.6±1.53 (8.7)*
scotopic ERG	OD	24.1±0.88 (25.9)	46.8±1.92 (50.6)	232.7±22.98 (186.7)*
	IOD	1.3±0.59 (2.5)	2.8±0.83 (4.5)	39.1±10.27 (59.6)*

Table 2 Averaged Transient rPERGs (mean ±SD, n=12)

Check size	Latency (ms)		Amplitude (μV)		
	P50	N95	P50	N95	N95/P50
28'	55.6±1.26 (58.2)	104.5±2.31 (109.0)	1.2±0.15 (0.8)*	2.5±0.21 (2.1)*	2.3±0.21 (1.9)*
56'	52.4±0.86 (54.1)	97.7±1.80 (101.3)	1.6±0.38 (0.9)*	2.2±0.17 (1.9)*	1.6±0.17 (1.3)*
112'	49.4±2.01 (54.3)	97.4±2.04 (101.5)	1.6±0.39 (0.82)*	2.3±0.12 (2.1)*	1.7±0.18 (1.2)*

Table 3 Flash VEPs (mean±SD, n=13)

	P1 (ms)	N2 (ms)	P2 (ms)	P1-N2 (μV)	N2-P2 (μV)
L-H	75.6±2.01 (79.6)	102.7±2.56 (107.9)	127.6±1.17 (129.8)	6.3±1.16 (4.0)*	8.3±1.06 (6.2)*
R-H	76.4±1.72 (89.0)	100.6±2.78 (106.1)	125.8±1.62 (127.4)	6.8±1.01 (4.8)*	8.5±1.07 (6.4)*
IHD	4.1±0.91 (5.1)	3.4±0.67 (4.7)	2.0±0.81 (3.6)	0.8±0.27 (1.34)	0.9±0.27 (1.44)
IOD	3.6±0.96 (5.5)	2.8±0.54 (3.9)	7.0±2.16 (11.3)	2.0±0.34 (2.7)	1.0±0.22 (1.4)

Table 4 Averaged Transient rPVEPs (mean ±SD, n=13)

Check size	Latency (ms)				Amplitude (μV)
	N75	P100	P50-N75	P50-P100	N75-P100
28'	79.7±1.40 (82.5)	113.6±4.39 (122.4)	26.9±2.55 (32.0)	57.6±2.01 (61.6)	6.9±1.25 (4.4)*
56'	81.9±3.90 (89.8)	115.7±3.15 (125.0)	31.6±4.53 (40.7)	65.5±4.05 (73.6)	7.3±1.28 (4.8)*
112'	83.3±3.18 (89.7)	116.8±4.11 (119.9)	31.9±3.77 (39.4)	66.1±3.75 (73.6)	7.9±1.32 (5.2)*

Note: age range 55-65 years. n=12(13). mean±SD. The measures in parentheses represent the upper limit values. Parentheses with asterisks represent the lower limit values. The measures in OD lines were for a single eye. IOD was the interocular difference. IHD was the interhemisphere difference.

Patient 1

Date of test: 15/11/93.

Place of test: Vision Sciences Department, Aston University.

Diagnosis: (R) AION?

Visual acuity when tested: OD=6/12; OS= 6/9.

RESULTS:

Flash ERGs

		a-wave (ms)	b-wave (ms)	a-b wave (μV)
scotopic ERG(18)	OD	22	45	225.0
	OS	23	50	300.0
photopic ERG(18)	OD	13	33	58.1
	OS	14	33	54.6
flicker ERG (18)	OD	18	26	31.9
	OS	15	27	30.0

Pattern reversal ERGs

	112'			56'			28'		
	latency (ms)		amplitude (μV)	latency (ms)		amplitude (μV)	latency (ms)		amplitude (μV)
	P50	N95	N95: P50	P50	N95	N95: P50	P50	N95	N95: P50
OD	48.0	88	4.7 : 4.4	47	89	4.8 : 3.3	48	101	4.3 : 3.9
OS	42.0	102	2.7 : 2.6	44	101	4.7 : 3.6	47	90	4.1 : 3.3

Flash VEPs (I4)

	P1 (ms)	N2 (ms)	P2 (ms)	N2-P2 (μV)
OD	74.0	104.0	130.0	12.5
OS	85.0	104.0	134.0	10.0

Pattern reversal VEPs

	112'		56'		28'	
	P100 (ms)	N2-P2 (μV)	P100 (ms)	N2-P2 (μV)	P100 (ms)	N2-P2 (μV)
OD			116.0	4.8	107	2.3
OS	119	3.5	107.0	4.8	111	2.8

Comments: *Flash ERGs* were normal in both eyes except that the amplitude of the scotopic ERG in the right eye was reduced 25% (60ms) compared with the right eye. *Pattern ERGs* were normal, implying no damge in the inner retina layers. *Flash VEPs* were normal and symmetrical, with large P3. *Pattern VEPs* to all the checksizes were reduced and larger positive waves at 140-180ms.

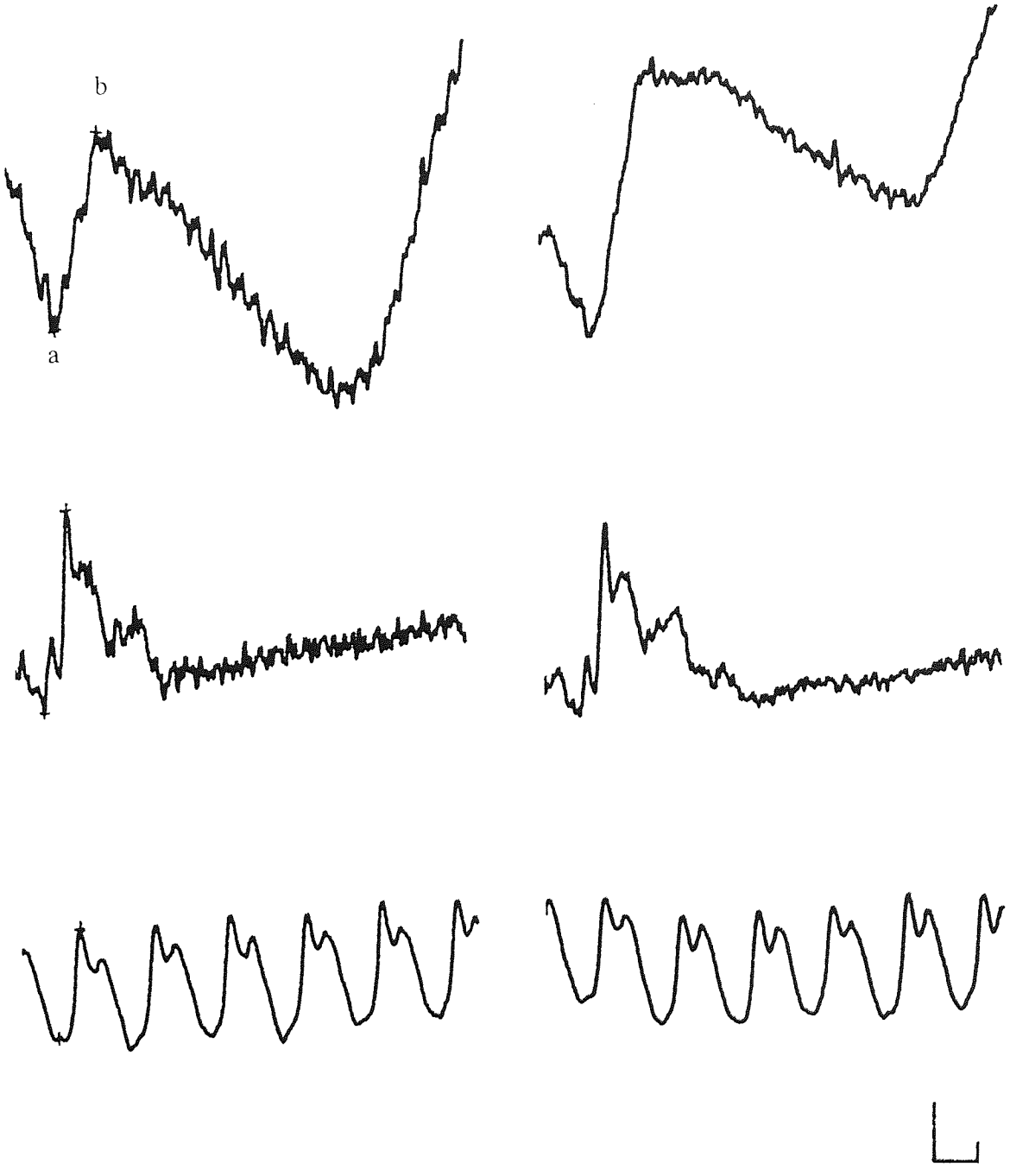


Fig. 7.1 Flash ERGs in patient 1. *Left column*: right eye (OD); *right column*: left eye (OS). *Calibr*: 60μV / 20ms (scotopic ERG) and 15μV/20ms (flicker and photopic ERGs).

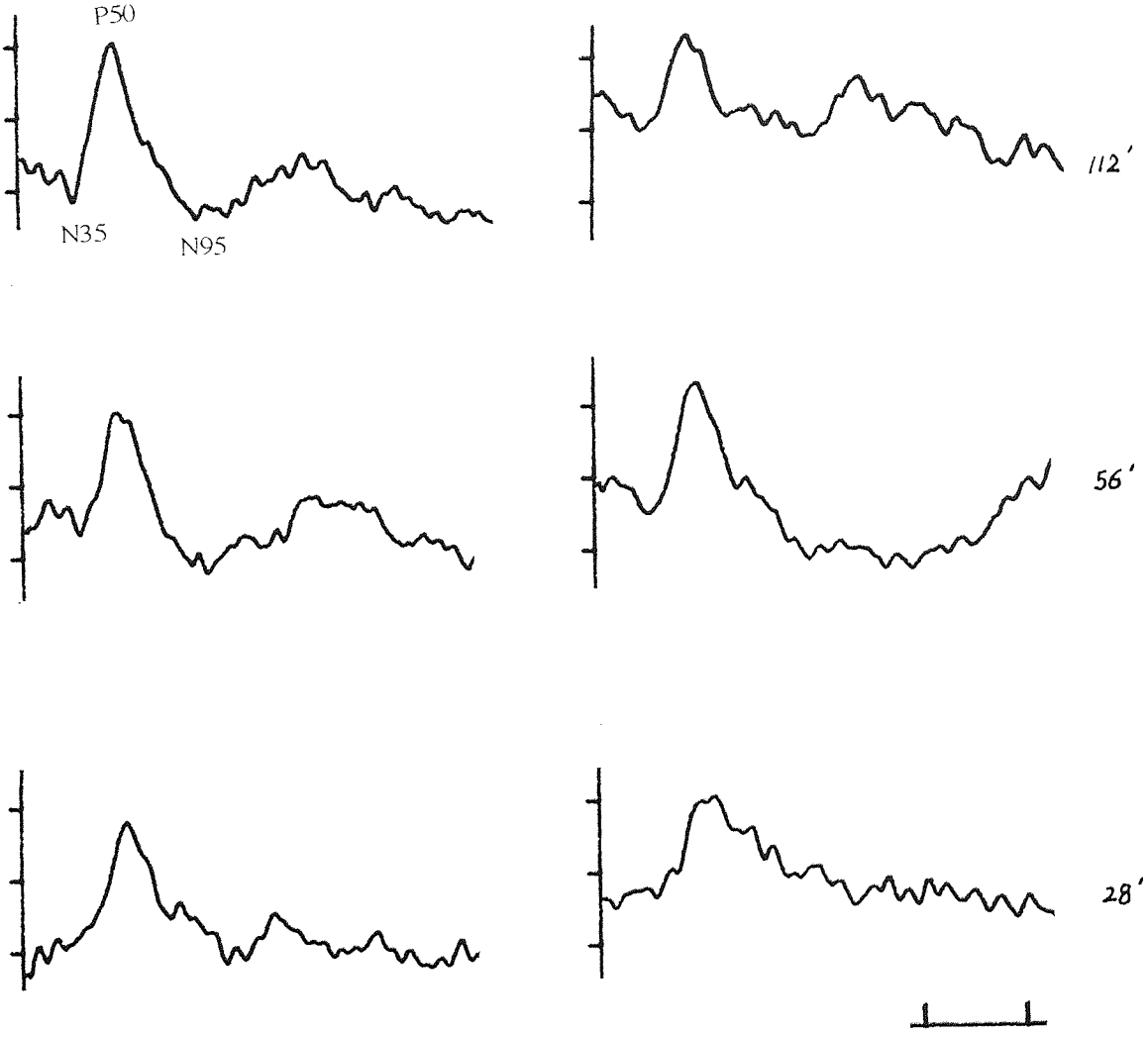


Fig 7.2 Transient rPERGs in patient 1 *Left column*: right eye (OD). *Right column*: left eye (OS). *Cali*: 1.87μV / 50ms.

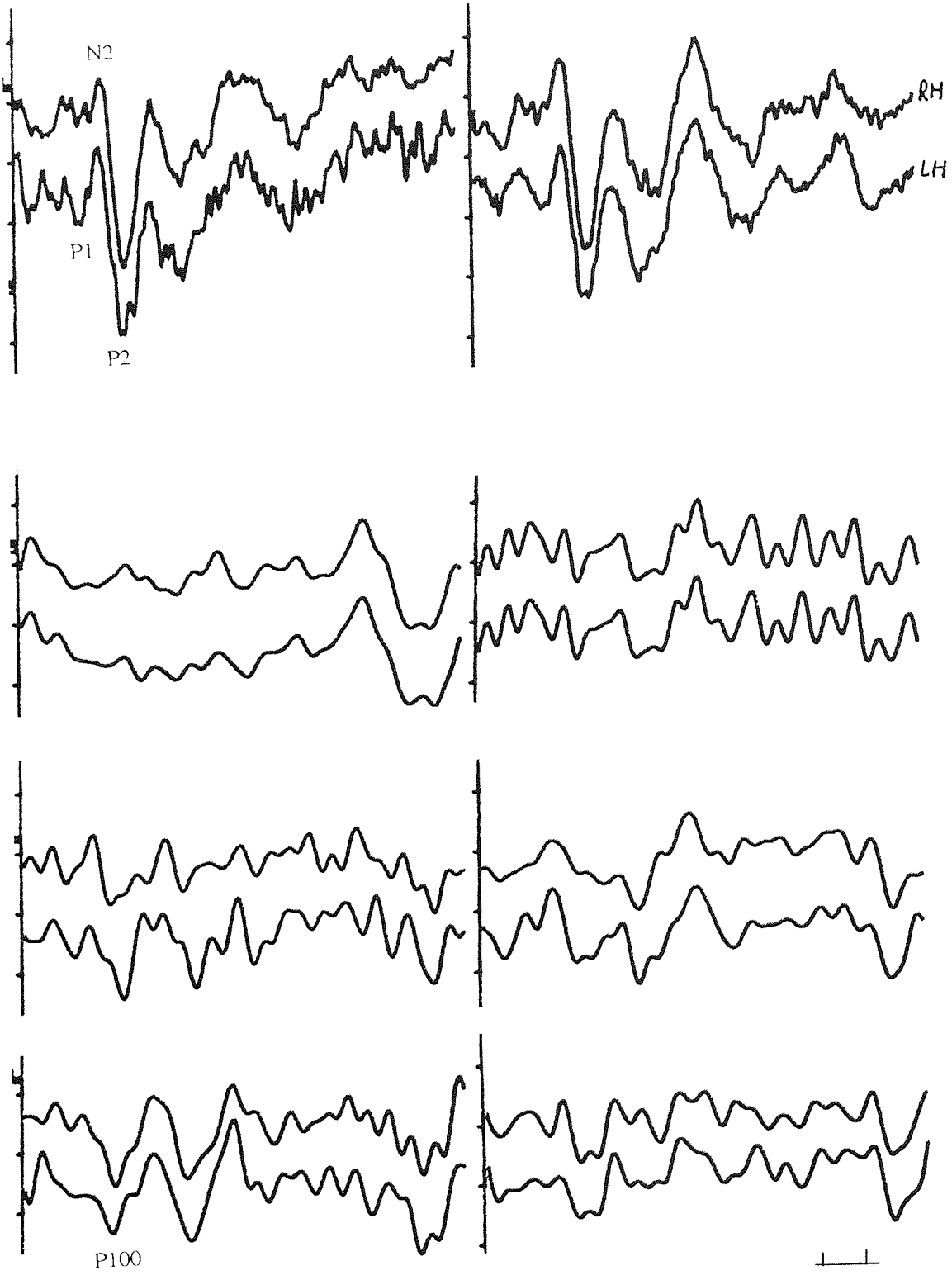


Fig 7.3 Flash VEPs (top) and transient rPVEPs in patient 1 *Left column*: OD. *Right column*: OS. *Calibration*: 3.75μV / 50ms.

Patient 2

Date of birth: 02/04/32.

Diagnosis: (L) AION?

RESULTS I (according to the records from the Birmingham Midland Eye Hospital (BMEH).

Test Date: 22/01/93. Visual acuity: OD-6/9; OS-6/36.

Flash ERGs

		a-wave (ms)	b-wave (ms)	a-b wave (μV)
scotopic ERG(I8)	**OD**	7.8	33	288.2
	OS	7.8	33	288.2
photopic ERG(I8)	**OD**	10.8	40	58.9
	OS	10.8	40	58.9
flicker ERG (I8)	**OD**	10.8	27	49.8
	OS	10.8	27	49.8

Flash VEPs

		P1 (ms)	N2 (ms)	P2 (ms)	N2-P2 (μV)
OD	I2	60	90	129	33.2
	I4	50	85	135	38.1
OS	I2	30	85	130	19.5
	I4	35	90	138	19.5

Pattern reversal VEPs

	2°		50'		25'	
	P100 (ms)	N2-P2 (μV)	P100 (ms)	N2-P2 (μV)	P100 (ms)	N2-P2 (μV)
OD	110	10.8	109	7.1	118	6.5
OS	107	11.9	104	6.0	114	8.1

Comments: All the measures of the *flash ERG* were normal to the age. The flash VEP amplitudes were reduced in the left eye. No evident delay was found. The responses were symmetrical in both hemispheres and both eyes. *PVEPs* were symmetrical and their latencies and amplitudes to three checksizes were in normal limit in both eyes.

RESULTS II (Vision Sciences Dept., Aston University Test date: 24/01/94.

Visual acuity--OD=6/9; OS= 6/9-2)

Flash ERGs

		a-wave (ms)	b-wave (ms)	a-b wave (μV)
scotopic ERG(I8)	**OD**	24	48	310
	OS	23	44	320
photopic ERG(I8)	**OD**	15	31	52.6
	OS	15	34	60.5
flicker ERG (I8)	**OD**	17	30	36.3
	OS	18	32	35.4

Pattern reversal ERGs

	112'			56'			28'		
	latency (ms)		amplitude (μV)	latency (ms)		amplitude (μV)	latency (ms)		amplitude (μV)
	P50	N95	N95: P50	P50	N95	N95: P50	P50	N95	N95: P50
OD	54	100	3.3 : 3.0	56	99	4.1 : 3.8	50	102	2.3 : 2.2
OS	(missed)			54	100	5.4 : 5.0	54	97	5.4 : 2.6

Flash VEPs (I4)

	P1 (ms)	N2 (ms)	P2 (ms)	N2-P2 (μV)
OD	61	92	117	20.1
OS	66	85	121	14.5

Pattern reversal VEPs

	112'		56'		28'	
	P100 (ms)	N2-P2 (μV)	P100 (ms)	N2-P2 (μV)	P100 (ms)	N2-P2 (μV)
OD	107	7.9	105	5.4	107	7.7
OS	110	8.9	110	9.0	110	7.5

Comments: *Flash ERG* were within normal limit. *Pattern ERGs* were normal in both eyes, implying no damage in the proximal retina. *Flash VEPs* were reduced in the left eye as in the first test (3 days earlier). *Pattern VEPs* showed 'W' waveforms in the left eye in response to large checks (112') but the amplitudes showed no abnormality. The results suggested a damage probably in the left prechiasmic optic nerve.

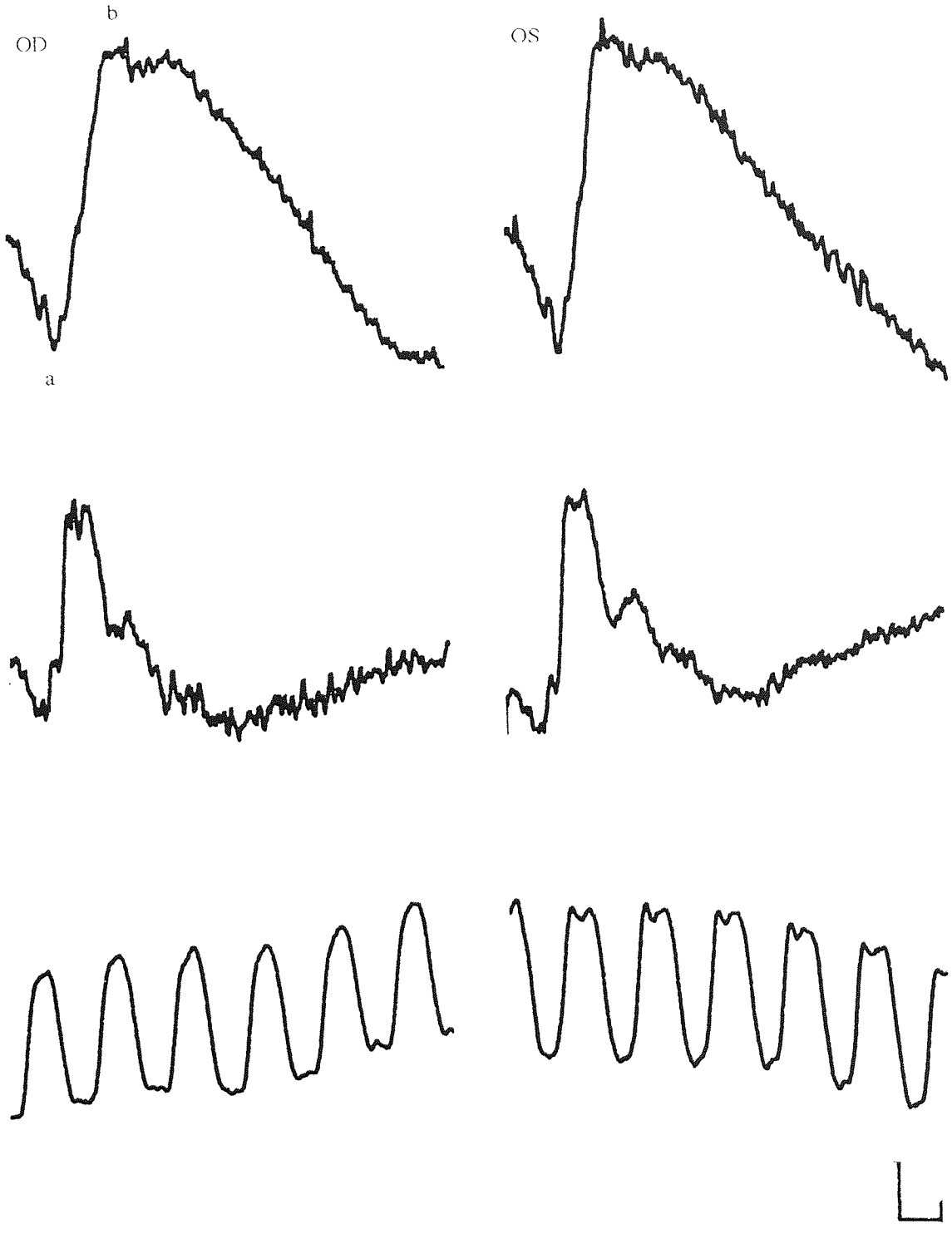


Fig 7.4 Flash ERGs recorded in patient 2 Cali: = 60μV / 20ms (scotopic ERG); 15μV / 20ms (photopic and flicker ERG).

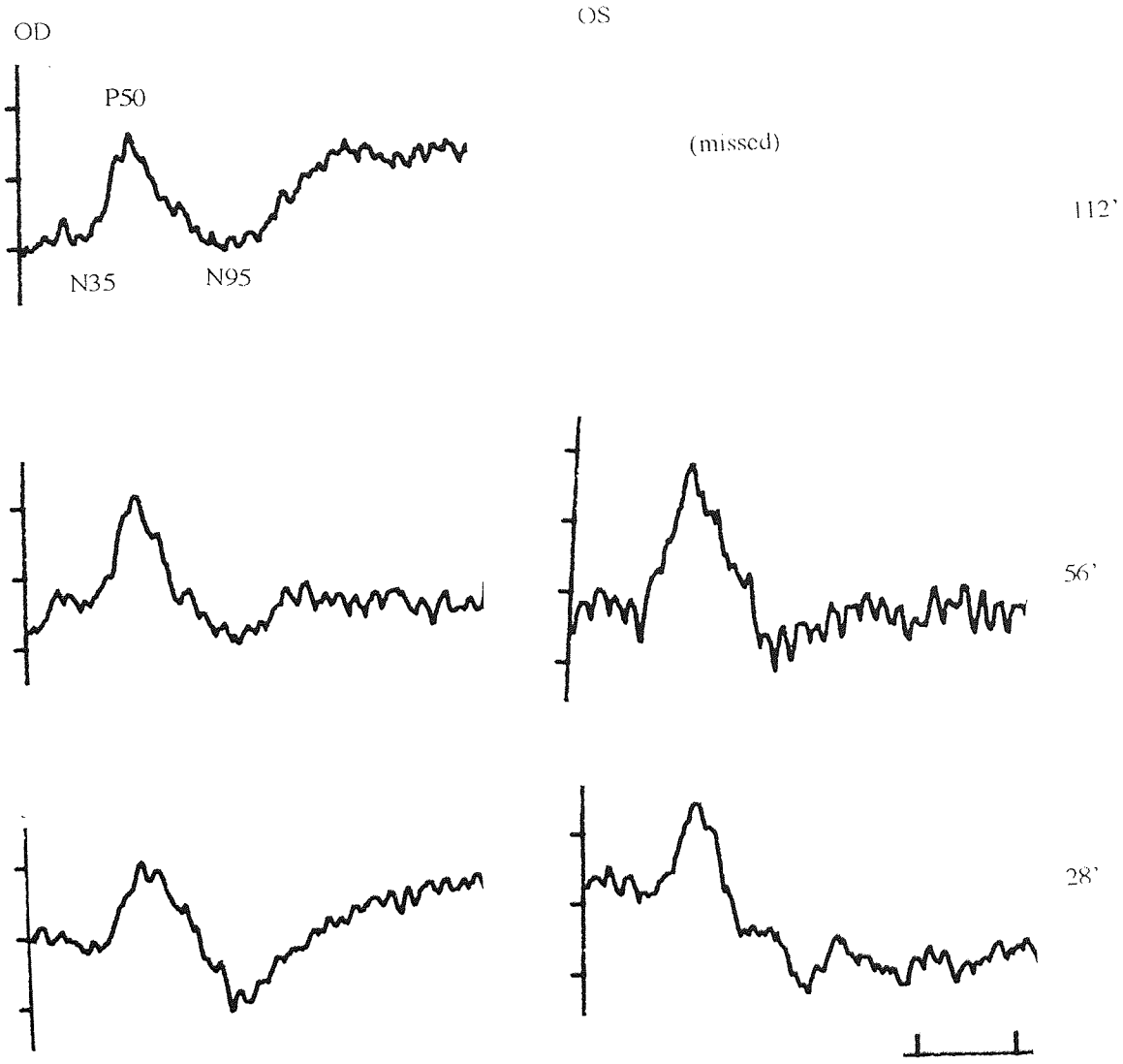


Fig 7.5 Transient rPERGs recorded in patient 2 Calib = 1.87μV / 50ms

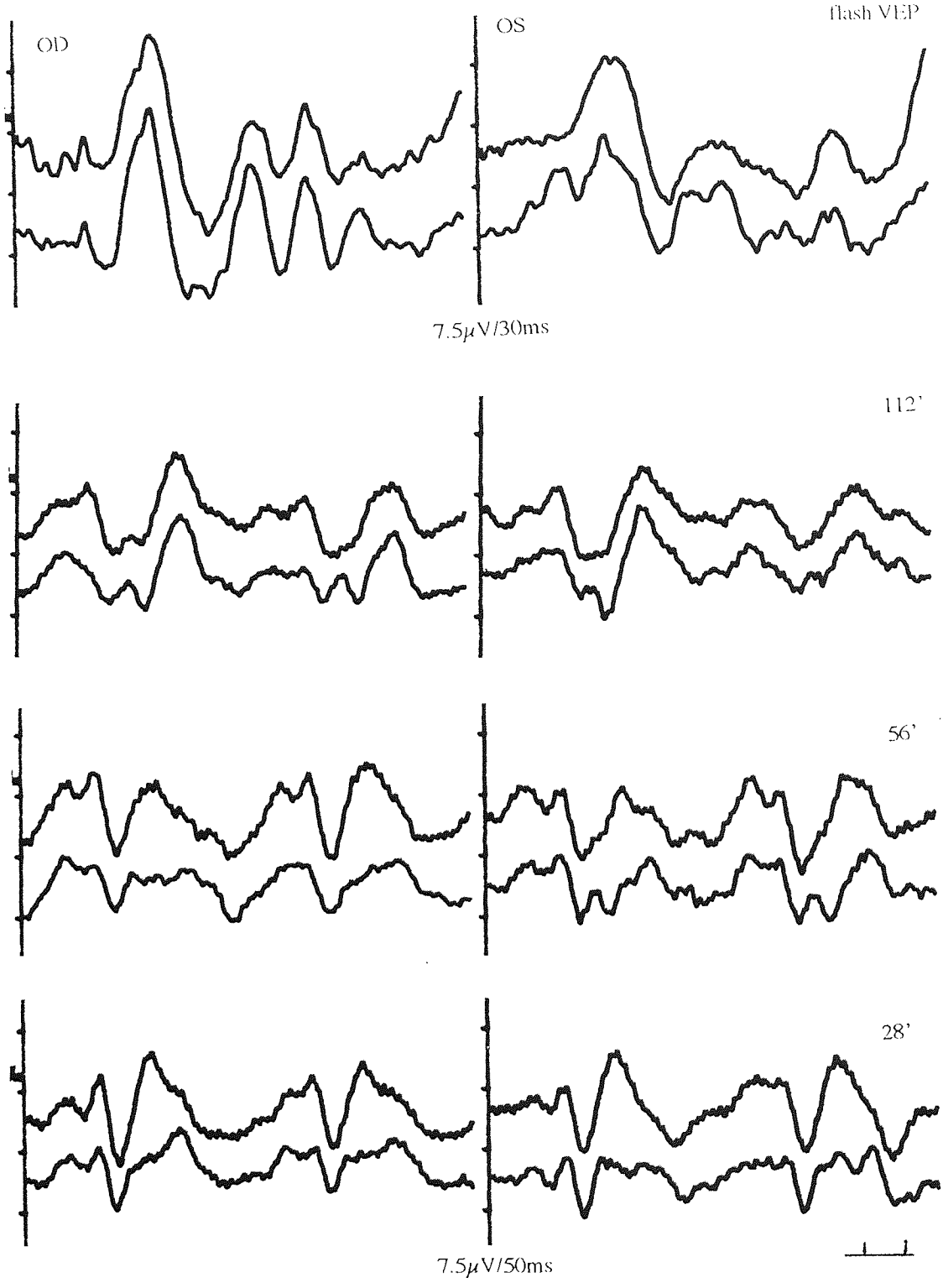


Fig 7.6 Flash VEPs (top) and transient rPVEPs in patient 2

Patient 3

Date of birth: 19/03/31.

Diagnosis: binoclar AION?

RESULTS I (according to records from BMEH. Test date-01/09/93. VA: OD=6/60; OS=6/36)

Flash ERGs

		a-wave (ms)	b-wave (ms)	a-b wave (μV)
photopic ERG(18)	OD	8	29	20.0
	OS	8	29	35.0
flicker ERG (18)	OD	18	28	11.7
	OS	18	28	18.7
scotopic ERG (18)	OD	18	39	61.0
	OS	14	34	104.9

Pattern reversal ERGs

(unrecordable)

Flash VEPs

		P1 (ms)	N2 (ms)	P2 (ms)	N2-P2 (μV)
OD	14	65	100	128	5.4
OS	14	70	105	127	5.4

Pattern reversal VEPs

	2°		50'		25'	
	P100 (ms)	N2-P2 (μV)	P100 (ms)	N2-P2 (μV)	P100 (ms)	N2-P2 (μV)
OD	(not recordable)					
OS	110	9.7	96	7.6	98	3.3

Note: All the *flash ERGs* latencies were normal but amplitudes were reduced, especially in the right eye. The *PERGs* were not obtainable. *Flash VEPs* in both eyes were just at normal lower limit and the responses were symmetrical and sychroneous between both hemispheres. *Pattern VEPs* was not recordable in the right eye and the response in the left eye kept normal to large checks but reduced to 28' checks.

RESULTS II (Vision Sciences Dept., Aston University Test date: 23/03/94.

Visual acuity--OD=FC; OS= FC)

Flash ERGs

		a-wave (ms)	b-wave (ms)	a-b wave (μV)
scotopic ERG(18)	OD	24.4	48.0	131.3
	OS	22.8	47.6	140-180
photopic ERG(18)	OD	15.2	29.2	40.9
	OS	17.2	33.2	34.1
flicker ERG (18)	OD	17.2	30.4	36.3
	OS	15.6	30.8	36.9

Pattern reversal ERGs

	112'		
	latency (ms)		amplitude (μV)
	P50	N95	N95: P50
OD	44	82	- : 1.3
OS	44	82	2.5 : 1.5

Flash VEPs (I4)

	P1 (ms)	N2 (ms)	P2 (ms)	N2-P2 (μV)
OD	75	102	129	6.1
OS	81	104	124	8.9

Pattern reversal VEPs

	112'	
	P100 (ms)	N2-P2 (μV)
OD	90	2.9
OS	106	3.6

Impression: *Flash ERGs* were normal ex cept the the scotopic ERGs were reduced, especially in the right eye. *PERGs* could be only recorded to checks of 112'. The response was normal in the left eye and reduced in the right eye, particularly N95. *Flash VEPs* were just on the lower normal limit in both eyes, with the response in the right eye slightly reduced. *PVEPs* in both eyes were reduced markedly and only recordable to large checks (112').

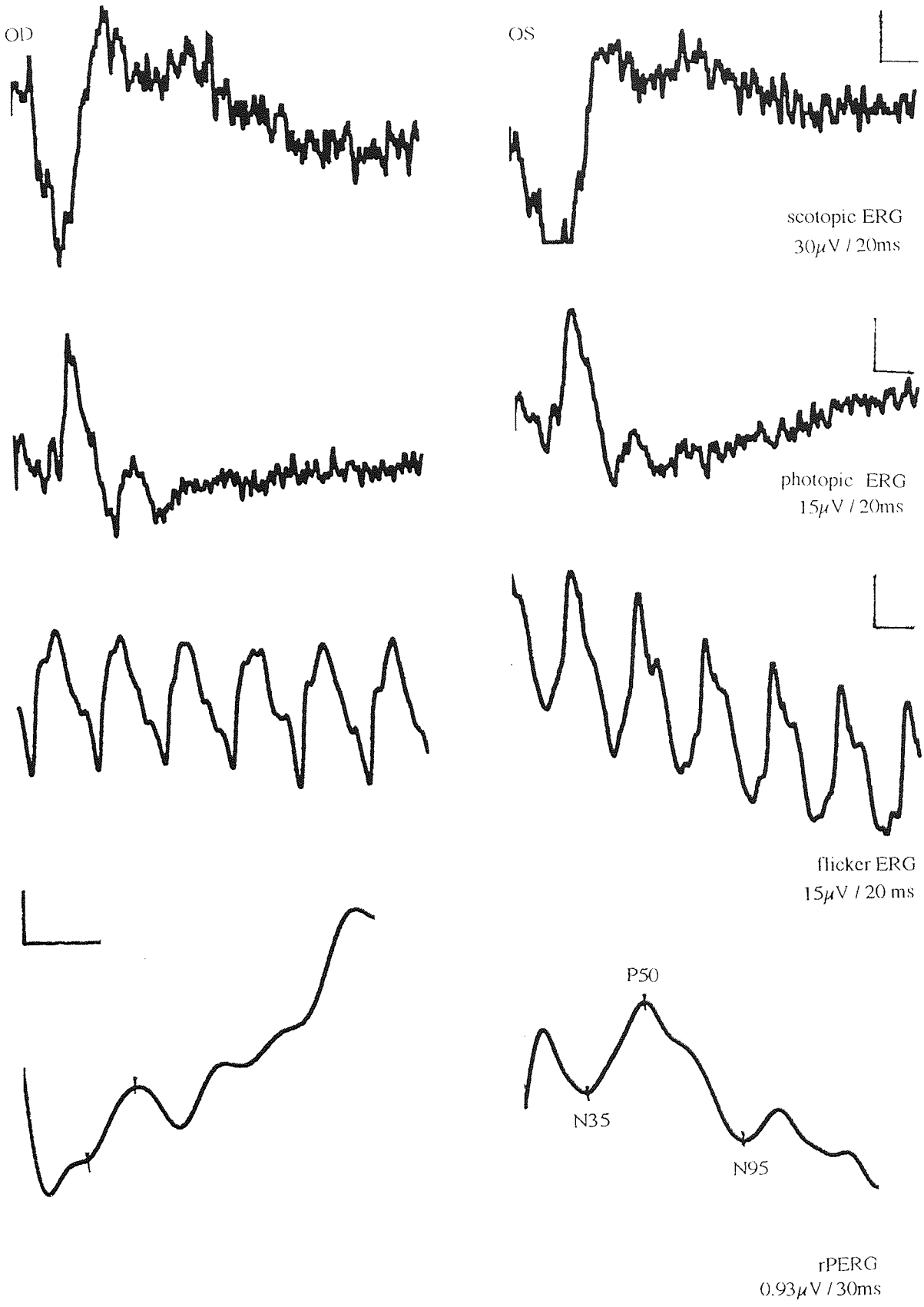


Fig 7.7 Flash ERGs and pattern reversal ERGs in patient 3

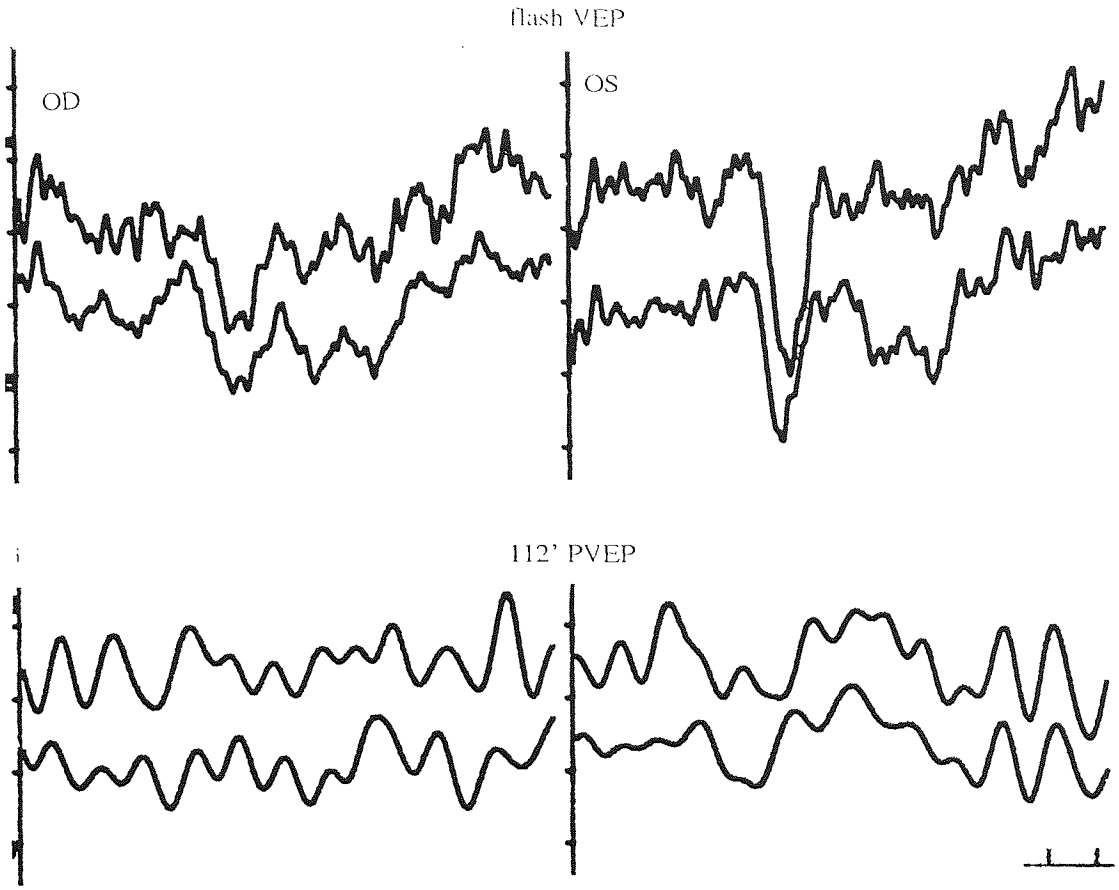


Fig 7.8 Flash VEPs (*top*) and pattern VEPs (*bottom*) in patient 3 (*Cali.* = 3.75μV / 30ms)

Patient 4

Date of birth: 02/04/32

Diagnosis: (R) AION?

Date of test: 21/09/94

Place of test:

Vision acuity when tested: OD=6/36; OS=6/18

RESULTS:

Flash ERGs

		a-wave (ms)	b-wave (ms)	a-b wave (μV)
scotopic ERG(I8)	OD	21	60	270.0
	OS	24	60	240.0
photopic ERG(I8)	OD	15	33	36.7
	OS	16	33	34.2
flicker ERG (I8)	OD	18	30	20.8
	OS	18	31	17.5

Pattern reversal ERGs

	56'			112'		
	latency (ms)		amplitude (μV)	latency (ms)		amplitude (μV)
	P50	N95	N95: P50	P50	N95	N95: P50
OD	50	96	2.1 : 1.0*	50	-	- : 0.7
OS	50	96	1.1 : 0.9	50-	-	- : 0.5

Flash VEPs (I4)

	P1 (ms)	N2 (ms)	P2 (ms)	N2-P2 (μV)
OD	-	78	124	5.8
OS	-	79	115	6.3

Pattern reversal VEPs

	112'		56'		28'	
	P100 (ms)	N2-P2 (μV)	P100 (ms)	N2-P2 (μV)	P100 (ms)	N2-P2 (μV)
OD	129	3.6	134	2.7	134	5.2
OS	127	8.6	134	8.3	125	8.5

Impression: *Flash ERGs* were normal in two eyes. *PERGs*, particularly N95, were reduced and the response to small checks (28') could not be recorded. The right eye was found difficult to follow the fast reversal stimulation (6Hz) and was in contrast to the left eye, suggesting an possible inner retinal damage. *Flash VEPs* was normal. *Pattern VEPs* in the right eye was delayed and reduced to all the checksizes.

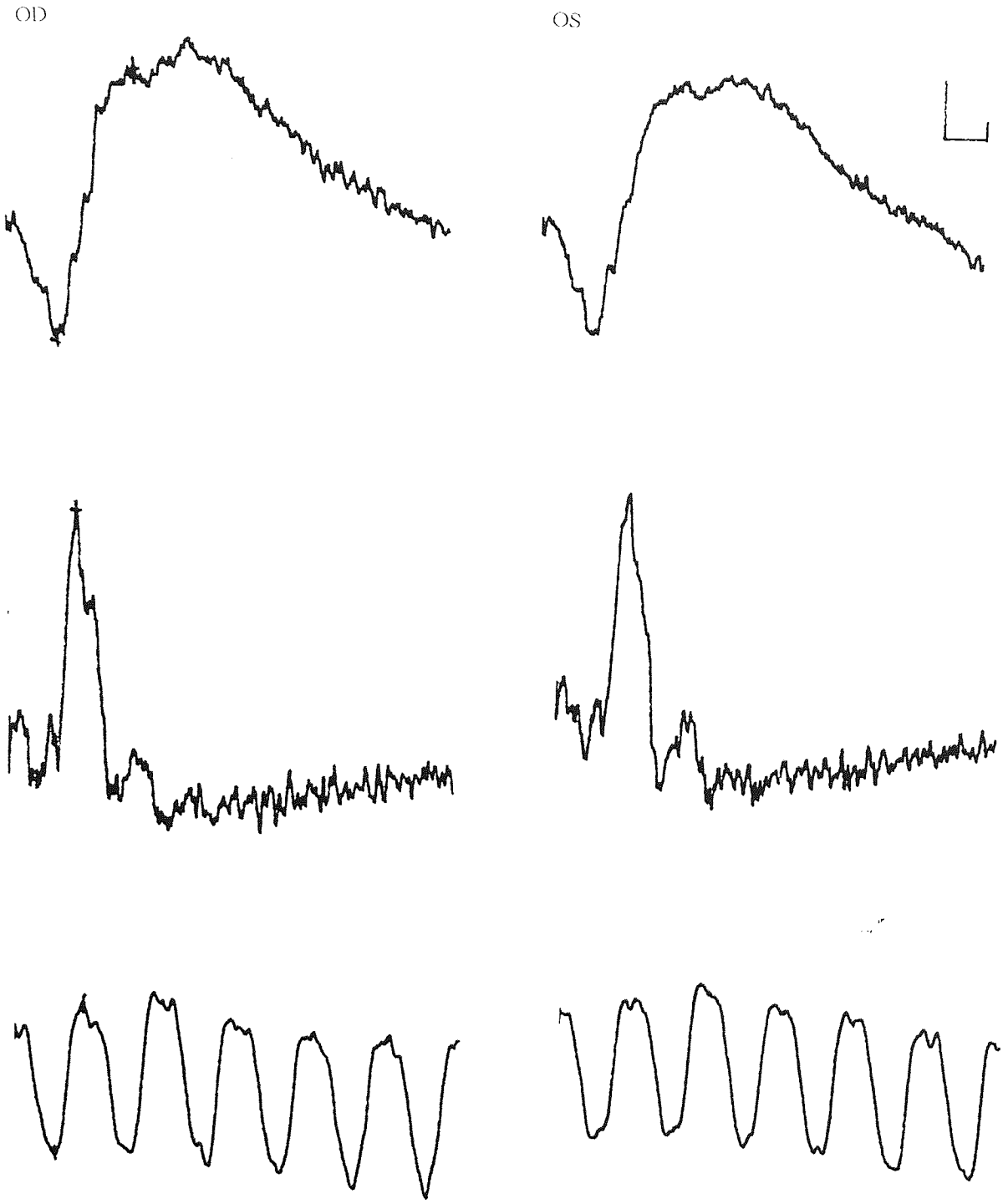


Fig 7.9 Flash ERGs in patient 4 (Calibration. = 50μV / 20ms -- scotopic ERG; 15 μV / 20ms --photopic and flicker ERGs).

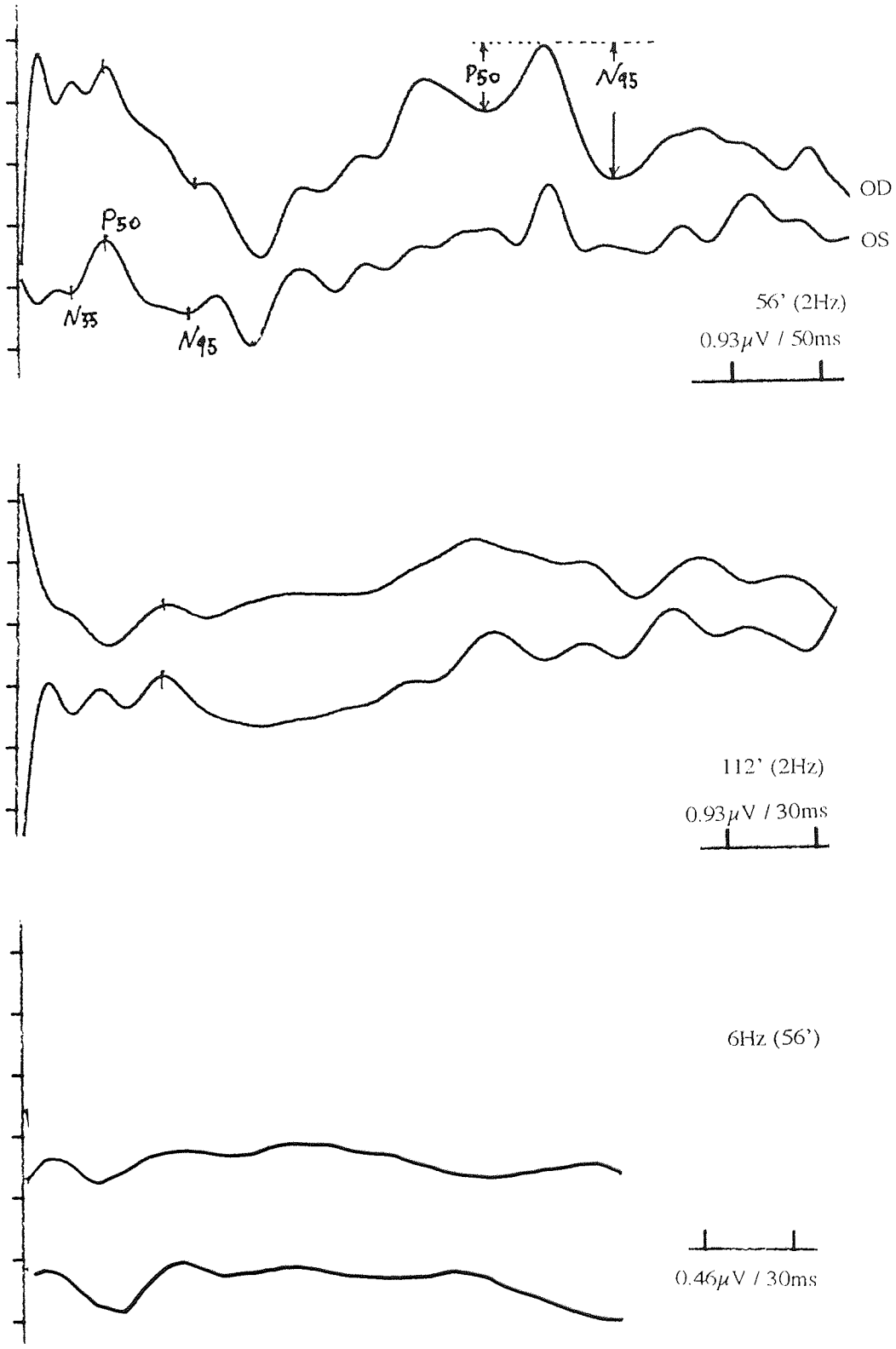


Fig 7.10 Pattern reversal ERGs in patient 4

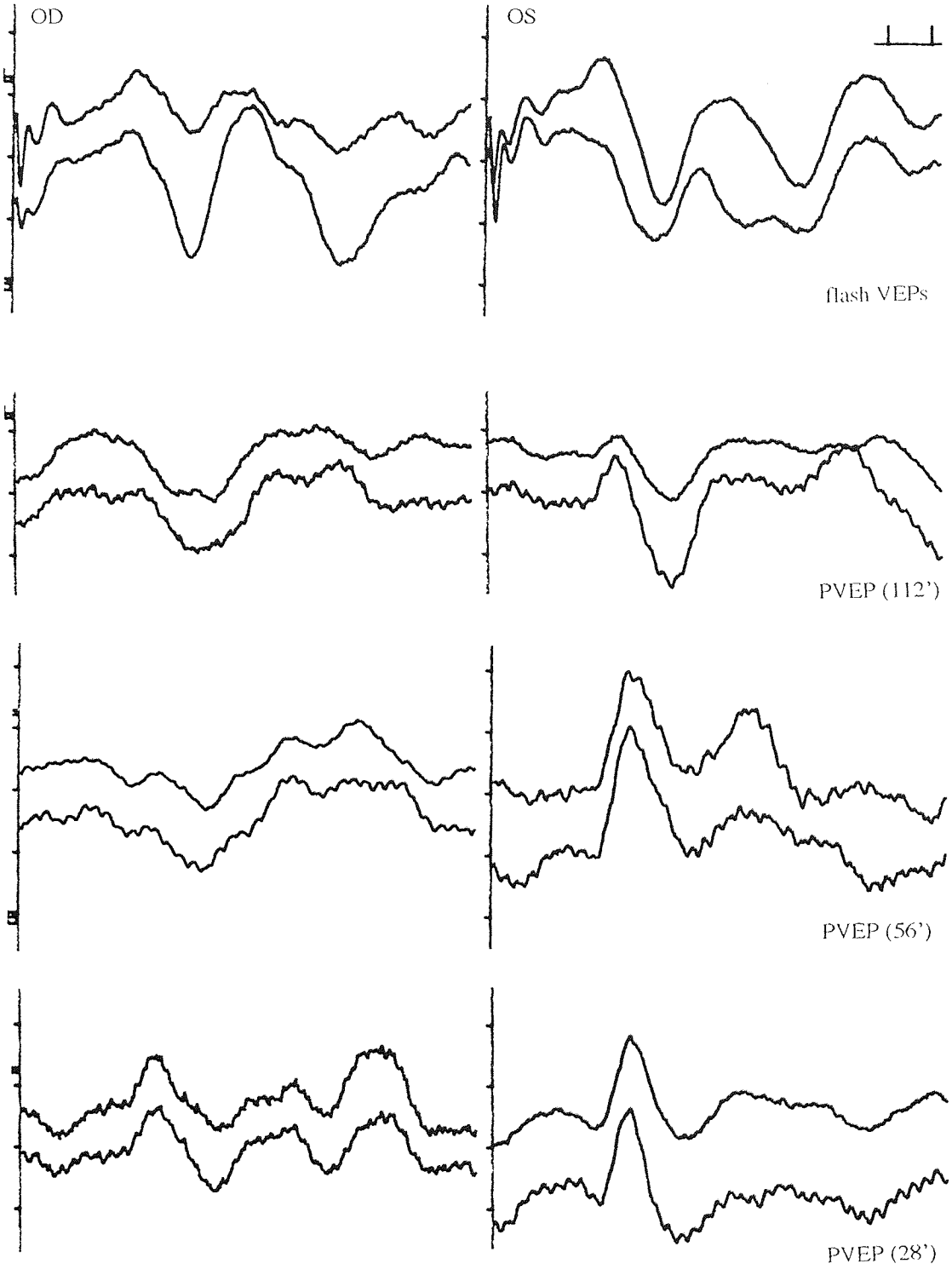


Fig 7.11 Flash VEPs and transient rPVEPs in patient 4 *Cali.* = 3.75μV / 30ms.

Patient 5

DOB: 29/10/29.

Diagnosis: (OS) AION? CSG? low & altitudinal field loss.

Medical history: cataract and glaucoma in both eyes, with more severe in the right eye. Right eye was more difficulty in colour perception than the left eye. The concentration and cooperation was poor during the tests.

RESULTS I (according to the records from the Birmingham Midland Eye Hospital (BMEH).

Test Date: 06/05/93. Visual acuity: OD-6/12; OS-6/9.

Flash VEPs

		P1 (ms)	N2 (ms)	P2 (ms)	N2-P2 (μV)
OD	12	64	91	129	8.1
	14	62	86	124	13.6
OS	12	59	82	130	4.9
	14	55	95	128	5.0

Pattern reversal VEPs

	2°		50'		25'	
	P100 (ms)	N2-P2 (μV)	P100 (ms)	N2-P2 (μV)	P100 (ms)	N2-P2 (μV)
OD	94	-	108	-	133	-
OS	108	-	110	-	150	-

Comments: The latencies of the *flash VEPs* were normal anf amplitudes of the left eye were reduced compared with those of the right eye. The amplitudes of the pattern VEPs were almost unrecordable and latencies of the responses to 25' checks were delayed.

RESULTS II---*Flash ERGs*

Date of Test: 19/08/93

Visual acuity: 6/9 (OD); 6/9 (OS)

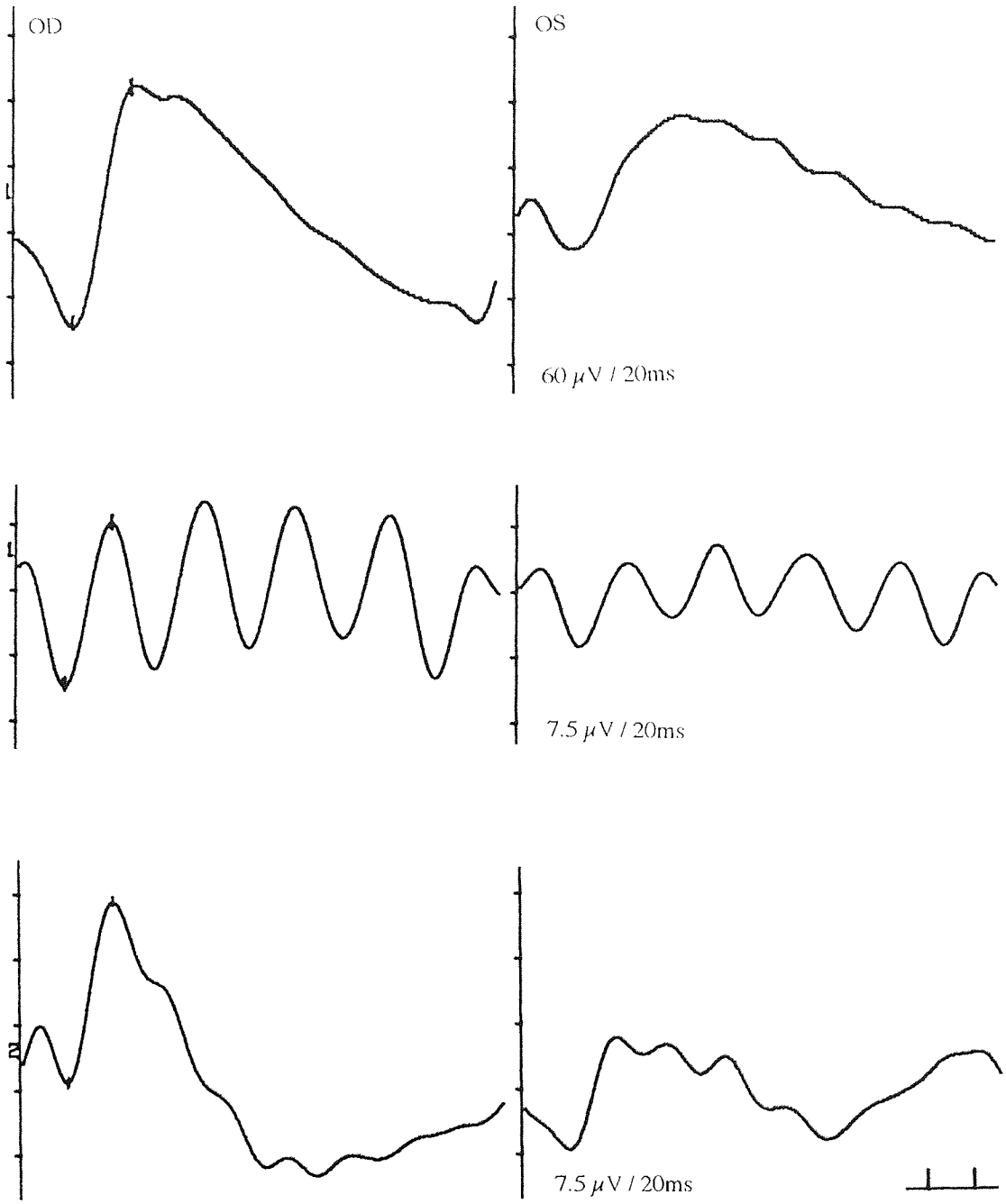
		a-wave (ms)	b-wave (ms)	a-b wave (μV)
scotopic ERG(I8)	OD	24.0	51.2	232.0
	OS	29.2	57.6	121.9
photopic ERG(I8)	OD	20.0	38.4	20.5
	OS	19.2	38.0	12.9
flicker ERG (I8)	OD	19.6	40.4	18.7
	OS	25.6	45.6	9.6

Date of Test: 28/03/94

Visual acuity: 6/60 (OD); 6/18 (OS)

		a-wave (ms)	b-wave (ms)	a-b wave (μV)
scotopic ERG(I8)	OD	24	57	273
	OS	28	52	120
photopic ERG(I8)	OD	22	42	16.0
	OS	22	42	5.9
flicker ERG (I8)	OD	26	40	28.0
	OS	26	42	14

Comments: *Flash ERGs* were reduced in the left eye and the abnormality did not progress after 7 months when the vision acuity was very poor.



VA = 6/9 (OD); 6/9 (OS)

Fig 7.12 Flash ERGs in patient 5. (DOT =19/08/93)

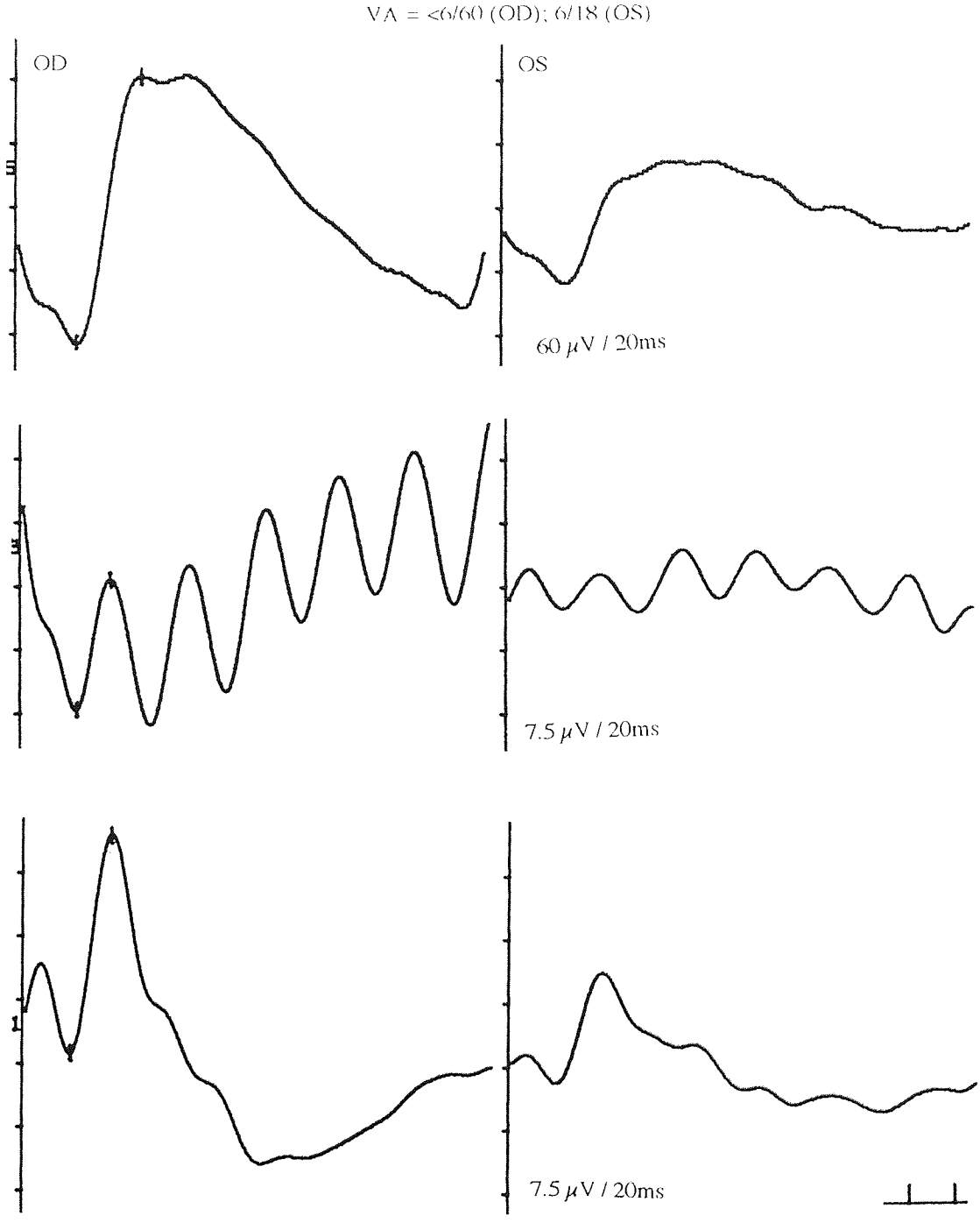


Fig 7.13 Flash ERGs in patient 5 (DOT = 28/03/94)

RESULTS III---*pattern ERGs*

Date of Test: 19/08/93

Place of Test: Vision Sciences, Aston University

Visual acuity: 6/9 (OD); 6/9 (OS)

Pattern reversal ERGs

	112'			56'			28'		
	latency (ms)		amplitude (μV)	latency (ms)		amplitude (μV)	latency (ms)		amplitude (μV)
	P50	N95	N95: P50	P50	N95	N95: P50	P50	N95	N95: P50
OD	50	89	1.3 : 0.5	55	110	2.1 : 0.8	56	107	(-) : 1.2
OS	60	105	1.9 : 1.2	50	115	3.2 : 1.6	55	123	1.9 : 1.3

Date of Test: 28/03/94

Place of Test: Vision Sciences, Aston University

Visual acuity: 6/36 (OD); 6/18 (OS)

Pattern reversal ERGs

	112'			56'			28'		
	latency (ms)		amplitude (μV)	latency (ms)		amplitude (μV)	latency (ms)		amplitude (μV)
	P50	N95	N95: P50	P50	N95	N95: P50	P50	N95	N95: P50
OD	68	(-)	(-) : 2.7	(unrecordable)			(unrecordable)		
OS	63	103	3.5 : 1.7	(unrecordable)			(unrecordable)		

Comments: *PERGs* were nearly normal when the subject was first time tested except that the N95 responsive to checks of 28' could not be found. Seven months later, the PERGs progressed makedly in the negative direction, suggesting a progresive development of the damage in the inner retina layers, especially of the right eye. The progress of the PERGs was consistent with patient's vision deterioration.

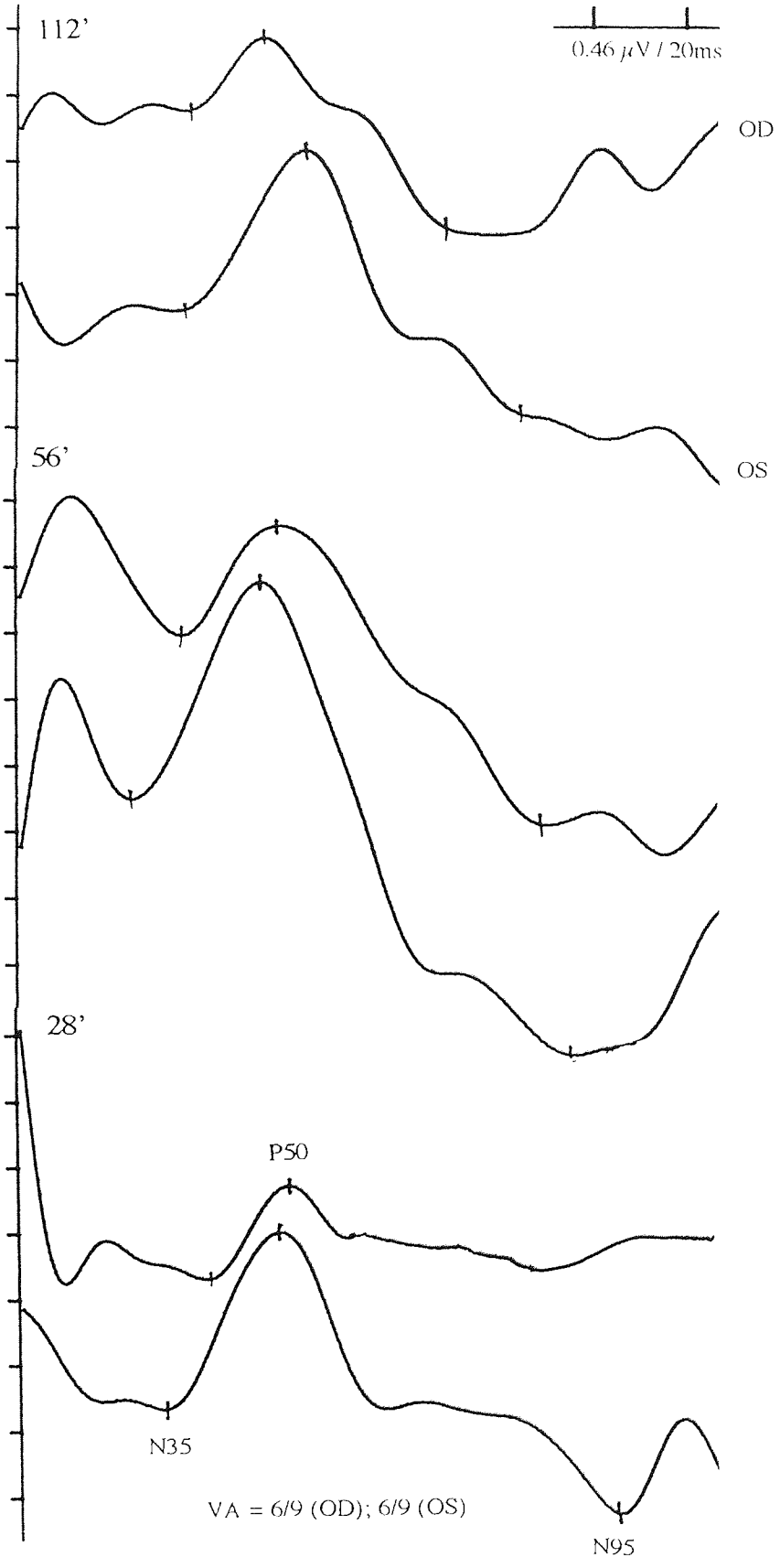


Fig 7.15 Pattern reversal ERGs in patient 5 (DOT = 19/08/93)

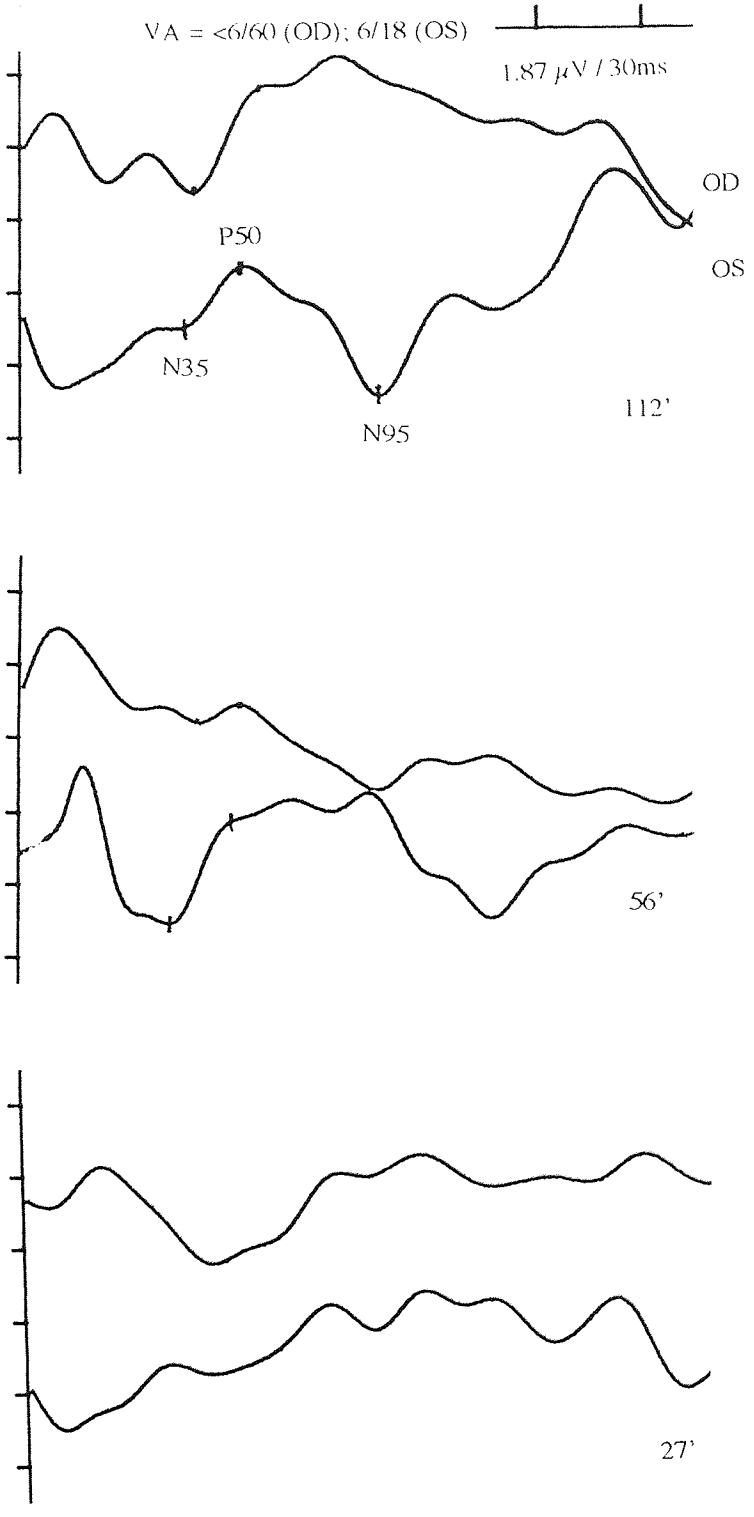


Fig 7.16 Pattern reversal ERGs in patient 5 (DOT = 28/03/94)

RESULT III---*flash VEPs and pattern VEPs*

Date of Test: 16/03/94

Place of Test: Vision Sciences, Aston University

Visual acuity: 6/36 (OD); 6/9 (OS)

Flash VEPs (I4)

	P1 (ms)	N2 (ms)	P2 (ms)	N2-P2 (μV)
OD	85	104	117	7.5
OS	88	104	142	7.4

Pattern reversal VEPs--I

	56'	
	P100 (ms)	N2-P2 (μV)
OD	107	7.7
OS	111	4.2

Pattern reversal VEPs --II

	56' central 5°		56' 1/2 upper field		56'1/2 lower field	
	P100 (ms)	N2-P2 (μV)	P100 (ms)	N2-P2 (μV)	P100 (ms)	N2-P2 (μV)
OD	119	5.8	not recordable		not recordable	
OS	96	4.8	112	3.8	not recordable	

Date of Test: 28/03/94

Place of Test: Vision Sciences, Aston University

Visual acuity: 6/60 (OD); 6/18 (OS)

Flash VEPs (I4)

	P1 (ms)	N2 (ms)	P2 (ms)	N2-P2 (μV)
OD	92	108	134	6.2
OS	67	108	150	7.9

Pattern reversal VEPs

	112'		56'		28'	
	P100 (ms)	N2-P2 (μV)	P100 (ms)	N2-P2 (μV)	P100 (ms)	N2-P2 (μV)
OD	126	2.3	138	5.0	175	3.8
OS	106	1.9	101	3.7	106	5.4

Impression: *Flash VEPs* were delayed in the left eye and the delay developed progressively fast. *Pattern VEPs* were reduced in the left eye. 'Central 5°' PVEPs were delayed in the right eye, indicating a possible macular dysfunction in that eye. The The responses from the lower half field were poor in both eye, suggesting a binocular altitudinal loss.

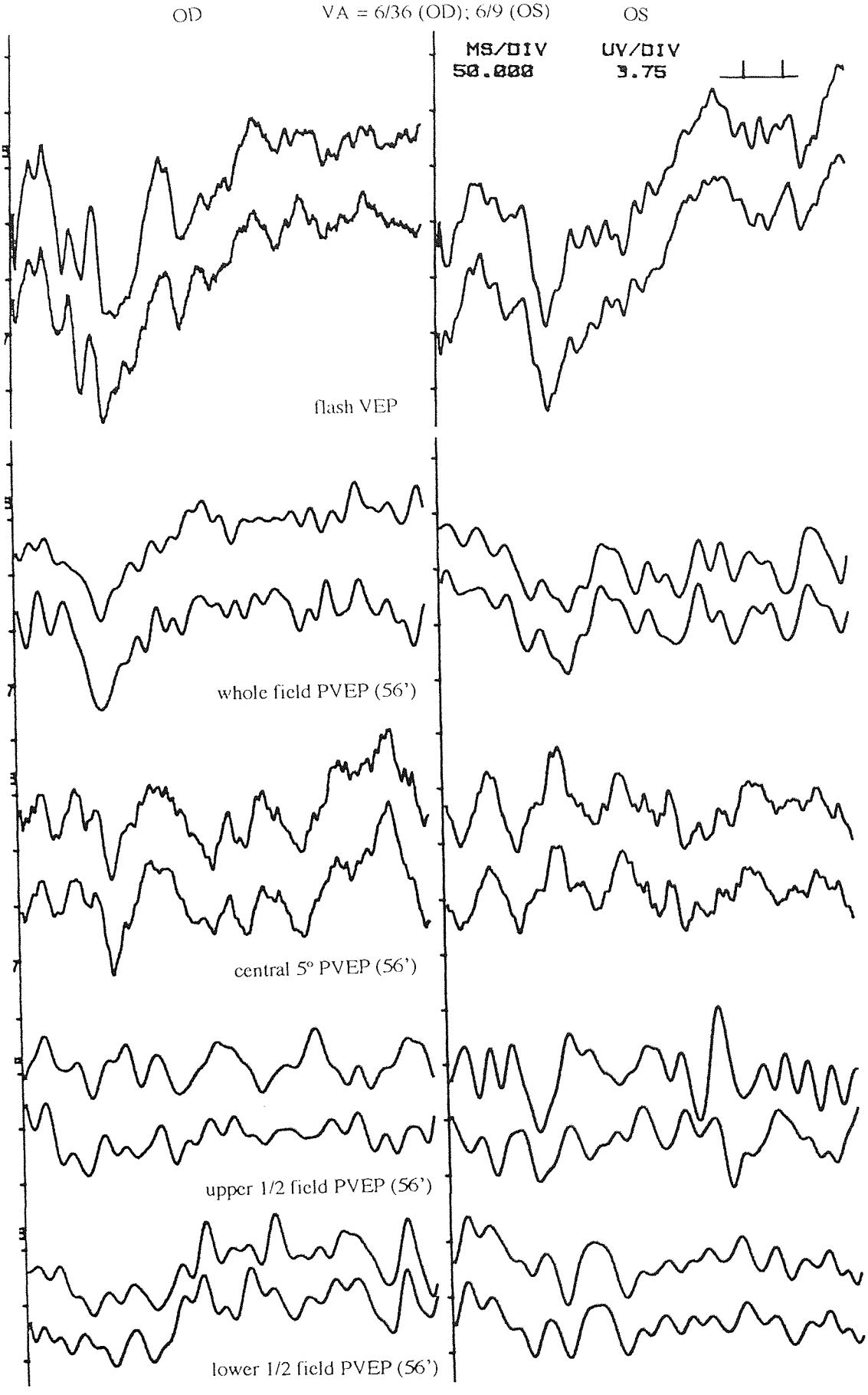


Fig 7.17 Flash VEPs and pattern reversal VEPs in patient 5' (DOT=16/03/94).

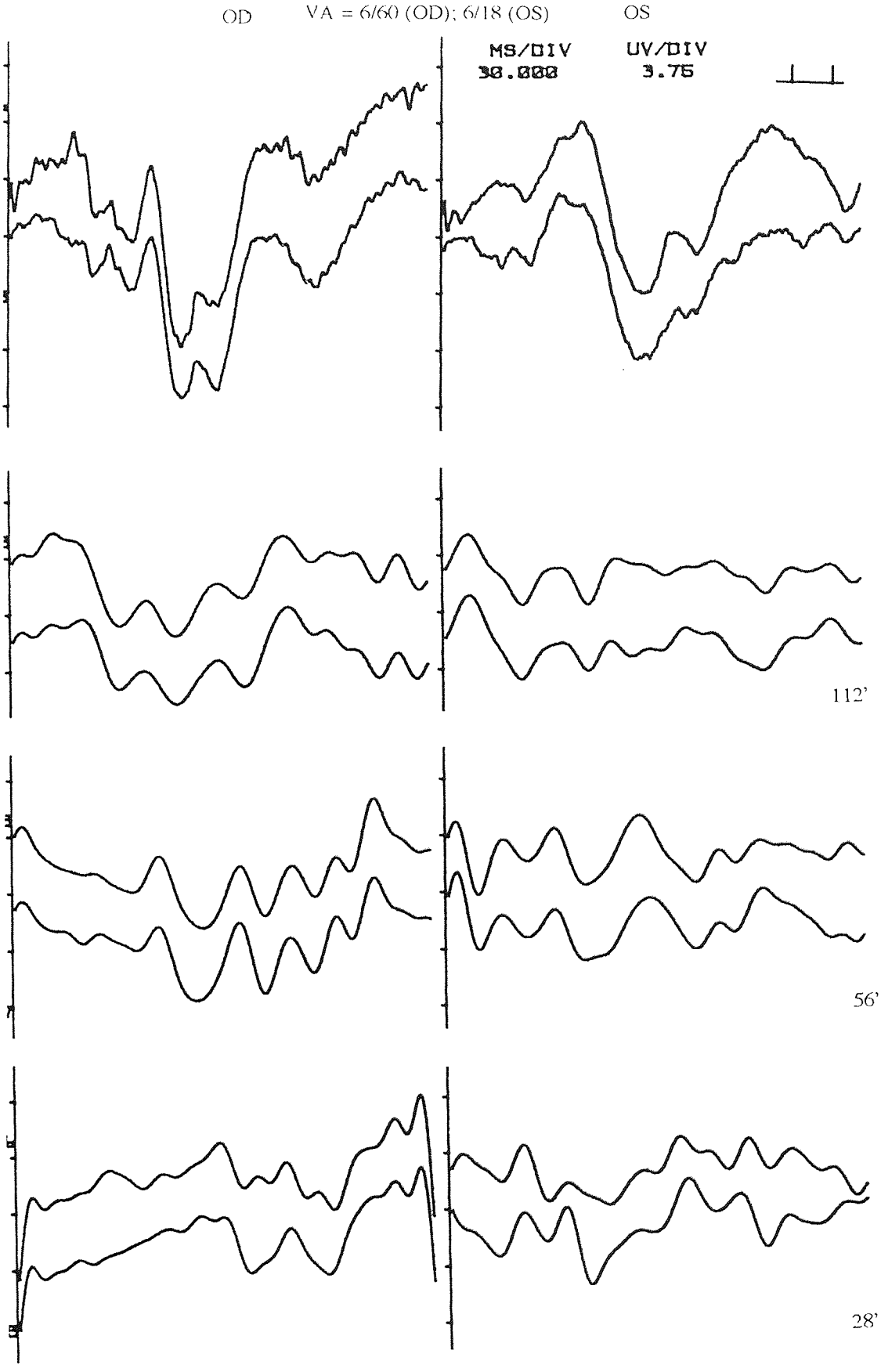


Fig 7.18 Flash VEPs and pattern reversal VEPs in patient 5 (28/03/94)

Patient 6

Date of birth: 27/01/1911.
Date of test: 28/03/95.
Place of test: Vision Sciences, Aston University.
Referred from: Wolverhampton Eye Hospital.
Diagnosis: (R) s/t retinal vein ischaemia + 2 artery occlusion (April, 1994).
Treatment: laser treatment.
Visual acuity when tested: OD=6/36; OS=6/18
RESULTS:

Flash ERGs

		a-wave (ms)	b-wave (ms)	a-b wave (μV)
scotopic ERG(I8)	OD	29	45	120
	OS	26	53	120
photopic ERG(I8)	OD	21	35	5.4
	OS	18	31	9.9
flicker ERG (I8)	OD	20	34	7.5
	OS	20	32	12.3

Pattern reversal ERGs

	112'			56'			28'		
	latency (ms)		amplitude (μV)	latency (ms)		amplitude (μV)	latency (ms)		amplitude (μV)
	P50	N95	N95: P50	P50	N95	N95: P50	P50	N95	N95: P50
OD	48	78	0.7 :0.4	47	78	0.7 : 0.4	54	-	- : 0.5
OS	54	84	1.5: 0.8	45	80	1.3 : 0.7	57	85	1.5 : 0.8

Impression: *Flash ERGs* were reduced in both eyes and *pattern ERGs* were reduced in the left eye.

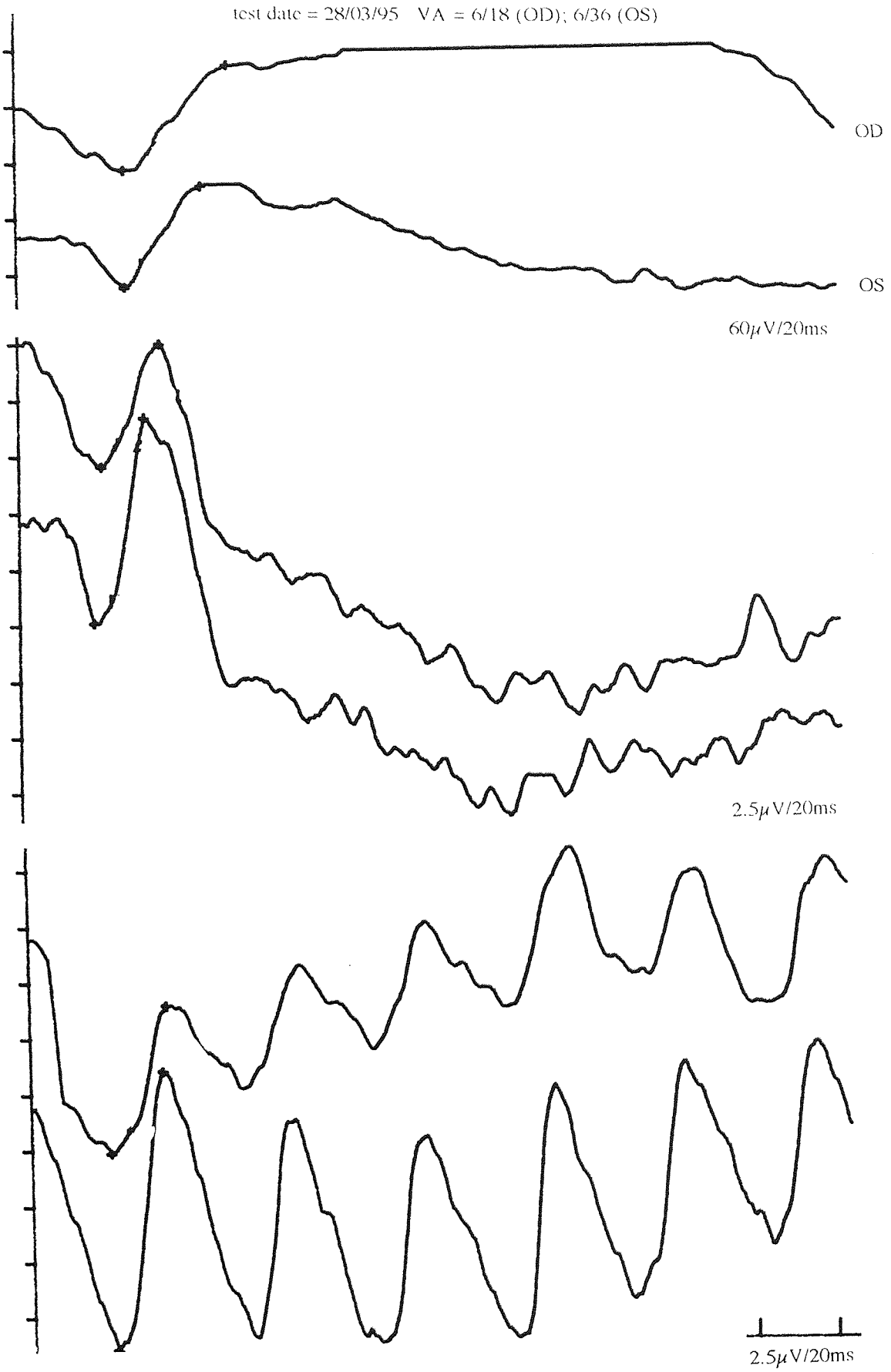


Fig 7.19 Flash ERGs and pattern reversal ERGs in patient 6

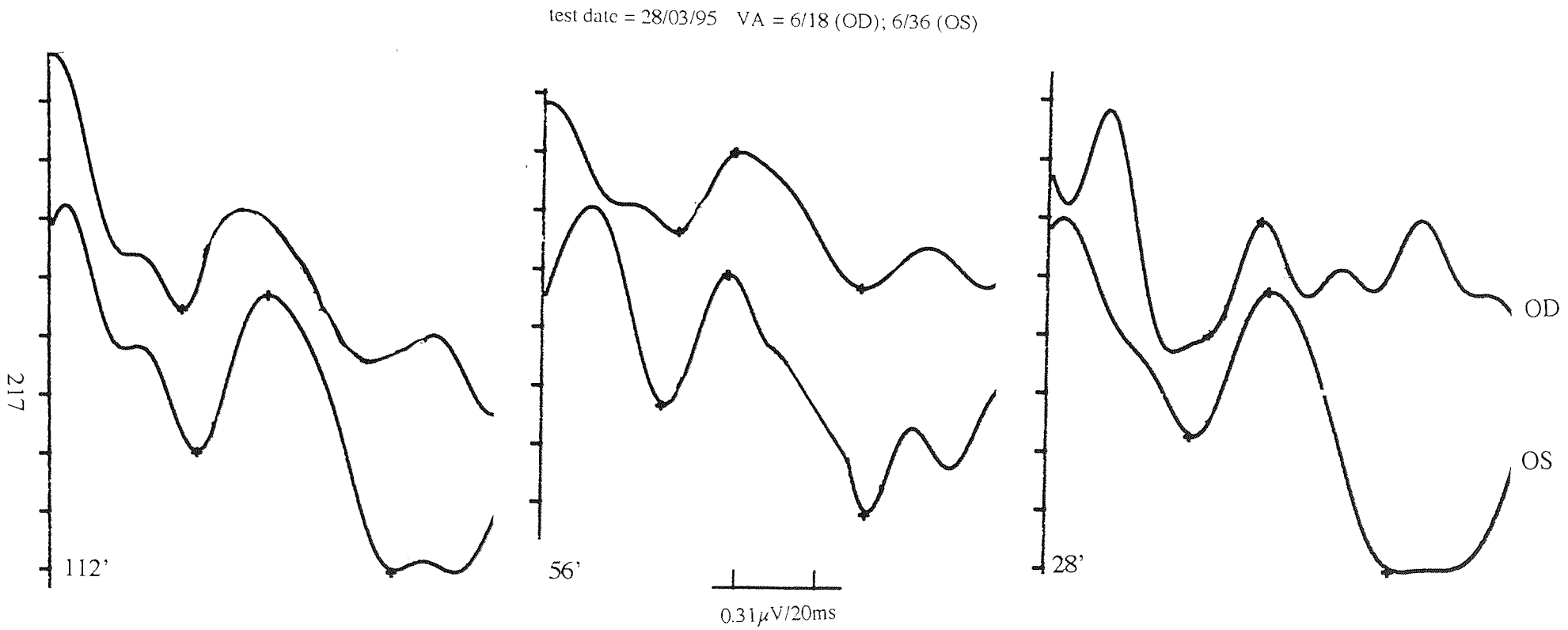


Fig 7.20 Pattern reversal ERGs in patient 6

Patient 7

Date of birth: 02/06/24
Date of test: 10/05/95
Diagnosis: (R) Retinal Ischaemia
Place of test: Vision Sciences Department, Aston University.
Visual acuity when tested: OD=6/36; OS=6/6.
RESULTS:

Flash ERGs

		a-wave (ms)	b-wave (ms)	a-b wave (μV)
scotopic ERG(18)	OD	28	48	108.5
	OS	28	50	205.4
photopic ERG(18)	OD	14	30	33.6
	OS	17	30	41.4
flicker ERG (18)	OD	24	33	15.6
	OS	23	31	25.0

Pattern reversal ERGs

	56' latency (ms)		amplitude (μV)
	P50	N95	N95 : P50
OD	54	87	0.9 : -
OS	50	87	1.6 : 0.9

Note: *Flash ERGs* and *pattern ERGs* were reduced in the right eye, especially the scotopic ERG. The results suggest an even retinal damage throughtout all the retinal laminae of the right eye.

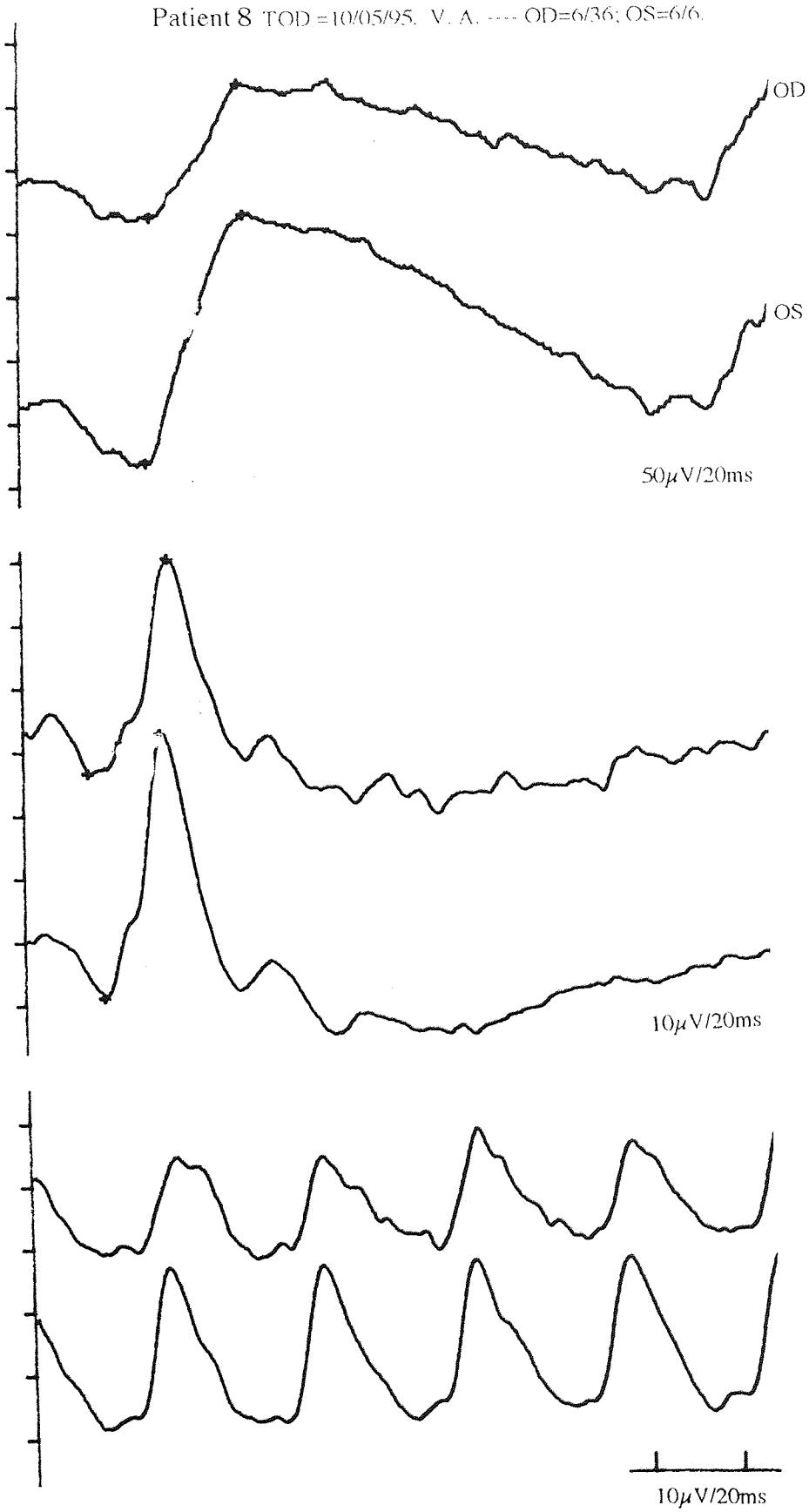


Fig 7.22 Flash ERGs in patient 8.

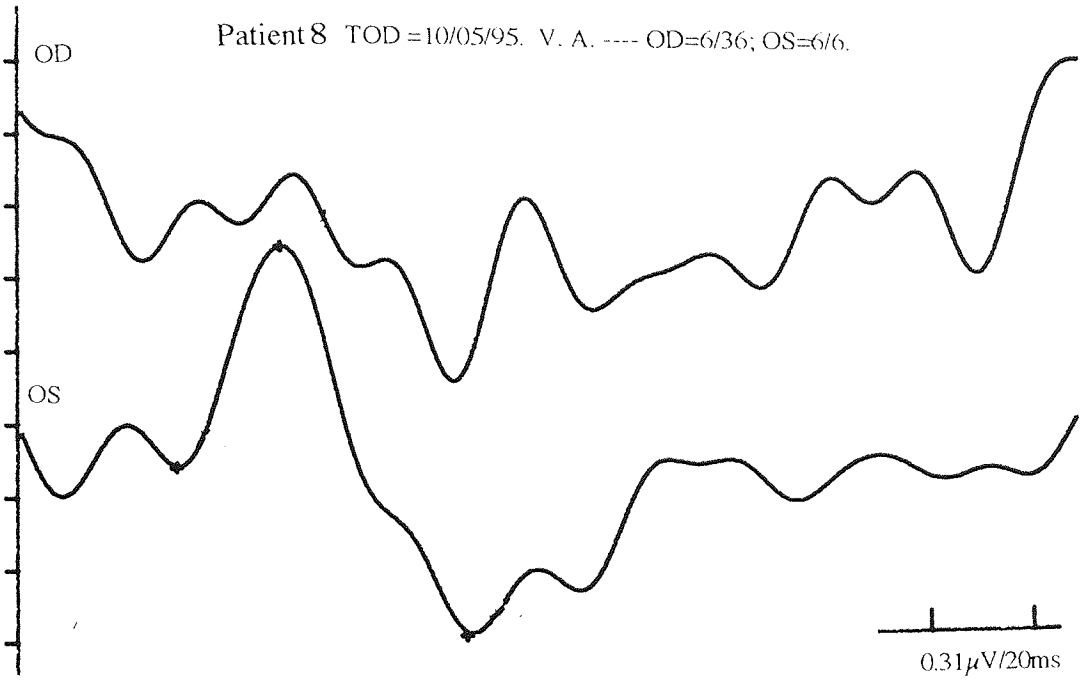


Fig 7.23 Pattern ERGs in patient 8

Patient 8

V.A.: OD=6/12; OS=6/36
Date of birth:
Diagnosis: (R) Retinal Ischaemia (CRAO), occurred in 13/05/95
Treatment: no laser treatment.
Other medical history: systematic hypertension; no diabetes; cateract operation in 1991
Date of test: 17/05/95
Place of test: Vision Sciences Department, Aston University.
Visual acuity when tested: OD=6/36; OS=6/12.
RESULTS:

Flash ERGs

		a-wave (ms)	b-wave (ms)	a-b wave (μV)
scotopic ERG(I8)	OD	27	57	164.1
	OS	28	52	175.8
photopic ERG(I8)	OD	18	36	35.4
	OS	20	38	33.5
flicker ERG (I8)	OD	26	36	22.9
	OS	26	37	24.5

Pattern reversal ERGs

	112'			56'			28'		
	latency (ms)		amplitude (μV)	latency (ms)		amplitude (μV)	latency (ms)		amplitude (μV)
	P50	N95	N95: P50	P50	N95	N95: P50	P50	N95	N95: P50
OD	-	-	- : -	-	-	- : -	-	-	- : -
OS	44	94	2.3 : 1.5	46	90	2.5 : 1.7	50	88	1.9 : 1.3

Note: Scotopic ERGs were reduced in both eyed. Other *flash ERGs* were normal. Pattern ERGs in the right eye were unrecordable to three chechsizes: 112', 56', 28', suggesting ischaemic damage involves more proximal retinal part.

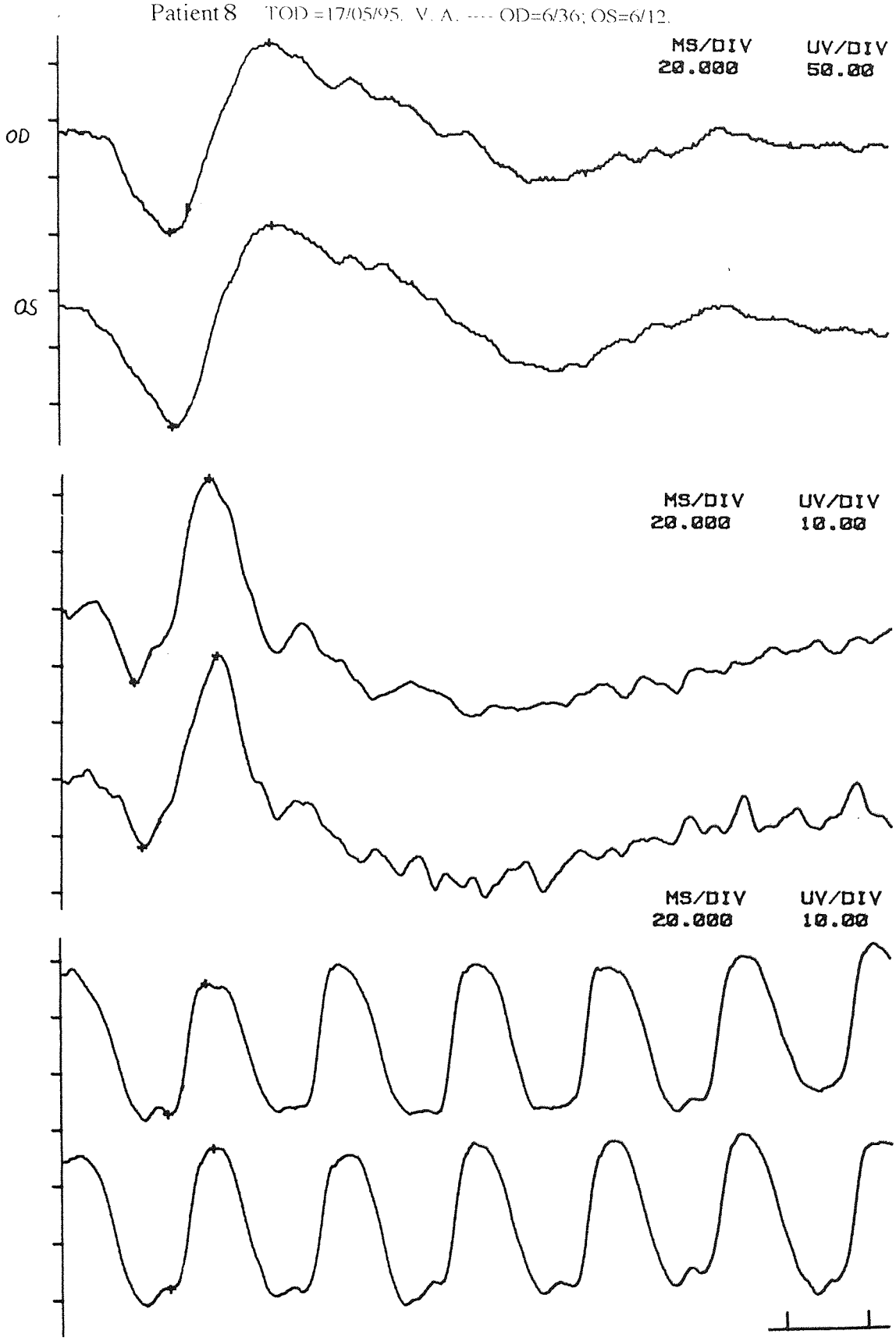


Fig 7.24 Flash ERGs in patient 8

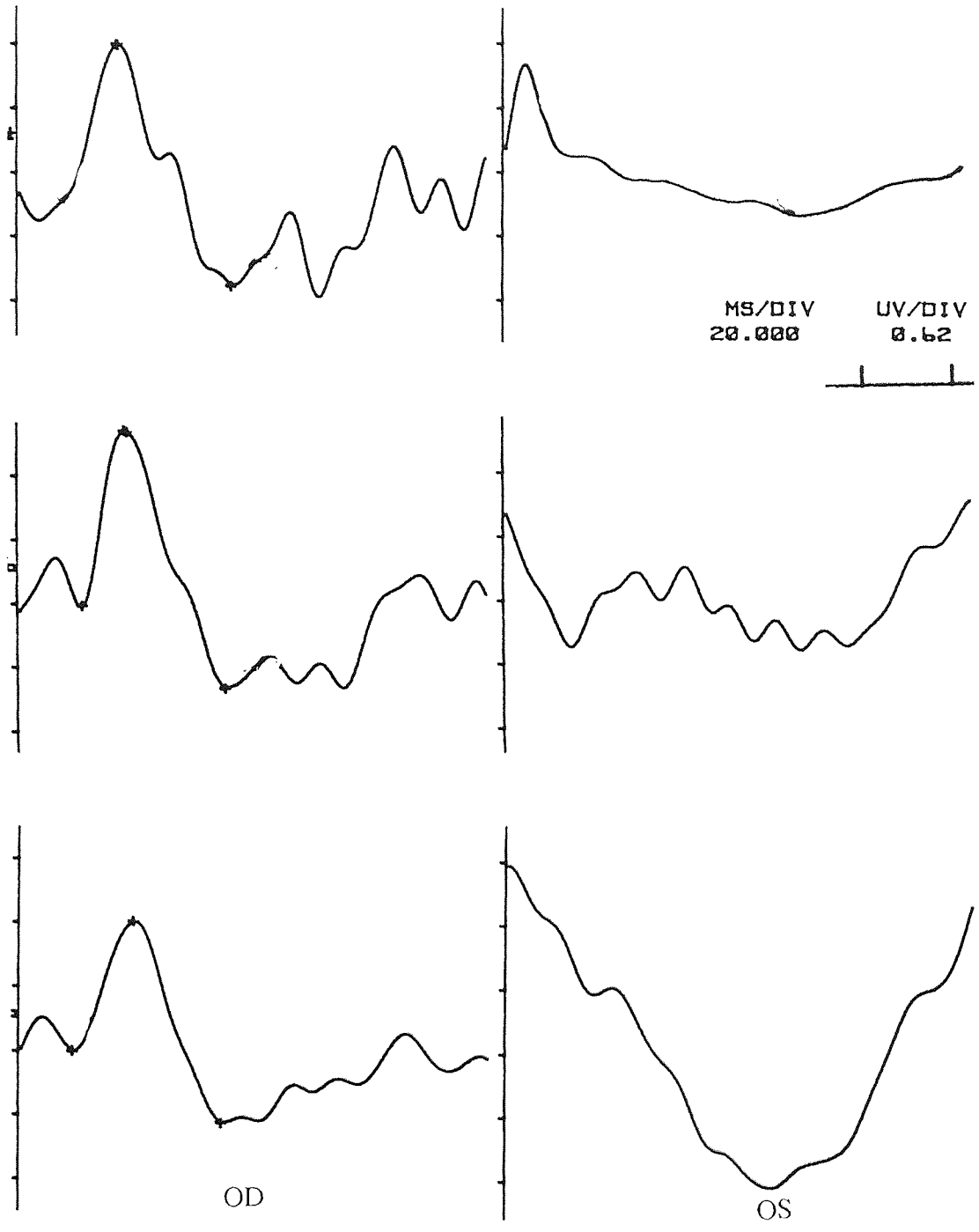


Fig 7.25 Pattern ERGs in patient 8

Case Analyses

AION

Patient 1 (01/23/19) Suspected AION (R).

The patient visited the unit at 15/11/93 with a visual acuity of 6/12 (OD) and 6/9 (OS). All the tests, including flash ERG, flash VEP, pattern ERG and pattern VEP were made at the same day. Flash ERG was normal although the response in the right eye (with worse vision) was slightly reduced. Both pattern ERG and VEP were normal, with a large P3 in the PVEP.

Patient 2 (01/04/32) Suspected AION (L).

The records obtained on the date 22/01/93 at the Birmingham Midland Eye Hospital showed that flash ERG and pattern VEP were normal; flash VEP in the effected eye (with visual acuity of 6/36 in OS) was reduced and normal in the better eye (visual acuity was 6/9).

The same tests were repeated in the Clinical Neurophysiology Unit of Aston University at 24/01/94. Flash ERGs were normal. Flash VEP was similar to the first record in the Hospital, with obvious reduction of the amplitude in the left eye. Pattern VEP carried a large P3, representing a 'W' waveform. Pattern ERG was tested and showed normality to three checks. The noticeable facts were that at the date of test, the patient's vision in the affected eye had recovered from 6/36 to 6/9-2 and the electrodiagnostic tests showed no clear change related with the vision improvement.

Patient 3 (19/03/31). Suspected binocular AION.

According to the records from the Hospital, both eyes had bad vision at the first visit (01/09/93), right eye being 6/60 and left eye being 6/36. The electrophysiological tests showed that flash ERGs and flash VEP were normal; Pattern ERG could not be recorded and pattern VEPs were not recordable in the worse eye and reduced to small checks (28') in the better (left) eye.

The tests were conducted at 23/03/94 when the patient visited the Unit with a vision of fingering counting in both eyes. The results showed that flash ERGs were normal but the scotopic ERG was reduced in both eyes; flash VEP was still normal; pattern ERGs could be got when large checks were used with a reduced amplitude (especially the N95); pattern VEPs could be recorded to large checks with a reduced amplitude.

Patient 4 (02/04/32). Suspected AION (R).

Flash ERGs and flash VEP were normal; pattern ERGs were effected and showed an abnormal reduction in both eyes; the right eye (vision = 6/36) was found difficult to follow the fast reversal patterns (6Hz); pattern VEPs were delayed and reduced in response to all sizes of the check in both eyes.

Patient 5 (29/10/29). Suspected AION (R).

The following studies were run on this patient. The patient had a few years history of glaucoma and colour perception difficulty, mainly in the right eye and showed a progressive vision deterioration during one years, from 6/12 (OD) and 6/9 (OS) to 6/60 (OD) and 6/18 (OS).

The first flash ERG was recorded in the Unit at 19/08/93, which was three months after patient's visit to the Hospital. Patient vision was recovered from 6/12 (OD) and 6/9 (OS) to 6/9 in both eyes. The flash ERG was reduced in the left eye. The abnormality did not develop 7 months later (28/03/94) when patient visited for the second time the Unit, although her vision was deteriorated severely (OD = 6/60; OS = 6/18).

The flash records (06/05/93) from the Hospital showed that the patient's flash VEP were normal when the patient had a vision of 6/12 (OD) and 6/9 (OS). The flash VEP in the left eye was found delayed when the patient visited the Unit at 16/03/94. This delayed seems to follow the vision deterioration since the acuity at this time was 6/36 (OD) and 6/9 (OS).

The first pattern ERGs were recorded in the Unit at 19/08/93 together with flash ERG (visual acuity = 6/9 in both eyes). Pattern ERGs showed normal except that N95 to checks 28' was effected. 7 months later, the abnormality of the PERGs developed severely, especially right eye (vision 6/60).

The first record for the pattern VEP was got at 06/05/93 and showed that the response were almost unrecordable to three checks. At this time, her vision was 6/12 (OD) and 6/9 (OS). For the second time (16/03/94) pattern VEPs were recordable, although the vision was severely deteriorated (OD = 6/36 and OS =6/9). Central pattern VEP (5 degrees) was delayed in the right eye. Combined with the patient's history of glaucoma, macular dysfunction were

suspected. The interior half field stimulation produced poor pattern VEPs in both eyes, suggesting the location of the AION and nonarteritic type of the AION.

RI

Patient 6 (27/01/11). Diagnosed s/t retinal vein ischamia + 2/4 artery occlusion (OD). Laser treatment. The patient was referred to the Unit by the Wolverhamton Eye Hospital. The vision was 6/36 (OD) and OS (6/18). Flash ERG was reduced in both eyes and pattern ERGs were reduced in the left eye.

Patient 7 (03/09/13). Diagnosed retina ischamia (OD).
Laser treatment. The vision was 6/36 (OD) and 6/6 (OS). Flash ERGs, especially scotopic ERG, and pattern ERGs were reduced in the right eye.

Patient 8 (11/03/19). Diagnosed CRAO (OD).
The patient received no laser treatment when tested and had a vision of 6/36 (OD) and 6/12 (OS). Flash ERGs were normal except the scotopic ERG. Pattern ERGs in the right eye were unrecordable to all the checks.

Discussion

One of the most important reasons for clinician to refer these patients for the electrophysiological tests was to trace the causes of the sudden loss of vision of a patient over 50 years old, which is typical of clinical symptoms of the disease. According to the development of the disease, the patients were usually at the acute stage when tested. Such that the relation between vision and responses evoked by flash and pattern stimulation during the progress of the disease was a visible criterion for the investigator.

Flash ERG was found normal in most of the cases (Patients 1, 2, 3) even though the vision has dropped to finger counting (Patient 3). In the patient with abnormal ERG, the abnormality did not change even though the vision was severely impaired (Patient 5). It seems that the flash ERG has no clear relation with vision deterioration in patients with suspected AION. The following-up studies (Patient 5) demonstrated that the flash ERG could be unaffected even when the vision and other tests were clearly abnormal. This assumption was

consistent with other reports (Francois, 1962), in which flash ERG was abnormal only when the retinal arterial occlusion was involved.

The deterioration of vision could be accompanied by a reduced flash VEP (Patient 1). A phenomenon noticed was that in some of the patients, flash VEP showed a 'W' waveform (Patients 1, 2 and 5). This type of waveform appearing in patient with AION was reported by Harding (1980) and interpreted by the author as a replacement of a positive component or a delayed P1-N1-P2 complex and the patients with this waveform had a history of temporal arteritis. As flash ERG, flash VEP were not effected accordingly to the deterioration of vision (Patients 2 and 3).

The abnormality of the patients with suspected AION could be tested more likely by pattern stimulation and was represented mainly by the response amplitude. Only one case (Patient 4) which showed combined reduced and delayed pattern VEP. A fact was noticed that usually the responses (PERG and PVEP) to small checks was effected first and the N95 of the PERG was more sensitive than the P50 (Patients 4, 5). In one patient, on which we did following-up studies, we found that the progress of the PERG abnormality was consistent with the vision deterioration. Usually, the abnormality was reflected in the amplitude rather than the latency change.

When the vision was dropped severely, the obtainment of the pattern responses depends upon largely on the extent of the patient's concentration and cooperation, since the responses were still recordable at vision 6/60 in some patient (as patient 5) or worse (Patient 3). The applicable values of the electrodiagnostic tests to those with vision less than 6/36 due to pathological reasons were much less. The worse vision influences directly getting the response due to the disability of patient's focusing on the target. In such cases, the flash responses could be entirely normal (Patient 3) that the high contrast between pattern and flash responses accompanying severely impaired vision could be one of the characteristics of the suspected AION.

The patients with RI usually have a combined abnormality in flash ERG and pattern ERGs in the eye with bad vision. This is the clear difference between the AION and RI. The abnormality of flash ERG was reflected in their amplitude reduction. While the pattern ERGs were almost unrecordable in these cases. One of the important facts we noticed was that the extent of the

abnormality in the ERGs and the extent of vision deterioration appears to be consistent. The abnormality seems to have no clear relation with the laser treatment.

Summary

An important characteristics of the AION was that patients usually had normal flash ERG when the other tests were abnormally reduced. The pattern responses were correspondingly effected when the vision was effected but there was no clear proportional relation between the vision deterioration and the extent of abnormality. The combined abnormality of the flash ERG and pattern ERG accompanied by the corresponding vision deterioration was prominent in patients with the RI. This contrast in abnormality between the two diseases is the main electrophysiological characteristic we obtained from the present observation.

CHAPTER 8.

THE CHARACTERISTICS OF THE TRANSIENT REVERSAL PERGS (SUMMARY ON THE EXPERIMENTAL PARTS)

As a method of system signal analysis, the advantages of the transient analysis in analysing the retinal response to pattern stimulus have been recognised by ERG investigators and widely used in clinical observations. Since all the information is included in one visible process, the integrity of the information from the retina is believed to be reliable to reflect the whole process from stimulation to response of the retina, if compared with the steady-state analysis. Yet, this visible process is also believed to consist of multiple subprocesses by their deflection directions of the response peaks. More likely these subprocesses lap over each other along the time course of the response and form the visible waveform of the transient PERG. This has been demonstrated in a report by Korth and Armington (1976) that peaks N35, P50 and N95 appeared at different luminance intensity and could also exist at the same intensity.

Experimental and clinical investigations have demonstrated the functional difference between the two potentials of the transient rPERG evoked by reversal patterns. It was thus assumed that such function differentiation is subserved by those different subprocesses and furthermore different neuronal mechanisms. One of the difficulties in interpreting the mechanisms of the negative potential is that this part of response is involved by more than one process. There are some modified methods to measure the negative potential: Korth and Armington (1976) used later negative potential; Arden and Vaegan (1982) advocated to measure the negative potential from the level of the N35; and Holder (1987) used the N95 : P50 ratio to describe the related retinal neurons' damage. The meanings of the 'negative potential' in these reports are different. Clearly, the authors realised that the later part of the N95 transient is functionally different from the whole negative potential. This assumption has been confirmed by some clinical observations that the later part of the negative potential is significantly affected when the inner retinal layers are damaged. In a report by Hull and Drasdo (1990) the authors presented such description on the complexity of the negative potential: '*the negative component must start fairly close to the peak of the positive component to produce the typical sharp decline*'.

In our investigation, we noticed that the coefficient of variation in N95 was higher than in P50 and waveform variation mainly occurred in the negative potential. The main feature was that on the negative potential, the deflection displayed a junction, which we termed notch. According to the waveforms we recorded under the present experimental conditions, the transient rPERGs were divided into I, II, and III types. Type I and II described the waveforms with such variations. Type I described the response with a smooth negative potential. The non-biological factors were examined to differentiate their effects on recording biological signals. The examination demonstrated that the waveform variation was more likely of biological origins.

According to the theory of principle component analysis (PCA) (Regan, 1989), it was assumed that such waveform variations resulted from the difference of spatially independent subprocesses summing along the time. By the aid of the low frequency attenuation, these three types of response were decomposed into two processes. It appeared that the subcomponents met at the time course where the notch appeared or vise versa. It was thus convincing that the response was composed of at least two major processes which over lap each other and peak at 50ms and 95ms after the stimulation onset; and the appearance of the notch or the waveform variations resulted from the difference of the timing process of each subprocess. The analysis provided a theoretical possibility of the constitution of the response by a visualised decomposing process. Other methods of composing the transient rPERG were reported such as by Hess and Baker (1984), in which the response was demonstrated to consist of a fast wave with a duration of 100ms and and a slow wave, which produces a slope baseline between two fast responses.

The physiological meanings of such notch appearance was still not clear. In the clinical part, we recorded pattern ERG on some patients with ischaemic optic neuropathy and chronic retinal ischaemia. The transient rPERGs were found to reduced in such cases, especially the negative potential, or N95. When the later part and the early part of the negative potential was examined, it was found that reduction was prominent between the visible notch and N95 peak. A typical example was recorded on a young patient with acute optic neuritis (suspected MS): the later negative potential was severely reduced while the early part of the N95 was slighly affected. Yet there was no sufficient cases being obtained to confirm a clear proportional relation between its reduction and the extent of damage in the optic nerve or the retinal ganglion cells.

This analysis on the waveform interpreted partially the large N95 amplitude variation in the

youth. Yet, in the elderly, the normal variation was otherwise found mainly in the positive potential P50. The result of natural senescence is known to produce a loss of accommodation and thus vision, especially near vision. It was presumed that the reduction of the retinal illumination (RRI), contrast loss (CL) and retinal neuron damage were the basic related factors producing such age-related changes. These factors were found to be the main causes for the PERG amplitude loss in the elderly. The experiments demonstrated that the P50 amplitude loss was contributed mostly by the RRI and the N95 loss mostly by contrast loss as well as neuronal damage. These amplitude loss apparently was mixed in the 'normal' rPERG in the elderly.

Furthermore, in the normal elderly, the vision was found normal when a certain degree of refractive errors existed. It was presumed that such errors were related to the amplitude loss. With defocus lenses, their vision was found normal when the refractive errors varied between ±0.25 - ±1.65D, confirming a possibility that the PERGs recorded in those elderly could be varied largely but within normal limit. Secondly, the PERG records that P50 was more sensitive to defocus than N95 confirmed this suggestion. Besides, the observation on the PERG by different size of checks showed that both P50 and N95 were effected during aging, but P50 was prominently reduced. All these observations suggested that the luminance-related response represented by the P50 amplitude was more severely affected by aging; and the factors should be considered when the elderly PERGs were analysed.

In addition to the observation on the normal variations of P50 and N95 in the youth and the elderly, we observed that effects of contrast as well as luminance on the response in the youth. The result confirmed that N95 was more sensitive to their changes than P50. This sensitivity was much more higher when the potential after the visible notch was subtracted from the whole negative potential. The reduction was particularly clear at the darkness, implying that it was this part of the negative potential which is subserved by the retinal central-surround organisms. The results suggested that the pattern specific component (response), represented by the N95, of the transient rPERG was more sensitive to contrast as well as luminance levels of a pattern than the luminance related component.

A few cases were reported to probe the electrodiagnosis values on some diseases with suspected damage in the inner retinal layers such as anterior ischaemic optic neuropathy (AION) and retina

ischaemia (RI). It was found that when the inner retinal layers, such as the ganglion cells were impaired, the presentation of the abnormality in the transient rPERG had no distinct difference. All the cases showed a prominent reduction of the whole response, especially the negative potential. When the etiology was analysed, the combined examination of flash and pattern ERG was necessary. The results showed that the AION usually had a normal flash ERG and only when the retinal circulation was involved such as in the case of RI, was the flash ERG effected. Recording response from visual cortex by flash and pattern stimulation showed that the comprehensive examination of all these tests could display the location, the extent as well as the etiology of some diseases.

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ABSTRACT OF POSTER PRESENTED AT THE 33TH INTERNATIONAL SOCIETY OF CLINICAL ELECTROPHYSIOLOGY OF VISION. 1995, ATHENS

Report of the Waveform Variations of the Transient rPERG

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The commonly reported PERG components evoked by patterns reversed at low rate (ie, the transient rPERG) are composed of a negative (N35)-positive (P50)-negative (N95) complex. It was found, with our experimental conditions, that the transient rPERG waveform varied among individuals, especially the negative potential, N95, which has been found valuable in detecting the functions of retinal ganglion cells. The studies on the negative waveform brings out a new description of the component by the aid of waveform analyses. It was noted that in the middle of the negative potential of the partial transient rPERG we obtained, there was a notch, being time locked with the stimulation as other peaks did. Using the low frequency attenuation, the wave after the notch was filtered and timing course of the left 'process' was equal to the one unprocessed, implying that the transient rPERG consists of two processes and their spatial and temporal summation resulted the waveform variations.

ABSTRACT OF POSTER PRESENTED AT TH BRITISH OPTOMETRY AND VISION SCIENCES. 1995 SEPTEMBER. BRADFORD UNIVERSITY

EFFECTS OF CONTRAST VARIATION ON THE TRANSIENT RPERGS

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Contrast between neighbouring black and white checkerboard patters was varied to observe the transient rPERG. The response was recorded under six contrast levels, 80%, 57%, 36%, 23%, 14% and 9% on 12 normal eyes adapted in dark environment. It was found that the latencies were little effected by contrast changes except part of the negative potential before a visible notch ($p < 0.05$). P50 latency was slightly prolonged. Amplitudes showed a linear decrease when contrast level was decreased and the negative potential (N95) showed a higher sensitivity to contrast changes than the positive potential (P50). Analyses on contrast gain demonstrated a similarity. The 'N', from the P50 peak to the notch showed an almost identical contrast gain as the P50. Subtracting it from the negative potential induced such assumption that it is probably this part of the negative potential which subserves the central-surround mechanisms represented, as commonly reported, by the negative potential (N95) of the transient rPERGs..