UNIVERSITY OF SOUTHAMPTON

An Investigation into the Origin of the Early Visual Evoked (Sub-Cortical) Response

By

Andrew Paul Larwood

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CONTENTS

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ABSTRACT

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AN INVESTIGATION INTO THE ORIGIN OF THE EARLY VISUAL EVOKED RESPONSE

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In the time between the onset of the electroretinogram and the occipital scalp recorded visual evoked potential following a flash of light, a series of small 'oscillatory' potentials may be recorded over wide areas of the scalp. These early 'oscillatory' potentials have been variously attributed to either a sub-cortical generator or wavelets of the electroretinogram.

In this study an attempt has been made to resolve this discrepancy and to establish the origin and scalp distribution of these early 'oscillatory' potentials evoked by stimulating the visual system with the use of flashes of light.

In addition, a review of the early literature and work concerning this evoked potential is included and results established in earlier work are compared with the results found in this study.

The effect of varying the test stimulus, ie rate, colour (wavelength), intensity and background illumination with respect to evoking the electrophysiological potential will be presented to show that the early oscillatory potentials are recordable and maximal from electrode position Pz.

The evidence of this study clearly indicates that these early visual potentials are not related to the ERG or cortical evoked potential in response to a flash of light. Separating the early visual oscillatory potentials from the ERG using scotopic and photopic conditions indicates that the generator site for these potentials is probably from an intracranial post-chiasmal source, and not volume conducted potentials generated by the retina.

KEY WORDS AND ABBREVIATIONS

Visual Evoked Responses
Technique
Electroencephalogram (E.E.G.)
Evoked Potential (E.P.)
Electroretinogram (E.R.G.)
Visual Cortical Evoked Potential (V.C.E.P.)
Visual Evoked Sub-Cortical Potential (V.E.S.P.)
Millisecond (msec)
Millivolts (mV)
Microvolts (uV)

LIST OF ILLUSTRATIONS

LIST OF TABLES AND GRAPHS

TABLES

GRAPHS

GLOSSARY OF SPECIAL TERMS AND ABBREVIATIONS

AER	Auditory Evoked Potential
AET	Aetate. Age at time referred to
α Rhythm	Alpha Rhythm. The usual dominant rhythm of an EEG of frequency between 8 and 14Hz of posterior distribution and usually responsive to stimuli
Amp	Amplitude, usually expressed in millivolts (mV) or microvolts (uV)
Artefact	Any electrical activity recorded which is not part of the VEP. This might be a 'physiologial' artefact due to such causes as the basic EEG, eye blinks, myographic potentials or a 'physical' artefact produced by 50Hz mains interferance, faulty connections or amplifier noise
β Rhythm	Beta Rhythm. An EEG rhythm of over 14Hz
Candela	SI unit of luminous intensity; defined as the luminous intensity, in the horizontal direction, of a surface of 1/600,000 square metre of a black body at the temperature of freezing platinum under pressure of 101325 Nm^{-2}
CRO	Cathode Ray Oscilloscope
C/sec	Cycles per second, or Hertz
δ Rhythm	Delta Rhythm. An EEG rhythm of less than 4Hz

Derivation	The electrode placements from which the recording or response is obtained
EEG	Electroencephalogram. A graph of the spontaneous electrical activity of the brain
EMG	Electromyogram. The recorded electrical activity of active muscle
ER/EP	Evoked Response/Evoked Potential
ERG	Electroretinogram. The recording of the electrical response of the retina, usually to a flash of light
Foot Lambert	A unit of luminance; the luminance of a uniform diffuser emitting one lumen per square foot
Hz	Hertz or cycles per second
IFSECN	International Federation of Societies of EEG and Clinical Neurophysiology
International 10-20 System	The system of electrode placement for EEG recommended by the IFSECN
Latency	The time interval between the stimulus and the response
Lumen	The amount of light emitted per second in unit solid angle of one steradian by a uniform point source of one candela intensity
Luminance	The luminous intensity of any surface in a given direction per unit of orthogonally projected area of that surface on a plane perpendicular to the given direction

Msec	Millisecond (1/1000 second)
P/F	Patterned Flash
P/R	Patterned Reversal
Sample	Each individual piece of EEG taken after the stimulus
Sample time or sweep time	The duration of EEG stored in the averager after each stimulus
SD	Standard Deviation
SER or SSEP	Somato-Sensory Evoked Response
θ Rhythm	Theta rhythm. An EEG rhythm of between 4 and 7Hz
um	Micrometre (1/1,000,000 metre)
uV	Microvolts (1/1,000,000 volts)
VA	Visual Activity
VEP	Visual Evoked Potential)
VER	Visual Evoked Response) Synonymous
WNL	Within normal limits
XY Plotter	Automatic writer of which the pen moves in a lateral direction 'X' and a vertical direction 'Y'

CHAPTER 1

INTRODUCTION

The visual Evoked Potential to flashes of light was demonstrated by Adrian & Matthews as early as 1934. They showed that rhythmic electrical responses could be recorded from electrodes placed over the occipital cortex in response to a regularly repetitive light flash stimulus and then termed 'photic following'. The light flash stimulator, the electronic stroboscope, was devised by Grey Walter in 1946 and this instrument was utilised by early workers investigating the visual evoked potential (VEP), (Barlow & Brazier 1957; Calvet et al 1956; Cobb & Dawson 1956, 1960; Ciganek 1958, 1959).

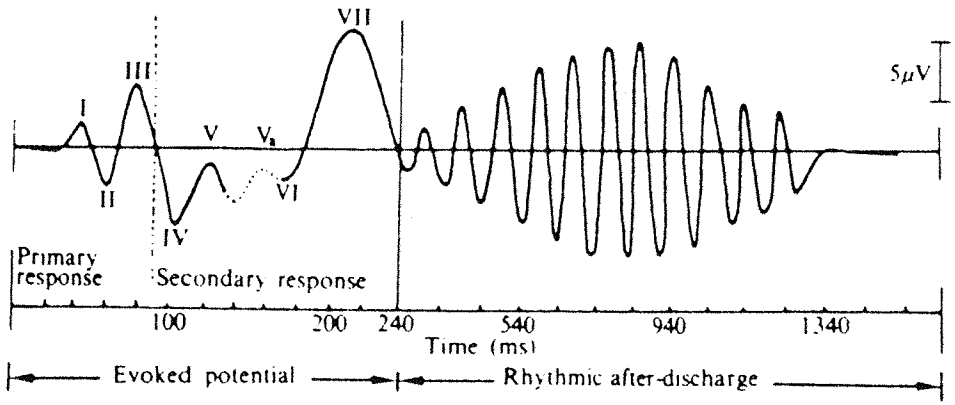
In routine EEG examinations, the response to a flashing light stimulus is a useful provocotive technique having clinical significance in subjects that show a photo-convulsive response, first described by Grey Walter (1946) and more extensively by Jeavons & Harding (1975), or in some non-infective encephalopathies such as Batten-Mayou disease (Carels et al 1960; Pampiglione & Harden 1973).

The absence or presence of the 'photic driving or following' response rarely has clinical significance in normal subjects and indeed less than 10% of normal controls have clearly observable responses in the raw EEG. Normal control subjects occasionally show 'photic following' responses not only to relatively fast frequency light flashes but also to single flashes. In addition, harmonics and sub-harmonics of the stimulus frequency can be observed. In some subjects the amplitude of the 'photic following' is large enough to be observed in the raw EEG without the need for averaging techniques.

Early investigation of the visual evoked potential (VEP) in humans (Cobb & Dawson 1960; Ciganek 1961), figure 1, showed a polyphasic waveform consisting of several positive and negative components (Ciganek 1961 and Gastaut & Regis 1965) starting at about 20 msec and continuing until 250 msec after the stimulus.

FIGURE 1

SCHEMATIC REPRESENTATION OF THE HUMAN FLASH



Three components can be recognised : a primary response, a secondary response, and a rhythmic after-discharge. Note the different time-scales. Symbols I-VII indicate the successive components of the VEP.

In the earlier work, a degree of uncertainty existed about the polarity of the first occipital potential following the flash stimulus and also of its origin. Much discussion took place with regard to the origin of the small early waves with two main theories being submitted as to the origin. The first theory stated was that the early waves sometimes referred to as 'oscillatory potentials' were of cortical origin. The second, and at that time most likely origin for these waves, was the passive current spread or volume conduction of the electro-retinogram (ERG) since the latency of the 'b' wave of the ERG coincided approximately with the latency of the first of the early waves (Cobb & Morton 1952; Calvet, Cathala, Hirsch & Scherrer 1956; Monnier 1957, Ciganek 1958). Furthermore, animal experiments have revealed high frequency, small amplitude wavelets (also called 'oscillations', 'oscillatory potentials', 'ripples') being recorded from all levels of the visual system from retina, optic nerve, lateral geniculate nuclei, optic tract and visual cortex areas 17, 18, 19 (Doty & Kimura 1963; Hughes 1964; Steinberg 1966; Wachtmeister & Dowling 1978; Crapper & Noell 1960; Yokoyama et al 1964; Ogden 1973; Faterhand 1978). Many workers previously found latencies for the first of the series of waves ranging from 20 msec (Gastaut & Regis, 1965); 28 msec (Ciganek 1961); 35 msec (Vaughan & Hull 1965); 40 msec (Allison et al 1977); 13-24 msec (Cracco & Cracco 1978); 21 msec (Harding & Rubinstein 1980); 10 msec (Van Hasselt 1972); 13 msec (Pratt, Bleich & Berliner 1982); 39 msec (Whittaker & Seigfried 1982). As can be seen from this selection of work undertaken investigating the early waves elicited by a light flash stimulus, variation in latency ranging from 10 msec to 40 msec is clearly apparent. The degree of variation, some 30 msec, is, in neurophysiological terms, quite extreme considering the anatomy and physiology of the visual pathways, the variations of which could be attributed to different methods of acquiring the data, ie electrode montage, electrode reference site, bandwidth of the amplifiers, stimulus rate, intensity, duration and wavelength of light used in the investigations and this has added to the conflicting reports as to the origins of these somewhat negelected evoked potentials.

Over the years, loss of interest in short-latency potentials occured predominantly due to the development of the pattern reversal stimulus and its first application clinically (Halliday 1972, 1973) and by the nature of the response itself. Short latency VEP's were generally of low amplitude, extremely variable and showed poor repeatability as compared to the more consistent and less variable later components that have latencies between 75-145 msec, especially the major positive component (P100 or P2) that is best evoked by pattern reversal stimuli, usually a black and white chequer board generated by slides or TV monitors. The flash VEP has been described as being more unreliable and more variable than the pattern reversal VEP and therefore less suited to clinical situations where precise quantification of waveform statistics are required (Halliday 1981, 1982).

However, although the pattern reversal VEP is the visual stimulus most widely used, this technique does not evoke early components of the VEP. In addition, the use of a flash stimulus to elicit a VEP largely eliminates the need for the subject to maintain stable fixation and focusing on the stimulator/stimulus, a requirement necessary when using the chequer board type stimulator. Furthermore, pattern reversal VEP are sensitive to refractive errors in the subject being tested, whereas the flash VEP is less affected by the opacity of the media of the eye, eg cataracts (Thompson & Harding, 1978) or major eye injuries (Crews, Harding & Thompson, 1978). Also the flash VEP can be used on newborn infants where the evoked potential to a light flash stimulus was recorded but appeared unreliable both during wakefulness and active sleep, but reliable during quiet sleep (Ellingson, Lathrop, Danahy & Nelson 1972). These workers also concluded that the flash VEP was a useful method in estimating the maturity of development of the visual pathway from term birth to 18-24 months where it reaches adult levels and that in adults VEP's tended to be reliable during both wakefulness and sleep but especially during slow wave sleep (SWS).

The flash VEP has also been of use in investigating patients that present with hysterical/pyschogenic blindness, on comatosed or anaethetised patients, in lesions of the optic pathway causing homonymous hemianopia (Vaughan, Katzman & Taylor 1963; Creutzfeldt & Kuhnt 1967; Harding, Thompson & Panayiopopoulos 1970) and in orbital surgery, (Harding, Smith & Yorke 1987; Costa de Silva; Warg & Symon 1985), in surgical decompression of the optic chiasm from pituitary adenomas (Sedgwick, Pickard, Tawana, Lakhbir, 1983) and as a non-invasive method of intracranial pressure estimation (York, Legan, Benmer & Watts 1984). As has been stated above, the origin of the early scalp recorded VEP's is still debatable, having definite schools of support from learned authors from around the world.

Review of Literature

In January 1960, Cobb & Dawson, using superimposition techniques (Dawson 1947), found a clear surface positive potential with a latency of between 20 and 25 msec and amplitude of 1-1.5 uV after the flash. In addition, a series of faster waves were seen superimposed on the variable slow waves which succeeded the first EEG deflection and it was thought that the latency of the faster waves (8-11 msec) corresponded closely with the oscillatory potentials of the ERG. Cobb & Dawson tried to determine the location of this EEG response and also the polarity, using widely spaced electrodes covering the midline, above and below the inion or external occipital protrubance and to the left and right of the centre line. The electrodes were connected in a bipolar chain such that an upward deflection occured as a result of one side of the amplifier becoming more negative than the other.

The maximum potential was located when the gradients of the potentials phase reversed. This was determined to be 6 cm above the inion on the midline. Closer spacing of electrodes was found to reduce the amplitude of the responses.

The initial positive deflection at 20-25 msec was followed by a negative deflection with a latency of 35-45 msec and a larger amplitude positive potential at 60-70 msec. The responses obtained by Cobb & Dawson using the superimposition technique appeared very variable from one stimulus presentation to the next which they concluded was due solely to the randomness of the background EEG activity.

However, the responses from averaged records within subjects were fairly consistent over varying periods of time indicating a high degree of confidence within subjects. As with all forms of stimuli applied to the sensory system, the evoked potential is related to the stimulus strength. The response obtained usually having a large amplitude with maximum intensity stimuli as compared with weaker stimuli.

Furthermore, the latency is also increased but the degree of increase is less than the degree of decrease in amplitude. In Cobb & Dawson's study, a decrease in flash intensity from 32 joules to 2 joules resulted in a 10 msec increase in latency from 20-25 msec to 30-35 msec and a reduction in amplitude by 50%. Cobb & Dawson concluded that the early positive potential over the occiput following a light flash stimulus is analogous to the response found over the scalp (somatic sensory receiving area) after a peripheral stimulus indicating the arrival of the afferent volley at the cortex.

In the same year, Ciganek published more definitive results following earlier work in 1958 and 1959. Using an electrode derivation of Oz-Pz from 10-20 system of electrode placements, the evoked response obtained had two separate contributions.

The evoked potential with initial negative deflection of 39 msec (2.9uV), positive deflection of 53 msec (2.5uV) and a negative potential of 73 msec (5.2uV). These first three I, II and III waves formed the primary response and were consistent from subject to subject and were unaffected by changes in stimulus rate up to 10 Hz. The later waves IV-VII (> 90 msec) were considered to form the secondary response of the flash VEP and were affected by stimulus rates above 10 Hz. Ciganek determines that waves I-III were unchanged during sleep except for a prolongation of latency whereas later waves IV-VII can be elicited by sound. These results supported the assumption that the primary response (waves I, II, III) are evoked in area 17 following a specific pathway. The localisation of the primary response was thought to be widely distributed but maximal in the centre line and in the occipital region. Figure 1.

The secondary response was regarded to be evoked by non-specific diffuse pathways because of its long latency, disappearance at high stimulus rates and the effect of sleep on the waves both in latency, morphology and amplitude.

Following the secondary response is the rhythmic after-discharge (Barlow & Brazier 1957; Calvet et al 1956; Ciganek 1958; Cobb 1950) which has a frequency of 8-12 Hz (240-1340 msec) and is thought to be related to the alpha rhythm. It is variable and dependent on levels of physchological awareness. The rhythmic after-discharge is prominent in individuals who possess a distinct, well established alpha (∝) rhythm when the eyes are closed and the subject is relaxed.

Ciganek concluded that the primary response was localised predominantly in the centre line and in the occipital region. For many years the evoked potential to a light flash stimulus and its physiological origin were unquestioned, especially as the flash of light from a stroboscope used as a stimulus was superceded by the pattern reversal stimulator which generated much more interest in the clinical and research establishments worldwide.

During the 1970's a number of workers identified short latency auditory and somatosensory evoked potentials which arose from subcortical areas that were recorded from the human scalp (Jewett et al 1970; Cracco & Cracco 1976). In 1978, Cracco & Cracco identified similar short latency potentials evoked by visual stimulation, recorded from the human scalp. These short latency potentials had previously been recorded in animal experiments, especially from over anterior frontal regions and simultaneously from the optic nerve and optic tracts (Doty & Kimura 1963; Doty et al 1964; Steinberg 1966). Oscillatory potentials similar in latency and configurative morphology have been recorded from the ERG of animals and man (Granit 1933; Cobb & Morton 1953; Cobb & Dawson 1960; Yokoyama et al 1964).

The ERG oscillatory potentials are thought to have been generated by the membranes of the inner plexiform layer of the retina, involving the axon terminals of the bipolar cells, the process of the amacrine cells and the dendrites of the ganglion cells (Ogden 1973) but however, the ERG oscillatory potentials were attenuated in sustained light adaptation conditions whereas the oscillatory potentials from the optic nerve and optic tract of the cat appeared maximal over the anterior regions (Steinberg 1966).

It was concluded that these oscillatory potentials recorded over anterior frontal regions were due to a combination of electrical activity from retinal cells and optic nerve and tract but the experiments had at this particular time not clearly demonstrated the origin of the oscillatory potentials to specific physiological pathways or anatomical structures within the visual pathway.

With respect to the oscillatory potentials recorded over central, parietal and occipital regions, Cracco & Cracco (1978) clearly demonstrated that the amplitude, frequency and short onset latency of the oscillatory potentials is comparable to potentials recorded from the lateral geniculate body, optic radiation and cortex of animals.

Although there appears to be agreement in the literature concerning the early potentials generated by visual stimuli in animal experiments, the converse is true when applied to the human population as previously defined by the preceding extracts.

There still exists considerable diversity of opinion as to their origin, a problem that is undoubtedly confounded by inter-laboratory differences in stimulus and recording parameters.

As an example of variations in technique, the bandwidths of the amplifiers used by early workers range from 30-1000 Hz (-3dB points, 6dB/octave roll off) (Pratt, Bleich & Berliner 1982); 100-2500 Hz (-3dB) (Cracco & Cracco 1978); 1-1000 Hz and 60-200 Hz (24 dB/octave roll off) (Whittaker & Seigfried 1982); 30-500 Hz and 66-700 Hz (Harding & Rubenstein 1980, 1981); 100-1500 Hz (-6dB or -12dB/octave roll-off (Sanarelli et al 1988).

The frequency of the 'oscillatory potentials' have been reported to be between 80-170 Hz, therefore bandwidth of the filters is important in determining the frequency and more importantly the latency of the early wavelets. In this study, selectively changing the bandwidth of the recording system is used as a method of determining the effect of filters on the potentials and with this in mind, both analog and digital filters were employed.

Other parameters were changed to elicit and evaluate the origin of the oscillatory potentials, along with differing stimulus parameters such as wavelength of light, luminosity and intensity and also the type of stimulus used, ie Ganzfeld, LED goggles or Stroboscope (Allen et al 1981; Lehmann et al 1969).

The ERG has been advocated as one possible origin of some of these components (Allison, Matsumiya, Goff & Goff 1977; Gambi, Rossini, Pirchio and Marchionna 1981) whereas others strongly deny this possibility (Perry & Childers 1969; Vaughan 1966).

The optic nerve is suggested by others (Van Hasselt 1972; Honda 1977; Siegfried 1980) but the optic tract, lateral geniculate body and geniculo-calcarine tract have also been proposed (Riggs 1969; Picton & Hink 1974; Cracco & Cracco 1978; Harding 1978) in addition to the visual cortex itself (Nakamura 1978). In 1978, Harding & Rubinstein developed a technique to investigate the first 50 msec post stimulus interval to record short latency photically evoked potentials which are unrelated to the ERG and independent of the cortical VEP. They called these elicited responses Visual Evoked Sub-cortical Potentials (VESP) (Harding & Rubinstein 1979, 1980, 1981; Rubinstein 1981).

Harding & Rubinstein found a major triphasic potential positive-negative-positive (PNP) complex of mean latency P23 msec, N28 msec, P34 msec that occured in 86% of subjects investigated with a maximal potential being recorded with active electrodes placed on the mastoid process or equi-distant between electrodes T4 and T6 or T3 and T5 of the 10/20 international electrode placements referenced to Cz. The potential (VESP) was recorded bi-laterally even with the occlusion of an eye suggesting that is is generated post-chiasmally and not from the retina or the optic nerve (pre-chiasmal structures).

The most plausible structure in the optic pathway at this juncture was concluded to be the lateral geniculate bodies. The potential (VESP) was considered to be a far field evoked potential similar to the Brainstem Auditory Evoked Potential that can be recorded on the scalp in response to auditory stimuli such as clicks and tone bursts/pips. The far field concept was devised by Jewett & Williston in 1971 to accentuate the components of the BAEP due to the generator sites of the BAEP being a considerable distance from the recording electrodes, ie within the brainstem structure.

Pratt, Bleich & Berliner in 1982 conducted experiments to resolve conflicting descriptions of the short latency photically evoked potentials that existed from different authors. The two major contributions that were quoted were studies from Van Hasselt (1972) and Cracco & Cracco (1978).

Pratt, Bleich & Berliner (1982) recorded short latency (oscillatory) visual evoked potentials at different surface locations on the scalp and also examined the effects of eye position and stimulus intensity on the potentials. In determining the surface distribution of the short latency or oscillatory potentials, a non-cephalic reference site was used in the hope of siting the generators of these potentials. The site used as the non-cephalic reference was the seventh cervical vertebrae (CV VII). The results from this study, as demonstrated in the literature, suggest that a series of components recorded within the first 100 msec following photic stimulation were volume conducted activity generated by a subset of the visual system which is activated by luminosity changes. The response obtained can be divided into three sections with the first four or five components being generated within the retina with subsequent components being generated in the optic nerve or tracts and later components of thalamo-cortical origin. The authors admit to the fact that instead of categorising the different group of components within the response, there seems to be considerable overlapping of activity from different generators which summate at the surface, which would be expected considering the different orientations of the numerous dipoles of the specific structures within the visual pathway.

But once again, clear evidence for the localisation of the generators that give rise to specific components of the short latency or oscillatory potentials in response to a flashing light stimulus or the breakdown of contributions from each section of the pathway to specific components of the response evoked is inconclusive.

Further studies in the latter part of 1982 by Whittaker & Siegfried attempted to investigate the high frequency end of the recording spectrum of the VEP's, most of which appear at relatively low frequencies. This is determined by the selected setting of the filters or bandwidth of the amplifiers. In addition, a further attempt at topographical localisation or distribution of 'wavelets' was performed to determine whether any part of the early VEP components was passively conducted from the retina, whether the topographical distribution of wavelets or oscillatory potentials was diffuse or centered over the visual cortex and whether the short latency potentials (ie, wavelets) were generated by different mechanisms compared with the generation of the P100 response. By varying stimulus, wavelength and retinal luminance and by comparing the effects of these stimulus variables on latencies of wavelets of the ERG with the P100 response, then the evoked potentials that had different relations to stimulus variables would have different generators. The results indicated that the evoked 'wavelets' of 30-40 msec following the onset of a light flash suggested the possibility that the earliest wavelets were of subcortical or retinal origin. Earlier work by Siegfried & Lukas (1981) concluded that the wavelets or oscillatory potentials recorded between Oz and Cz are not passively conducted from the retina due to the difference in the spectral sensitivity of ERG wavelets and VEP wavelets. Wavelets occuring prior to 70 msec after flash onset from posterior regions were thought to be generated from the occipital pole of the cerebral cortex rather than from diffuse cortical or subcortical areas. In conclusion, wavelets recorded between 35 and 70 msec were more likely to be generated from occipital cortex rather than retinal, subcortical or diffuse cortical sites.

More recent studies by Sanarelli, Rossini, Rizzo et al 1988, 1989; using combined lens corneal, nasopharyngeal and scalp electrodes (Fpz, Fz, Cz, T3, T4, Oz) referenced to either earlobe or to a non-cephalic site such as the shoulder or cervical spine seven (CV7) have demonstrated short latency sinusoidal wavelets to bright flashed stimuli. In this investigation the bandwidth used was 100-1500 Hz (-6 or -12 dB/octave roll off).

The results obtained showed the lens corneal ERG response to have the same morphology and configuration of components as the nasopharyngeal recording electrode (and Fpz referenced to ear), even though anatomically the nasopharyngeal electrodes are situated posteriorly and inferiorly to the eyeball. If the eye is considered as a dipole, with the positivity at the anterior pole of the eye then the responses obtained should be a mirrored image of the lens corneal ERG response. From the work of Sanarelli et al (1988, 1989), this was not demonstrated. See figure 2.

Latencies measured for the oscillatory waves in the ERG, corneal, nasopharyngeal and Fpz electrodes referenced to the earlobe could be grouped between 15 and 45 msec after the flash stimulus. Latencies at posteriorly placed electrodes to Cz were between 15 and 40 msec after the flash and at scalp locations behind the vertex, Cz, the oscillations of triphasic configuration started with a latency of 35-45 msec. At temporal electrodes, the alternating wavelets had an initial latency of 25 msec following flash stimulus. The simultaneous recording showed a phase reversal of the responses between the electrodes Fz and Cz independent of reference site which may support the hypothesis that propagation of the impulse along the various sections of the visual pathway are orientated in different planes and therefore the volume conducted far-field potentials generated show polarity inversions and phase reversals at different scalp locations as demonstrated by the varying initial latencies recorded at different scalp locations.

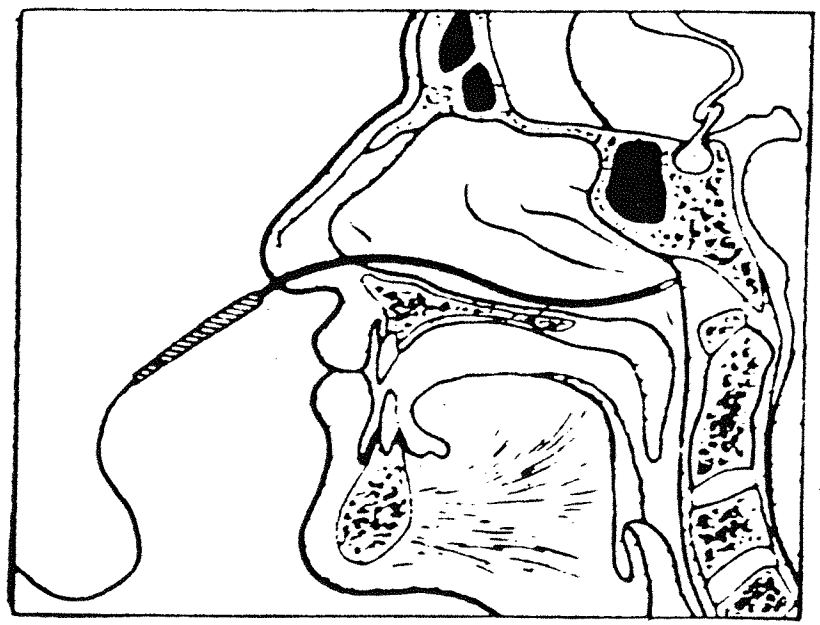


FIGURE 2

POSITION OF THE NASOPHARYNGEAL ELECTRODE USED IN THE WORK OF SANARELLI ET AL 1988, 1989.

Sanarelli et al concluded that 'local retinal' electrical activity is volumetrically diffused through extra cranial layers on wide scalp and facial areas, including periocular and frontal regions up to the scalp vertex and the ipsilateral earlobe (Rush & Driscoll 1968; Nakamura 1978; Rubenstein & Harding 1981). In addition, the oscillatory activity that Sanarelli and co-workers recorded at mid-posterior sites may reflect subcortical and cortical activity but in the presence of a normal flash ERG it is difficult to define which part of the scalp recorded short latency oscillating visual potentials is generated subcortically.

Summarising the earlier literature, flash VEP's present several components with different latencies. These components have been associated with different functions of the visual system and/or with different locations within the brain. The flash VEP can be separated into three components; a 'primary' component (latency 29+/- 2 msec) with a minimum of inter-individual variability; a secondary component (latency approximately 90 msec) which is more variable and a rhythmic after-discharge with enormous variability within and among subjects (latency 135-350 msec, average 250 msec). The primary component does not change when the subject is alert or in the various stages of sleep and remains present at high flash frequencies and is considered to originate in the primary visual cortex (Brodmann's area 17). Figures 3(a) and 3(b).

A consideration when measuring the latency of components that are generated at a distance is the conduction velocity along nerve pathways. In man, most of the optic nerve fibres are thinner than 1 um (Chacko 1948). For a myelinated fibre with a diameter of 1 um, the propagation velocity of nerve impulses is about 6 msec. If the total length of the direct pathway from the eye to the visual cortex is about 20cm, then the time between the onset of the photoreceptor response and the arrival of the afferent volley in area 17 will be about 35 msec (adding a few milli-seconds to include synaptic delays). This value of 35 msec corresponds to the latency observed for the primary VEP component, suggesting that the short latency response is generated in the primary receiving area of the visual radiation from the lateral geniculate nucleus (Ciganek 1961; Reits 1975).

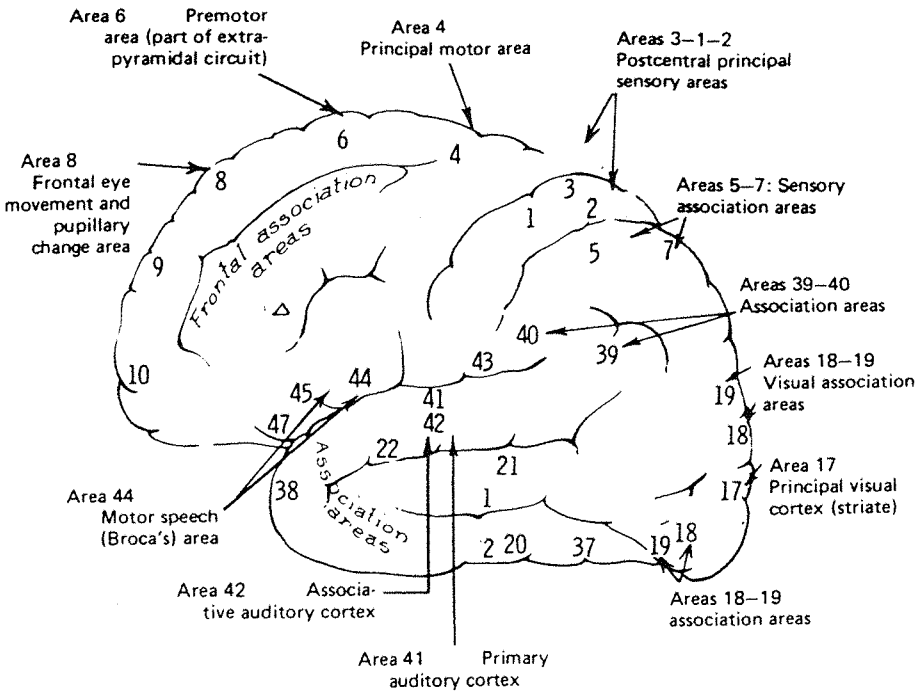


FIGURE 3A

The lateral aspect of the cerebrum. The cortical areas are shown according to Brodmann with functional localizations.

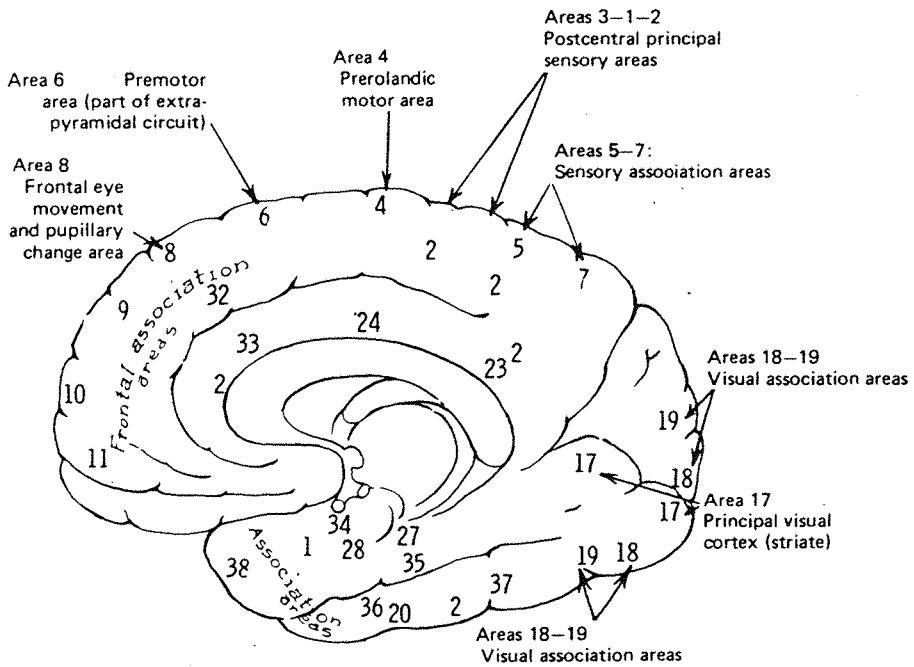


FIGURE 3B

The medial aspect of the cerebrum. The cortical areas are shown according to Brodmann with functional localizations.

Recent studies using depth recordings have suggested that parieto-occiptal oscillating activity following flash stimuli mainly reflects the immediate reverberation of subcortical and intracortical circuits within the optic radiations and the calcarine cortex both in the monkey and in man (Kraut et al 1985; Fava et al 1986).

From the review of the literature, a fair degree of inconsistency is apparent between authors investigating these low amplitude evoked responses.

That the responses evoked by a flash light stimulus can be recorded from electrodes placed on the scalp is in no doubt but the topographic distribution, generator sites and importance of these early wavelets, oscillatory or short latency potentials is still debatable. Many of the observations by authors about each others methodology is interesting and varied, especially as many of the variables such as stimulus rate, wavelength and luminance or intensity are not comparable, just as the differing recording methods of each investigator will affect the responses obtained for each experiment. Had many of the authors conducted the same experiments as each other, a greater understanding of these early scalp recorded VEP's would have been obtained, hence this study.

Initially, a comparative study of Harding & Rubinstein's work was undertaken using the stroboscopic light flash stimulus to see if it was possible to replicate their findings and secondly by using LED goggles as the stimulus to investigate if a different light source both in wavelength and intensity, but without the 'click' artifact of the strobe, could generate the evoked potentials.

Further work investigated the difference between various wavelengths of light, intensity, background illumination, photopic and scotopic responses with eyes open or closed and the scalp distribution of the evoked responses. In addition, a method of separating the early responses (oscillatory potentials) of the ERG from the proposed 'sub-cortical' components was devised.

From the literature, the light flash stimulus still has a place in clinical research neurophysiology for evoking an electrical physiological event. In this study, the origin of early scalp recorded VEP in a normal control group of volunteers is investigated and the results obtained are compared with findings from other authors. In addition, various parameters of the stimulus are changed in order to determine the optimum recording technique for evaluation of the early scalp recorded VEP's and its use in the ophthalmological armoury of the neurophysiologist.

CHAPTER 2

ANATOMY AND PHYSIOLOGY OF THE VISUAL PATHWAYS

In order to understand the principle of recording an evoked response to a stimulus, whether it is a visual, auditory or an electrical stimuli, an understanding of the anatomy and physiology of the particular sensory system under investigation is required. In the preceding sections, I have over-simplified the anatomy and physiology of the visual system and have dwelt upon those areas that have significant relevance to the evoked responses obtained in this study. Readers can find numerous references to anatomical or physiological aspects of the visual system in the reference appendix.

The Eye

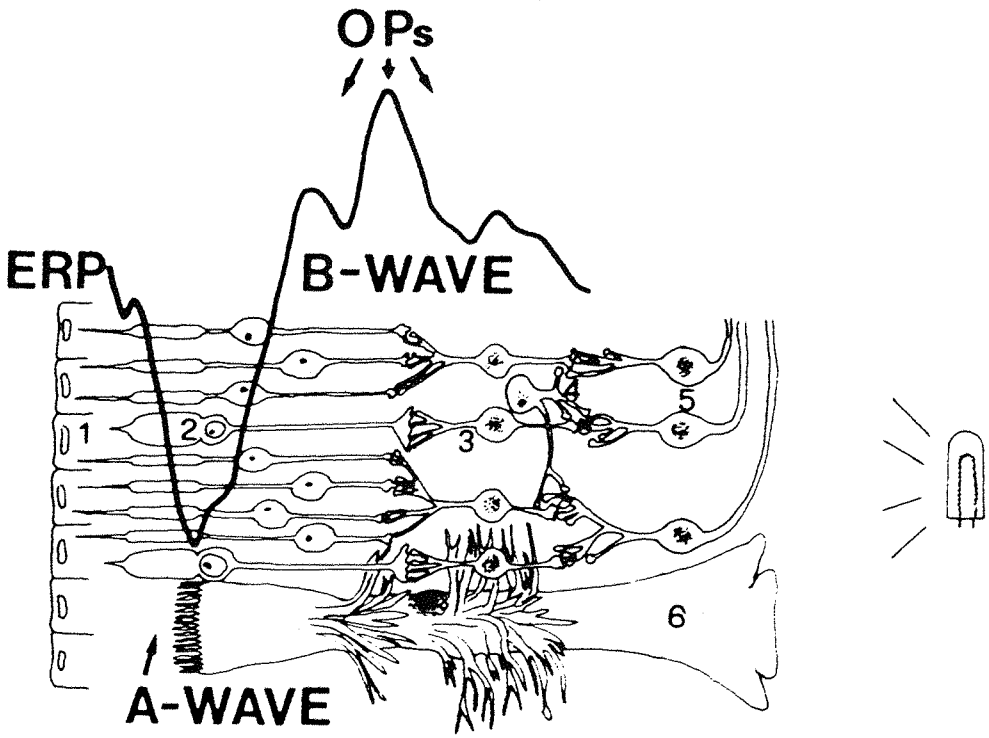
Electromagnetic energy (light) reflected from or produced by any object passes through the transparent cornea through the medium called the aqueous humour to the lens. The thickness of the lens is controlled by the ciliary muscles which act to focus the image sharply upon the retina. Objects brought into attention are focused upon a region of high activity, the fovea. The fovea is the small depression in the surface of the retina that is free of blood vessels. Light has to pass through the layers of the retina to activate the photoreceptors, the rods and cones. The cones have their highest density in the region of the fovea centralis with rods being almost absent. With increasing distance from the fovea, the density of the rods increases whereas the density of the cones decreases.

The Retina

The retina is the light sensitive portion of the eye containing cones which are diurnal and responsible for colour vision and the rods which are mainly responsible for nocturnal vision. In addition, the retina contains the nerve cells of the first and second sensory neurones of the visual pathway which are arranged vertically in 3 cell layers of the retina. Figure 4.

The outer nuclear layer contains the photoreceptors, rods and cones; the inner nuclear layer where the bipolar cells are located and thirdly, the ganglion cell layer. The axons of the retinal ganglion cells form the optic nerve bundle and leave the eye and travel to the brain. Separating the 3 layers are two synaptic layers, the outer plexiform and inner plexiform layers. The former separates the outer and inner nuclear layers with the latter separating the inner nuclear layer and the ganglion cell layer. In addition to the photoreceptors, bipolar cells and ganglion cells, there are two types of interneurons called horizontal and amacrine cells which are located in the outer and inner plexiform layers respectively. The horizontal cells synapse with other horizontal cells, bipolar cells and photoreceptors whereas the amacrine cells synapse with other amacrine cells, bipolar cells and ganglion cells.

Throughout the 3 layers of the retina, glial cells known as Müller cells are prominent. These cells maintain a stable environment for the other cells to function. The Müller cells also play an important role in the generation of the electroretinogram, ERG, described later. The density of the cell types is not uniform throughout the retina. Cones, bipolar and ganglion cells have their highest densities in the foveal region making synaptic contact in a ratio of 1:1:1, resulting in the fovea occupying over 60% of the visual cortex. This is known as the cortical magnification factor. In the peripheral retina, the outputs of many rods and some cones, converge to a small number of bipolar cells and finally to an even smaller number of ganglion cells, the output of which occupy a small area of the visual cortex.



COMPONENTS OF THE CLINICAL ERG

Components	Principal origin
· ERP	· Photoreceptor outer segment
· A-wave	· Photoreceptors
· B-wave	· Bipolar cells, Müller cells
· OPs	· Inner plexiform layer, amacrine cells

FIGURE 4

FLASH ERG COMPONENTS AND SCHEMATIC RETINAL STRUCTURE

1 : Pigment epithelium
2 : Photoreceptors
3 : Bipolar cells
4 : Amacrine cells
5 : Ganglion cells
6 : Muller cells

Two Visual Pathways

Two visual pathways are distinguished : The retino-geniculo-striate pathway and the retino-tectal pathway. Both pathways originate in ganglion cells of the retina whose axons form the optic nerve to travel to the optic chiasma. It is at this juncture that half the fibres from each optic nerve cross over the midline of the brain and travel as the contralateral optic tract to the lateral geniculate nucleus of the thalamus or to the tectum of the midbrain.

Axons from the retinae are divided into fibres that originate from either side of a vertical line through the fovea. The crossing of nerve fibres is not haphazard, the fibres originating from retinal ganglion cells located in the nasal hemi-retinae cross over the midline whereas those from the temporal hemi-retinae continue on the same side of the brain. This results in visual events that occur to the left of a fixation point are registered in the right side of the brain and vice versa. Figure 5.

The optic tract fibres terminate in two major structures; in the lateral geniculate nuclei of the thalamus and in the superior colliculi of the tectum. To complete the retino-geniculo-striate pathway, the principle cells of the lateral geniculate nucleus send their axons via the internal capsule and optic radiations to terminate in area 17 of the occipital lobe (striate cortex). Fibres from the superior colliculus terminate in the pre-tectal nucleus and to association areas of neo-cortex lying around the visual cortex after first relaying in thalamic nuclei such as the lateral posterior nucleus. The functions of the two visual pathways, although related to the neuro-sensorium of vision, appear to be different. For example, human subjects with visual cortex lesions in area 17 of the occipital lobe are unable to 'see' visual objects. They are unable to describe them, yet, when asked to report the position of an object, they are able to indicate its position particularly if the object is moving. However, these 'blind' subjects are adamant that they cannot see the object.

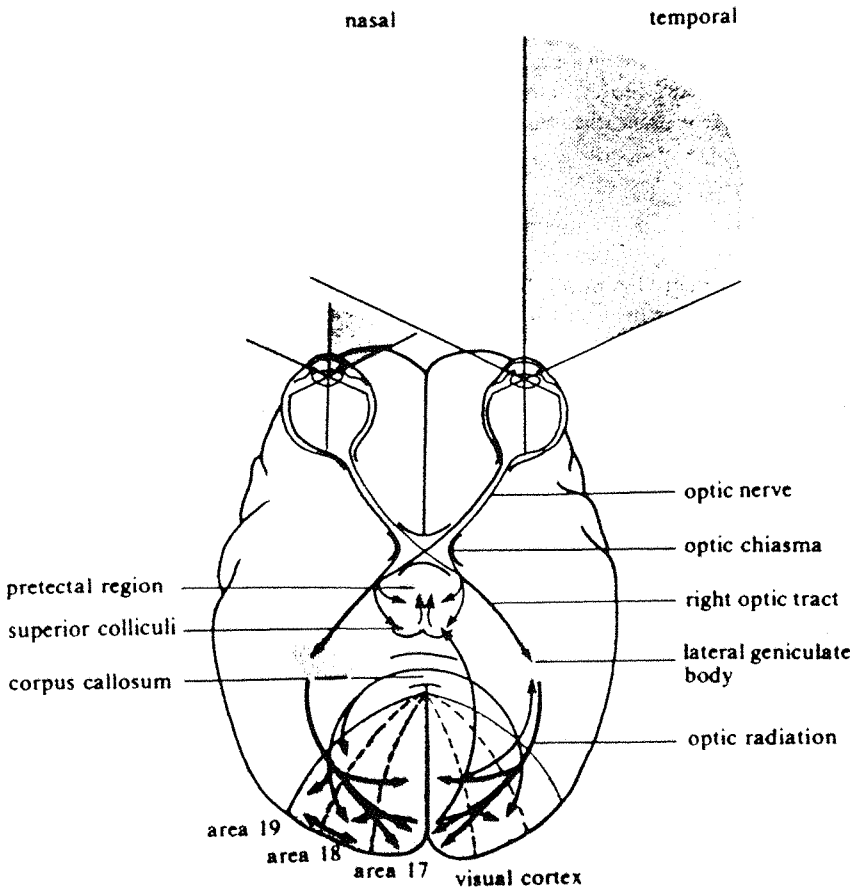


FIGURE 5

A schematic representation of the visual system of the human brain. The visual cortices of the left and right of the brain are joined by axons passing through the corpus callosum. The representation of areas, 17, 18 and 19 is very much simplified.

Similar lesions in other mammals have analogous effects. These animals cannot perform visual recognition or discrimination tasks but they are able to orientate towards visual stimuli. In contrast, lesions of the superior colliculus in mammals leave them able to perform visual discriminations. This implies that the integrity of the retino-geniculate-striate pathway is necessary for an animal to make visual discriminations, whereas the retino-tectal pathway is necessary for it to be able to orient towards visual cues.

Throughout the visual pathway there is well maintained spatial organisational heirachy from retina to visual cortex which allows specific parts of the retina to be stimulated and the response of the cortical neurons to be recorded from a particular and often predictable region of the visual cortex.

This organisation within the sensory pathway is not only dependent of anatomical contact between different parts of the pathway but also to the types of physiological receptive fields of the neurons within the retina, lateral geniculate nucleus and visual cortex as well as to the type of stimulus used to ellicit the evoked response.

Within the visual pathway, topographic representation due to neuronal convergence is maintained by the input from photoreceptors, rods and cones, to retinal ganglion cell axons terminating upon lateral geniculate nucleus cells, which in turn project their axons to discrete regions of cortical columns containing the cortical neurons that respond to the appropriate stimuli.

For example, the photoreceptors in the retina respond best to a diffuse light stimulus whereas the ganglion and geniculate cells respond best to a small spot or narrow bar of light. This is in comparison to the complex and hypercomplex cells of the striate visual cortex which respond best to a bar, line or edge that stops or to a corner or angle stimulus (Hubel & Wiesel 1962). Hence, in human evoked potential studies to visual stimuli, the best stimulus to evoke a response from cortical cells is a chequer board pattern of alternate light and dark squares.

Reversal of the pattern so that the light square becomes dark and vice versa evoked quite large potentials even though the light energy falling on the retina remains the same. The stimulus to evoke responses from photoreceptors is obviously a diffuse light source whereas the best stimulus for evoking a response from lateral geniculate cells are circular areas of light and shade. In this investigation, a bright light source is used as the stimulus in order to help differentiate between the electro-retinogram produced by the retina and the early evoked potentials, subcortical or cortical.

Visual Areas

The contralateral visual field is respresented in triplicate within the occipital lobe. The Primary Visual Area or Striate Cortex (Area 17) is situated around the calcarine fissure on the medial aspect of each hemisphere. The Second and Third Visual Areas or Pre-Striate Cortex (Area 18 and 19) surround area 17 in concentric fashion and include large areas of the occipital lobe. Area 19 also encroaches on the temporo-parietal cortex. All 3 visual areas receive fibres from the lateral geniculate body and area 17 projects fibres to area 18 which in turn activates area 19. Evoked potentials can be generated in the 3 visual areas by pulses of light recorded through the human scalp which will be demonstrated in this study.

The Evoked Potential

An Evoked Potential is an electrical response to a particular sensory stimulus which can be in the form of either visual, auditory or somatosensory. The Evoked Potential is usually of the order of a few microvolts in amplitude (5-20uV) and is usually mixed up with the spontaneous electrical activity of the brain, the EEG, which is assumed to be random. The EEG activity has a larger amplitude (20-200uV) than the Evoked Potential and therefore some method of signal extraction is necessary. The process of Signal Averaging is used in which to isolate an Evoked Potential. A repetitive stereotyped stimulus is presented and the scalp potential changes recorded for a set time period following presentation of the stimulus. The individual responses are lost in the random 'noise' of the EEG and in the other biological and non-biological artifacts encountered during recording, such as muscle potentials and 50 Hz mains interference. However, superimposition techniques reveal potential changes which are time-locked to the stimulus - the Evoked Potential (Dawson 1954). By the use of averagers, the signal enhancement or noise reduction is achieved which increases the amplitude of the signal relative to the noise. This is known as the signal to noise ratio.

In this technique the analogue signal is digitised and stored in an address in the averager. Each individual presentation of the stimulus triggers the averager, and the EEG activity together with the 'hidden' evoked potential are added together to give the sum of the individual trials. To obtain the 'averaged' evoked potential, the sum of the trials is divided by the number of sweeps or runs. The digital signal can then be converted back into an analogue form to be displayed for analysis. By averaging a large number of trials, the signal to noise ratio is improved by a factor of $\sqrt{N}$, ie, the average of the background activity has decreased by a factor of $\sqrt{N}$ and the evoked potential is discriminated from the decreased background noise. The use of averaging eliminates the random background 'noise'. As the number of repetitions increases the effective amplitude of the background activity decreases leaving a reproducible neural response.

The 'averaged' evoked potential is thought to be the result of graded post-synaptic potentials of sensory neurons rather than action potentials. The recording of EP's allows a non-invasive test of the sensory pathways of the nervous system from the receptor via the afferent pathways to the appropriate sensory cortex.

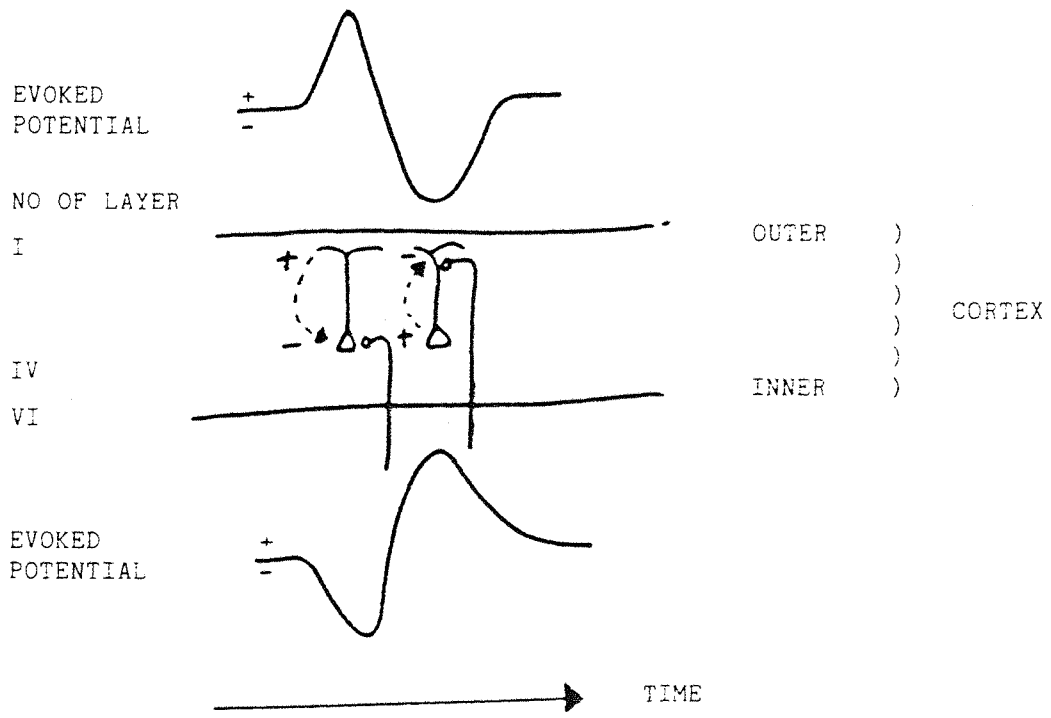
Evoked potentials recorded from the surface of the head or body are volume conducted and can be divided into two types:-

a) near field, recorded close to the generator
b) far field, recorded far from the generator

The amplitude of an EP decreases rapidly with increasing distance from the generator but then levels off (see figure 6). Anatomical studies suggest that afferent input to a group of neurones from a particular source usually makes synaptic contact on the dendrites or on the soma of the neurones. The afferants are from the thalamic relay nucleus which terminate directly or via stellate interneurons on or near pyramidal cells. The de-polarisation by excitatory impulses is recorded as a positive potential at the cortical surface.

Slightly later de-polarisation of apical dendrites by excitatory impulses activating the axodendritic synapses or by electrotonic invasion from the cell body evokes a surface negative potential. Beneath the cortex, a potential of similar waveform but opposite in polarity is recorded. While there is evidence for spatial differentiation most neurons probably generate both potentials sequentially. Hyperpolarisation of the cell body or dendrites by inhibitory synaptic action would evoke surface negative and positive potentials respectively.

Other neural elements are also activated by an afferent volley, eg stellate cells and basal dendrites of pyramidal cells, but due to their random orientation, the potential field produced by that activation is minimised.



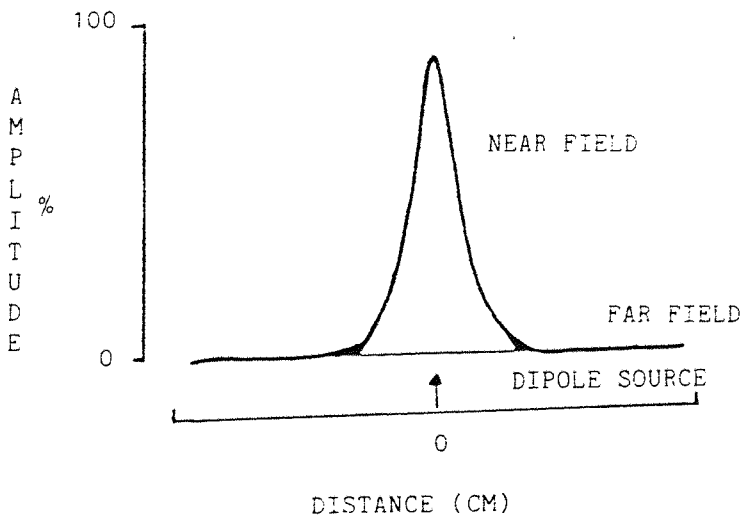


FIGURE 6

VOLUME CONDUCTION - NEAR AND FAR FIELD POTENTIALS

The spatial orientation of nerve cells or cell groups and the temporal pattern of synaptic activation of the nerve cells or cell groups are important determinants to whether the extracellular potentials can be recorded at a large distance (far field) from the active cells (Lorente de Nó, 1947). In addition, for the EP to be recorded to a synchronous afferent volley all the cells or group of cells would need to be de-polarised simultaneously. This would result in the individual potential fields being orientated in the same direction and would therefore summate giving rise to the evoked potential. This assumes that the individual nerve cells or neurones are all physically orientated in the same parallel plane known as an 'open field' (see figure 7). The closed field model of cells, ie cells orientated in different planes such as stellate cells and the basal dendrites of pyramidal cells will result in the potential fields of each cell cancelling the potential field of other cells. The net result is that no EP is recorded (Bishop & Clare 1952; Landau & Clare 1956; Towe 1966).

The amplitude of the early visual evoked potentials and the distribution of the waveforms from previous workers investigations indicate that these potentials are far field potentials recorded at a distance from the generator(s).

The Electro-retinogram

The ERG is the electrical response of the retina evoked by a flash of light and picked up at a distance, ie cornea or lower eyelid. The ERG consists of a series of waves, the a-wave, b-wave and c-wave. The two most important are the a-wave (PIII) and the b-wave (PII) (Granit 1933). The former wave is generated extracellularly along a radial path from the cell body of the photoreceptors into the membrane of the outer segments. The a-wave has two components - a1 and a2 representing activity of cones and rods respectively. The b-wave is generated by the cells of the inner nuclear layer especially the bipolar cells and the Müller glial cells. The c-wave (PI) is the extra-cellular current arising from hyperpolarisation of the apical face of the pigment epithelium in response to a decrease in extracellular potassium ions in the region of the inner segment of the photoreceptor layer.

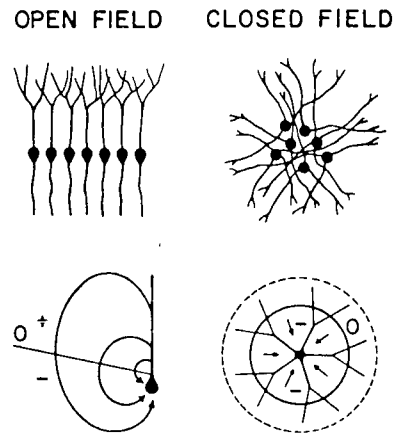


FIGURE 7

Predicted current flow and potential field produced by synchronous depolarization of the cell bodies of a row of neurones with parallel orientation (open field) and a group with cell bodies clustered in the centre and dendrites spreading radially (closed field).
Adapted from Lorente de Nó (1947b).

The integrity of the pigment epithelium and photoreceptors is an essential factor for the generation of the c-wave. In addition, there are ERG oscillatory potentials which are generated by the membranes of the inner plexiform layer of the retina involving the axon terminals of the bipolar cells, the processes of the amacrine cells and the dendrites of the ganglion cells. The normal range for a photopic (light adapted eye) is 75-150uV (microvolts) in response to a bright flash of light from a stroboscope. The normal scotopic ERG (dark adapted eye) in response to the same flash intensity will result in the b-wave of the ERG being at least double the amplitude of the b-wave amplitude in the photopic ERG (150-300uV), (Galloway, 1975).

Visual Subcortical/Cortical Evoked Potentials

The VEP can be divided into a Primary response, Secondary response and Rhythmic After Discharge (Ciganek 1960) (see figure 8).

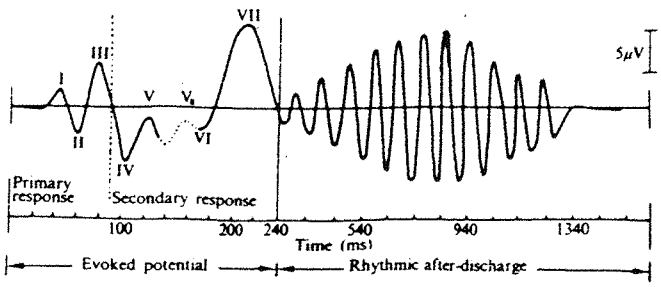
1. Primary response - (0-90 msec) Waves I-III. This includes the activity generated by the primary visual cortex (area 17) by a stimulus following a specific pathway. The P35 wave (I) probably represents the primary cortical positivity.

   In addition, early visual oscillatory potentials can be recorded from wide areas of the scalp to a visual stimulus. These oscillatory potentials have been designated N14, P18, N21, P24, N28, P33, N36, P39 (Craco & Cracco 1978). These potentials are believed to originate from structures such as the optic nerve and optic tract (Doty & Kimura 1963) and/or post-chiasmal areas such as thalamic or optic radiation (Harding & Rubinstein 1982). These authors recorded the visual subcortical evoked potential consisting of components P21, N29 and P34 complex possibly of superior colliculus or lateral geniculate nucleus origin.

   The retinal electrical activity (ERG) can also be recorded all over the head during this time period. The early visual oscillatory and visual subcortical evoked potentials could possibly be related to ERG oscillatory potentials (Ogden 1973).

2. Secondary response - (90-240 msec) Waves IV-VIII. This response could be the result of further processing by the primary visual cortex or produced by non-specific diffuse pathways (Ciganek 1960) or by corticothalamo-cortico reverberating circuits (Hubel & Wiesel 1971).

3. Rhythmic After Discharge - (240-1340 msec). This is related to the Alpha rhythm and is variable and dependant on levels of psychological awareness.



Schematic representation of the human flash VEP. Three components can be recognized: a primary response, a secondary response, and a rhythmic after-discharge. Note the different time-scales. Symbols I–VII indicate the successive components of the VEP.

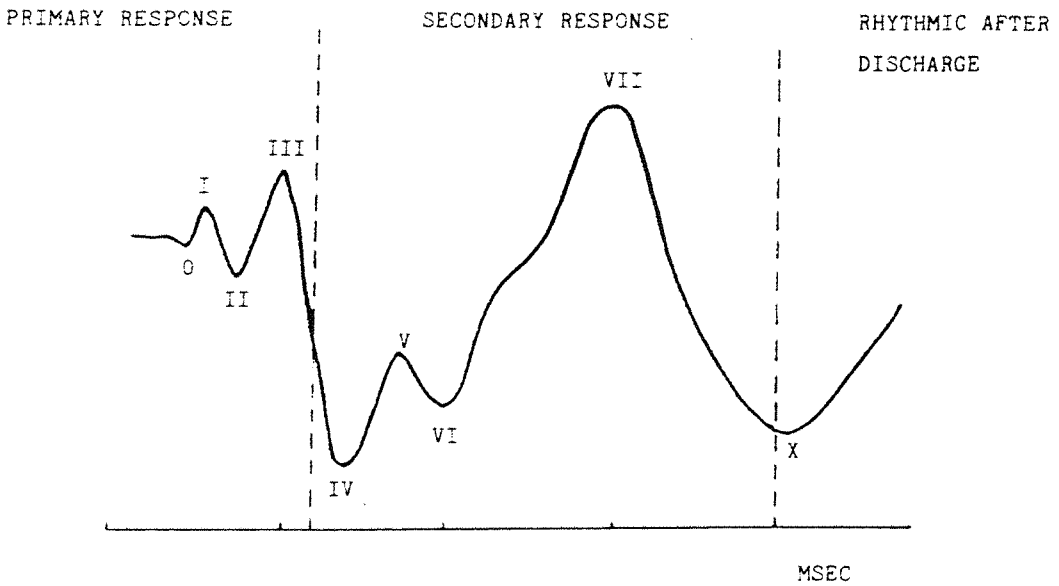


FIGURE 8

SCHEMATIC REPRESENTATION OF FLASH VEP

CHAPTER 3

EXPERIMENTAL METHOD/TECHNIQUE/RESULTS

Equipment

Nicolet Pathfinder II (Stimulator and Averager)

Technical Specification

Amplifier

Built in Nicolet SM200 biological amplifier with an input impedance of 10 megohms minimum (10MΩ) and a common mode rejection (CMR) greater than 90 dB at a frequency of 60 Hz. The amplifier noise level was less than 1uV r.m.s.

Sensitivity

This was set to 100 or 200 uV (full scale deflection) giving an amplification of x100,000 or x50,000 respectively. The displayed evoked potential could be further enlarged by using the display gain control. Relative negativity of the active electrode was denoted by an upward deflection.

Filters

Analogue filters were used with a bandpass of 5Hz-1500 Hz (-3dB) and a roll off of 12dB/octave. The effect of changing the upper and lower frequency limits on the evoked potential is reported as selectively changing the filters and can be used to separate and highlight different components of the evoked potential.

Averaging

The averager incorporated in the Pathfinder is a Nicolet 1280 processor which provides an 8 bits 'word length' for the Analogue Digital Convertor (ADC) and allows input voltage over a range of 10 volts so the effective resolution of the ADC is $10/2^8$ = 39mV per level.

This means that the peak amplitude of the signal has to be larger than 0.39uV (assuming an amplification factor of 100,000 times) for it to be recorded faithfully (Picton et al 1984), although a smaller signal could still be detected by longer averaging (Picton & Hink 1984). An analysis time of 120-150 msec after 10% post stimulus delay was used. The number of sampling points was 512 giving a sampling rate of approximately 4266.6 - 3413.3 points per second respectively. The sampling frequency was set to the highest possible rate that would avoid aliasing errors which, in theory, should be twice the highest frequency present in the signal, according to the Nyquist rate. The Nyquist rate represents the theoretical minimum value for the sample rate. In practice the sampling rate should be higher, preferably 4-5 times the highest frequency present in the signal. This oversampling reduces errors produced by the ADC and aliasing. Each trial consisted of between 200-500 sweeps, dependant on the physical and mental state of the volunteers, repeated twice and in some instances more than twice to ensure constancy of the response. In some cases it was necessary to accumulate more than 500 sweeps in order to improve the signal to noise ratio. Automatic artifact rejection was always employed. This ensured that a given response would be rejected if any data point beyond the first 10% of the sweep time exceeded 96% of the input sensitivity of the amplifier. This reduced the contamination of the evoked response by physiological artifacts such as eye movements, blink artifacts or high frequency muscle potentials. The raw EEG activity was monitored continuously throughout the recording procedure using a separate oscilloscope. This was necessary to observe the quality of the raw EEG signal and to identify potential electrical or physiological artifacts.

A Hewlett Packard XY Plotter was used to produce hardcopy of the evoked potentials acquired in this study.

Additional items required for this investigation:-

Nicolet Ganzfeld : Specifications -

Sphere Interior : 18" Interior diameter coated with Eastman Kodak 6080 reflectance paint

Strobe : Xenon Linear Flash Tube with glass filters to absorb ultraviolet and infra-red radiation.

Strobe Intensities : Range - from 0.25 to 1.5 selectable in 0.25 log unit steps. Remote filter selection allows strobe output to be varied over 5 log units.

Strobe Filters : 2" x 3" Kodak Wratten filters, Nos 26, 47, 47A, 47B (see figure 9 for Strobe Output Spectra).

Strobe Flash Rate : Externally controlled from 0.1-35 Hz depending on intensity setting.

Background Light : DC operated lamp with intensity selected from 1, 2, 5, 10, 15, 20, 25 and 30 footlamberts.

Strobe Output Liminance

Relative (log)	English (ft-ls)*	SI (cd m-2S)**
0.25	0.24	0.81
0.50	0.36	1.22
0.75	0.62	2.11
1.00	1.15	3.93
1.25	1.86	6.36
1.50	2.92	10.02

* Footlambert seconds

** Candela per square metre seconds

Strobe Output Spectra

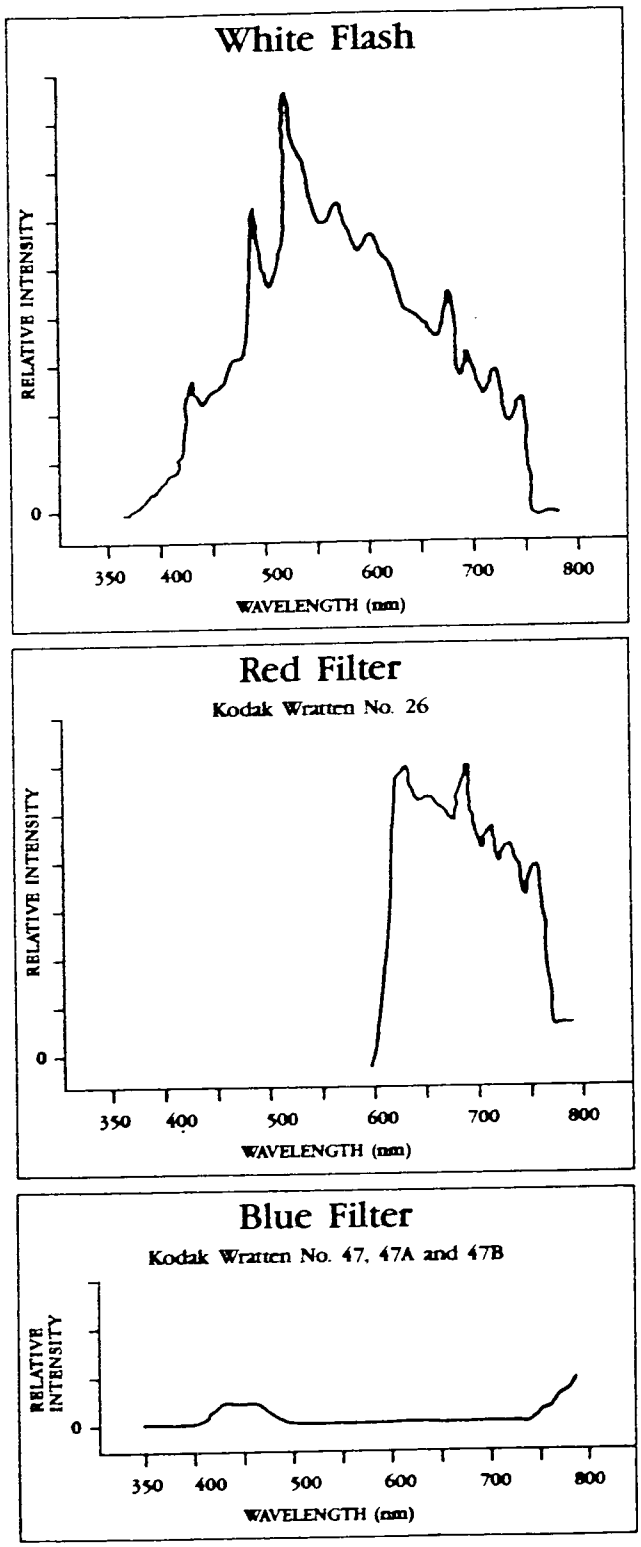


Figure 9

Nicolet L.E.D. Goggles 640 - 655nm : Intensity 100 - 600 mcd

Silver/Silver Chloride (Ag/Ag Cl) electrodes
Flexible collodion
Saline electrode gel (Dracard)
Syringes and Serrated blunt needles
Data disks
Tape measure
Air compressor
Chinagraph (wax) pencil
Plotting paper
Swabs
Acetone
Methylated spirit
Cotton buds
Skin pure (abrasive paste)
Micropore adhesive tape
Blenderm adhesive tape
Eye patch (black)

Method

The examination was carried out in a dimly lit room with the subject supine in a reclining chair. Silver/Silver Chloride (Ag/Ag Cl) non-polarisable electrodes were attached to the scalp of the volunteer using flexible collodion at the electrode positions O1, O2, C3, C4, Cz, A1, A2, T3.5, T4.5 and Fz (see figures 10 and 11) according to the international 10-20 system of electrode placement (Jasper 1958). Before the electrodes were applied, the head of subject was measured to determine the electrode positions of the 10-20 system. The electrodes T3.5 and T4.5 were placed half way between T3 and T5 and T4 and T6 respectively of the 10-20 system. The electrode site is prepared using an abrasive cream which removes the cornified layer of skin thereby reducing the electrode impedances. The electrodes are then applied and fixed in position by using flexible collodion which is dried using a cold jet of air from an air compressor. Saline (isotonic) gel is injected into the cup of the electrode through an aperture on the dome of the electrode. The saline gel forms an electrical double layer between the ions of the electrode (Ag/Ag Cl) and the ions (Na^+ Cl^-) in the saline gel. The gel is the 'bridge' between the electrical rhythms generated from the nervous system and the recording device. For good results, the electrode-scalp interface should be made as stable as possible. The electrode impedances were reduced and equalised to below 5 kilo-ohms - this is necessary to improve the common mode rejection ratio and signal to noise ratio of the amplifiers.

Connecting the electrodes to the Pathfinder allowed the raw EEG from the volunteer to be observed on the oscilloscope before averaging was started.

The electrodes used for recording the ERG were Silver/Silver Chloride electrodes attached to the right and left lower eyelids with Blenderm or Micropore adhesive tape. The skin of the lower eyelid was slightly abraded using Skin Pure abrasive paste and isotonic saline gel as the conducting medium. Again the impedances were measured and if necessary further reduced until the impedance value was 5 kilo-ohms or below.

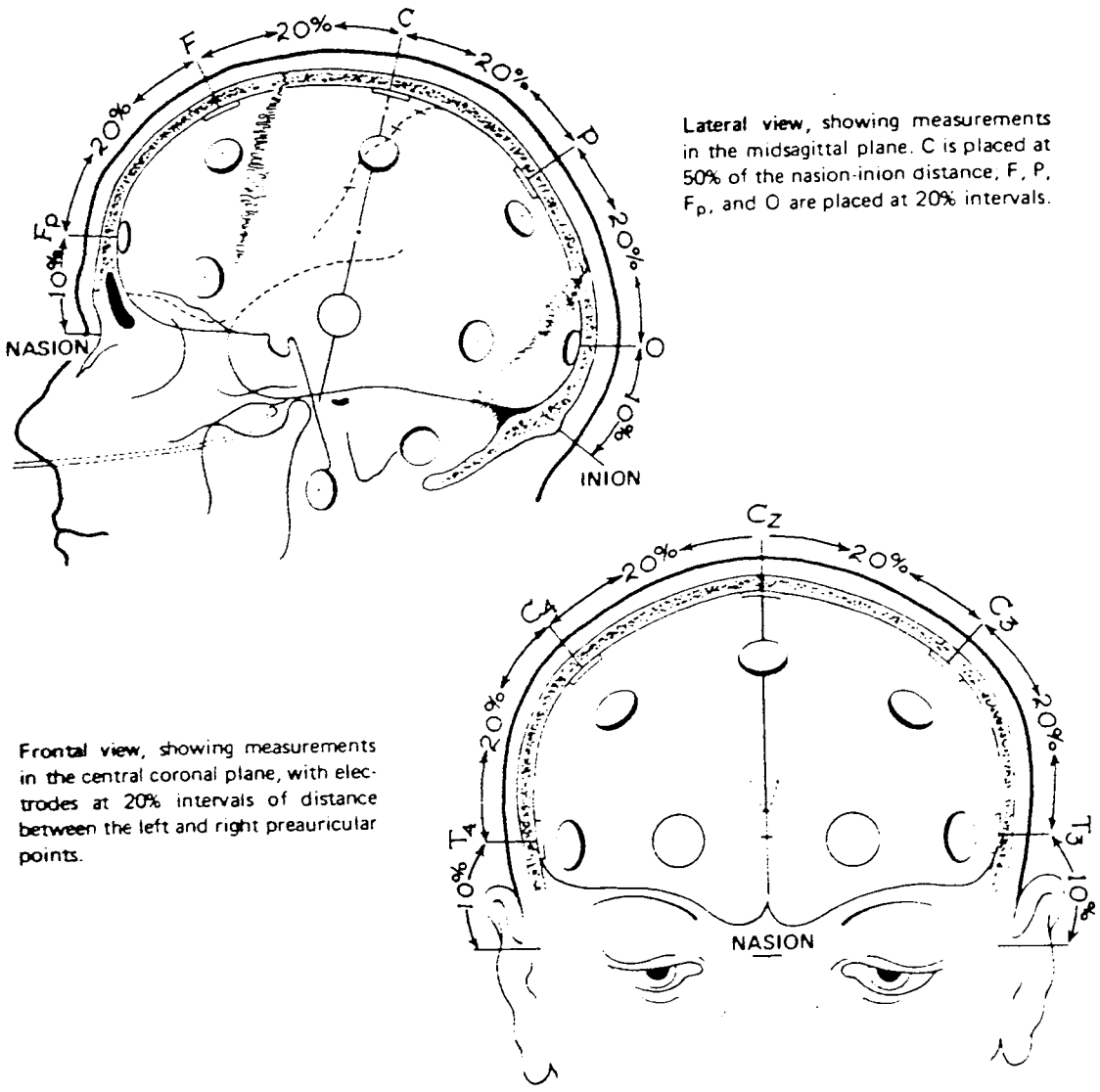


FIGURE 10

ELECTRODE PLACEMENTS IN THE 'TEN TWENTY' ELECTRODE SYSTEM

C = Central
F = Frontal
Fp = Frontal Pole
O = Occipital
P = Parietal

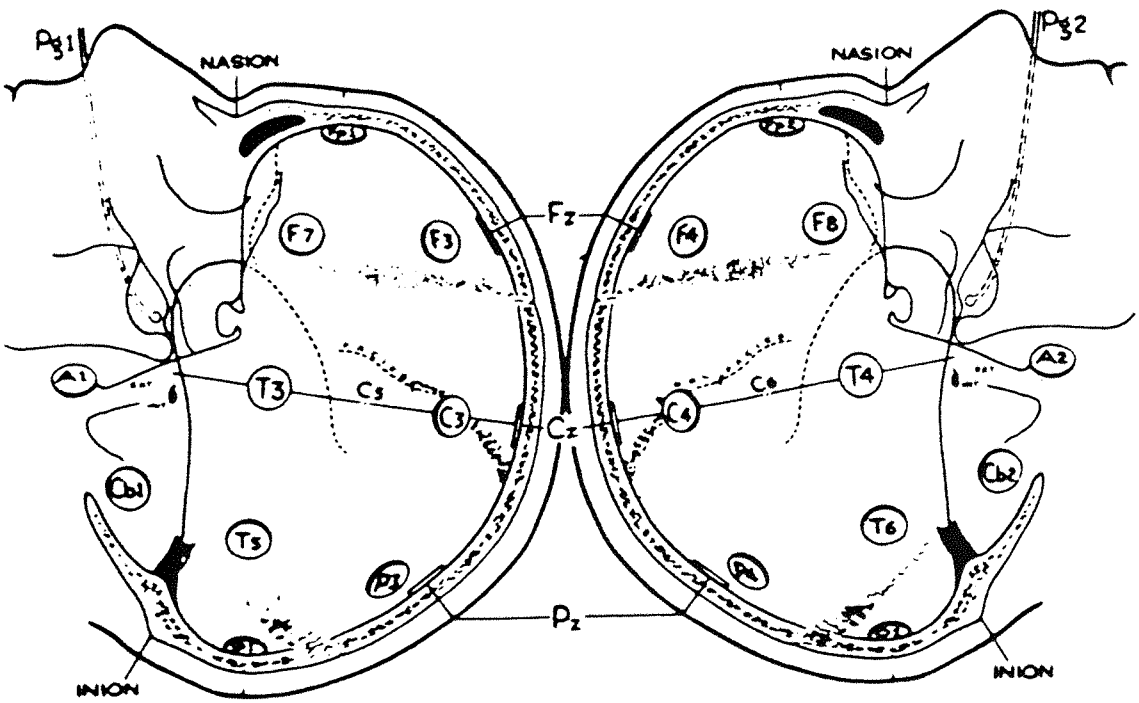


FIGURE 11

ELECTRODE PLACEMENTS IN THE '10-20' ELECTRODE SYSTEM

Silver/Silver Chloride disc electrodes were chosen for this study as opposed to more conventional corneal ERG electrodes like gold foil or DTL carbon fibre electrodes because of the extended duration of the examination of the experiment. Even with anaesthetic eye drops, movement of the gold foil or DTL fibre electrodes is more evident than with the skin applied electrodes. The major drawback of using skin applied electrodes compared to corneal electrodes is when measuring amplitude of the ERG and in identifying the oscillatory potentials. From this study, the results of recording the ERG with skin electrodes were comparable to those recorded using corneal electrodes except for amplitude comparison. Oscillatory potentials of the ERG could easily be identified with both methods.
Silver/Silver Chloride skin electrodes are easier to apply and can be routinely used in neonates or children without discomfort. In addition, the sterilising of Silver/Silver Chloride electrodes does not have to be as stringent as with corneal electrodes.
Furthermore, price is also a prime consideration when using gold foil over Silver/Silver Chloride electrodes, the latter being less expensive and generally have a longer recording life. The stimulus used in the first part of the study was a flash of light from a pair of goggles consisting of an L.E.D. display arranged in a chequer board pattern (5 x 3 L.E.D.'s) and giving a flash of 5 msec duration at a repetition rate of 4.7 flashes per second. The reason for using the L.E.D. goggles was firstly to see if the 'sub-cortical responses' recorded in Harding & Rubinsteins (1980, 1981) work could be replicated using a different light stimulus but using the same recording parameters and secondly as the 'sub-cortical responses' that were recorded were considered to be far field potentials, a light stimulus without the audible click artifact from stroboscopic stimulators was needed. The Audible Click stimulus is the stimulus of choice when investigating the Brain-Stem Auditory Evoked Potential (BAEP) or Middle Latency Response, now recognised as far field potentials and recorded at a distance. In Harding & Rubinstein's work, the results obtained were thought to contain an auditory component which contaminated the visual response. Using L.E.D. goggles removed this effect and the results obtained were from visual stimulation only.

Part 1

Using the Nicolet Pathfinder, seven channels of data were recorded simultaneously. Obviously the more channels available, the easier and more informative are the responses obtained for a specific time period. With several different aspects of the experiment, the 'mental' state of the volunteers whether awake or asleep, nervous or agitated, may have resulted in differences of the recorded responses with respect to amplitude and latency being measured. Responses obtained were recorded both with eyes open and closed and during wakefulness and sleep.

All the volunteers, aged 21-29 years (mean 24.2 years, 7 females, 3 males) were neurologically and ophthalmologically normal individuals who worked in the Department of Clinical Neurophysiology, Southampton. These volunteers were more relaxed than other populations of volunteers may have been due to their various experiences of tests used in neurophysiology, ie EEG and EP recordings and their knowledge of what was required.

Visual acuity was tested by means of a Snellen Test Chart, which comprises of a set of letters, the details of which subtend a visual angle of one minute when held 6m from the eye. The clinical measurement of visual acuity is carried out by determining the distance apart at which separate images can be resolved when placed at a known distance from the eye. Normal visual acuity is 6/6.

Electrode Montage

ERG

Channels 1 and 2 - Mono-polar recording from Left Lower Lid (LLL) referenced to A1; Right Lower Lid (RLL) referenced to A2.

Short Latency Visual EP - Channels 3 and 4 - Mono-polor recording

Subcortical Visual EP/Oscillatory Potentials - From T3.5 and T4.5 referenced to Cz.

Cortical Visual EP - Channels 5, 6 and 7 - Mono-polar recording from O1, Oz, O2 referenced to C3, Cz C4 respectively. Ground electrode was Fz.

Amplifier Settings

ERG	High Band Pass Filter	=	1500 Hz
	Low Band Pass Filter	=	5 Hz
	Sensitivity	=	200 uV/cm
	Time Base	=	150 msec
	Sweeps/Repetitions	=	As required
Short Latency VEP	High Band Pass Filter	=	1500 Hz
	Low Band Pass Filter	=	5 Hz
	Sensitivity	=	100 uV/cm
	Time Base	=	170 msec
	Sweeps/Repetitions	=	500
Cortical VEP	High Band Pass Filter	=	500 Hz
	Low Band Pass Filter	=	5 Hz
	Sensitivity	=	100 uV/cm
	Time Base	=	170 msec
	Sweeps/Repetitions	=	500

The study can be divided into 2 sections:-

1. Confirmation of the work carried out by Rubinstein & Harding, with traditional stroboscope light stimulus and then with red L.E.D. goggles.

2. Localisation or spatial distribution of the evoked potential over the scalp; whether it is related to the activity of the retina and how does changing the rate of stimulation and amplifier filter settings affect the evoked responses and is it possible to separate the evoked response from the ERG using specific wavelengths of light.

CHAPTER 4

RESULTS AND DISCUSSION

Results - In a normal control series aged 21-29 years (mean 24.2 years)

This section of results relates to the work performed using the criteria and methodology of Harding & Rubinstein with the addition of red LED goggles as the stimulus.

Before using the red LED goggles on the subject, the examination was undertaken using a xenon flash discharge tube as the stimulator. This was a Grass stimulator at intensity 4. From the manufacturer, the highest intensity of the Grass stimulator, intensity 16, represents 1,500,000 candle power for 10 microseconds at a distance of 10 inches. Therefore step 4 is one quarter of step 16. It was felt that before attempting to question or validate previous results obtained by various workers, a direct comparison should be made before changing either the stimulus or other parameters used in recording the evoked potentials. The results of this initial baseline using the xenon flash are shown in figure 12.

The responses shown are the non-corneal electro-retinogram and the early visual evoked potentials recorded using the electrode placements as suggested by Harding & Rubinstein. The latencies for the ERG are within normal limits when compared to published date (Ikeda 1976, 1982), ie 40-50 msec for the b-wave latency. The b-wave amplitudes of the ERG are reduced and are of the order of 14-17 uV (normal corneal range 0.1-1.0 mV); this is due to the fact that the responses recorded were obtained using Silver/Silver Chloride skin electrodes placed on the lower eyelids. In routine clinical ERG examination, gold foil or DTL electrodes are used which are placed in direct contact with the cornea of the eye, thus resulting in large amplitude potentials. For the purpose of this study, it was necessary to establish a baseline for ERG amplitude and latency using the xenon flash stimulus which in turn will enable a comparison to be made when using the red L.E.D. goggles.

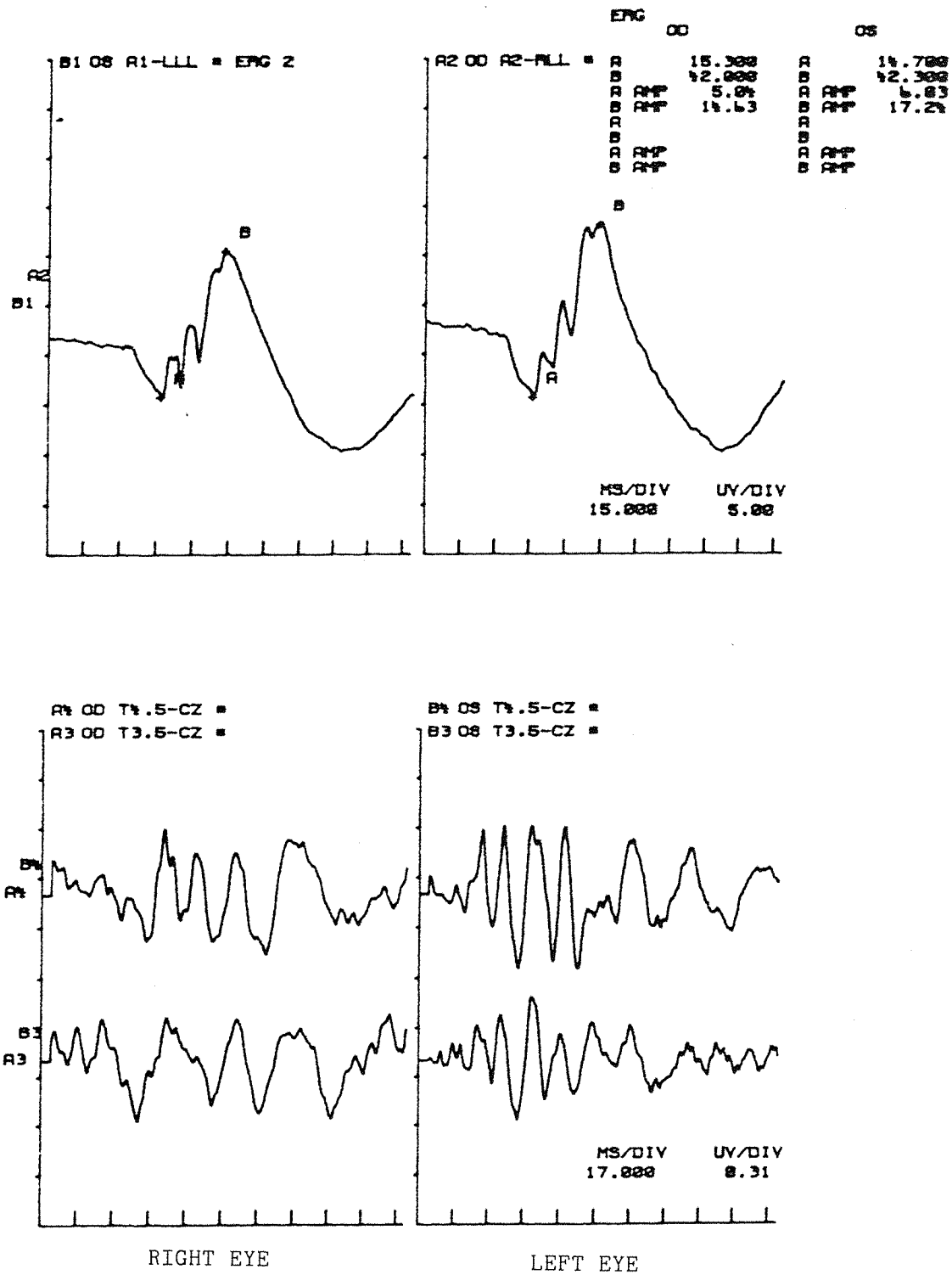


FIGURE 12

ERG AND EARLY VISUAL EVOKED POTENTIALS RECORDED IN RESPONSE TO A LIGHT (XENON) MONOCULAR FLASH STIMULUS

In addition, from figure 13 the amplitude of the early visual evoked potentials can be seen to be less than 1uV peak to peak amplitude. It will also be noted from the figure, that in this particular subject, a difference in morphology of the evoked response exists, not significantly between recording sites T3.5 or T4.5 but between which eye is stimulated. This difference is not evident in the ERG.

Having established that evoked potentials could be recorded following the flash from the xenon light stimulus using scalp electrodes over specified areas of the head according to Harding & Rubinstein, the stimulator was changed to a pair of goggles in which a chequer board array (5 x 3) of red light emiting diodes were mounted. The test was then performed with the goggles worn over closed eyes. The subject was requested to maintain eye closure in order to reduce contamination of the raw data by blink artifact, to standardise the procedure and to reduce the variable of eye opening/closing on the responses recorded. It also ensured that, should the subject fall asleep the responses would be recorded through closed eyes and therefore not be affected unduly. If the responses obtained showed marked differences with eyes closed between alert and sleep states, then this would be attributed to the physiological state and not to the eyes being open or closed. Figure 14 clearly demonstrates the combined recording of the non-corneal electro-retinogram, the early visual and cortical visual evoked responses to monocular stimulation from red L.E.D. goggles through closed eyelids from one of the volunteers examined. Two runs are superimposed to demonstrate reproducibility. Figure 15 shows ERG and early sub-cortical and cortical responses evoked with L.E.D. goggles. The cortical responses have been marked according to Ciganek's nomenclature.

Subsequent measurement of latency and amplitude for the a and b waves of the ERG, the most consistent identifiable waves, both positive and negative for the early visual evoked responses and the most prominent peaks and troughs of the cortical visual evoked responses were documented and listed in the accompanying tables. Graphical representation of the mean and standard deviation of the ERG latencies for both right (OD) and left (OS) eye are included for summary (see table 1 and graph 1).

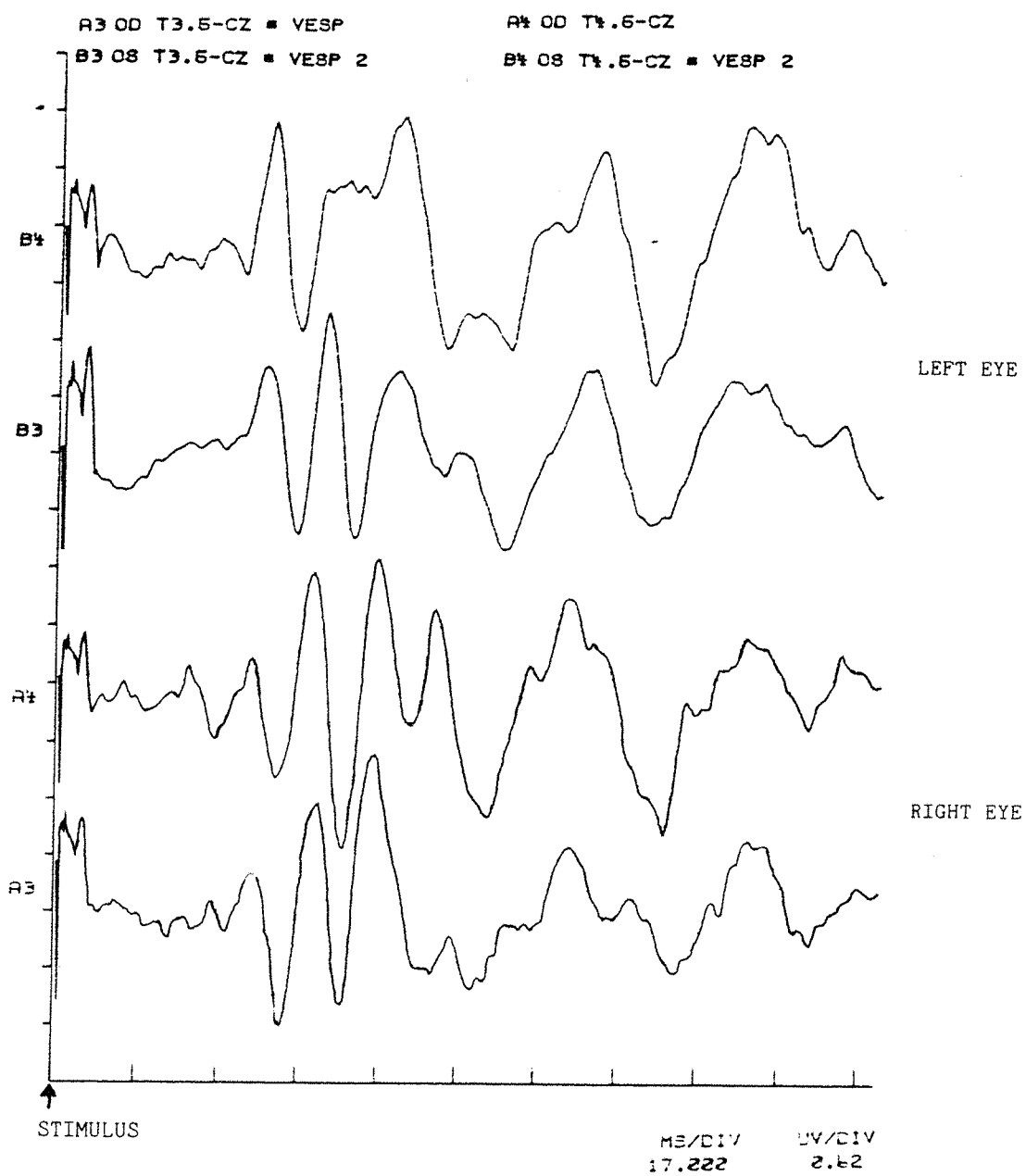


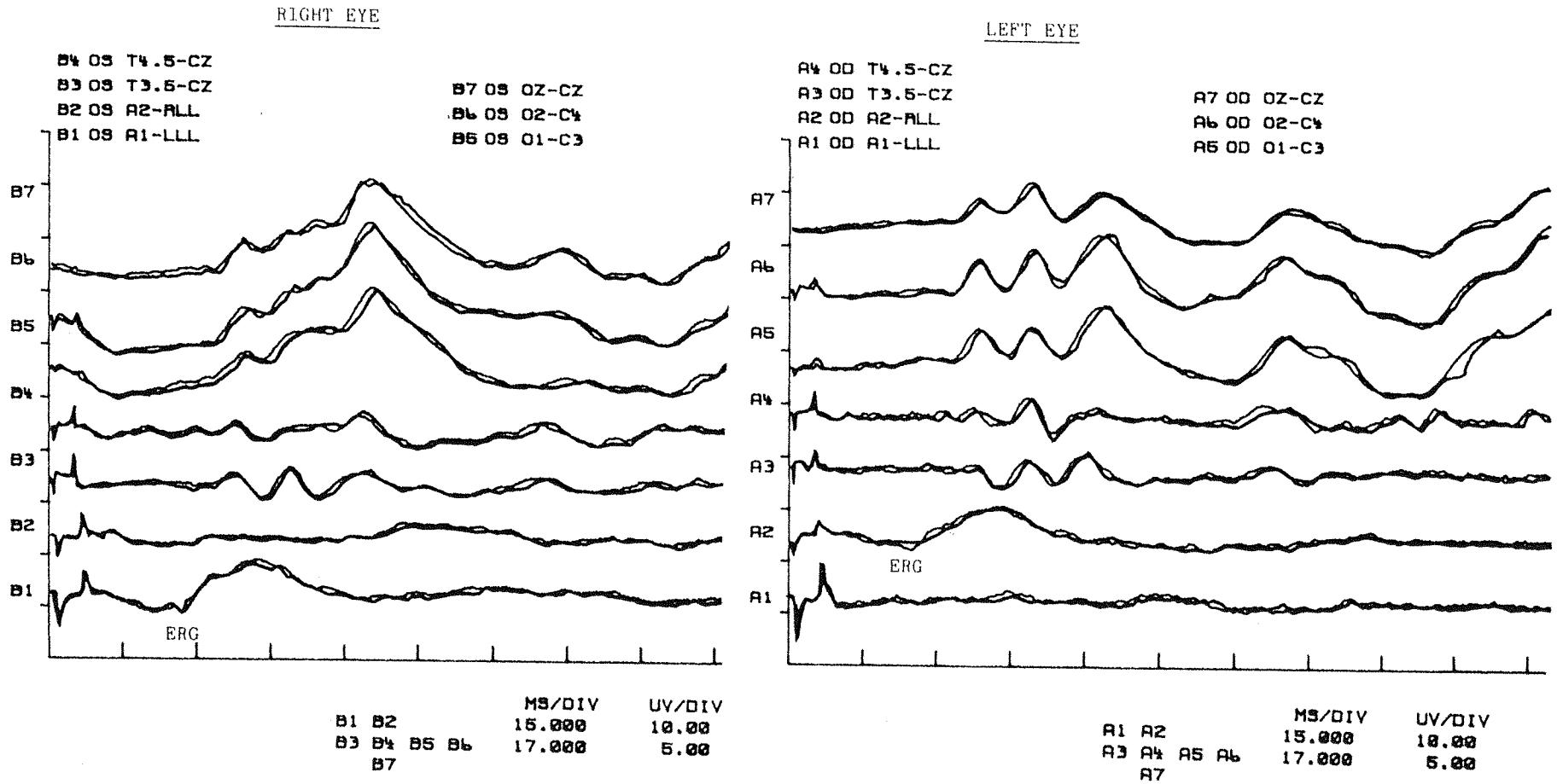
FIGURE 13

THE EVOKED RESPONSE OBTAINED BY MONOCULAR L.E.D. GOGGLE STIMULATION RECORDED AT T3.5 AND T4.5 REFERENCED TO Cz IN ONE SUBJECT (500 SWEEPS EACH RESPONSE).

FIGURE 14

SIMULTANEOUS RECORDING OF ERG, EARLY AND CORTICAL VISUAL EVOKED POTENTIALS TO MONOCULAR L.E.D. STIMULATION - OD AND OS

N.B. AMPLITUDE DIFFERENCES BETWEEN ERG AND CORTICAL EVOKED POTENTIALS



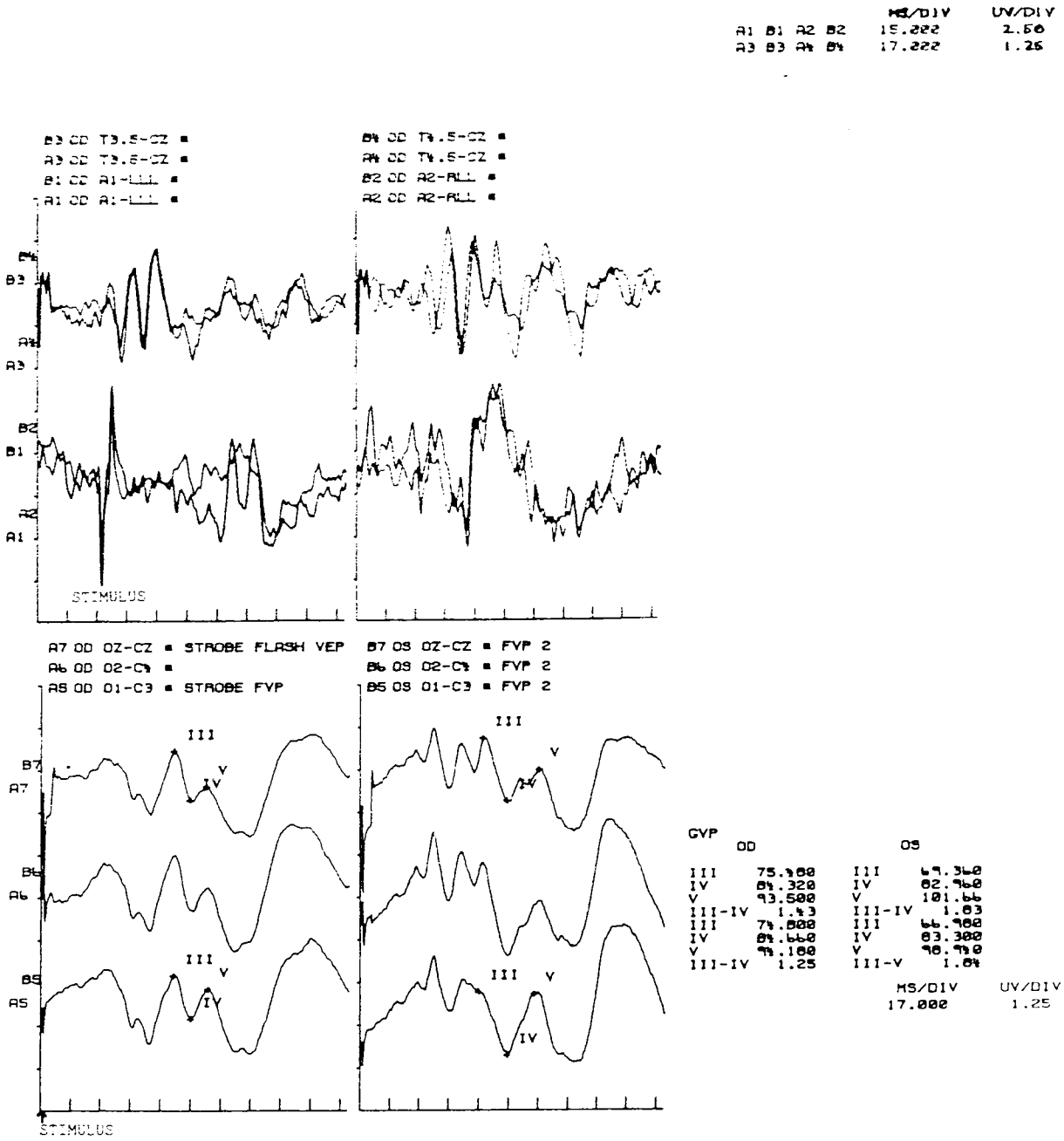


FIGURE 15

ERG AND VISUAL SUB-CORTICAL RESPONSE - TWO RUNS SUPERIMPOSED AND THE BOTTOM TRACE SHOWING THE CORTICAL VISUAL RESPONSE

TABLE 1

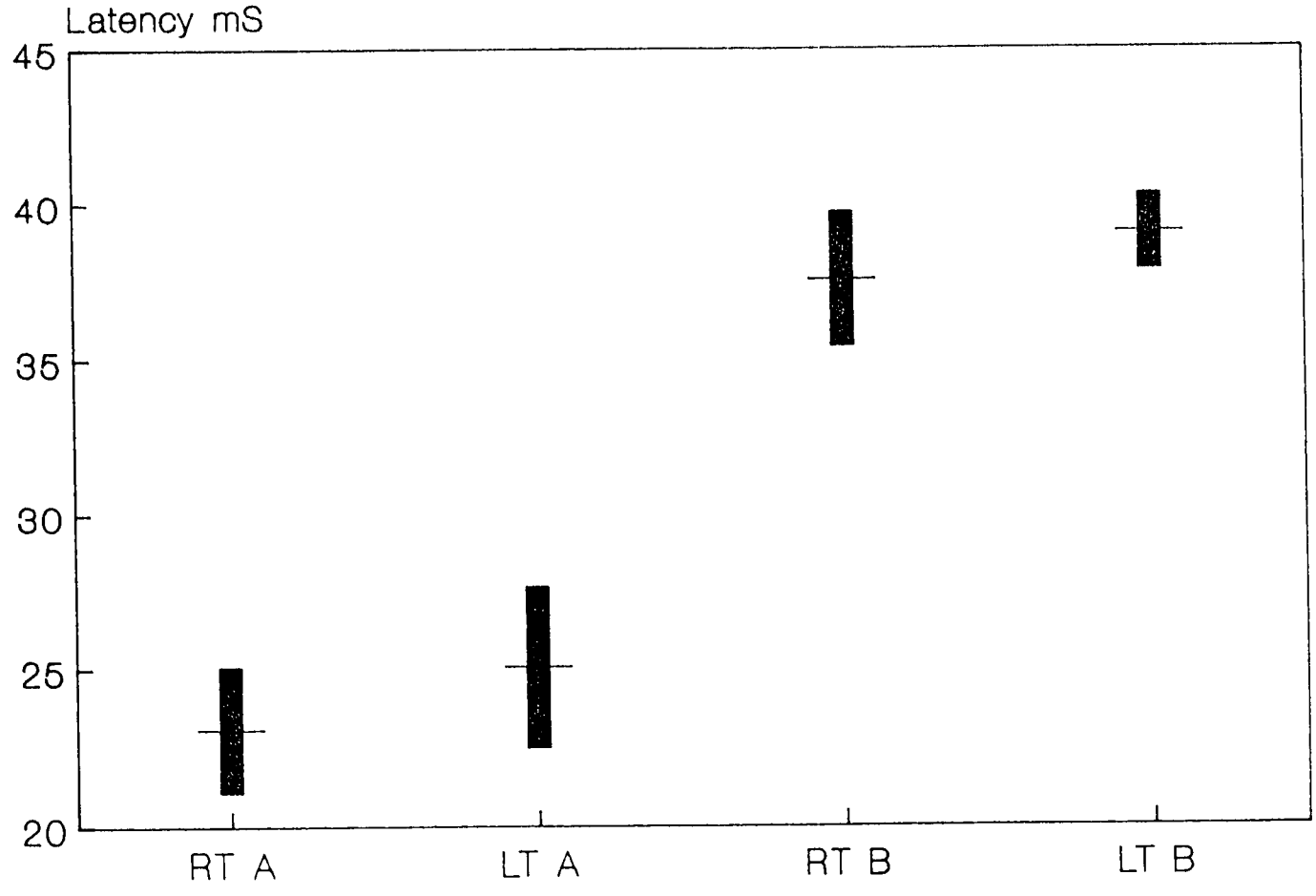
ERG - Latencies (mS)

Inits	Age	Lat mS RT A	Lat mS Lt A	Diff	Lat mS Rt B	Lat mS Lt B	Diff
C.B.	26	26.10	26.70	.60	38.40	40.20	1.80
B.M.	22	18.30	18.60	.30	41.40	41.40	.00
S.B-W.	21	22.50	25.50	3.00	34.80	38.40	3.60
S.T.	25	21.90	22.80	.90	39.30	40.20	.90
A.P.	21	22.80	25.80	3.00	33.90	38.40	4.50
N.H.	21	24.00	25.80	1.80	37.50	38.10	.60
S.P.	27	23.10	28.20	5.10	39.00	39.90	.90
T.N.	29	23.70	24.00	.30	38.70	37.80	-.90
E.G.	22	23.10	26.40	3.30	36.90	38.70	1.80
R.C.	28	25.20	26.80	1.60	35.80	37.50	1.70
VAR	9.0	3.95	6.66	2.24	4.64	1.47	2.32
MEAN	24.2	23.07	25.06	1.99	37.57	39.06	1.49
SD	3.0	1.99	2.58	1.50	2.15	1.21	1.52

Electroretinogram A and B Waves.

Mean +/- Standard Deviation

No. of Subjects = 10



GRAPH 1

Latency measurements for the early 'sub-cortical' visual responses (T3.5 - Cz and T4.5 - Cz) are listed with a summary table for the most consistently identifiable responses N29, P37 and N44. Graphical representation is also attached representing numerical data for the waves identified (see table 2 and 3, graphs 2, 3, 4 and 5).

Latency measurements for the cortical visual evoked potential recorded from occipitally placed electrodes (O2, Oz, O1) referenced to transverse midline electrodes (C4, Cz, C3) are also tabulated. The peak and trough of the cortical response were labelled using Ciganek's nomenclature. A comparison table between Ciganek's findings and those of this study is listed (Table 4, 5 and 6) showing the consistency and similarity between responses obtained from the visual cortex even though different stimuli were used in each study.

From the responses obtained to light stimulation, either xenon flash or red LED goggles, the ERG was the most consistent in both latency and amplitude and also in configuration. Although the ERG is composed of the activity of numerous different types of cells, all the components were recorded including the oscillatory potentials. These were more prominent when using the xenon flash stimulus although they could be identified in responses obtained using the red L.E.D. goggles. The amplitudes of the two ERG's recorded to different light stimuli were different giving an amplitude range for LED stimulation between the a and b waves from 3.5 to 12.5 microvolts. The measures for the stroboscope stimulus showed amplitude range between the a and b waves from 14.0 to 21.5 microvolts. The low amplitudes for the ERG's are attributed to a number of experimental conditions during the investigation. These include (i) recording the ERG with Silver/Silver Chloride skin electrodes placed on the lower eyelids, (ii) recording the ERG through closed eyes, (iii) recording of the ERG in photopic conditions and (iv) using a large number of sweeps.

TABLE 2

VISUAL SUB-CORTICAL EP (RIGHT + LEFT EYE T3.5-CZ)
POLARITY ACCORDING TO E.E.G.CONVENTION

NAME	N29	P37	N44	P52	N65
C.B.	N/A	34.00	43.80	49.90	64.90
B.M.	31.90	40.50	46.60	51.00	60.80
S.B-W.	29.60	35.70	43.50	55.10	68.70
E.G.	28.20	37.00	46.90	53.70	60.20
S.T.	29.30	32.30	49.60	53.40	68.70
N.H.	31.60	34.70	39.80	54.00	66.30
S.P.	31.70	31.70	44.50	58.20	74.80
T.N.	25.80	37.70	45.60	51.70	62.60
A.P.	30.90	33.60	49.60	54.00	59.50
B.M.	24.80	38.10	44.20	50.60	63.90
S.B-W	30.90	39.50	42.70	47.30	64.60
C.B	29.60	35.70	43.50	55.10	68.70
E.G.	26.70	38.40	42.90	53.00	67.60
S.T.	28.50	36.70	40.80	57.50	62.20
N.H.	25.50	34.30	42.50	49.30	71.00
S.P.	25.80	37.20	43.20	48.60	60.80
T.N.	29.20	43.20	48.30	51.70	66.30
A.P.	29.20	39.40	41.80	47.60	66.00
AVE	28.78	36.65	44.43	52.32	65.42
STD	2.25	2.90	2.74	3.05	3.98
VAR	5.07	8.39	7.49	9.32	15.81

VISUAL SUB-CORTICAL EP(LEFT + RIGHT EYE T4.5-CZ)
POLARITY ACCORDING TO E.E.G. CONVENTION

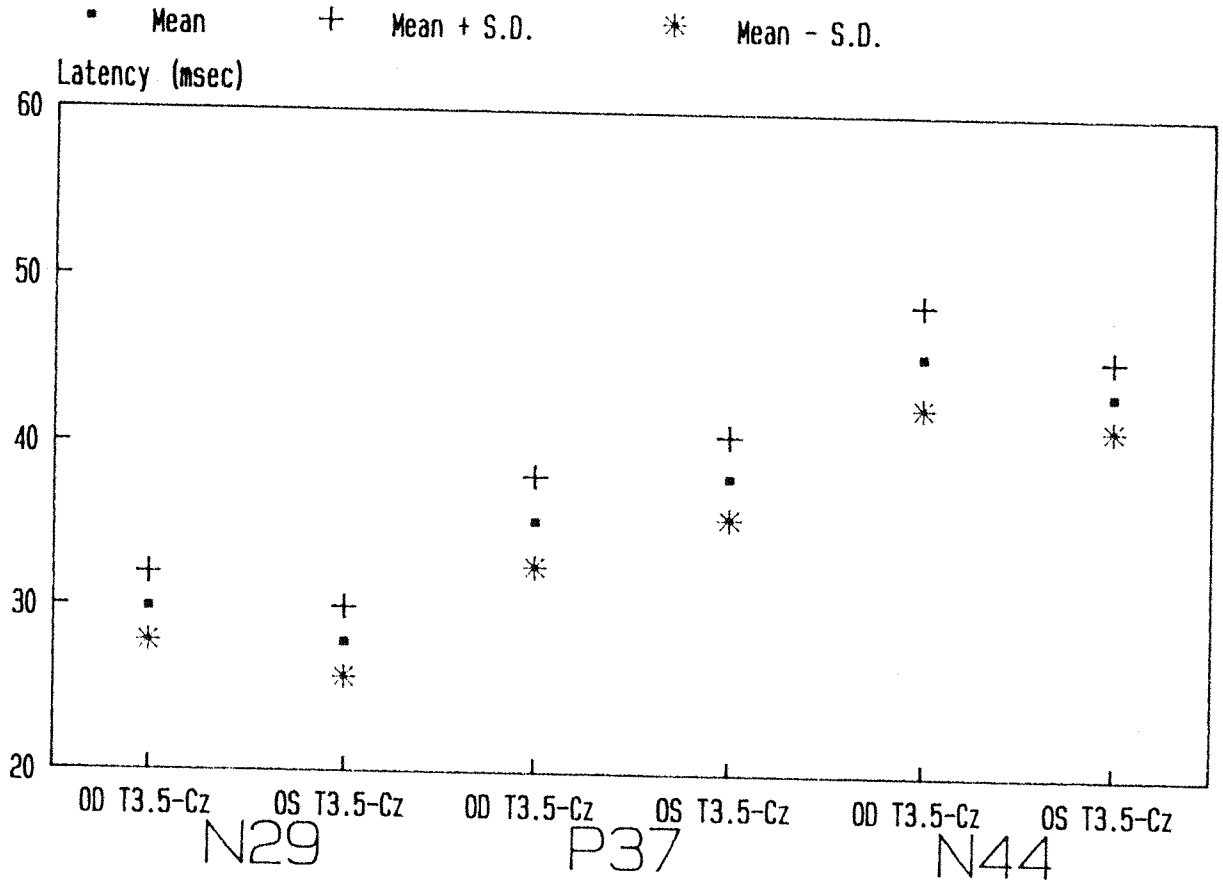
NAME	N29	P37	N44	P52	N65
B.M.	25.50	38.70	43.80	50.30	68.30
S.B-W.	24.10	35.70	43.50	51.30	74.10
C.B.	31.70	36.70	44.20	51.30	64.60
E.G.	30.20	38.40	47.20	56.80	66.30
S.T.	26.80	31.60	36.70	48.20	68.40
N.H.	23.80	37.00	43.20	49.60	71.00
S.P.	25.80	36.00	39.80	48.60	63.20
T.N.	34.70	39.10	43.80	51.70	69.30
A.P.	31.90	36.40	41.80	48.60	70.40
B.M.	28.20	39.10	48.90	53.70	64.20
S.B-W.	27.50	33.60	47.90	60.80	70.00
C.B.	28.90	41.10	46.60	57.80	66.90
E.G.	25.80	39.40	46.60	52.70	72.00
S.T.	25.20	32.90	47.90	53.00	68.30
N.H.	26.60	39.70	52.30	59.50	66.30
S.P.	24.50	41.80	64.90	74.80	80.60
T.N.	25.80	37.70	41.10	55.10	64.30
A.P.	29.90	38.00	43.80	54.40	76.80
AVE	27.61	37.38	45.78	54.34	69.17
STD	2.96	2.65	5.83	6.14	4.44
VAR	8.76	7.00	34.01	37.68	19.75

TABLE 3

EARLY FLASH VISUAL EVOKED POTENTIALS FROM 10 NORMAL ADULTS

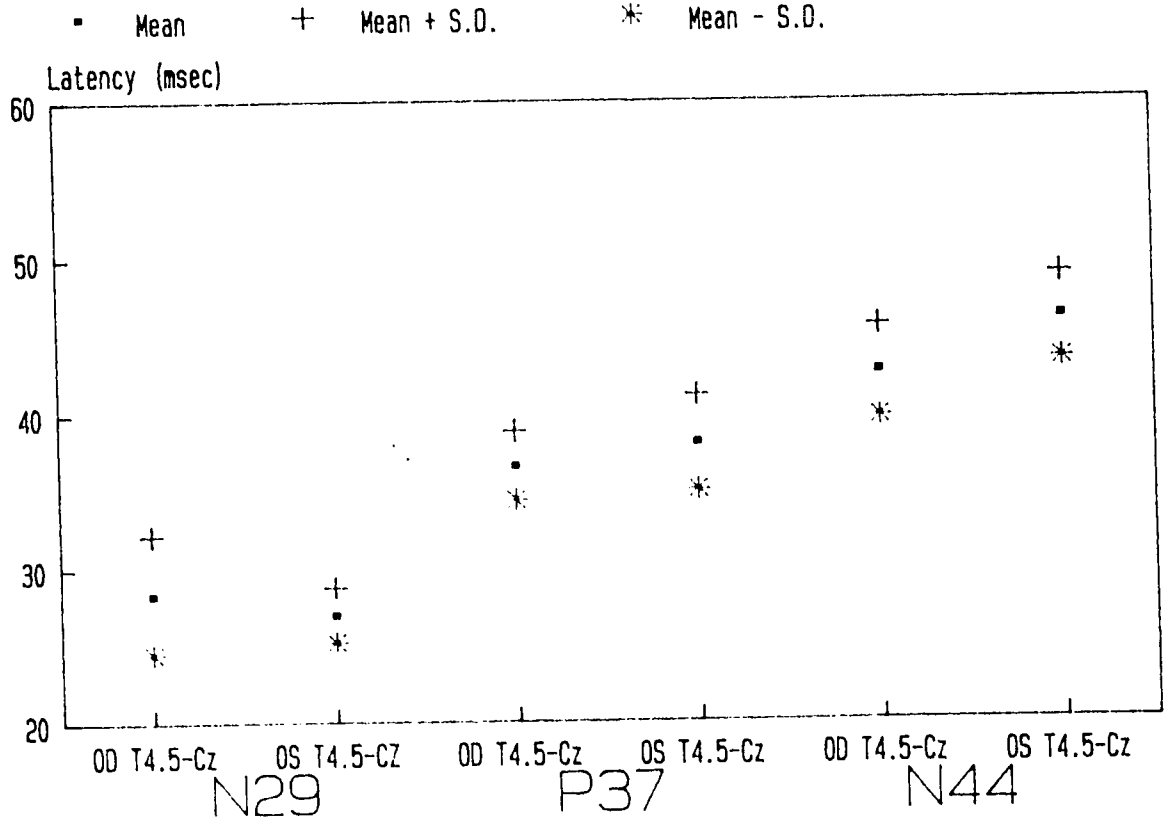
	T3.5-Cz Mean ± sd	T4.5-Cz Mean ± sd
Potential N29		
Right eye	29.87 ± 2.11	28.27 ± 3.90
Left eye	27.80 ± 2.14	26.90 ± 1.80
Potential P37		
Right eye	35.24 ± 2.80	36.62 ± 2.24
Left eye	38.05 ± 2.56	38.10 ± 3.07
Potential N44		
Right eye	45.50 ± 3.10	42.66 ± 2.97
Left eye	43.30 ± 2.10	46.11 ± 2.74

VISUAL SUB-CORTICAL EVOKED POTENTIALS
Early Potentials (OD & OS T3.5-Cz)



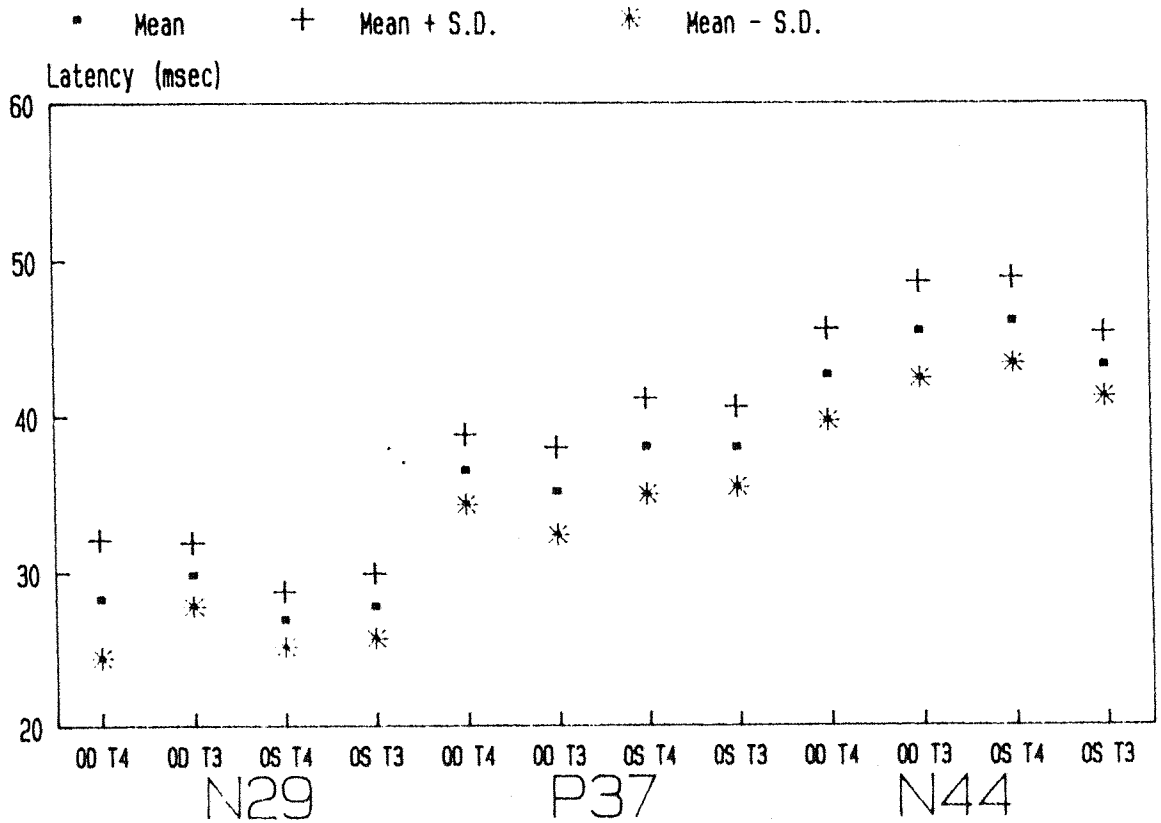
GRAPH 2

VISUAL SUB-CORTICAL EVOKED POTENTIALS
Early Potentials (OD & OS T4.5-Cz)



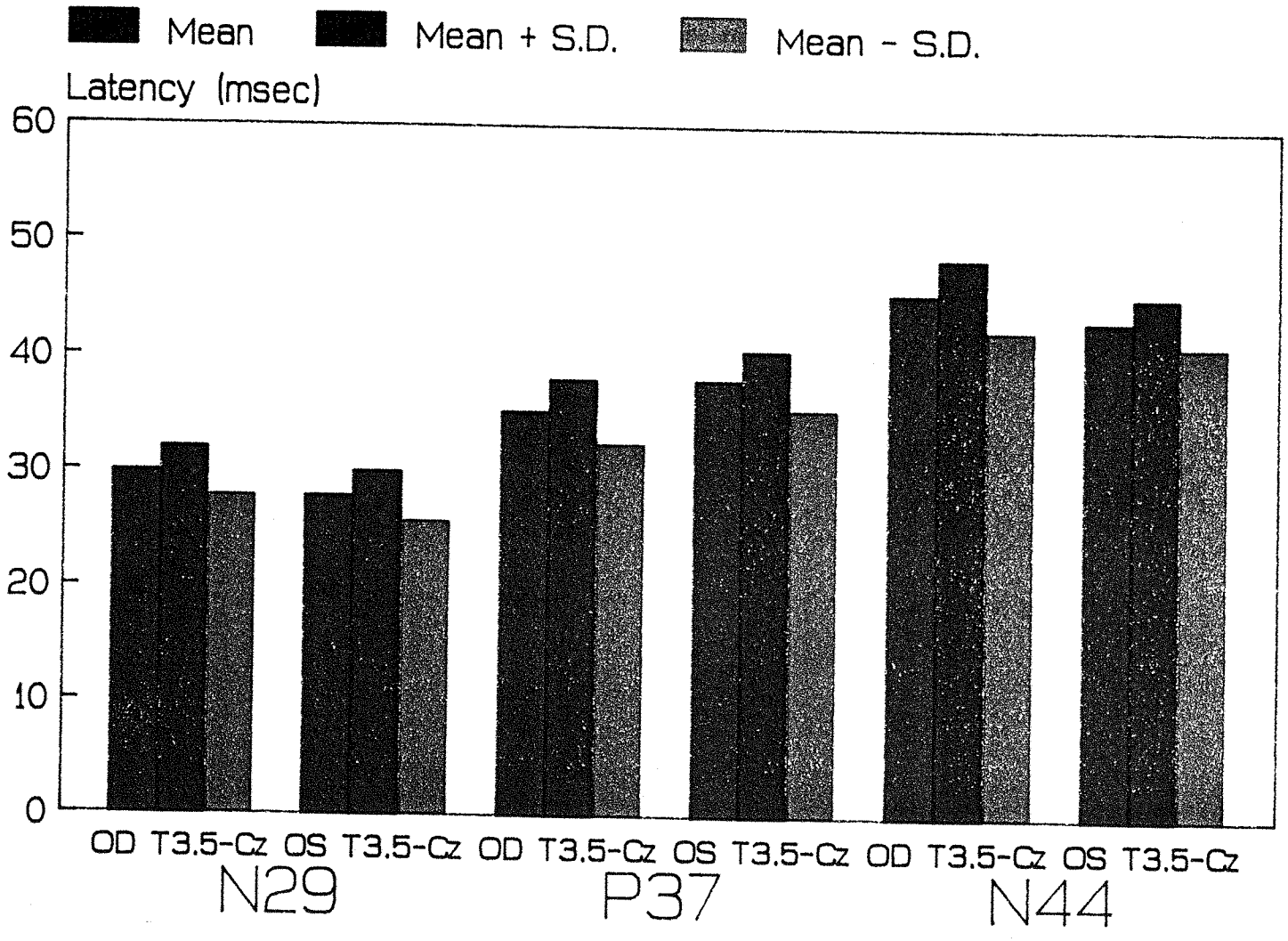
GRAPH 3

VISUAL SUB-CORTICAL EVOKED POTENTIALS
Early Potentials (OD & OS T4.5 & T3.5)



GRAPH 4

VISUAL SUB-CORTICAL EVOKED POTENTIALS
Early Potentials (OD & OS T3.5-Cz)



GRAPH 5

TABLE 4

VISUAL CORTICAL EP (RIGHT + LEFT EYE OZ-CZ)

POLARITY ACCORDING TO E.E.G. CONVENTION

NAME	I	II	III	IV	V	VI
S.T.	40.24	52.36	68.34	90.44	116.28	137.36
S.B-W.	44.88	52.70	72.40	99.90	132.00	147.50
E.G.	48.62	64.60	75.14	94.18	104.70	127.50
B.M.	47.26	51.60	69.02	91.10	112.50	139.00
N.H.	54.74	60.18	70.38	90.78	122.00	142.46
T.N.	57.12	60.20	75.14	98.60	123.45	156.74
A.P.	37.74	46.20	69.70	101.30	124.40	149.90
S.P.	40.46	54.40	62.20	94.18	122.06	135.60
C.B.	43.18	51.68	67.34	92.80	102.00	127.80
S.T.	51.34	55.08	70.04	93.80	115.90	144.80
S.B-W.	44.20	59.50	74.12	98.90	130.50	148.50
E.G.	52.70	68.00	82.30	92.50	122.00	134.90
B.M.	45.56	53.70	61.20	93.70	115.00	128.00
N.H.	57.12	61.54	65.60	93.50	118.30	135.60
T.N.	44.12	59.50	74.46	85.00	98.60	121.00
A.P.	54.70	62.90	74.80	105.70	128.96	154.40
S.P.	48.90	58.80	64.90	97.50	124.10	142.12
C.B.	48.20	57.40	67.60	100.30	136.30	151.30
AVE	47.84	57.24	70.26	95.23	119.39	140.25
STD	5.69	5.30	5.10	4.78	9.96	9.88
VAR	32.33	28.05	26.06	22.85	99.15	97.61

TABLE 5

COMPARISON OF VISUAL CORTICAL EP (CIGANEK v RESULTS OBTAINED)

	CIGANEK (Oz-Pz) (STROBOSCOPE)		LARWOOD (Oz-Cz) (L.E.D. GOGGLES)	
	AVERAGE	STD	AVERAGE	STD
I	39.12	4.18	47.83	5.68
II	53.40	4.42	57.24	5.29
III	73.33	6.36	70.26	5.10
IV	94.19	7.13	95.23	4.78
V	114.00	7.14	119.39	9.95
VI	134.55	9.92	140.24	9.87

TABLE 6

GRAND AVERAGE OF CORTICAL EP RIGHT & LEFT

L.E.D. GOGGLE STIMULATION

WAVES	RIGHT (OZ-CZ)	LEFT (OZ-CZ)
I	57.10	45.50
II	60.50	52.00
III	69.02	71.00
IV	96.20	96.50
V	121.00	122.40
VI	142.60	143.80

WAVES	RIGHT (O2-C4)	LEFT (O2-C4)
I	40.40	44.20
II	47.00	51.00
III	68.30	70.30
IV	96.50	96.50
V	123.70	124.10
VI	138.40	142.40

WAVES	RIGHT (O1-C3)	LEFT (O1-C3)
I	40.10	54.40
II	50.60	60.20
III	69.00	70.70
IV	94.80	97.20
V	121.70	124.40
VI	143.80	145.20

Using 300-500 or more sweeps (and hence light flashes) was necessary to average the early visual evoked potentials N29, P37 and N44 identified in this study from the raw EEG data. Constant presentation of light stimuli to the retina results in a reduced amplitude due to physiological hatituation of the photoreceptors.

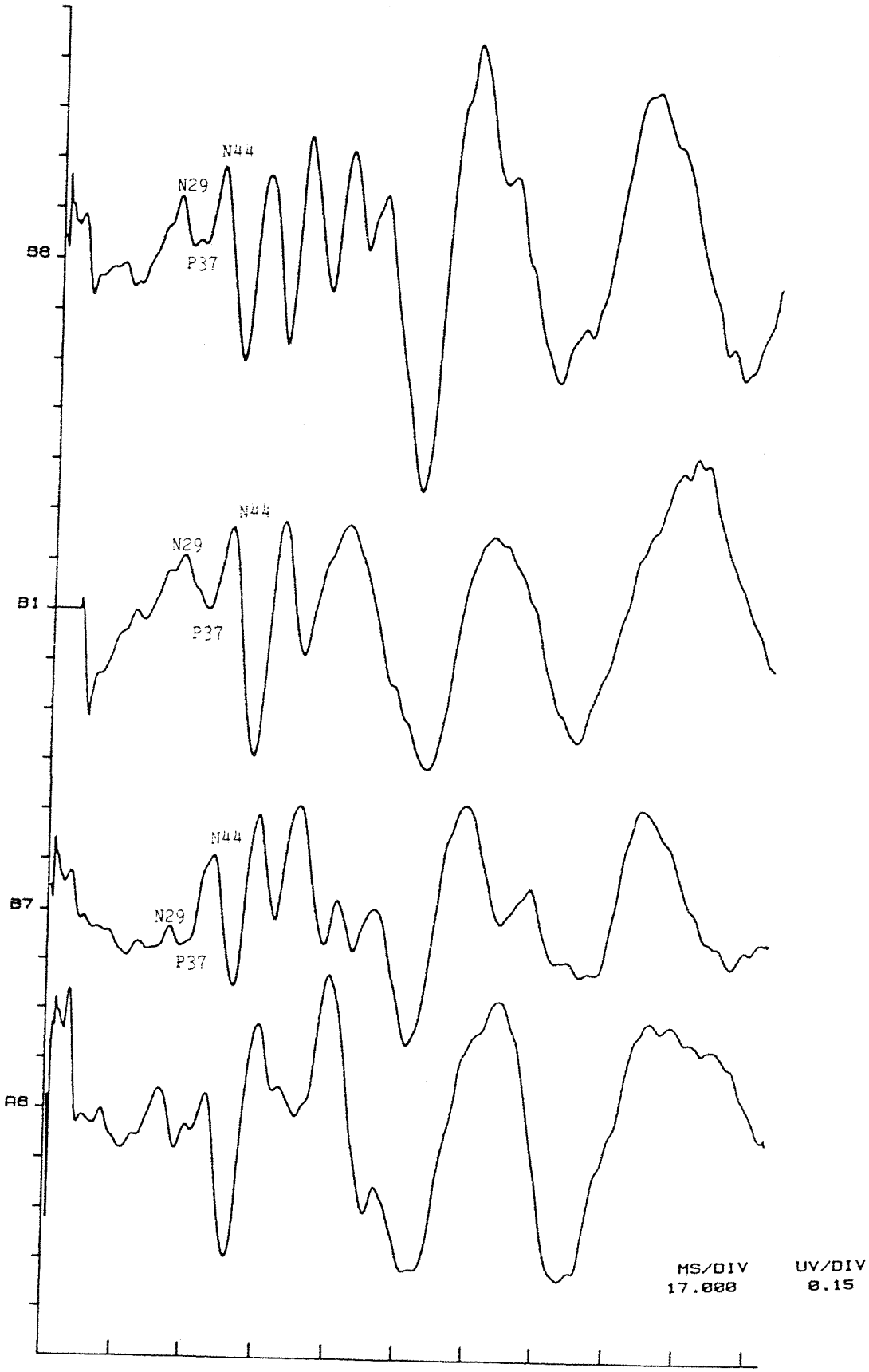
The ERG was clearly identifiable in all volunteers and showed good correlation within the subjects two eyes and between individuals used in this study (see Appendix A).

The early evoked responses (oscillatory or sub-cortical) waveforms were identified in all subjects studied but the degree of variability, both in morphology, the number of negative or positive components making up the response and the range of latencies and amplitudes recorded made the listing and selection of the major components slightly more difficult. The major components that could be identified consistently were (P20), N29, P37 and N44 when recorded from active T3.5 and T4.5 electrodes referenced to Cz. These were the average values obtained from the small population studied and could correspond to the P21, N29 and P34 components reported by Harding & Rubinstein. The P20 waveform identified in this study was seen in some of the subjects but not in all so was not included for discussion. At this stage, although there is a slight difference in latency between the findings of this study and those of Harding & Rubinstein, this was accounted for by the difference in light intensity of the red L.E.D. goggles compared to the flash from the xenon stroboscope. The N29, P37 and N44 peaks were shorter when using the stroboscope for stimulation and compared favourably with previous workers results.

Examples of the variability can be seen in figure 16 which clearly demonstrates the difference in number of the 'oscillatory potentials' and also to the negative and positive phases of each individual components. Clearly the potentials evoked are physiological in origin as the responses obtained can be replicated and duplicated with successive runs and also when the test is repeated after a time period of days or weeks between tests.

FIGURE 16

VSEP OBTAINED BY STIMULATING WITH RED L.E.D. GOGGLES USING HARDING AND RUBENSTEIN'S ELECTRODE PLACEMENTS.



To identify each peak it was necessary to perform one of two operations. The components could be labelled by identifying the major component (negative or positive) of the cortical visual evoked potential recorded from occipitally placed electrodes which was recorded simultaneously and labelled according to Ciganek (figure 1). Alternatively, all the responses obtained for stimulation of the right eye (OD) recorded at T3.5 referenced Cz added together and divided by the number of trials which gave the grand average. This was repeated for right eye stimulated with response recorded at T4.5 and for the left eye (OS) to T3.5 and T4.5. The idea behind this operation was to try and obtain an 'evoked potential template' against which the individual responses could be compared and measured.

The 'template' was used in all measurements to identify the most consistent negative and positive components. Only those components of the individual responses when compared to the 'template' showing the same phase negative or positive were included in determining the major components and annotating them N29, P37 and N44.

If the individual response had several negative and positive deflections within a short time period, the component closest to the 'template' component in that time period was counted. Multiple deflections that occured in some subjects were measured for both latency and amplitude but as some of the multiple negative and positive components did not occur in the majority of the subjects they were not included in the statistics.

The potentials recorded from occipitally placed electrodes (O1, Oz, O2) referenced to central electrodes (C3, Cz, C4) shows a similar response configuration to that obtained by Ciganek using Oz referenced to Pz. A comparison of wave latencies of Ciganek versus results obtained in this study is shown in Table 5.

Figure 17 shows the early visual and cortical visual evoked potentials recorded simultaneously to red L.E.D. stimulation but using different recording electrodes. The early 'sub-cortical' potential was recorded using T4.5 - Cz and the cortical visual potential recorded using Oz - C4 of the 10-20 system of electrode placement. It will be noted that the Primary and Secondary response of the cortical visual EP, according to Ciganek, is well-defined with the large slow wave components of the FVEP being prominent. The waveform has been labelled after Ciganek identifying the major components I, II, III, IV, V, VI and VII. The early visual evoked (T4.5 - Cz) response shows slightly reduced amplitude oscillatory potentials when compared with the cortical VEP but the later waves IV, V, VI and VII are greatly reduced in amplitude. The most consistent components of the cortical (occipital) FVEP are III, IV and V waves (corresponding in latency to N70, (N80), P95 and N120 msec).

All the subjects showed consistent and reproducible cortical responses to L.E.D. stimulation and between run variability in each individual was minimal but between subjects variability of waveform was evident as proven by previous workers using flash stimulation.

Comparison of the responses obtained using different recording sites shows similarity in the early components of both responses P20, N29, P37, N44 and figure 17 shows a good correlation between the early waves of the primary response and the oscillatory potentials.

The evoked responses obtained indicate that they are due solely to the light stimulus generated by the L.E.D. goggles and that the response does not have an auditory component from the click of the photic stroboscope stimulator as suggested by Harding & Rubinstein (1982).

V . S . E . P & V . C . E . P IN SAME INDIVIDUAL

(NOTE THE GOOD INTERPEAK RELATIONSHIP BETWEEN THE V.S.E.P. & V.C.E.P.)

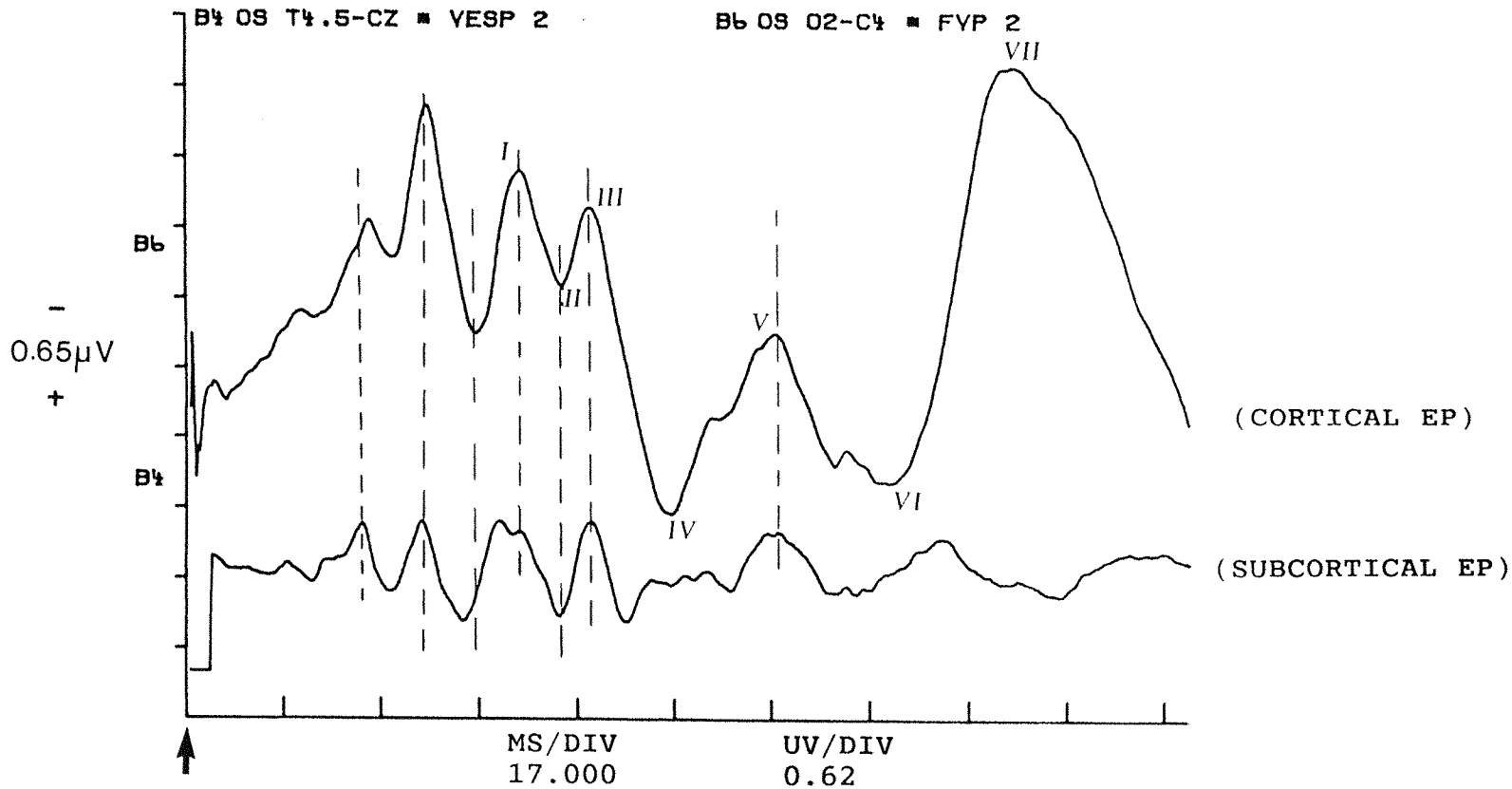


Figure 17

With reference to the topographic distribution of the early oscillatory potentials, Harding & Rubinstein using all electrodes referenced to Cz showed the maximum amplitude of the response to be centred around the mid-temporal/mastoid area, T3.5 and T4.5 whereas Cracco and Cracco (1978) showed the maximum potential to be found at electrode positions in midline and parasagittal leads than in temporal leads using ear reference leads with the maximum amplitude change seen at electrode location Pz and the minimum at electrode positions T3 and T4. In addition, Cracco & Cracco (1978) used cervical spine 7 as the reference electrode to help differentiate cephalic from non-cephalic reference site recording.

In this study the topography of the early oscillatory potentials was also investigated in the anterior-posterior temporal plane (electrode positions FPz, F8, T4, T4.5, T6, O2, Oz), anterior-posterior midline plane (electrode positions FPz, Fz, Cz, Pz, Oz) and in the central transverse plane (electrode positions T3.5, T3, C3, Cz, C4, T4, T4.5). These derivations were referenced to Cz, A2, A1 and CV7, shoulder and linked mastoid processes (A1 + A2).

Before investigating the topography of the early oscillatory potentials using the red L.E.D. goggles, a simple check between Harding & Rubinstein and Cracco & Cracco recording derivations was performed with the results displayed in figure 18. This figure clearly shows that the responses could be recorded using both derivations but that a polarity reversal of the waveforms is apparent. Selecting the best reference is obviously of great importance as it will determine the polarity of particular components of the evoked responses ellicited.

Figure 19 and 20 show the scalp distribution of the early oscillatory (sub-cortical) visual evoked potentials to goggle flash stimuli presented to the left eye referenced to an electrode on cervical spine 7; along the temporal, midline and central transverse electrode positions. The figures are identical with reference to the results displayed but differ in respect of showing the electrode positions as specified according to the International 10-20 electrode placement.

FIGURE 18

SUB-CORTICAL VEP AS RECORDED BY HARDING AND RUBINSTEIN (UPPER TRACE)

SUB-CORTICAL VEP AS RECORDED BY CRACCO AND CRACCO (LOWER TRACE)

TO SHOW POLARITY REVERSAL

MS/DIV 17.000 UV/DIV 0.62

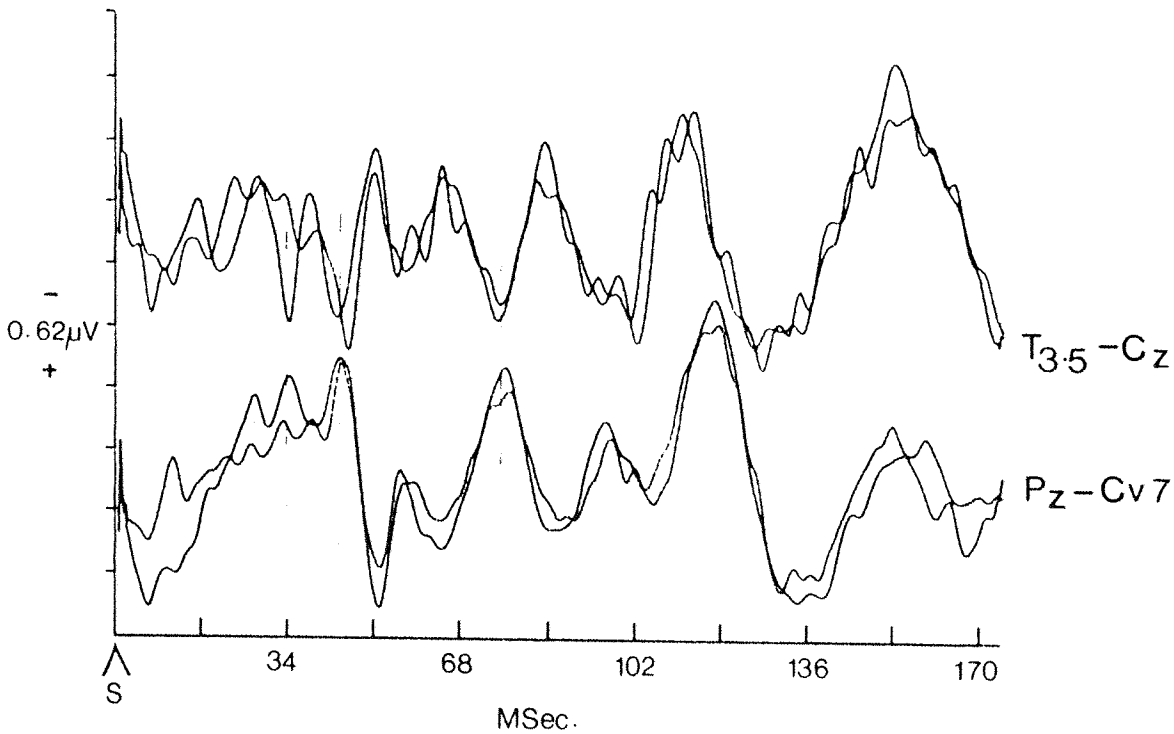


FIGURE 19

SUB-CORTICAL VEP TO GOGGLE FLASH STIMULUS

REFERENCE ELECTRODE ON CERVICAL SPINE 7

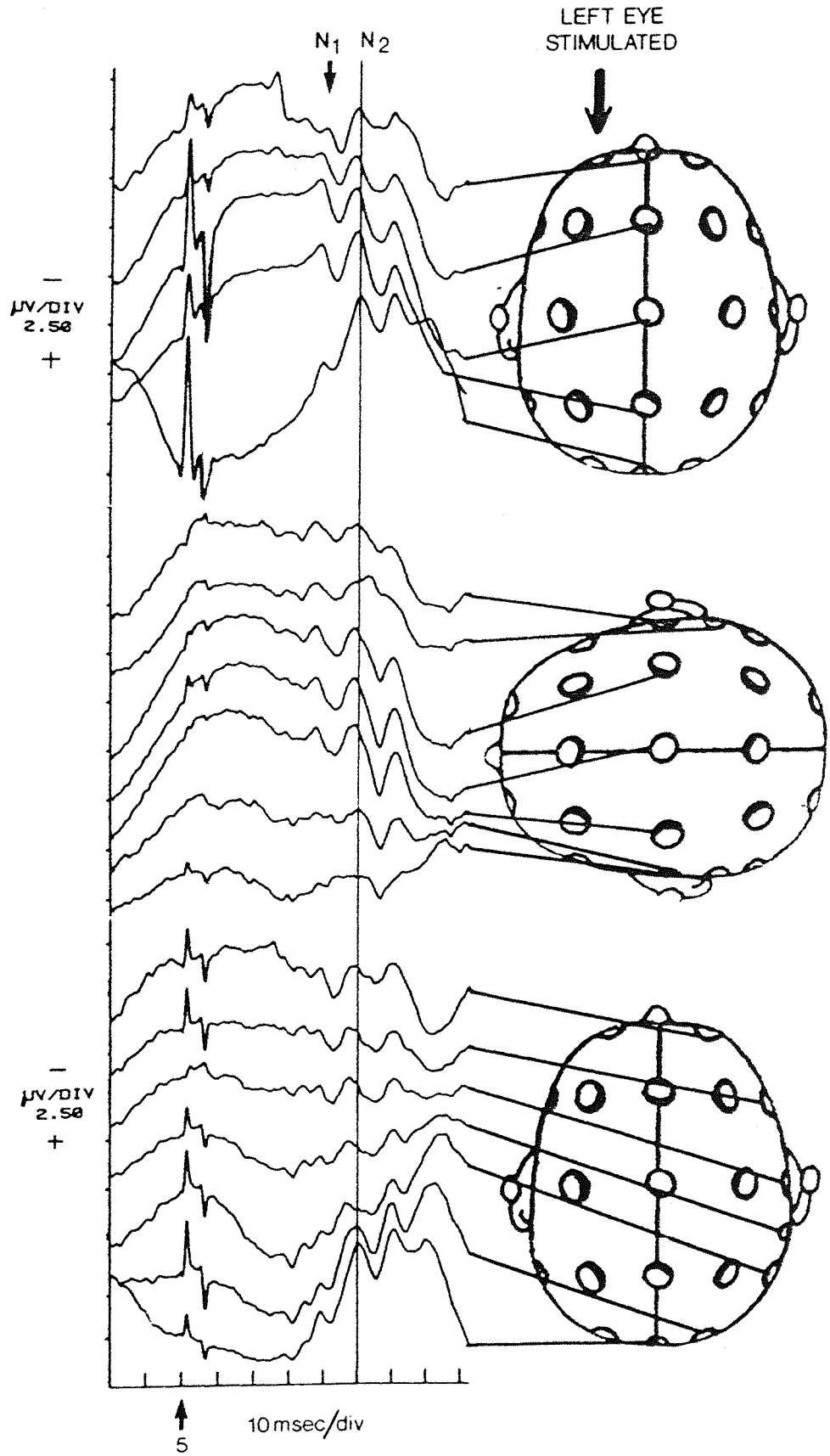
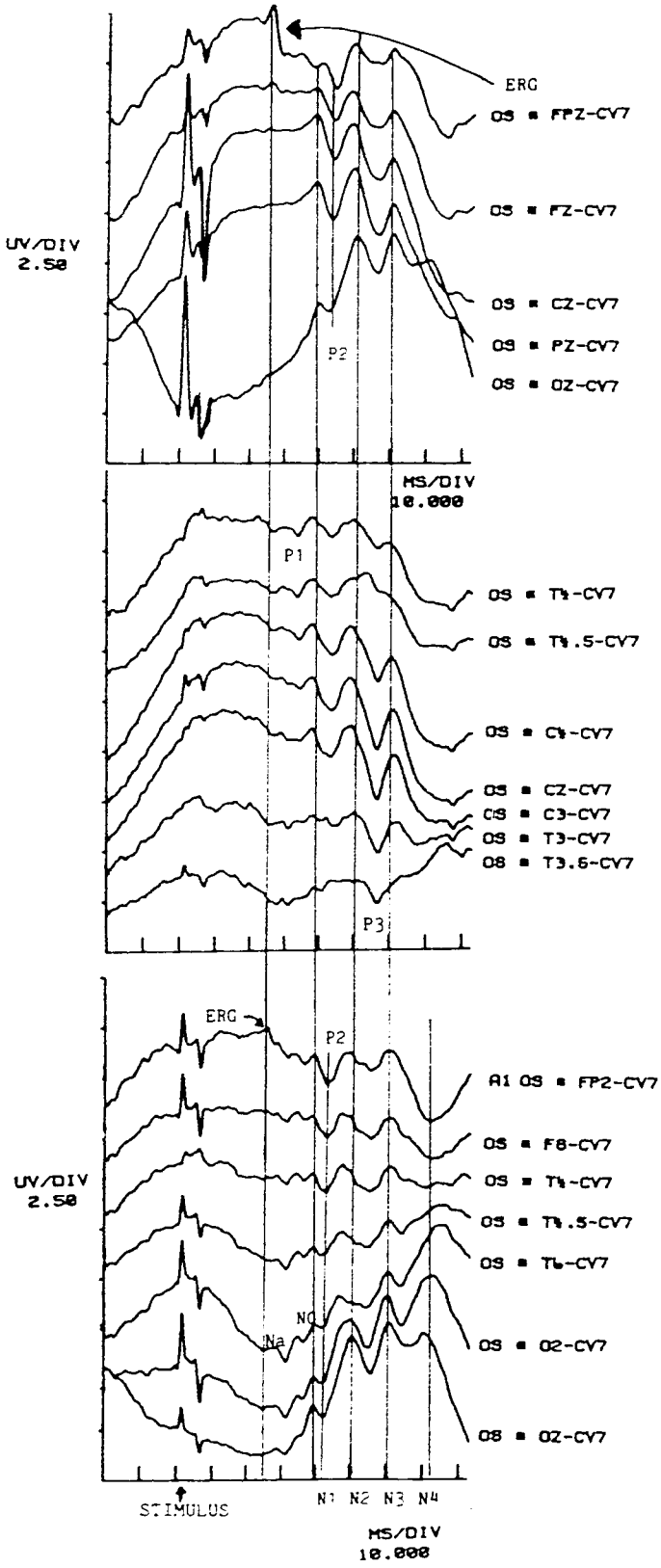


FIGURE 20

SUBCORTICAL VEP TO GOGGLE FLASH STIMULUS

REFERENCE ELECTRODE ON CERVICAL SPINE 7



NI DELAYED IN FPz - CV7 OR EVEN PHASE REVERSED.

P2 LATENCY IS SHORTER POSTERIORLY.

N2 LATENCY IS SHORTER ANTERIORLY.

THE A-WAVE OF THE ERG IS CLEARLY SEEN IN FPz AND FP2 ELECTRODE POSITIONS AS A NEGATIVE DEFLECTION WHEREAS IN OTHER POSITIONS IT IS EITHER ABSENT OR SHOWING A VERY SMALL POSITIVE INFLECTION.

N3 IS ABSENT BOTH AT T3.5 AND T4.5.

N2 LATENCY IS SHORTER IN ELECTRODE POSITIONS CLOSER TO THE MIDLINE.

N1, P2, N2 WAVES ARE ABSENT IPSILATERAL TO STIMULATED EYE AT ELECTRODE POSITIONS T3.5.

P3 IS THE MOST PROMINENT COMPONENT.

N2 LATENCY IS SHORTER AT ANTERIORLY POSITIONED ELECTRODES.

P2 LATENCY IN ANTERIOR/POSTERIOR TEMPORAL, MIDLINE AND TRANSVERSE DERIVATIONS IS CONSTANT.

The components of the response have been labelled for descriptive and reference purposes only with N or P for indicating the polarity according to the EEG convention, ie negative is upward.

The ERG can be seen in the first (Fpz - CV7) and 13th (Fpz - CV7) traces (top to bottom). The main feature of this series of evoked responses is that the P2 - N2 amplitude is greatest and maximal at electrode positions Cz, Pz, Oz, C3 and C4. It is also of interest that the P2 latency is shorter posteriorly whereas the N2 latency is shorter anteriorly. The component N1 - P2 is maximal in amplitude at Pz and Cz. The component N1, P2 and N2 are absent (T3.5 - CV7) ipsilateral to the stimulated eye (trace 12). There is also a phase reversal of the later part of the waveform (N4 or P5) focused around the T4 - CV7 and T4.5 - CV7 electrode positions (traces 15 and 16). Similar results using cephalic reference electrodes (Cz, A1, A2) or another non-cephalic reference site (shoulder) were obtained with the exception of the evoked responses obtained when using Cz as a reference.

When using Cz as reference the responses were inverted or showed an apparent phase reversal (see figure 21 - Comparison of OS stimulation). To confirm this 'phase reversal', a bipolar derivation of electrode placement was used in the central transverse plane (see figure 22 - OD bipolar chain). The responses obtained clearly demonstrate a 'phase reversal' about the Cz electrode position with maximum amplitude shown in the T4 - C4 and C3 - T3 electrode connections, the responses of which appeared as mirrored images. The results obtained would strongly indicate that the electrode position Cz is active. This demonstrates the error made by Harding and Rubinstein regarding Cz as 'inactive' with the maximum potential being measured at T3.5 or T4.5 electrode positions. The 'phase reversal' is a consequence of how the electrodes are connected to the amplifier inputs and would indicate that in a 2-dimensional plane, it would appear as a 'phase reversal' about Cz but is in fact simply a reflection of the physical connections in the circuitry.

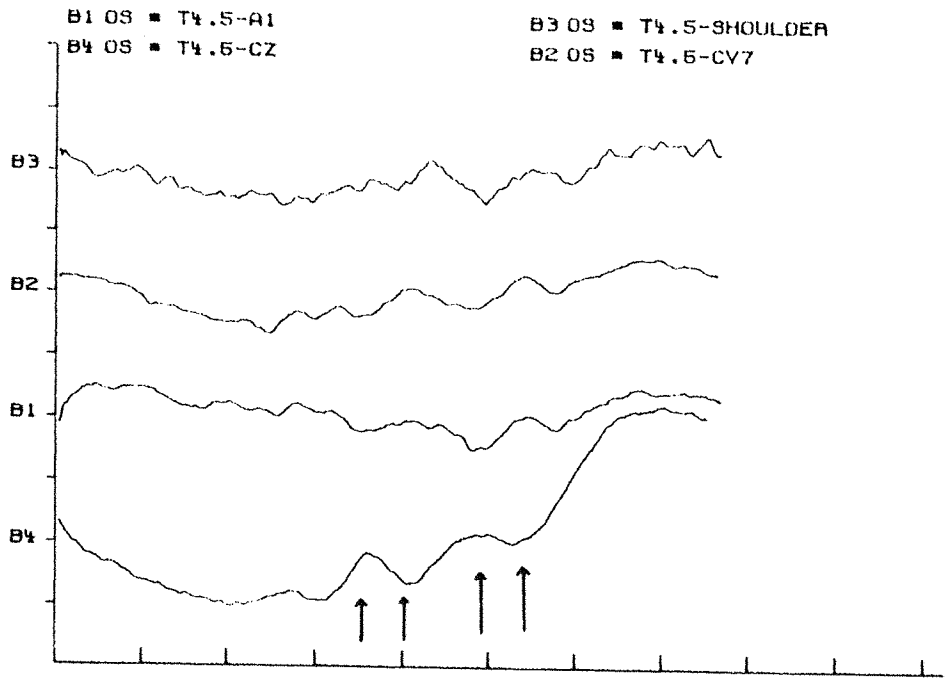
FIGURE 21

COMPARISON OF LEFT EYE STIMULATION WITH
T4.5 - CV7
T4.5 - CZ
T4.5 - A1

T4.5 - SHOULDER

MS/DIV 10.000 UV/DIV 2.50

NB: INVERSION OF T4.5 - CZ; This, along with the bipolar derivation would strongly indicate that the electrode position CZ is active. This demonstrates the error made by Harding and Rubinstein regarding CZ as "inactive".

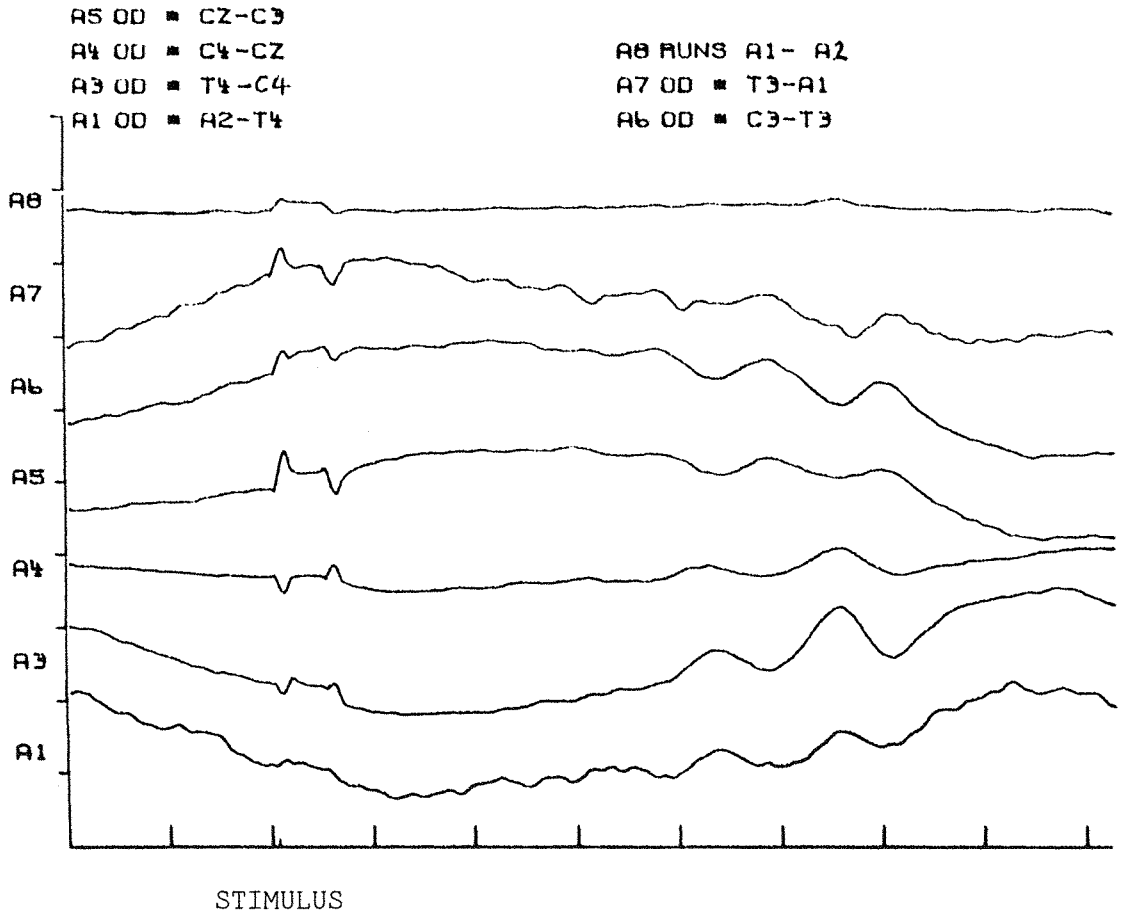


REVERSAL OF PHASE

FIGURE 22

TRANSVERSE BIPOLAR ELECTRODE CHAIN. RECORDING THE POTENTIAL DERIVED FROM STIMULATION OF RIGHT (OD) EYE.

MS/DIV	UV/DIV
10.000	2.50



A1 - A2

T3 - A1

C3 - T3

Cz - C3

C4 - Cz

T4 - C4

A2 - T4

The transverse midline bipolar derivation shows a phase reversal of voltage situated between electrodes C3 and C4 centred about Cz. This degree of symmetry and "focusing" of the potential in this electrode derivation clearly indicates that the response is represented bi-laterally even though only one eye is stimulated.

The 'phase reversal' in Figure 21 would indicate that the applied voltage at Cz in the T4.5 - Cz lead was positive, with respect to the applied voltage at T4.5 and that in the other 3 derivations, the applied voltage at T4.5 is less negative than at the A1, shoulder or CV7 sites.

Many workers have advocated not using earlobes or the mastoid processes (A1 or A2 electrode positions) as reference sites due to the large contamination by the electroretinogram and the cortically generated visual evoked responses.

In this study, to act as a control, one channel of the electrode A2 referenced to A1 or vice versa was used and it can be seen from figure 22, OD bipolar chain, that no consistent response was recorded when compared with other active electrodes Cz, Pz, Oz when referenced to A1 or A2 or (A1 + A2) electrodes.

The large negative deflection N4 at around 70 milliseconds (figure 20) corresponds with N80 or III of the primary response of the flash VEP after Ciganek (1968). In addition, regardless of the electrode position when referenced to CV7, N2 and N3 are consistent in latency but vary in amplitude being maximal in midline and central electrode positions and recorded as far forward as FPz and posteriorly at Oz. Components N2 and N3 are less well defined at electrode positions T3.5 and T4.5. The time separating the oscillatory components is also very consistent being of the order of 10-12 msecs, between successive negative components (N1, N2, N3 and N4). Lower amplitude less well defined oscillatory components were seen in the temporal chain of electrodes referenced to CV7 having latencies of 20-27 msecs (P20).

These were labelled Na, Pa, Nb, Pb and were of maximal amplitude in T4, T4.5 and T6 electrode positions and could reflect the triphasic complex of short latency potentials (P20 (P23), N26 (N28), P34) of Harding & Rubinstein (1980) but of opposite polarity due to the different reference site used in the recording.

These components Na, Pa, Nb and Pb were not evident in responses recorded from the lower eyelid or in the midline electrode positions. However, very low amplitude components were seen in midline transverse electrode positions, but these were very variable. There appears to be three distinct sections to the complex evoked resonses to flash stimuli, namely the ERG component, the oscillatory wavelets, thought to arise from sub-cortical structures, and the cortical visual evoked potential - primary and secondary responses. The generators of this complex evoked potential arise from the retina, optic nerve and tract, lateral geniculate nuclei, optic radiations and visual cortex.

The ERG and cortical evoked potential have been well documented and with the oscillatory potentials from sub-cortical generators there is a tendency for responses to overlap in the time domain and to a lesser degree in the frequency domain. In order to try and establish whether the oscillatory components recorded are of ERG or sub-cortical/cortical origin, a simplified method of recording was devised in order to try and separate the ERG response from the oscillatory potentials thought to arise in sub-cortical and cortical structures.

Having established from previous distribution studies that the potential of the oscillatory potentials ((P20), N29, P37 and N44) were maximal at or close to Pz electrode position regardless of reference electrode position, a simple recording technique to separate the early flash VEP (oscillatory potentials) from ERG to L.E.D. goggle stimulation was investigated.

The technique used was to record evoked responses from different sites on the face and scalp referenced to a common electrode position.

The responses could then be subtracted from each other which has the effect of common components related to each active electrode and reference electrode cancelling each other, leaving the desired component of interest. It can be simplified by illustrating with the equation:-

$$(A - ref) - (B - ref) = A - B$$

As it was necessary to try and evaluate the oscillatory potentials and their origin, the following electrode positions and derivations were used; Pz, A1, A2, RLL (right lower lid), LLL (left lower lid).

The channels recorded were:-

1) Pz - LLL
2) Pz - RLL
3) A1 - LLL
4) A2 - RLL
5) A1 - A2

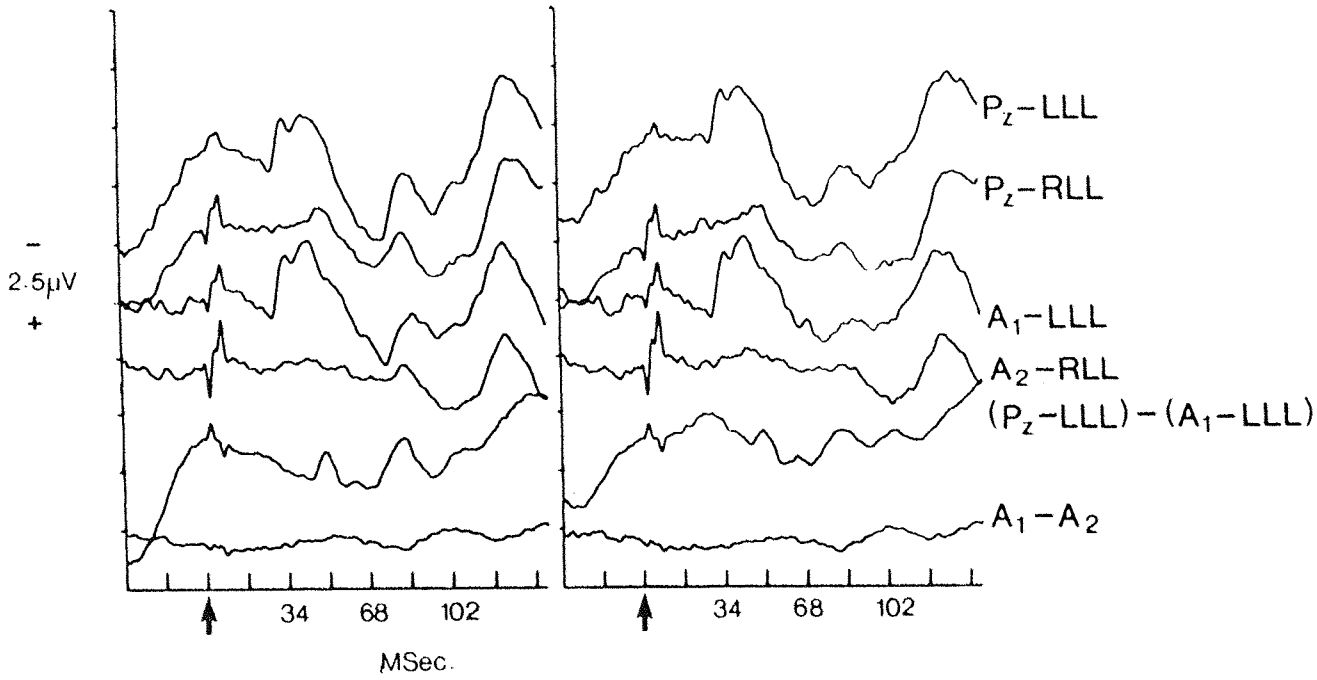
The previous amplifier settings, as stated in the methodology, were used in this examination. The visual stimulus were the red L.E.D. goggles.

Figure 23 shows the responses obtained with left eye stimulation to goggle flash with separation (off-line or on-line) of the ERG from the early visual evoked potentials. Two runs are recorded in order to ensure replication of the responses and performed with eyes closed.

Taking the top trace of figure 23, Pz - LLL left eye stimulated clearly shows the ERG response to goggle flash stimuli whereas the response from Pz - RLL shows no clearly identifiable ERG, although a component of similar latency to the early visual evoked potential is present in Pz - RLL derivation and later components (68-130 msec) are clearly identified from both recordings suggesting that these are probably the cortical responses described by Ciganek and others, (waves III, IV and V) to flash stimuli.

FIGURE 23

GOGGLE FLASH VEP: SEPARATION of ERG FROM EARLY VEP
L,R = LEFT, RIGHT
LL = LOWER EYELID
A_1 A_2 = L&R MASTOID ELECTRODES
STIMULATE L. EYE
2 IDENTICAL RUNS



Responses A1 - LLL and A2 - RLL again show that the ERG is only seen from the eye stimulated, OS (A1 - LLL) even though later components similar in polarity and latency but showing lower amplitude are in evidence again indicating the cortically generated (waves III, IV and V) flash VEP and the potential distribution of this evoked response to recording or reference electrode sites (A1 and A2) mastoid processes.

In order to separate the ERG from the early visual or oscillatory potentials, the following subtraction was performed:-

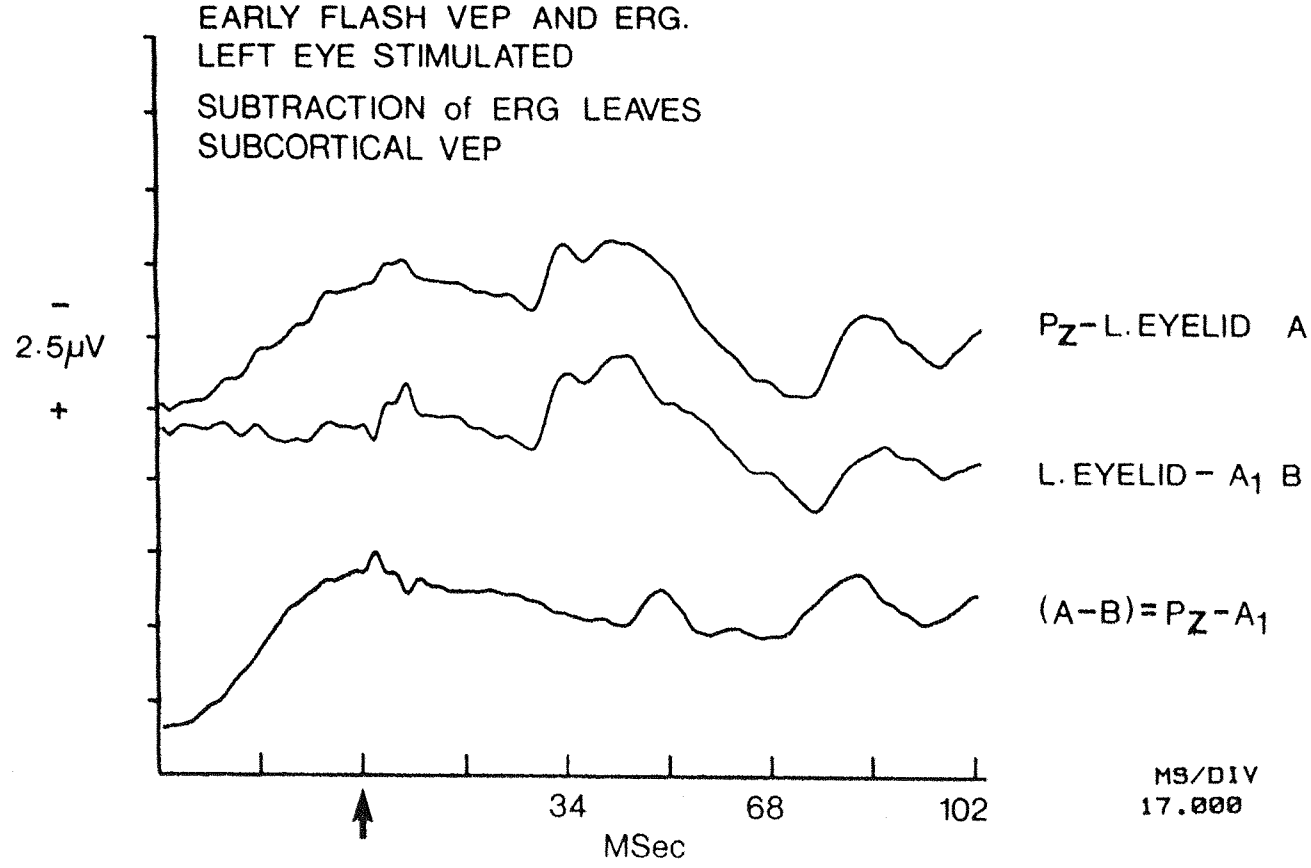
Trace 1 (Pz - LLL) - Trace 3 (A1 - LLL) = (Pz - A1)

The result is clearly demonstrated is trace 5 of figure 23. This shows the early components which cannot be related to the ERG oscillatory potentials. The last trace shows the evoked response of the electrode derivation (A1 - A2) which is of very low amplitude and has a positive component at approximately 85 msec, a negative component at 102 msec followed by a further positive 120 msec deflection.

These components were of such low amplitude, even absent in some instances, as to be negligible when compared to the responses obtained from other derivations. The main reason for this apparent low amplitude (or absent) response is that, whichever eye is stimulated, the dipoles post chiasmically are of opposite planes, opposed at 180° to each other, thereby the responses measured at these locations will tend to cancel each other out. For this reason, combined electrodes (A1 + A2) are suitable for use as a reference site.

Figure 24 shows three responses; the first two traces the ERG is demonstrated but when these two responses are subtracted, the 'hidden' component is clearly identified, indicating that this evoked response is not generated by the retina or pre-chiasmal structures, but is generated by post-chiasmal or cortical structures.

FIGURE 24


EARLY FLASH VEP AND ERG.
LEFT EYE STIMULATED
SUBTRACTION of ERG LEAVES
SUBCORTICAL VEP
−
2.5μV
+
PZ-L.EYELID A
L.EYELID - A1 B
(A-B)=PZ-A1
34
68
102
MSec
MS/DIV
17.000

Further evidence that the oscillatory potentials are generated from post-chiasmal structures is evident by the response being recorded bilaterally to monocular stimulation. Also of interest is that a component of similar latency to the early visual or oscillatory potentials was recorded in the Pz - RLL derivation to left eye (OS) stimulation indicating further that there is no contribution from the retina to the oscillatory potentials that are generated sub-cortically or cortically.

Selective Filtering

If these results had been obtained using a narrower bandwidth instead of 5-1500 Hz, then the large negative offset on which the oscillatory potentials are superimposed, could have been filtered out making latency and amplitude measurements easier. The major reasons for not doing so was not to introduce timing errors and phase distortions into the evoked response. Later results will be shown in which the effect of selectively filtering the response can introduce latency errors.

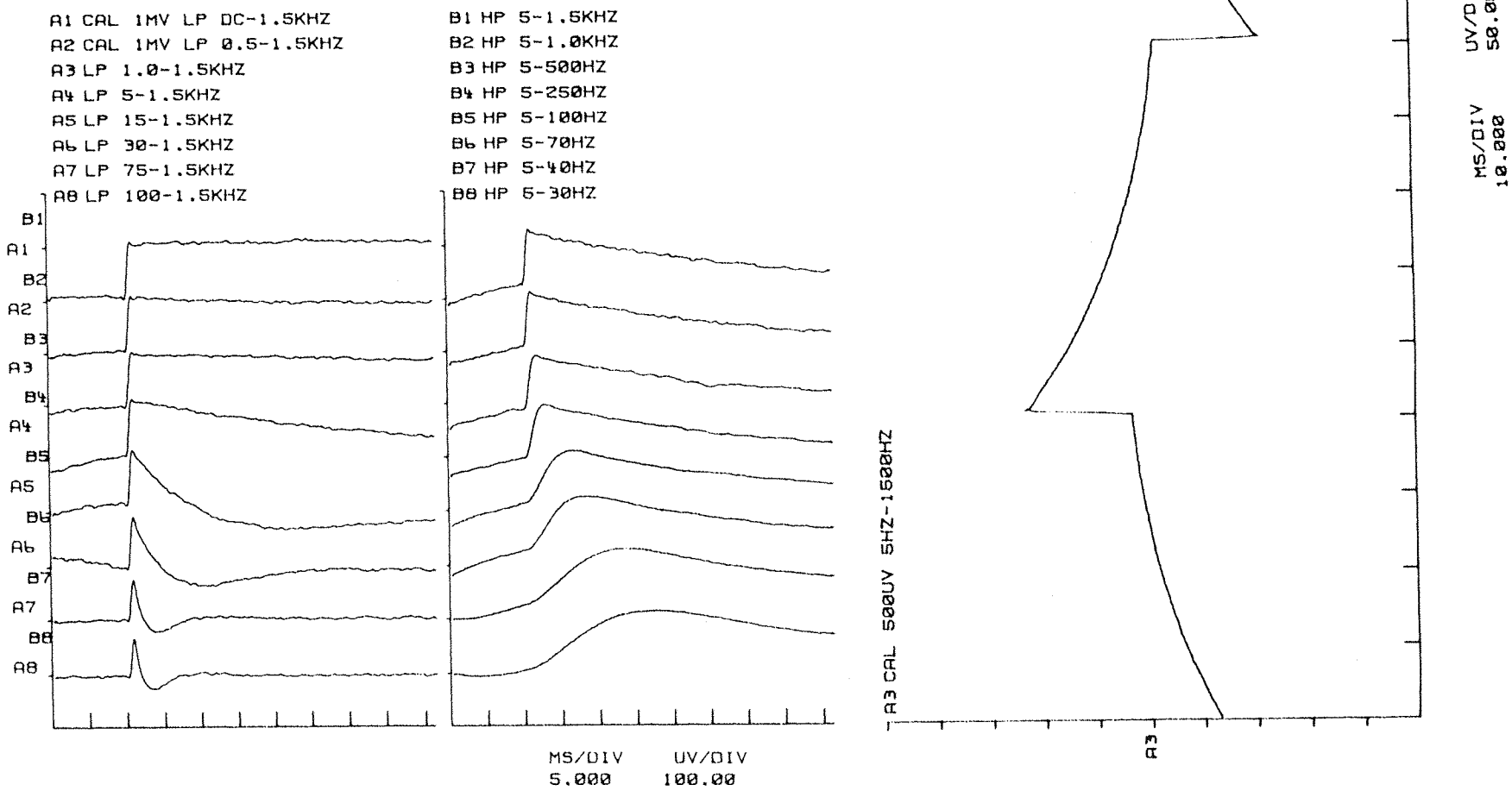
As previously mentioned, the methodologies of various workers are very different. One of the most consistent differences between authors is the use of filters and amplifier bandwidths ranging from 30-1000 Hz, 100-2500 Hz, 1-1000 Hz, 60-200 Hz, 30-500 Hz, 66-700 Hz and 100-1500 Hz for each study. In this investigation the bandwidth of the amplifiers was 5-1500 Hz for all measurements recorded.

To see if selective filtering on the evoked response could be of benefit in enhancing the response or in separating the individual components, the effect of different low and high pass filters was determined.

Initially, the effect of filters on a constant signal such as a square wave of known amplitude should be investigated. This is shown in figure 25 where the effects of changing the low frequency filter (high pass filter) and keeping the high frequency filter (low pass filter) constant and vice versa.

FIGURE 25

EFFECT OF CHANGING THE LOW AND HIGH PASS FILTERS ON A SQUARE WAVE CALIBRATION SIGNAL (1MV)



It is clearly demonstrated that the effect of changing either the high or low frequency filters has altered the calibration signal, both in morphology, latency and amplitude. It has also shown how changing filters can introduce phase distortions and timing errors of the components.

The effect of the bandwidth used in this study, 5-1500 Hz (-3dB, 12dB/octave roll-off) is shown to the left of the figure for comparison.

The effects of filter changes on a physiologically evoked signal is illustrated in figures 26 and 27. The evoked response is to flash (goggle) stimuli with the T3.5 referenced to Cz derivation. The effects on the evoked respones are more related to changing the high frequency (low pass filter) rather than the low frequency (high pass filter). The high frequency value where changes are noted is at 325 Hz (-3dB) and the low frequency value where changes are apparent is at 50 Hz. Therefore, for optimum recording of the early oscillatory potentials to visual (flash) stimuli a 50-325 Hz bandwidth is necessary. Although narrow bandwidths can be used to exclude various components like the ERG or slow components of the cortical flash VEP to enhance other components of interest, accidental exclusion of components under investigation may also occur.

This is why, in the opinion of the author, the responses evoked should be acquired with a wide open amplifier bandwidth or the maximum possible. If selective filtering is necessary, then digital filtering would be the method of choice and can be performed post acquisition if a computer and microprocessor that can access the data is available.

FIGURE 26

EFFECTS OF VARYING THE LOW FREQUENCY FILTER ON OSCILLATORY POTENTIALS TO FLASH STIMULI (HIGH FREQUENCY FILTER CONSTANT AT 1500 Hz)

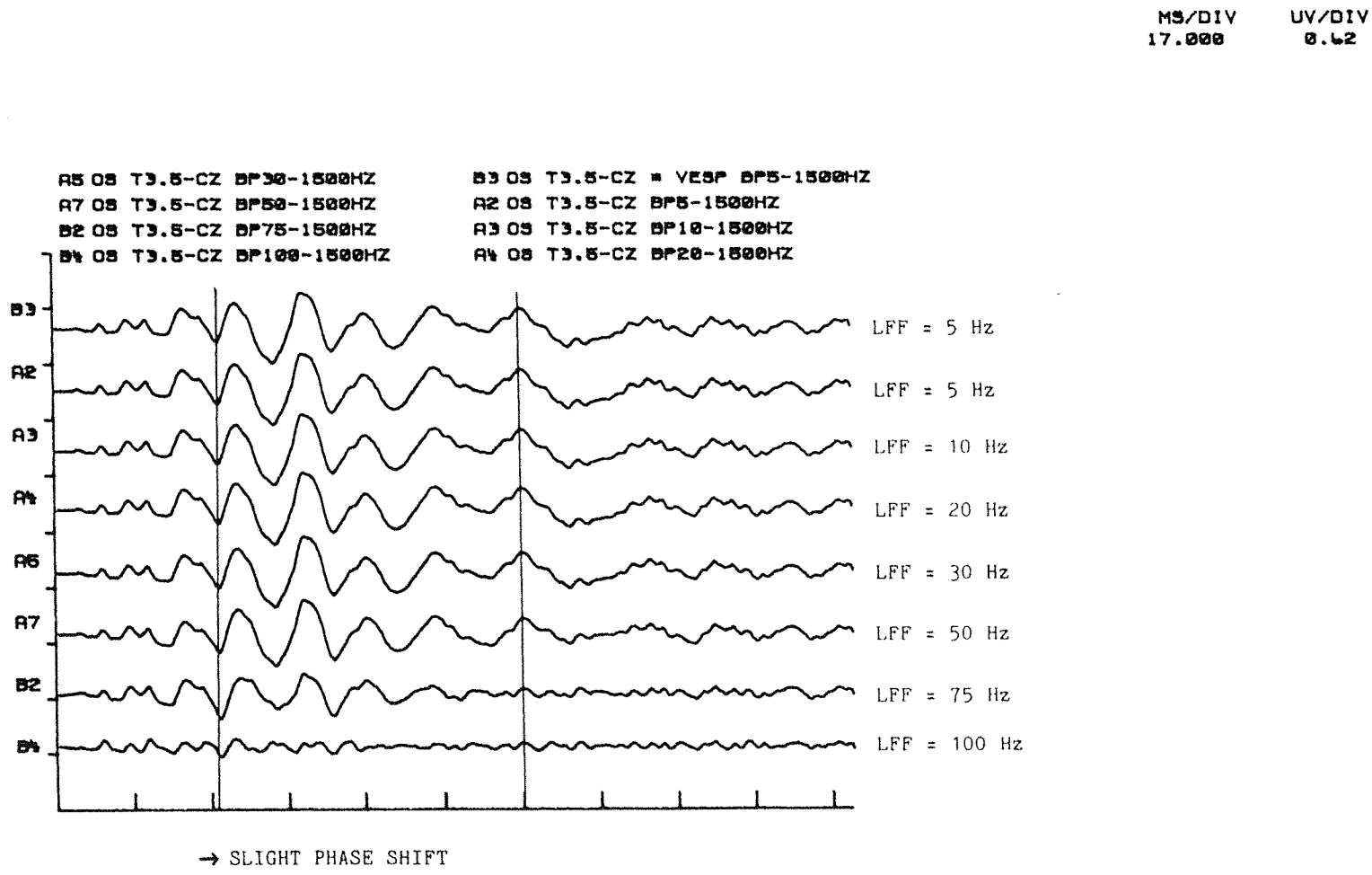
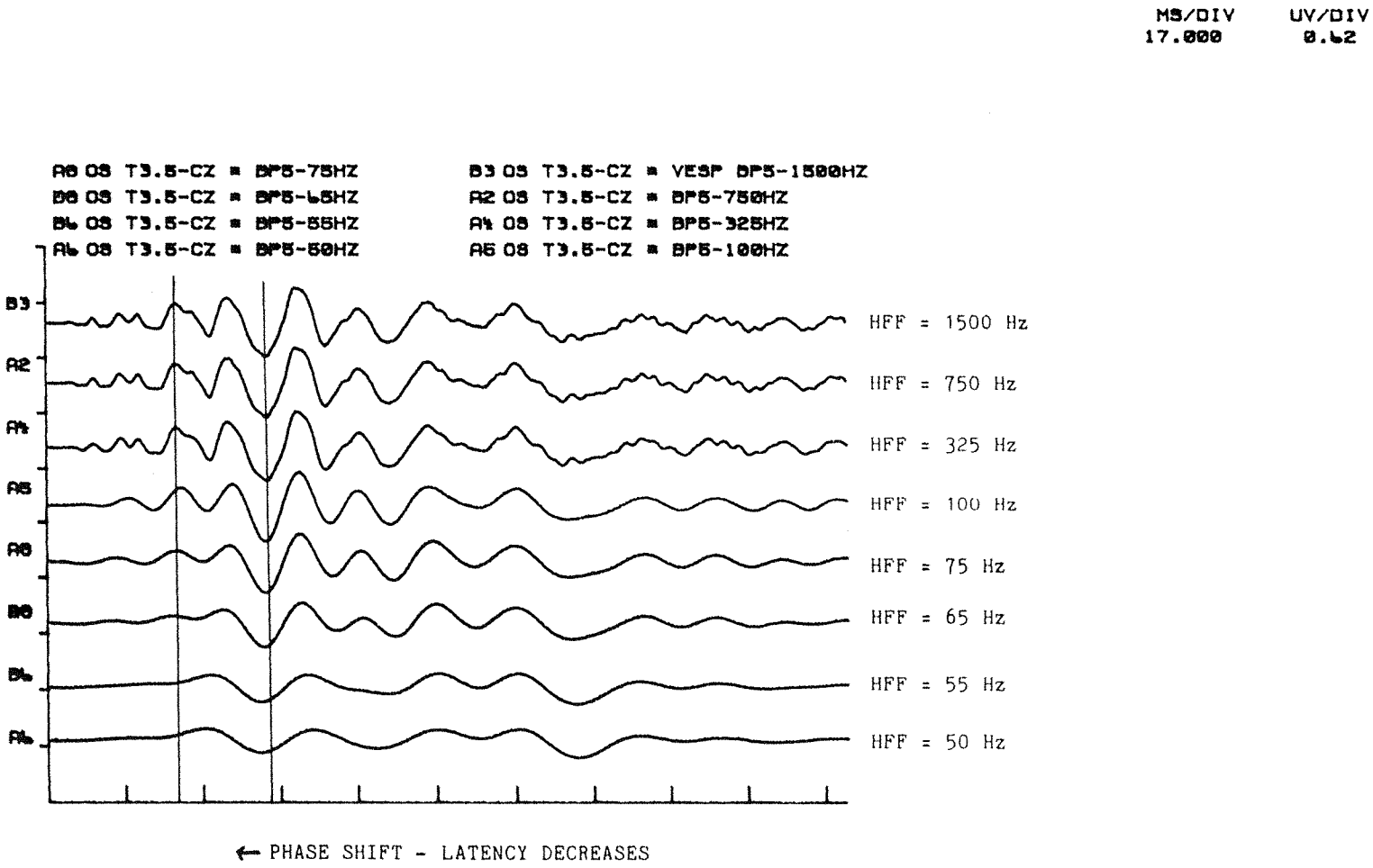


FIGURE 27

EFFECTS OF VARYING THE HIGH FREQUENCY FILTER ON OSCILLATORY POTENTIALS TO FLASH STIMULI (LOW FREQUENCY FILTER CONSTANT AT 5 Hz)



Stimulus Presentation

Monocular versus Binocular Stimulation

In monocular stimulation, the amplitude of the recorded evoked responses were of lower amplitude (on average 20% lower) when compared with binocular stimulation with the exception of ERG. The ERG recorded was equal in amplitude as the response obtained is from all the cells of the stimulated eye whereas the oscillatory or early visual evoked potentials will be the result of only half the population of neurones being stimulated with monocular presentation due to the division of the optic fibres at the optic chiasm to the left and right hemispheres. With binocular stimulation, both visual pathways to the right and left hemispheres conduct impulses to the occipital cortex so the effect will be an increase in amplitude which in some instances was double to that of monocular stimulation.

The whole neuronal population is available for stimulation by binocular stimulation and the difference in amplitude between monocular and binocular stimulation can be attributed to this fact.

The reason for the difference in amplitude can be attributed to the composition of the lateral geniculate body into six nuclear layers with layers 2, 3 and 5 (from the inside outward) receiving signals from the temporal portion of the ipsilateral retina, while layers 1, 4 and 6 receive signals from the nasal retina of the opposite eye, and the columnar organisation of neurons in the visual cortex. Pairing of layers from the two eyes plays a role in fusion of vision from the two eyes because corresponding retinal fields in the two eyes connect with respective neurons that are approximately superimposed over each other in the successive layers.

As previously described, the complexity of the receptive fields at each level of the visual pathway becomes greater from the cells in the retina to the neurons in the primary visual cortex. In the primary visual cortex, the neuronal population is arranged in columns, each column containing about 100,000 neurons, extending throughout the 6 layers. Signals from the lateral geniculate body terminate in layer 4 and secondary signals are transmitted to layers 2, 3, 5 and 6.

Most of the neurons in layer 4 respond in a similar way to the cells in the lateral geniculate body, that is to spots of light, borders or lines. The neurons in the outer and inner layers are more selective, responding to lines or borders oriented in certain directions. This further degree of selective responsiveness is attributed to the simple, complex and hypercomplex cells that respond to line orientation, displayed line orientation and length of lines or borders respectively.

Visual signals from the two separate eyes are relayed through separate lateral geniculate body neuronal layers. The signals are still separated from each other when they arrive in the layer 4 of the primary visual cortex, but due to the colums being partially interlaced with each other, the signals from one column begin to converge with the signals from adjacent columns so that by the time the complex and hypercomplex cells are excited, the signals have merged, resulting in a larger amplitude signal recorded at the surface of the scalp when both eyes are stimulated.

This is perhaps why the alternating pattern chequer board is the stimulus of choice when investigating the visual evoked potentials as the main recording area for the pattern VEP is from area 17 where the highest density of hypercomplex cells is evident. Transmission of visual signals from the primary visual cortex to the visual association areas (Brodmann areas 18 and 19) occurs where the visual information is further processed. The evoked potential activity at these areas can also be recorded but due to the complex receptive fields of the neurons in these areas, the VEP recorded over areas 18 and 19 are of low amplitude and poorly defined. Simple visual patterns such as lines, borders or angles fail to cause excitation of specific neurons and therefore a minimal poorly defined evoked potential is recorded at scalp locations over areas 18 and 19, even with both eyes stimulated. Hence, binocular stimulation that activates all layers of the lateral geniculate body and hence adjacent columns of primary visual cortical neurones will give rise to larger amplitude evoked potentials. However, monocular stimulation is of clinical importance when trying to detect asymmetries of latency, amplitude or morphology of response in the visual pathways to establish localisation of pathological changes.

The results of monocular right eye and binocular presentation are demonstrated in figure 28 which shows the evoked responses.

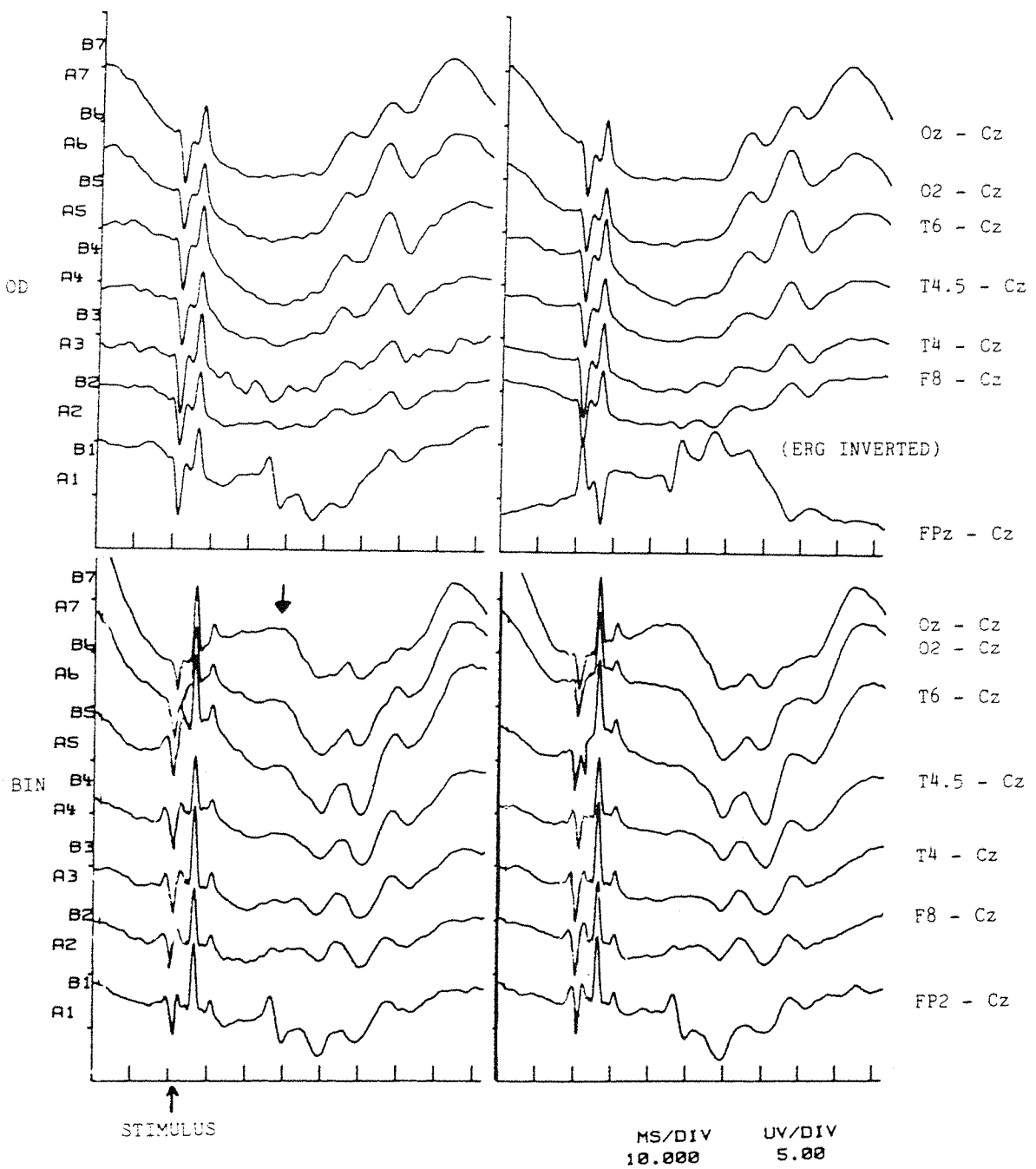
This shows the ERG in both instances to be of similar amplitude but the oscillatory or early visual evoked potential to be of different amplitudes being highest at electrodes Cz to the F8, T4, T4.5 and T6. To binocular stimulation compared with monocular later components to the flash stimuli in T6, O2 and Oz derivation are better defined in monocular stimulation versus binocular stimulation which may be the result of the different orientation of the dipoles within the posterior portions (Meyer's loop and optic tracts) of visual pathways of the two hemispheres. The initial negative deflection (20 msec) seen in binocular stimulation is not in evidence in monocular stimulation at electrode sites from T4 through to Oz. This would again indicate a cumulative effect of structures contributing to the generation of the early oscillatory potentials. It could be argued that the waveform shown has the same phases with negative and positive at the Fpz-Cz derivation as the Oz-Cz derivation which would indicate volume conduction of the ERG. The evidence is against this theory in the monocular stimulation illustration showing no negative potential at approximately 20 msec, even though the ERG potential is of equal amplitude in both forms of stimulation.

If this is correct then the origin of the early visual evoked potentials or oscillatory waves can be more precisely located. The definition of these components and their potential distribution would indicate that the generator of these early components to visual (flash) stimuli must be located within that portion of the visual pathway whose dipoles are orientated in a fan-like pattern and in a vertical, slightly posterior tangenital plane, thus giving the maximum potential at electrodes Pz, and to a lesser degree Cz and Oz respectively, regardless of which reference is used.

FIGURE 28

EFFECT OF MONOCULAR OR BINOCULAR FLASH STIMULATION ON AMPLITUDE OF EARLY VISUAL EVOKED POTENTIALS

MONOCULAR STIMULATION - UPPER TRACES
BINOCULAR STIMULATION - LOWER TRACES



Stimulus Rate and Intensity

Another variable used in the investigation of the oscillatory or early visual evoked potentials is the rate of stimulus presentation. Cracco & Cracco (1978) found the optimum flash frequency to be 7 Hz. This frequency was also utilised by Sanarelli et al (1988, 1989) in their studies. Other workers have used flash stimulation frequencies varying between 2/sec (Pratt et al 1982) up to 35/sec (Ciganek 1960).

Ciganek in 1960, concentrating more on the cortically generated evoked potential to light flash stimuli, reported that at frequencies below 10 Hz, all waves/components of the Primary and Secondary responses (I, II, III, IV and V) were recorded. Above 10 Hz only waves I, II and II could be reliably recorded with the later waves becoming poorly defined or even absent.

It was reported from previous work that stimulation rate does not have a major impact on whether the early oscillatory potentials are recorded. However in this study, initially, the stimulation rate was set at 4.7/second. The reason for selecting an odd number was to reduce the chance of the stimulation rate, which is time locked to the trigger of the averager, being synchronous with 50 Hz mains interference. The study was further conducted with flash frequencies below 4.7/second at 3.5/second and above at 8.4/second and 11.5/second. See figures 29 - 33. The electrode derivations for recording the effect of stimulation rate on the evoked response were the same as used to separate the early visual potentials namely channel 1 : Rll - (Al + A2); channel 2 : LLL - (Al + A2); channel 3 : Pz - (Al + A2); channel 4 : Pz - RLL. The time base for this measurement was kept constant at 120 msec and the figures show at higher stimulation rates two responses are obtained for both the ERG recording channels and also for the early visual potentials.

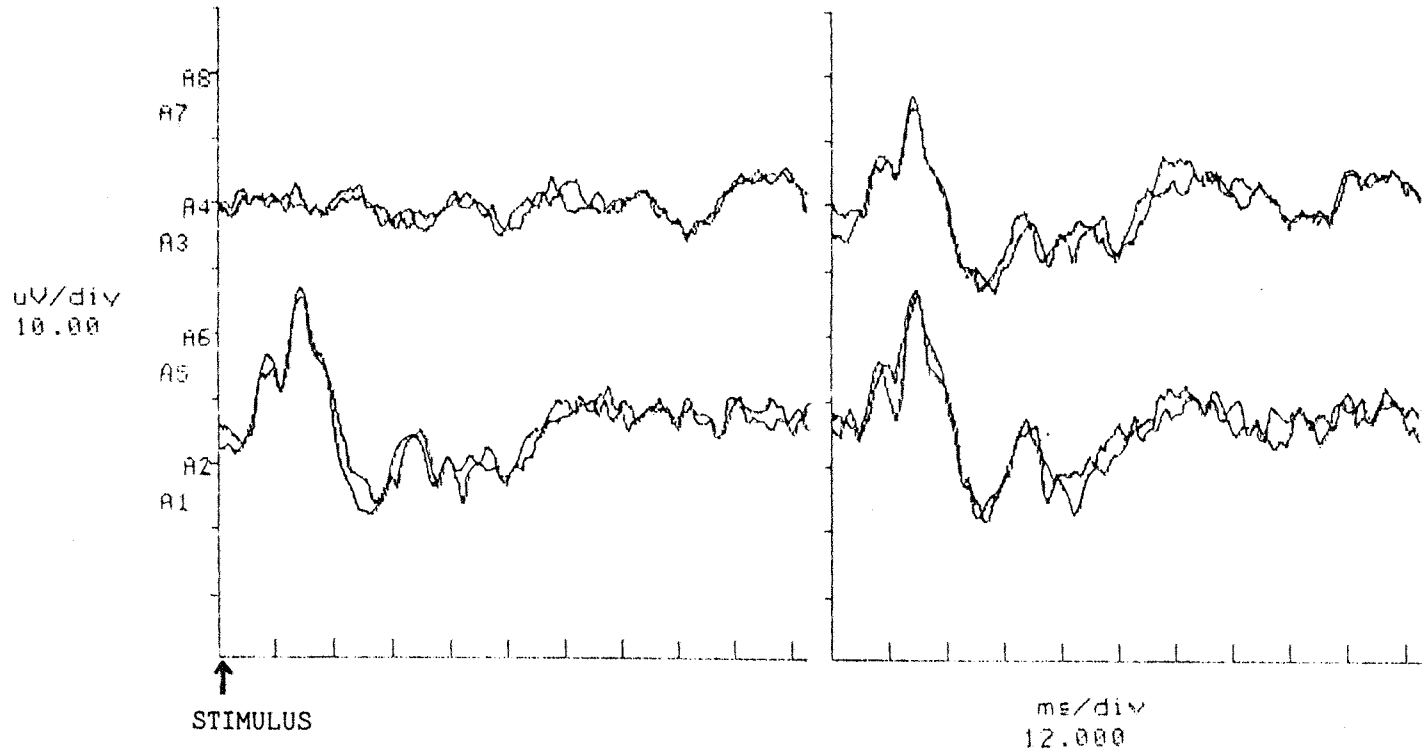
Taking the responses from subject A for rates at 3.5, 8.4 and 11.5/second, the amplitude of the ERG is of higher amplitude, approximately 10-15% increase, at low flash rates which is to be expected as at lower stimulation rates, habituation of the retina cells is not as marked as when stimulated by higher stimulation rates.

With high stimulation rates, the ERG response is predominantly photopic in origin. High stimulation rates are used in the assessment of cone-mediated retinal responses, in the clinical environment by measuring the flicker ERG function. The amplitude of the photopic flicker ERG wavelets reduces as the stimulation rate increases which is consistent with the findings in this study of stimulation rate effect.

Furthermore, the amplitude of the evoked response in channel 4 (Pz - (A1 + A2) is higher, approximately 40-50% higher, at faster stimulation rates than at lower rates and also the configuration of the response is better defined. No change in latency of the early response between the different stimulation rates was observed in any of the volunteers studies, which further implies that the early oscillatory potentials to a visual stimulus are not related to the current spread or volume conduction of the ERG to more posterior regions.

FIGURE 29

EFFECT OF STIMULATION RATE ON THE ERG AND EARLY VISUAL OSCILLATORY POTENTIALS



SUBJECT A

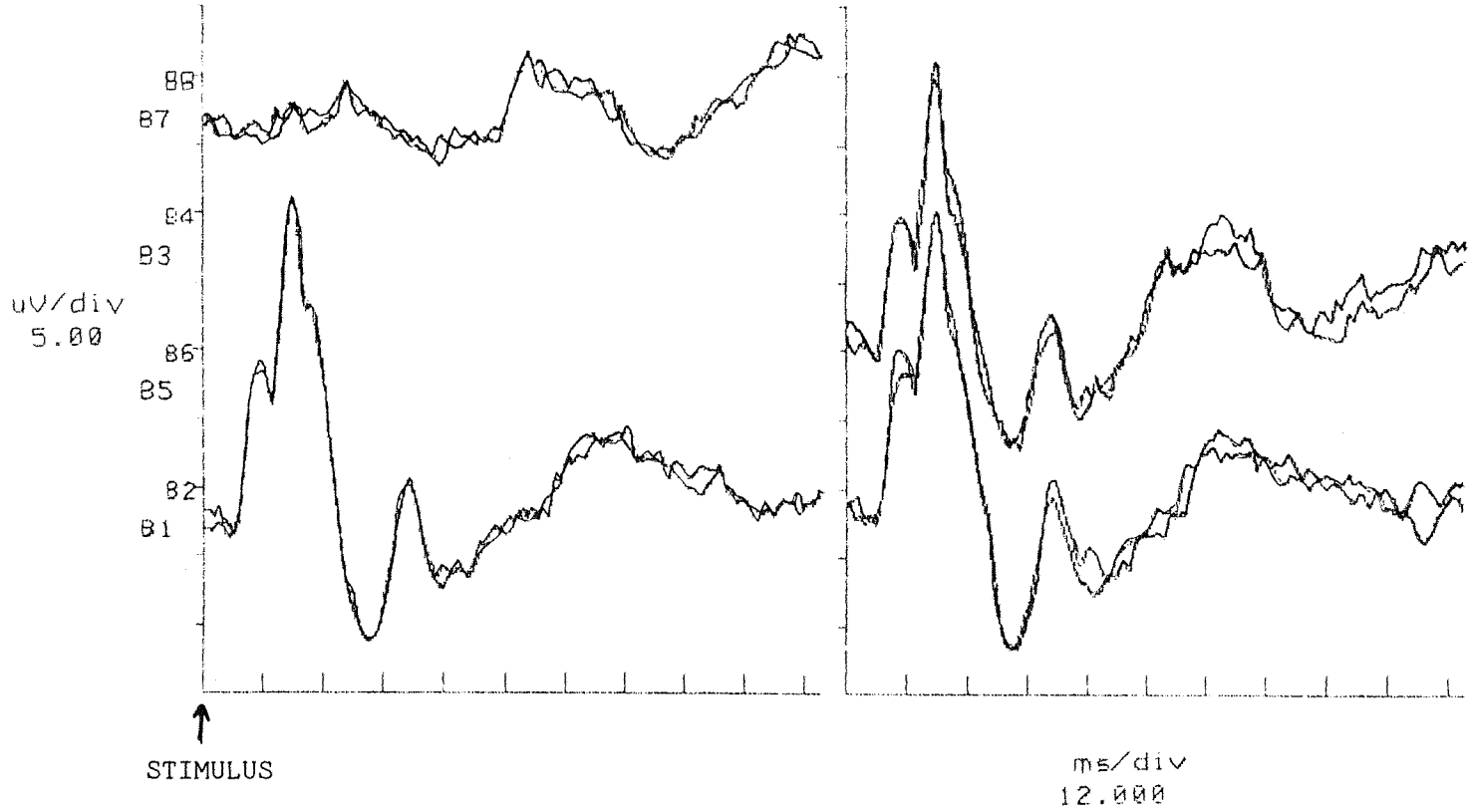
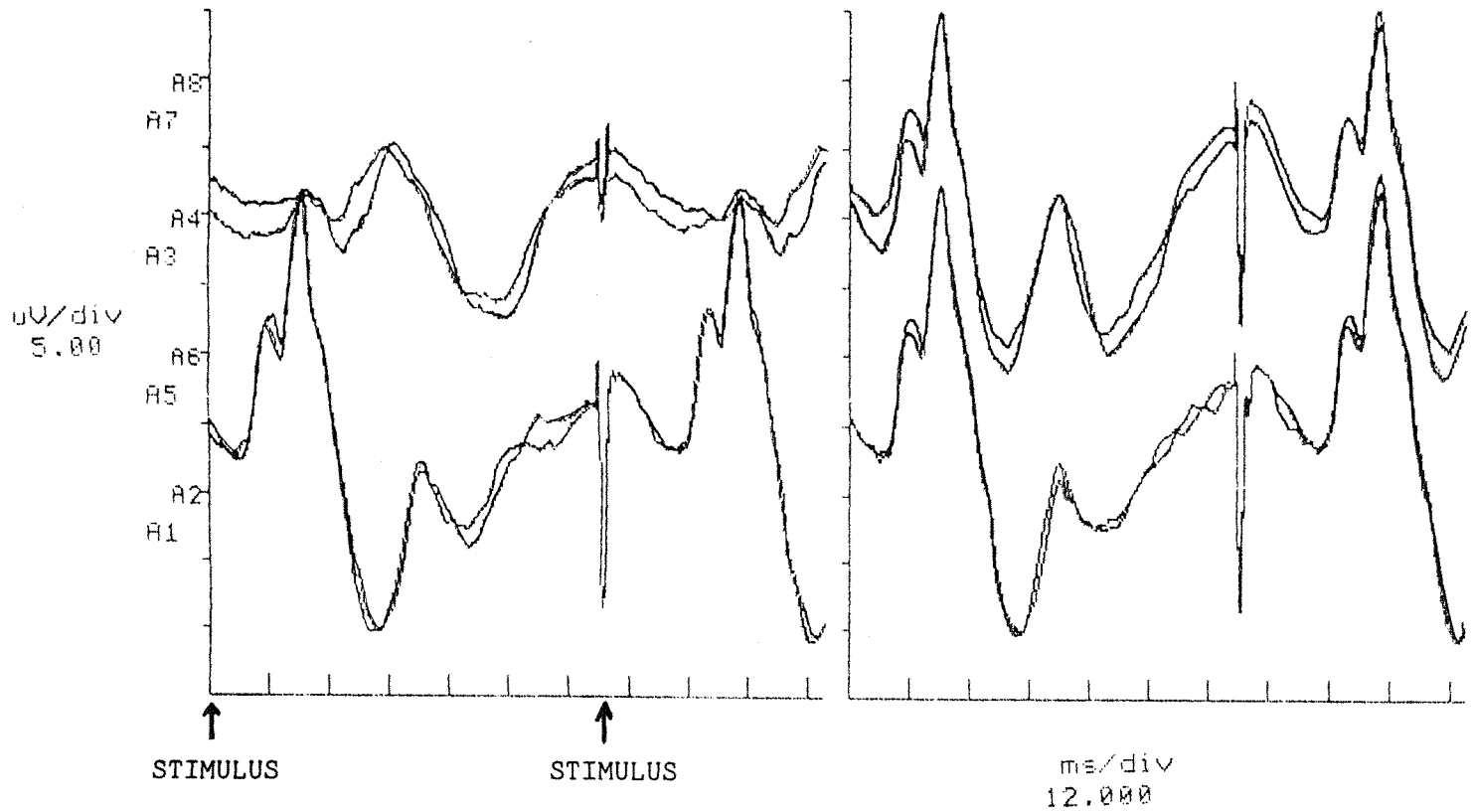


FIGURE 30

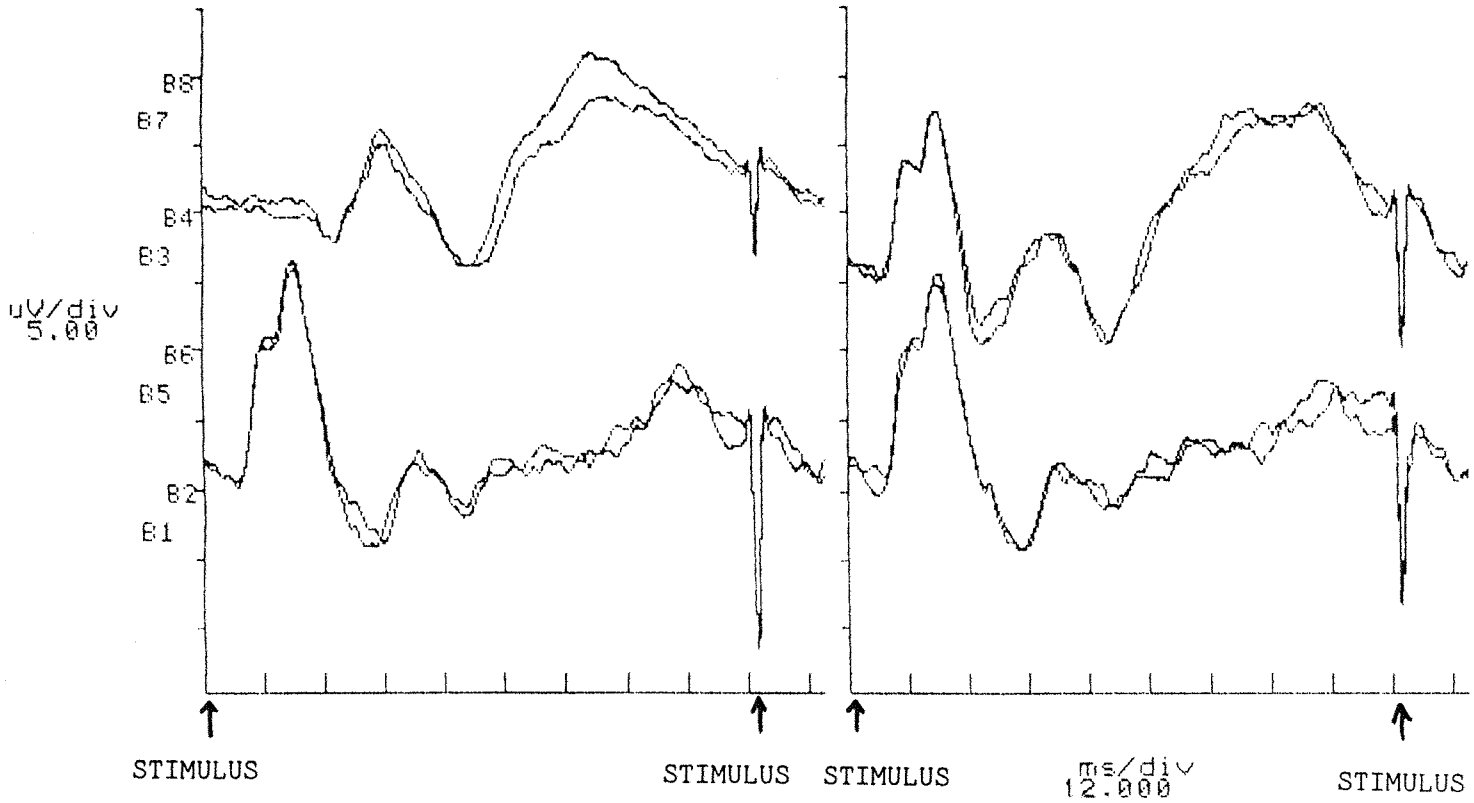
EFFECT OF STIMULATION RATE ON THE ERG AND EARLY VISUAL OSCILLATORY POTENTIALS



SUBJECT A

FIGURE 31

EFFECT OF STIMULATION RATE ON THE ERG AND EARLY VISUAL OSCILLATORY POTENTIALS



B2 BACKGROUND 10FT LAMBERT
B3 LOG INTENSITY 1.5
B1 RATE 8.4/SEC RED FILTER

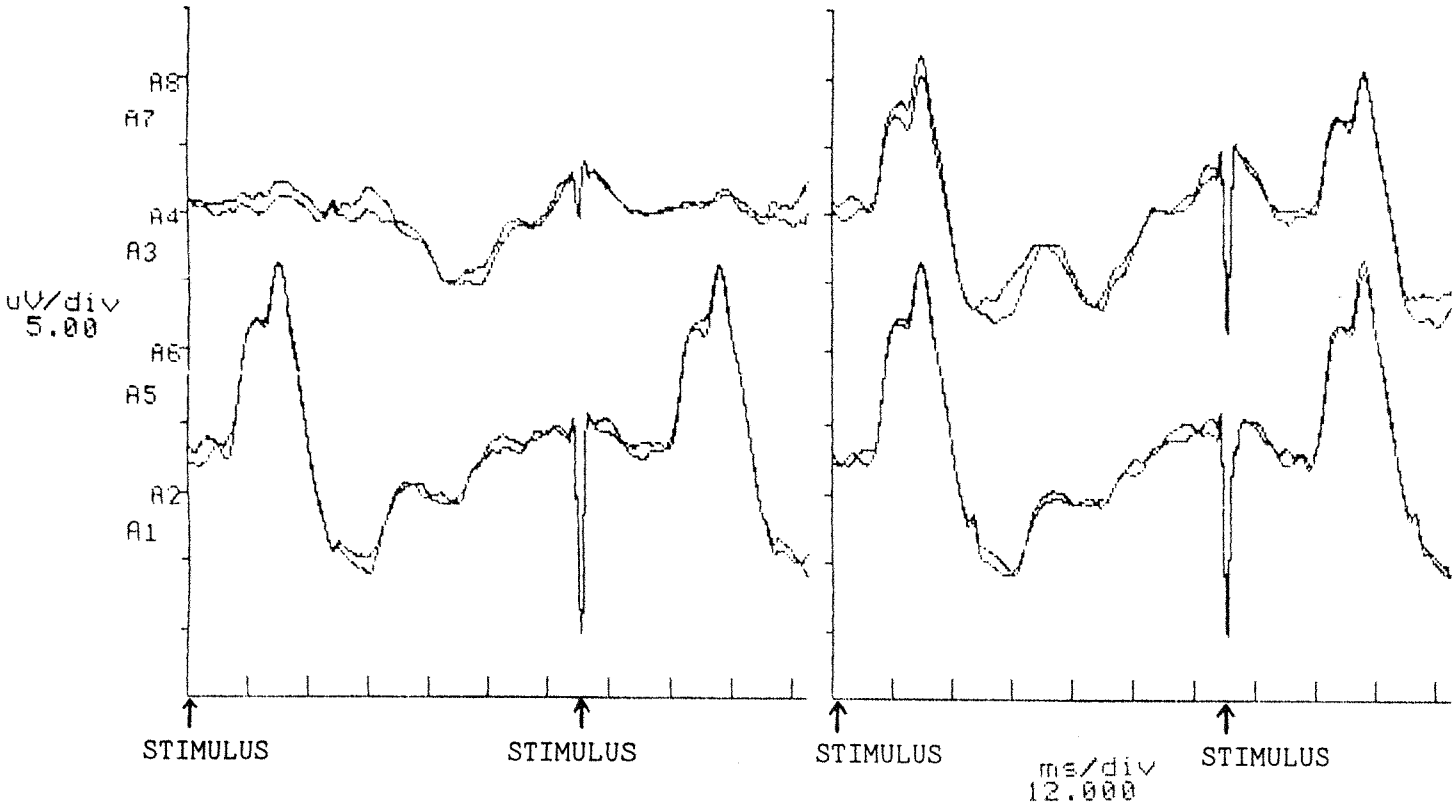
SUBJECT B

FIGURE 32

EFFECT OF STIMULATION RATE ON THE ERG AND EARLY VISUAL OSCILLATORY POTENTIALS

FIGURE 33

EFFECT OF STIMULATION RATE ON THE ERG AND EARLY VISUAL OSCILLATORY POTENTIALS



SUBJECT B

A2 BACKGROUND 10FT LAMBERT
A3 LOG INTENSITY 1.5
A1 RATE 11.5/SEC

Part II

In this section of the study, the Ganzfeld stimulator was used in place of the red L.E.D. goggles. The main reason for this change was to observe the effects of changing the colour of the stimulus, mainly red and blue, presented to obtain photopic and scotopic responses and to further delineate the evoked response into ERG and 'sub-cortical' components.

The strobe output spectra for the Nicolet Ganzfeld is described in the previous section on methodology.

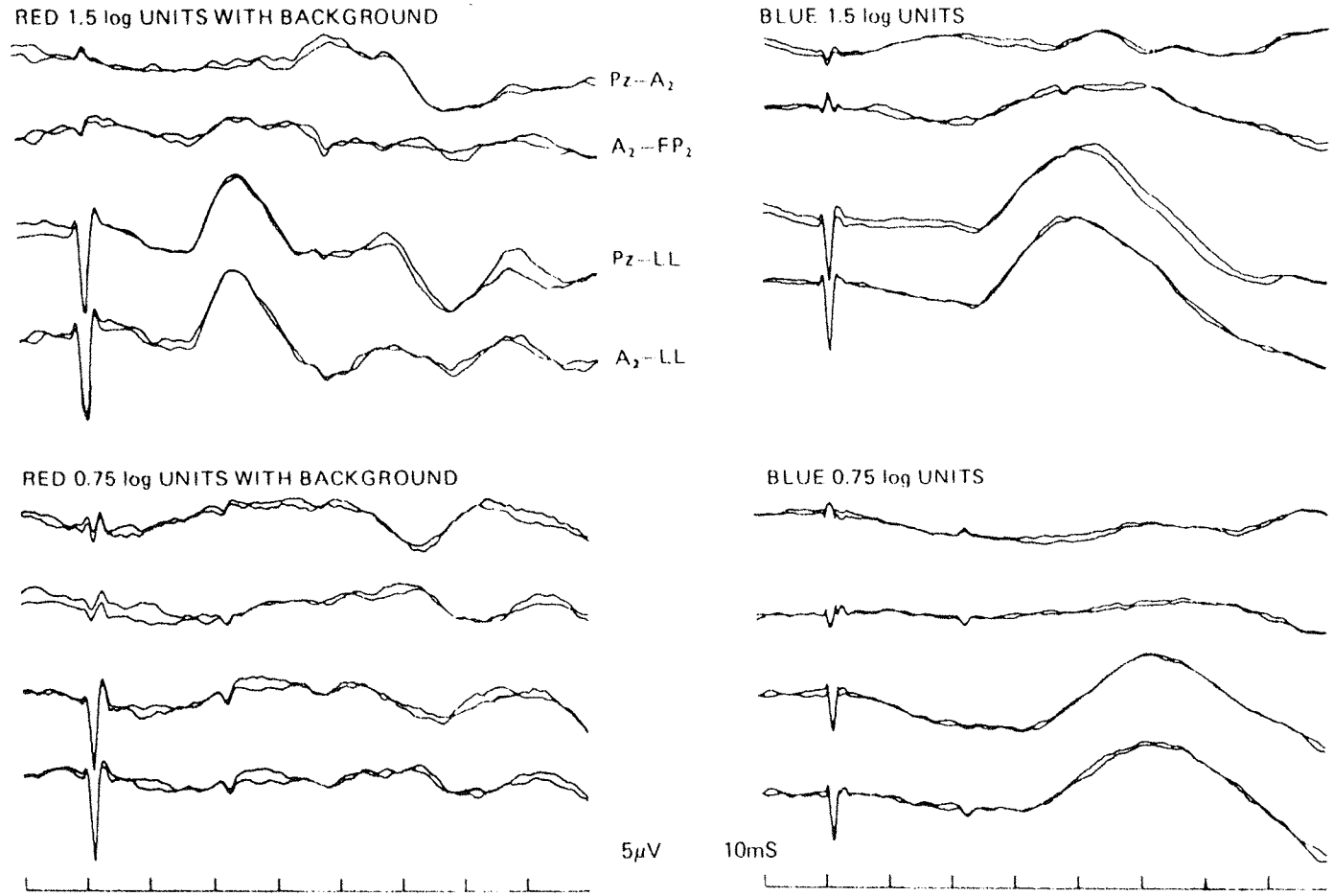
The parameters used for this part of the investigation are identical except the rate of stimulation to those used to obtain the EP with red L.E.D. goggles. Therefore, the only change is in the visual stimulus. Each subject was tested with different coloured filters, with, without and with varying degrees of background illumination, together with different levels of intensity. The Ganzfeld is much better suited for examination of the retina in response to light flashes as the whole retina is stimulated by the diffuse reflectance of the light from the dome of the Ganzfeld. With L.E.D. goggles or standalone stroboscopes, only part of the retina is stimulated, ie that part of the retina which is at right angles to the incidence of the light source.

The electrode derivations were the same as those used in previous examinations and the method of subtraction of one channel from a second channel was used to separate the ERG and oscillatory potentials.

Figure 34 shows the responses obtained by using red and blue light at two intensities. When stimulating the subject's eyes binocularly, background illumination at 30 foot lamberts was used with the red filter (Kodak Wratten No 26). With blue filter stimulation (Kodak Wratten No 47), no background illumination and a lower flash rate frequency was employed.

FIGURE 34

FLASH ERG AND SUB-CORTICAL VEP TO RED AND BLUE LIGHT AT 2 INTENSITIES



This ensured that with the red filter plus background illumination the ERG and early visual oscillatory potentials recorded were a photopic response whereas with the blue filter, no background illumination and with a lower frequency stimulus presentation, the response obtained is scotopic (see figure 35a).

The photopic (cone response) ERG was best recorded with a red light flash, intensity of 1.5 log units (2.92ft-L-S or 10.02 cd m-2S) with background illumination of 30 foot lamberts. The results show the reproducibility of the response and also the low amplitude early visual potentials from electrode derivation Pz - A2. Decreasing the stimulus intensity of the red flash to 0.75 log units (0.62ft-L-S or 2.11 cd m-2S) greatly reduced the photopic ERG response and the amplitude of the early visual evoked potential.

It should be noted that the decrease in intensity resulted in an increase in the latency of the a-wave of the ERG from 16-17 msec to 23-25 msec) but no significant change in latency of the early visual EP was observed (35 msec at 1.5 log versus 37 msec at 0.75 log intensity).

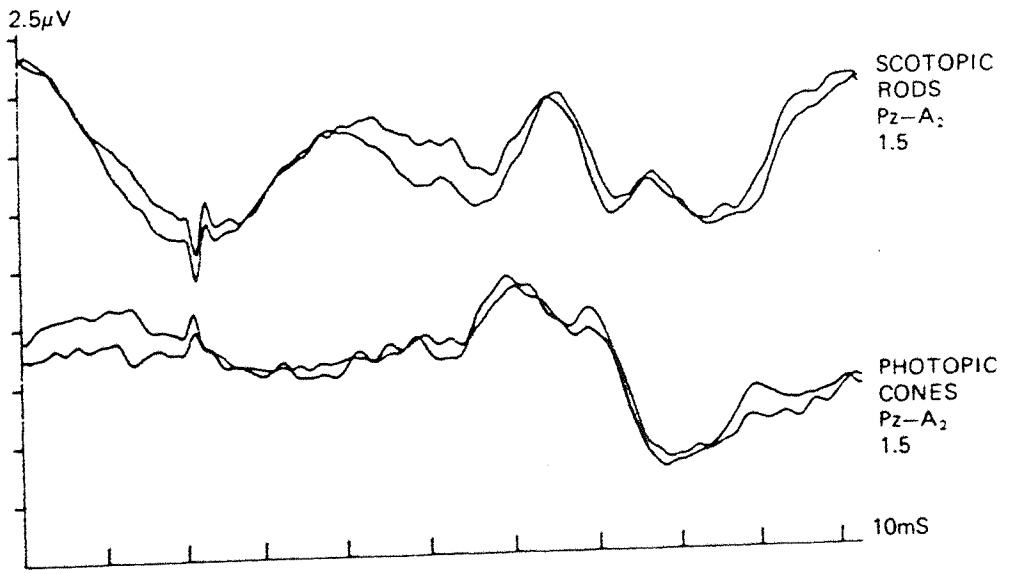
Using the blue light stimulus, no background illumination and lower stimulation rate (1.3/sec), the scotopic (rod response) ERG was recorded at both intensities. No amplitude difference between the two intensities was observed but a definite latency shift of on average 10 msec (intensity 0.75 log units) to 25 msec (intensity 1.5 log units) was noted in all eyes tested. The early visual oscillatory potentials to blue flash stimuli were of much lower amplitude compared to the red flash stimuli. At intensity 0.75 log units, there is only a very slight negative deflection from the baseline, which although reproducible between successive runs and subjects had a mean latency of 50 msec and average amplitude range of 0.5 uV - 1.0 uV. It was difficult to really establish the peaks or troughs of this component and the mean latency measured for this potential could not be reliably identified in all subjects.

FIGURE 35(a)

SUBCORTICAL FLASH VISUAL EVOKED POTENTIAL

BLUE OR RED FLASH

Intensity in relative log units



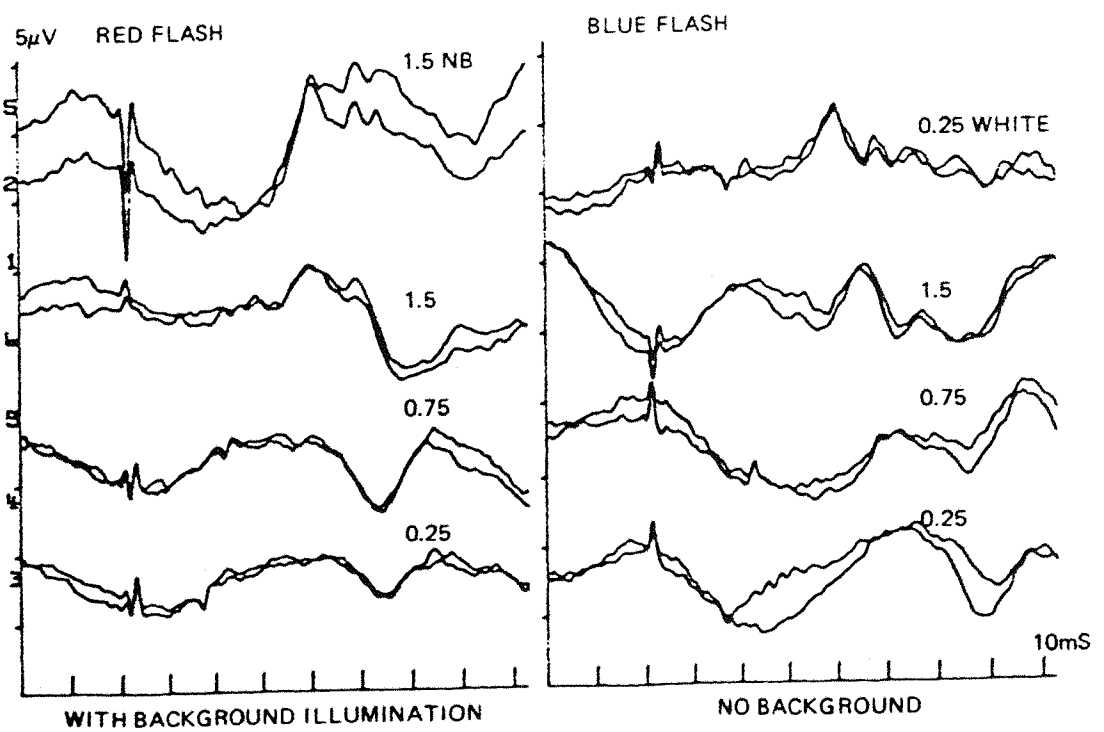


FIGURE 35(b)

CHANGING THE INTENSITY OF THE FLASH EFFECTS, THE AMPLITUDE AND CONFIGURATION OF THE EARLY VISUAL OSCILLATORY POTENTIALS

At flash intensity 1.5 log units, the early visual oscillatory potentials to blue light stimulation were much better defined having a W shaped configuration. The mean latencies for the P1 (P20), N1 (N27), P2 (P37), N2 (N44) components were 36 msec, 45 msec, 55 msec and 60 msec respectively. The difference between the red and blue responses may be the result of the cones being more sensitive than the rods to the red end of the spectrum. In addition, by using background illumination of 30 foot lamberts, only that part of the ERG related to cone function is determined and measured. The amplitudes between the components of the early visual oscillatory potentials to the red and blue flash stimuli are shown in the following table:-

	P1-N1	N1-P2	P2-N2	N2-P3
Red flash 1.5 log + background 30 ftls	3.5-4uV	2-3uV	1.5-2uV	4-6uV
Blue flash 1.5 log	3-5uV	3-5uV	2-2.5uV	1.5-3uV

The major and significant amplitude difference to red and blue flash stimuli on the early visual oscillatory potentials is in the N2 - P3 section of the evoked response being higher for a red than for a blue flash stimulus. The other N - P amplitude measurements showed no significant difference which would lend support that the origin of the early visual oscillatory potentials is from a structure(s) which has an input both from the rods and cones. By recording the ERG it is possible to separate out that activity generated by the retina which is volume conducted and has a wide topographic distribution.

Figure 35b shows the evoked responses recorded to varying levels of intensity from 0.25 log units to 1.5 log units for red and blue flashes. The response to a white flash, intensity 0.25 log units is shown for comparison. This shows a much more sinusoidal waveform with shorter latencies but similar morphology to the red flash intensity 1.5 log units without background.

It should be noted that the evoked responses to a red flash stimulus, with and without background illumination, although similar in morphology, the response with no background illumination has a much higher amplitude between the P1 - N1 components. Figure 36 shows in more detail the type of response (ERG and early visual oscillatory potentials) recorded to blue and red flash stimulus (rods or cones).

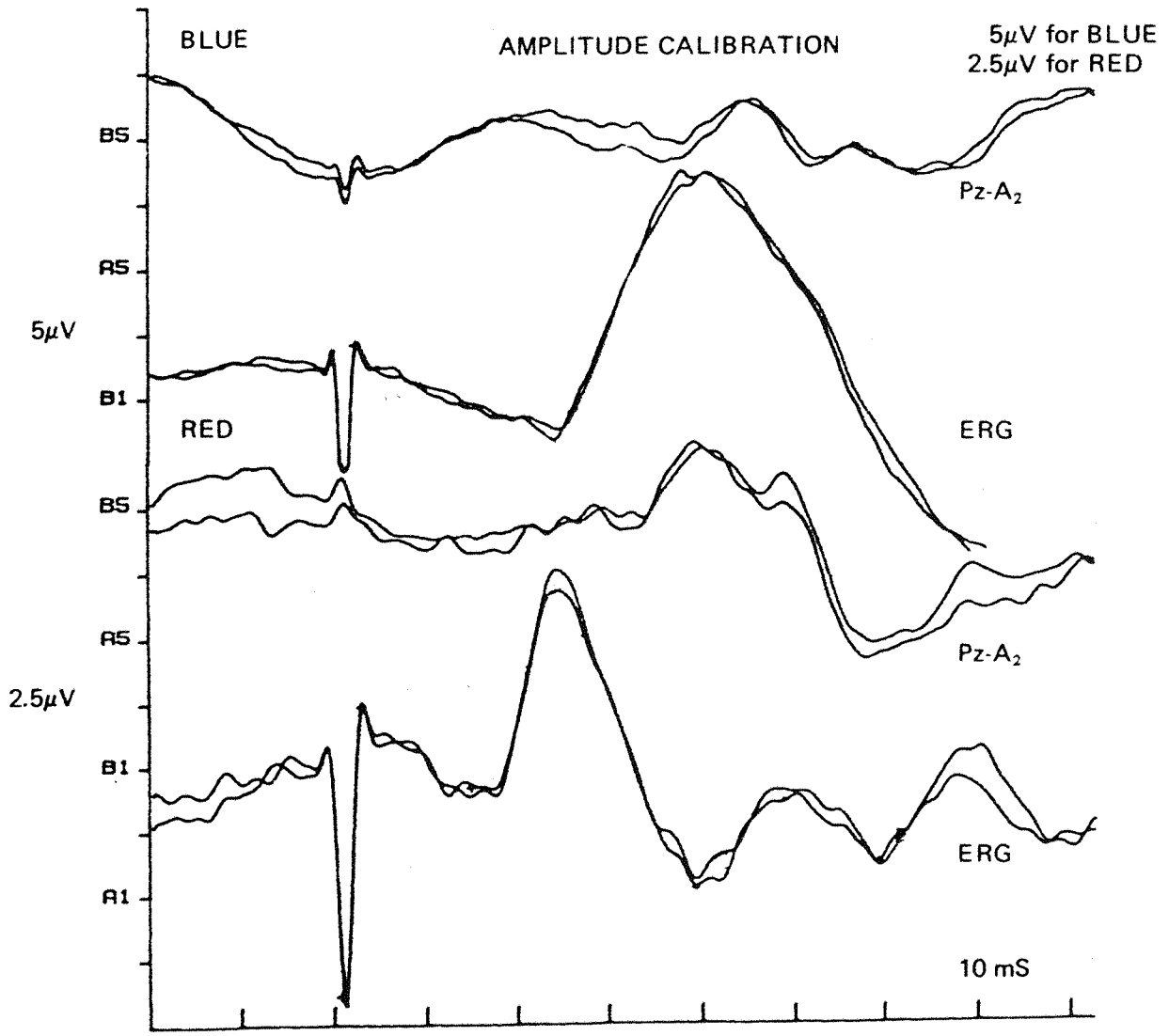
Having identified, established and confirmed that early oscillatory potentials can be recorded to a visual (flash) stimulus, it was concluded that additional variables should be investigated. The effects on recording the evoked response investigated were eyes open and eyes closed; with and without background illumination. Finally, a measure of the power and frequency spectra of the ERG, early visual oscillatory potentials and cortically generated flash evoked response was performed.

Results obtained were divided into the following categories:-

1a) Red flash intensity log 1.5 background illumination 30 ft lamberts - eyes open
1b) Red flash intensity log 1.5 background illumination 30 ft lamberts - eyes closed
2a) Red flash intensity log 1.5 no background illumination - eyes open
2b) Red flash intensity log 1.5 no background illumination - eyes closed
3a) Blue filter intensity log 1.5 background illumination 30 ft lamberts - eyes open
3b) Blue filter intensity log 1.5 no background illumination - eyes open

FIGURE 36

SUBCORTICAL FLASH EVOKED POTENTIAL ($Pz-A_2$)
and ELECTRORETINOGRAM (A_2 – LOWER LID) TO
TO BLUE OR RED FLASH (RODS OR CONES)



In all categories, the electrode derivation used is Pz referenced to (A1 + A2); binocular stimulation; rate 4.7/sec; LFF = 5 Hz; HFF = 1500 Hz; amplifier sensitivity = 100uV; runs of 300 sweeps were averaged to check reproducibility and then added together. The results are shown in figures 37-42.

Examining the results of test 1 (figures 37 and 38), red flash stimulus intensity log 1.5 with 30 foot lamberts background illumination with eyes open and closed showed that the wide open filtered responses were of similar morphology, especially the first 4 components having the same number of negative and positive phases. The major difference was the later components probably of cortical generation (N145). This component was widespread and diffuse lasting approximately 45 msec on average when the eyes were closed. With eyes open, the later components were better separated and sinusoidal making identification, latency and amplitude measurements easier. The power spectra was different for eyes open and closed, being maximal at 18.7 Hz for eyes open to 8.9 Hz for eyes closed. Digitally filtering the responses (LFF = 30 Hz, HFF = 100 Hz) clearly enhanced the oscillatory potentials.

The results to the second test (figure 39 and 40) are to a red flash stimulus, no background illumination but with eyes open or closed. The early oscillatory potentials are well defined, being of slightly higer amplitude with the eyes closed. The maximal power spectrum occured at 9.76 Hz for eyes closed and at 11.39 Hz for eyes open. In test category 3 (blue filter intensity log 1.5, eyes open, with and without background illumination, 30 foot lamberts), the evoked responses to a blue flash stimulus was clearly recorded. More 'oscillations' occured with a background illumination of 30 foot lamberts as compared with no background illumination. Furthermore, the amplitude of the oscillatory potentials was much higher with background illumination. The power spectra was different for the two test conditions being maximal at 4.88 Hz for background illumination and 13.02 Hz for the no background parameter.

FIGURE 37

EARLY VISUAL OSCILLATORY POTENTIALS TO A RED FLASH STIMULUS

TEST CATEGORY 1(a) (SEE TEXT FOR DETAILS)

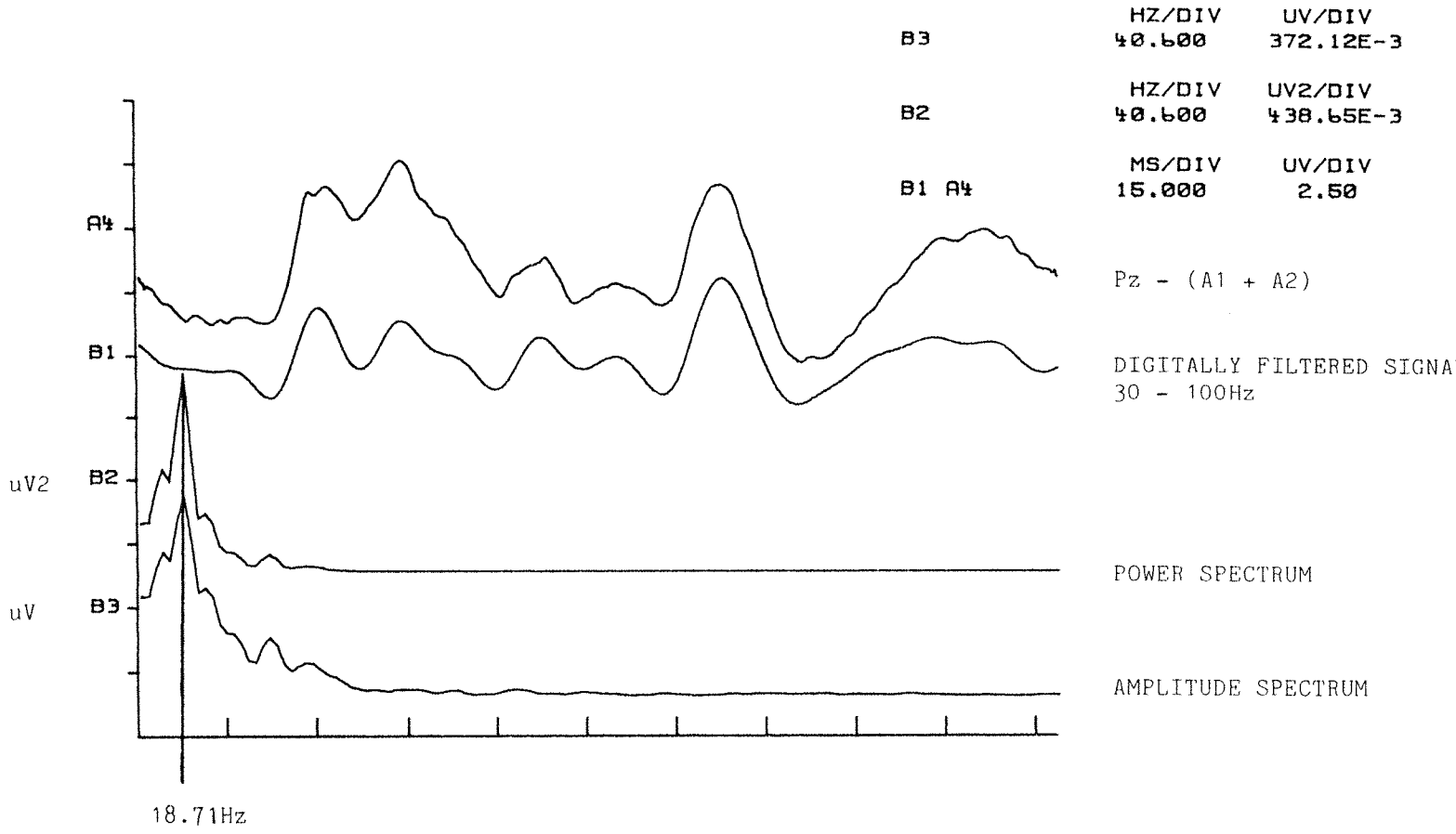


FIGURE 38

EARLY VISUAL OSCILLATORY POTENTIALS TO A RED FLASH STIMULUS

TEST CATEGORY 1(b) (SEE TEXT FOR DETAILS)

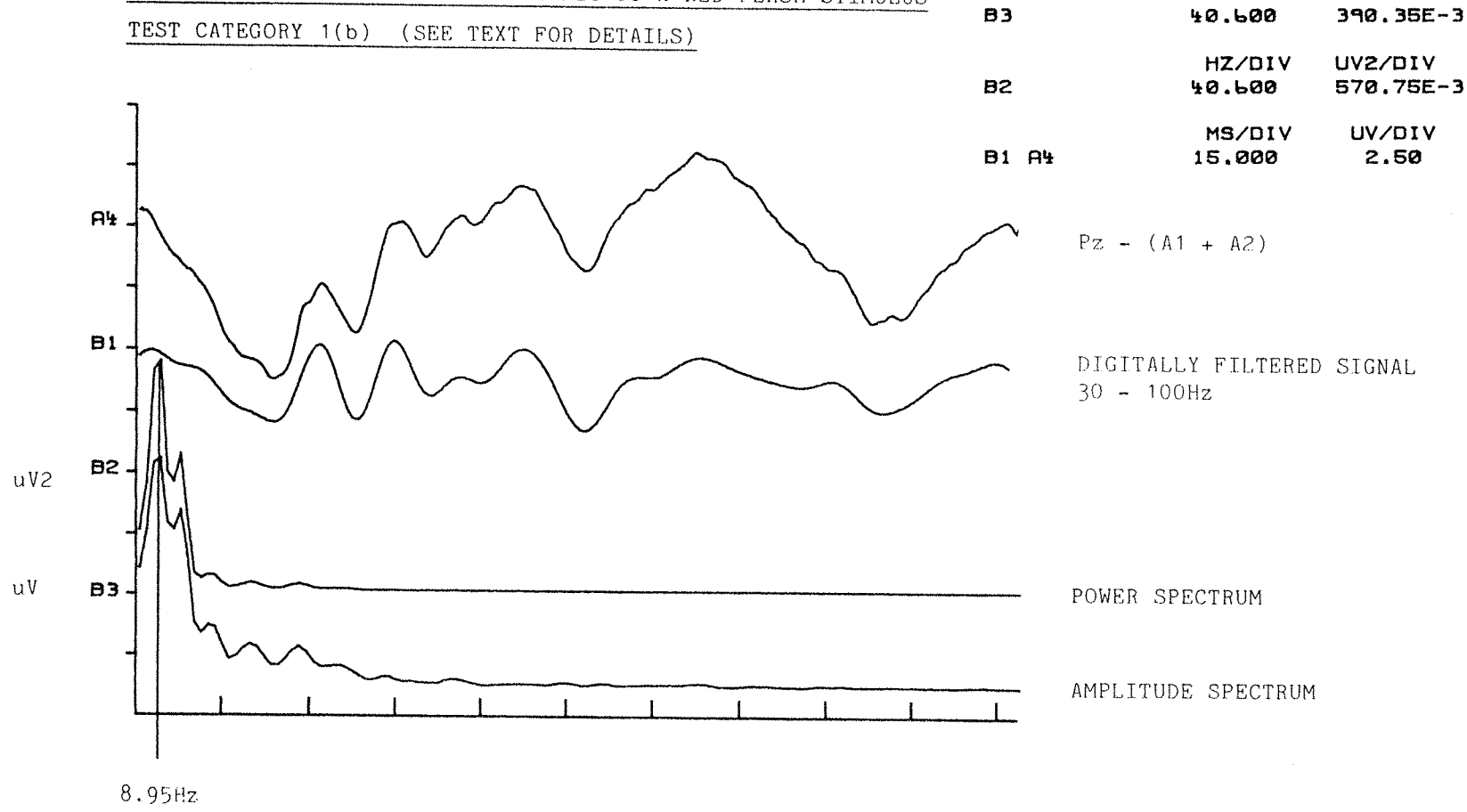


FIGURE 39

EARLY VISUAL OSCILLATORY POTENTIALS TO A RED FLASH STIMULUS

TEST CATEGORY 2(a) (SEE TEXT FOR DETAILS)

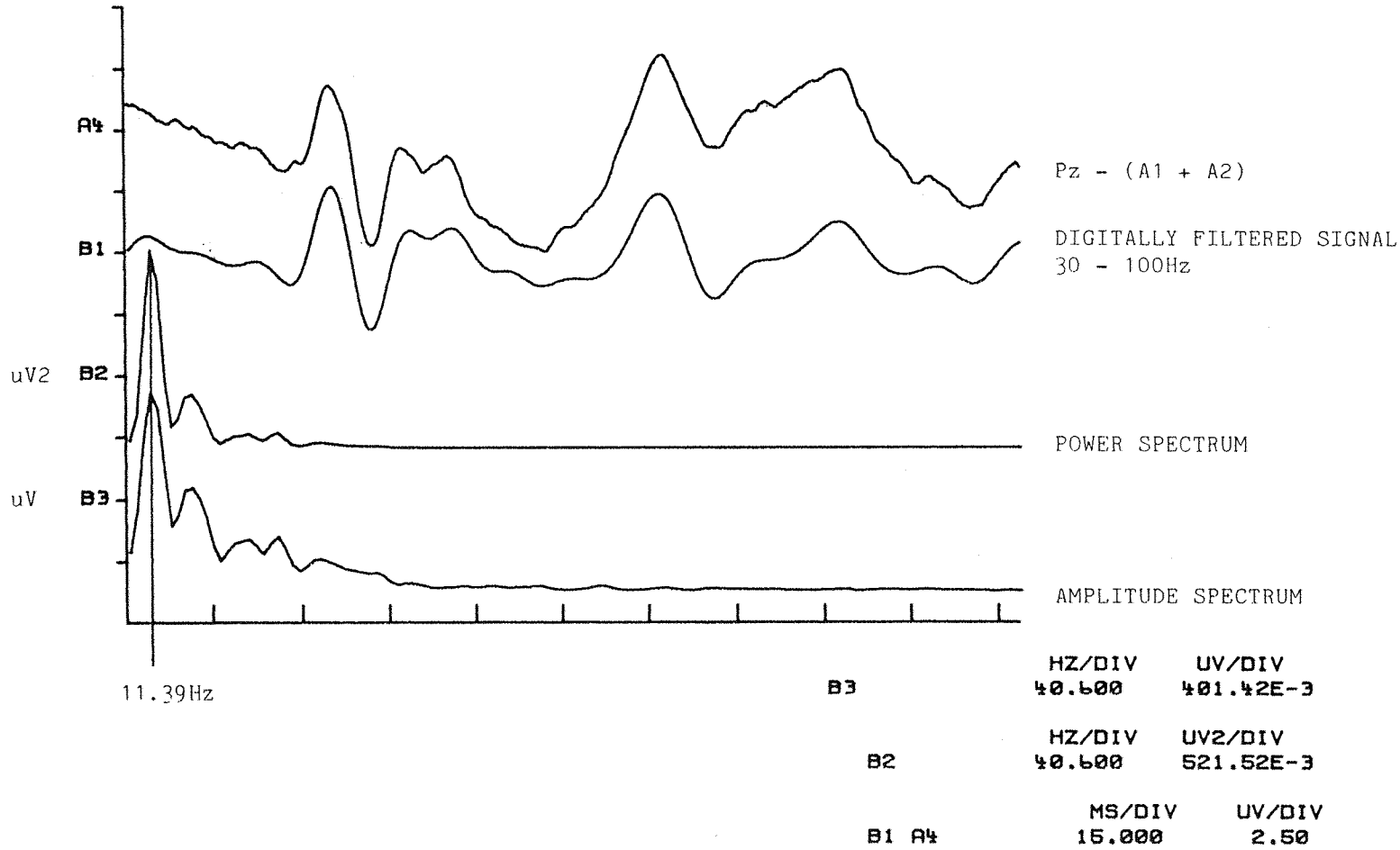
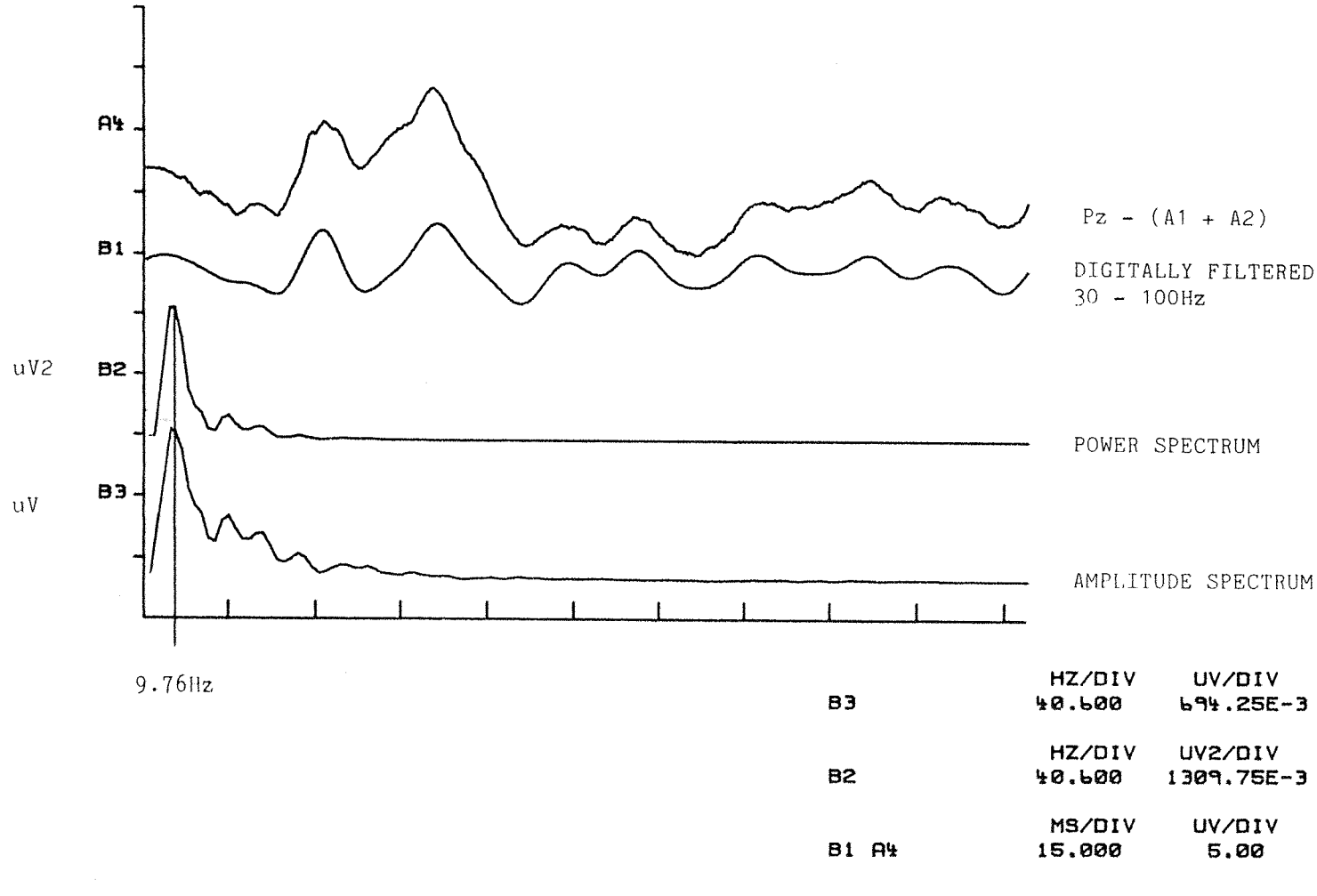


FIGURE 40

EARLY VISUAL OSCILLATORY POTENTIALS TO A RED FLASH STIMULUS

TEST CATEGORY 2(b) (SEE TEXT FOR DETAILS



In the preceeding examinations, the parameters which could be considered the best for elliciting the early visual oscillatory potentials are the following:-

1. Wide open amplifier bandwidth to acquire raw data then digitally filter post acquisition.
2. Highest flash intensity possible.
3. Background illumination equal to or greater than 30 foot lamberts.
4. Pz - (A1 + A2) electrode derivation.
5. Binocular or monocular stimulation for lateralisation detection.
6. Perform test with eyes open.
7. Repetition rate at 4.7/second.
8. White or red light flash stimulus.

The results of the power spectral analysis between each test category show that the major frequency component which is generated by the structure(s) responsible for the early visual oscillatory potentials is affected by changes of wavelength of light, intensity of background luminance and also the added effect of closing the eyes. Closing the eyes effectively reduces the intensity of the flash stimulus and introduces a 'red' filter between the stimulus source and the eye/retina, which will alter the wavelength of light used in the Ganzfeld.

By measuring the power spectra of the combined recording for the electroretinogram, early visual oscillatory potentials (sub-cortical visual evoked potentials) and the cortically generated visual evoked response to a bright flash stimulus, it can be concluded that by keeping the same amplifier and recording parameters for evoking these three potentials, the evoked potentials are generated by three separate structures within the visual pathway.

FIGURE 41

EARLY VISUAL OSCILLATORY POTENTIALS TO A BLUE FLASH STIMULUS TEST CATEGORY 3(a)

(SEE TEXT FOR DETAILS)

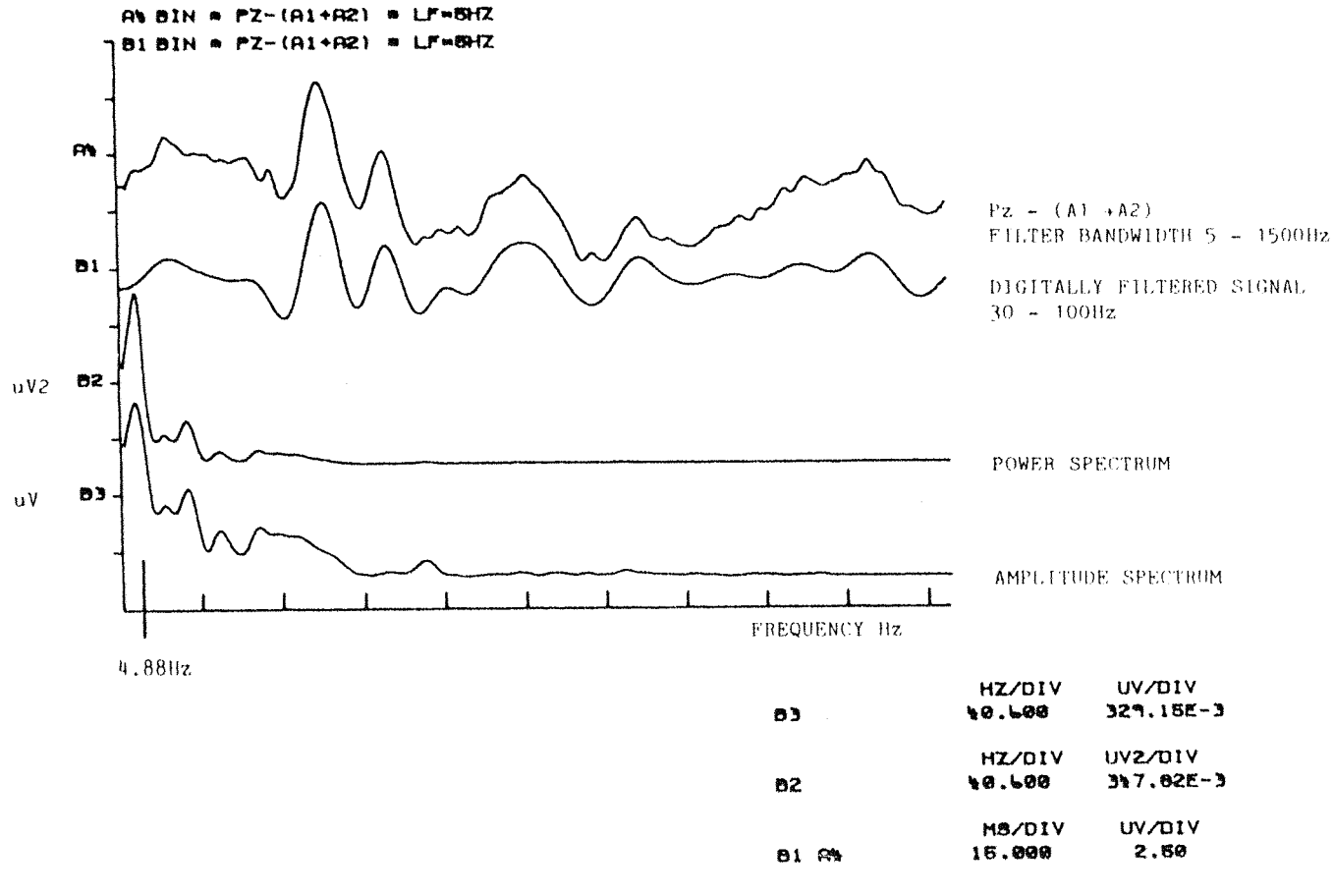
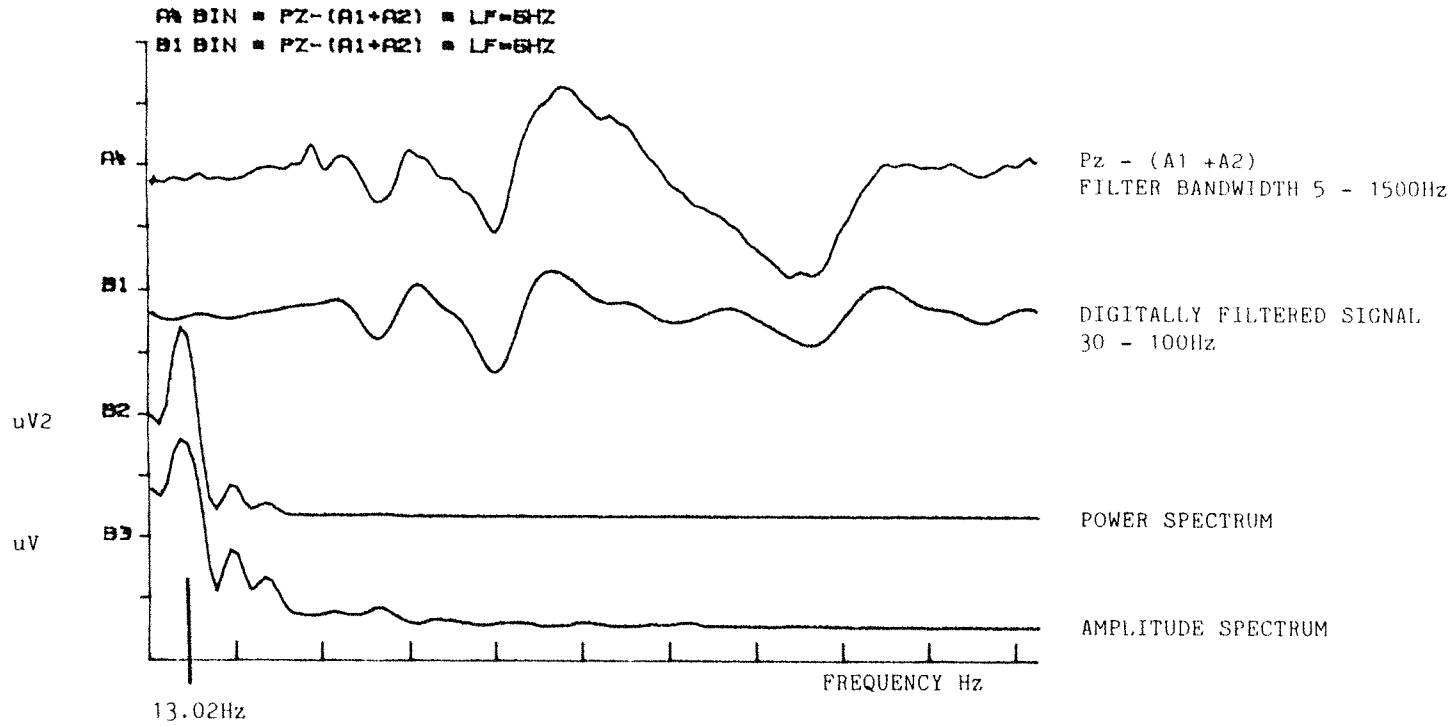


FIGURE 42

EARLY VISUAL OSCILLATORY POTENTIALS TO A BLUE FLASH STIMULUS TEST CATEGORY 3(b)

(SEE TEXT FOR DETAILS)



	HZ/DIV	UV/DIV
B3	%0.600	32%.%7E-3
	HZ/DIV	UV2/DIV
B2	%0.600	32%.00E-3
	MS/DIV	UV/DIV
B1 A%	15.000	2.50

Figures 43 - 45 show the power spectrum for the skin ERG, the oscillatory potentials and the flash VEP (occipital cortex) with frequency peaks at 7.323 Hz, 22.35 Hz (with harmonic at 45.2 Hz) and 8.61 Hz respectively. The frequency spectra shown are the result of adding all the responses obtained from the volunteers and each individual response and frequency spectrum compared. Without doubt, the early visual oscillatory potentials can be recorded from scalp electrodes to a flash stimulus.

Many investigators have shown these potentials to be oscillatory and sinusoidal in morphology, with the degree of oscillation being very dependant on the amplifier filter bandwidth used in each method. This study has clearly demonstrated that the topographic distribution of the early visual oscillatory potentials are to be found maximal at or very close to the electrode position Pz of the International 10-20 system of electrode placement (Jasper 1958).

Evidence from this study has also demonstrated that the early visual oscillatory potentials are not volume conducted potentials from the retina which is in keeping with the work of Harding & Rubinstein (1988, 1989) but have a subcortical generator. Sanarelli et al concluded in their work that the early visual oscillatory potentials could not be recorded in patients with retrobulbar neuritis posterior to Cz electrode position but could be recorded from electrode positions over the frontal scalp. In addition, they also found oscillatory wavelets over the frontal scalp positions although of reduced amplitude in patients suffering from retinopathies like retinitis pigmentosa, where the ERG was non-recordable.

These results indicated that in the presence of a normal flash ERG it is difficult to define which part of the scalp recorded, short latency oscillatory visual potentials to bright flashes is generated in sub-cortical visual structures.

FIGURE 43

FLASH ELECTRORETINOGRAM AND ITS POWER SPECTRUM

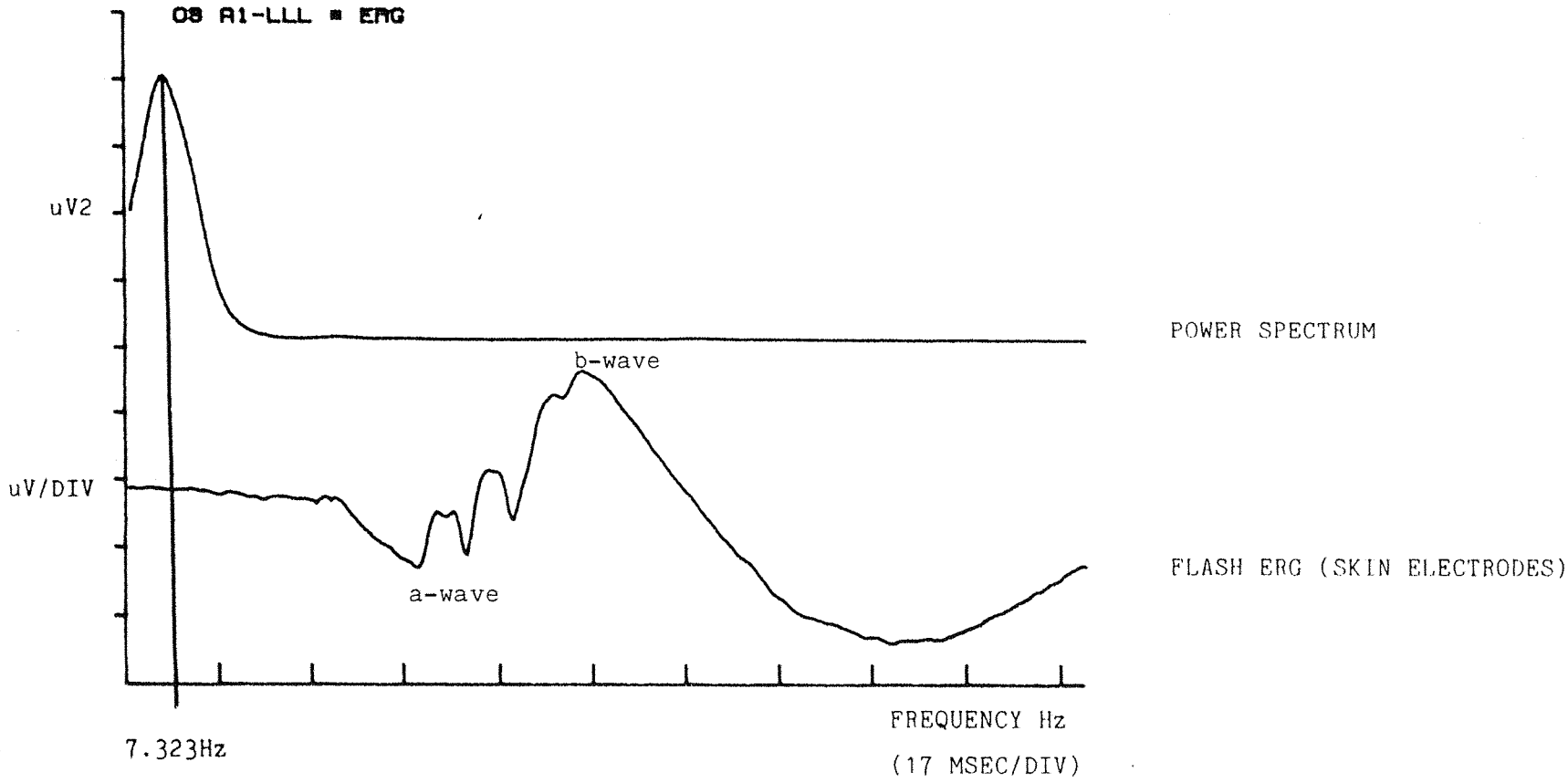


FIGURE 44

EARLY VISUAL OSCILLATORY POTENTIALS TO FLASH STIMULUS (RED L.E.D. GOGGLES)

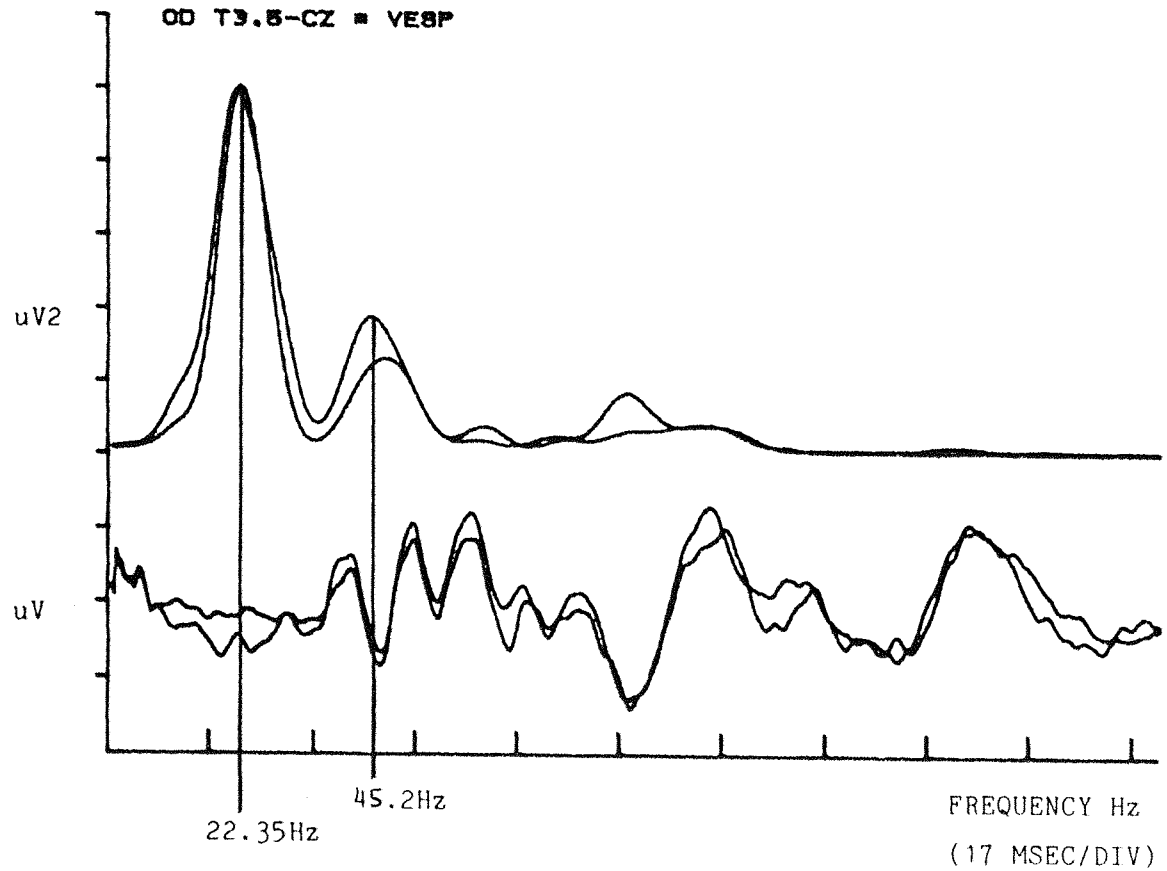
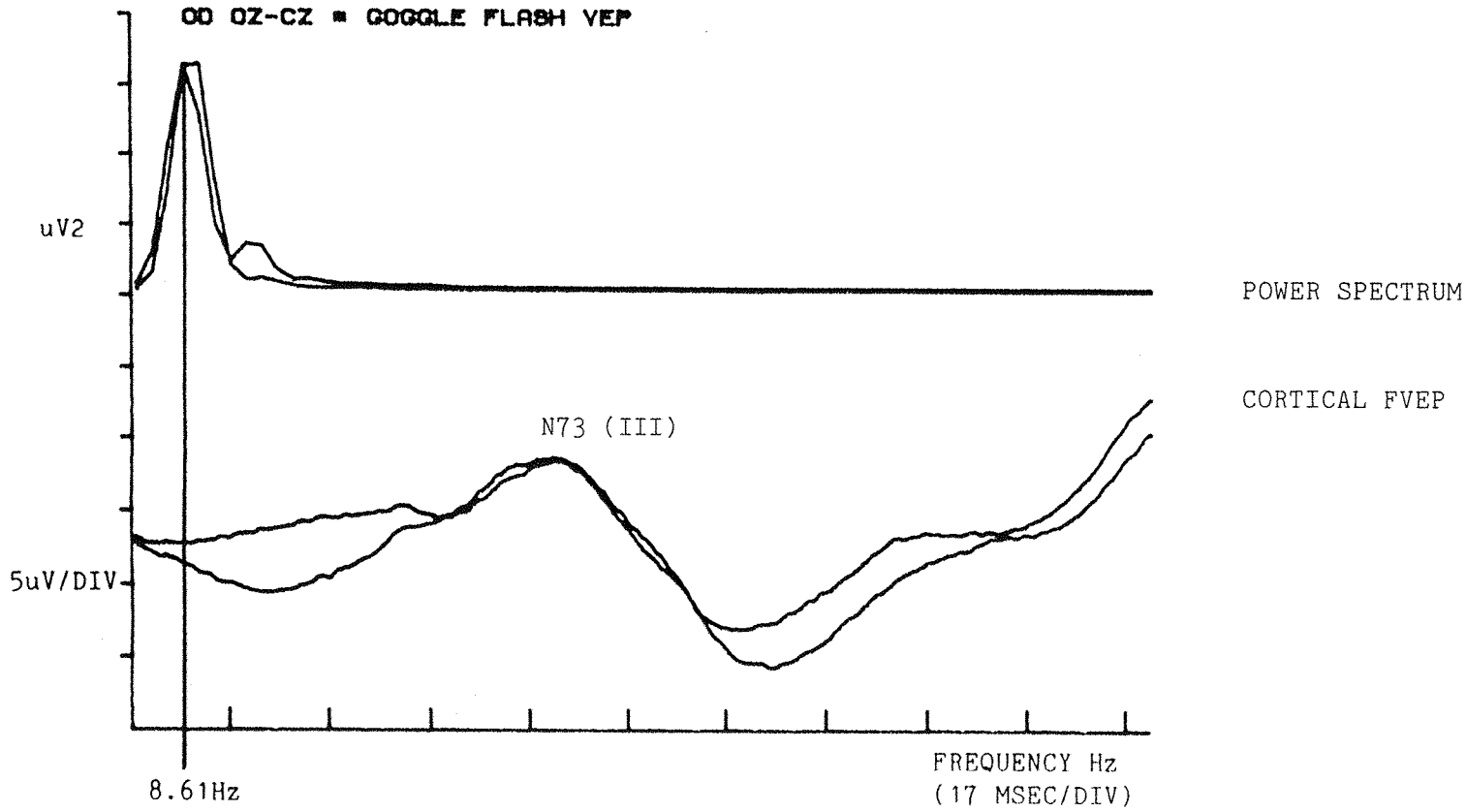


FIGURE 45

VISUAL CORTICAL EVOKED RESPONSE TO A FLASH STIMULUS (RED L.E.D. GOGGLES)



The evidence from this study concludes that the early visual oscillatory potentials recorded over scalp positions to a bright flash stimulus are generated from an intracranial, probably sub-cortical source which is not related to the electroretinogram but may have some overlap with the primary response of the cortically generated flash VEP (waves I, II, III). The evidence for this conclusion is that the oscillatory potentials can be separated from the ERG, that the response is recorded bilaterally to monocular stimulation, oscillatory potentials are generated by selectively stimulating the rods and cones separately and in combination, frequency analysis shows a frequency difference for the ERG, oscillatory potentials and the cortical FVEP and the scalp distribution excludes a retinal source.

It is in the opinion of the author that every effort should be made in recording the early oscillatory potentials to visual flash stimuli when investigating patients that present with lesions of the optic nerves and tracts and also of the thalamocortical radiations and visual cortex as the absent or presence of the short latency oscillatory potentials can help differentiate between lesions in different sections of the visual pathway (Borda 1977), from the retina through sub-cortical structures to the visual cortex.

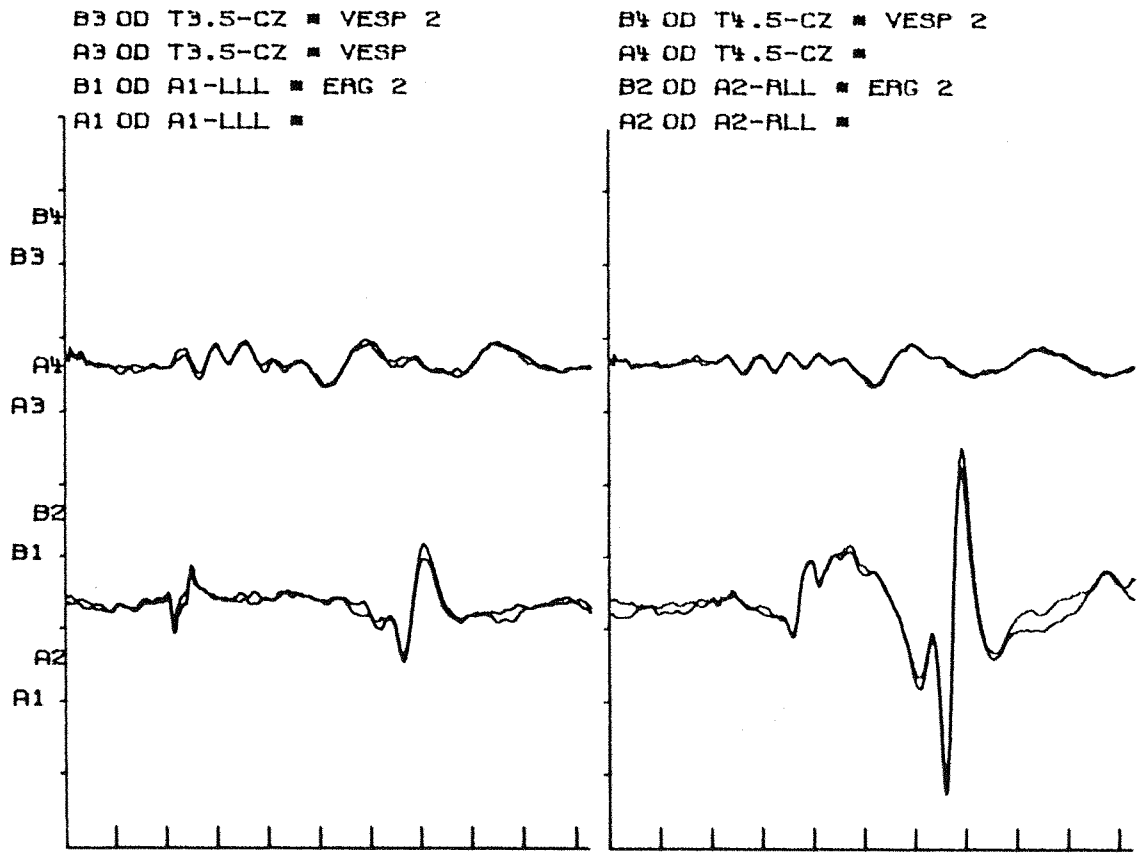
Further work is required to evaluate the effectiveness of this technique on selected groups of patients each suffering with a clinically proven disease process affecting the visual pathways. Knowing the sites of the lesions from CT scanning or nuclear resonance imaging or the clinical history and applying this technique will reveal more information on the exact generator as to the source of these early visual oscillatory potentials in humans.

APPENDIX A

COMBINED ERG AND EARLY OSCILLATORY POTENTIALS RECORDED TO

VISUAL FLASH STIMULUS (GOGGLES L.E.D., RED)

	MS/DIV	UV/DIV
A1 B1 A2 B2	15.000	10.00
A3 B3 A4 B4	17.000	5.00



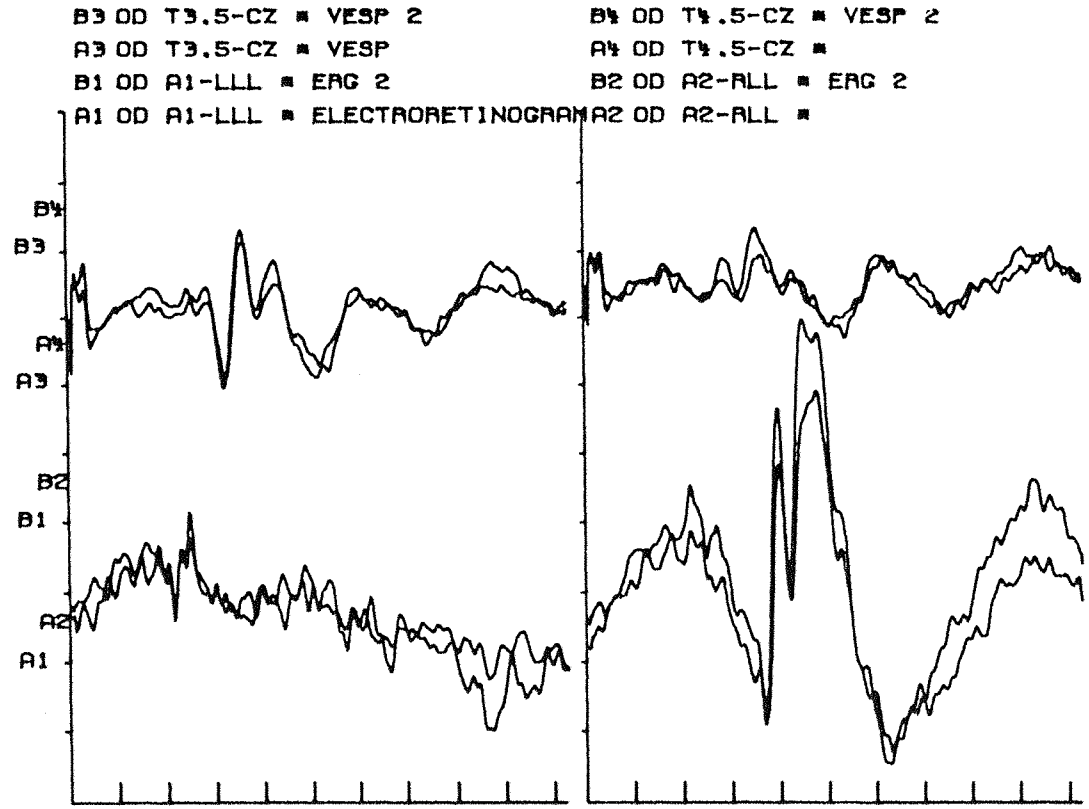
EARLY OSCILLATORY POTENTIALS

ERG

COMBINED ERG AND EARLY OSCILLATORY POTENTIALS RECORDED TO

VISUAL FLASH STIMULUS (GOGGLES L.E.D., RED)

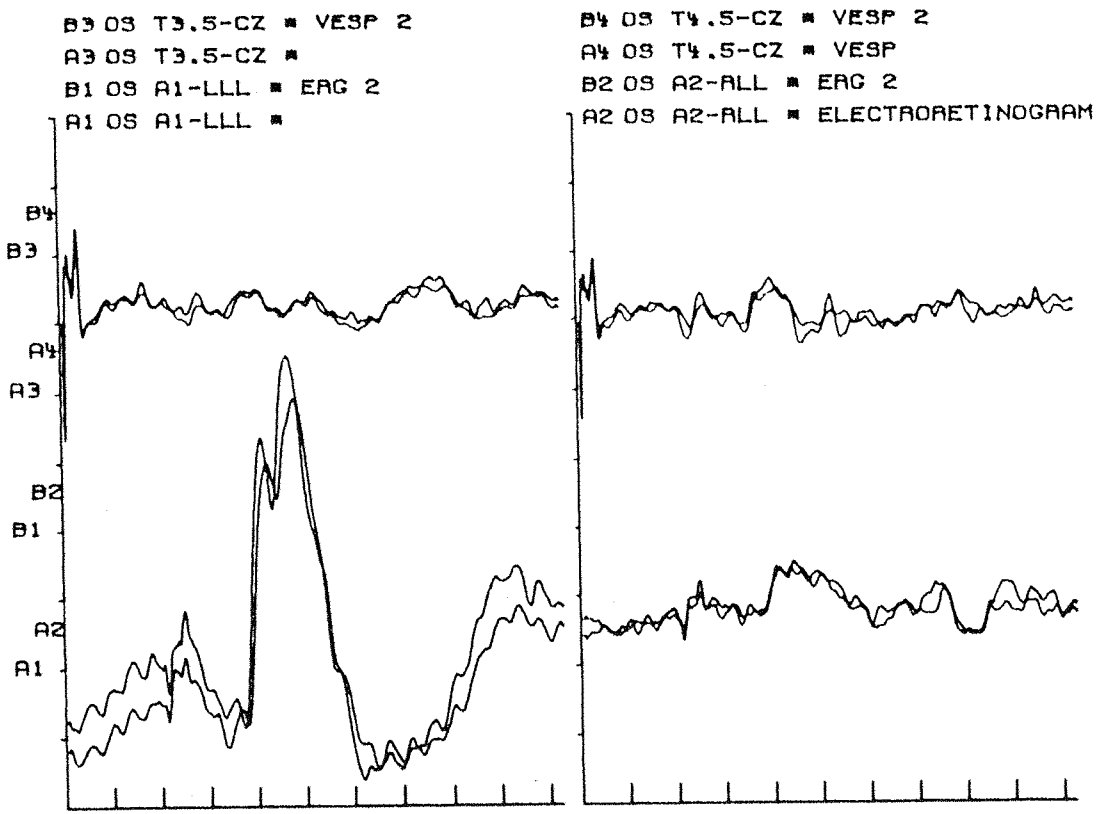
	MS/DIV	UV/DIV
A1 B1 A2 B2	15.000	1.25
A3 B3 A4 B4	17.000	0.62



COMBINED ERG AND EARLY OSCILLATORY POTENTIALS RECORDED TO

VISUAL FLASH STIMULUS (GOGGLES L.E.D., RED)

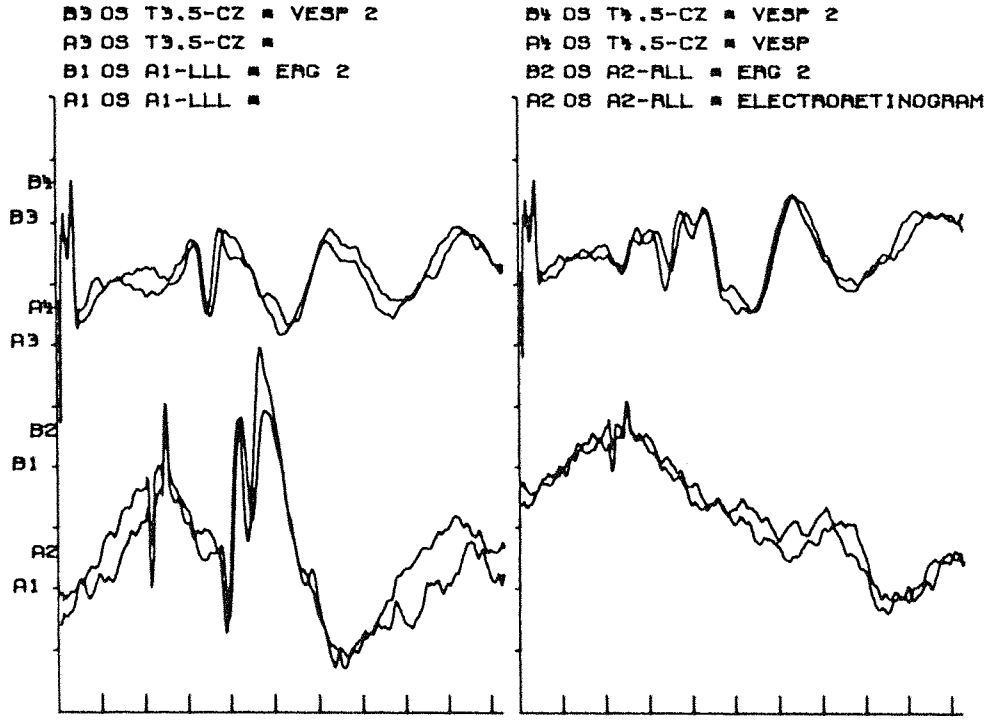
	MS/DIV	UV/DIV
A1 B1 A2 B2	15.000	2.50
A3 B3 A4 B4	17.000	1.25



COMBINED ERG AND EARLY OSCILLATORY POTENTIALS RECORDED TO

VISUAL FLASH STIMULUS (GOGGLES L.E.D., RED)

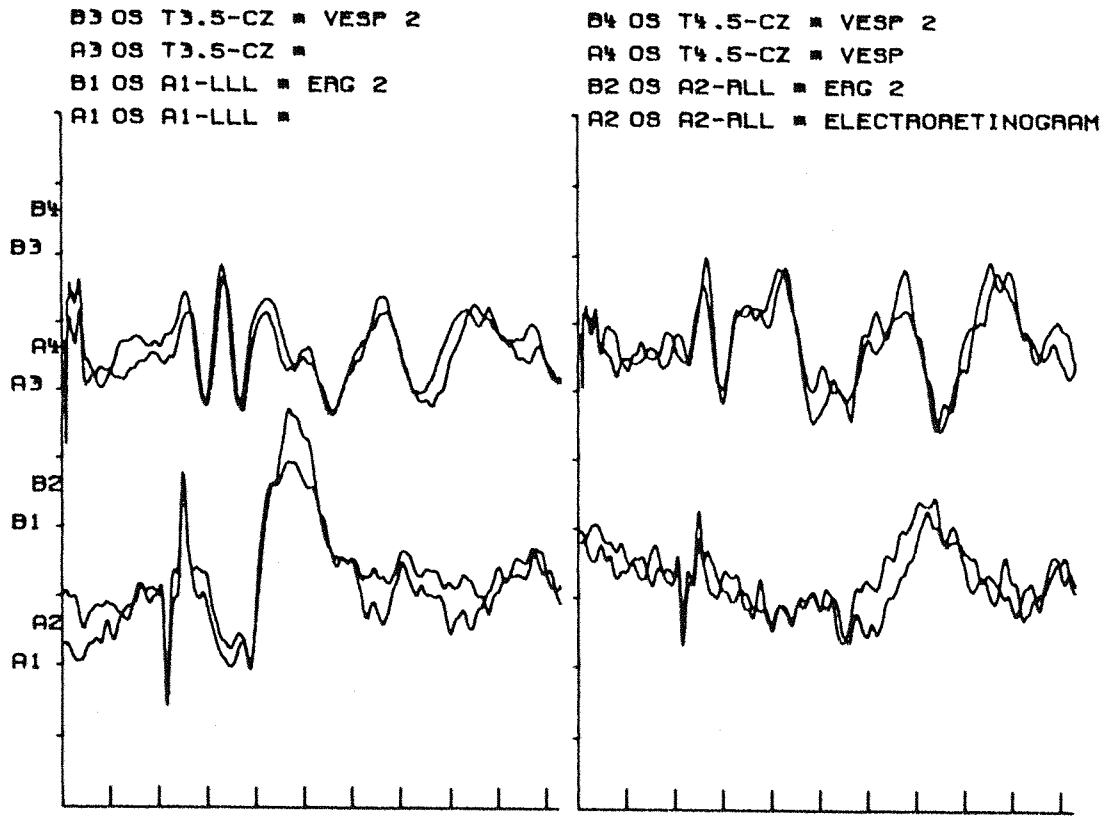
	MS/DIV	UV/DIV
A1 B1 A2 B2	15.000	1.25
A3 B3 A4 B4	17.000	0.62



COMBINED ERG AND EARLY OSCILLATORY POTENTIALS RECORDED TO

VISUAL FLASH STIMULUS (GOGGLES L.E.D., RED)

	MS/DIV	UV/DIV
A1 B1 A2 B2	15.000	2.50
A3 B3 A4 B4	17.000	1.25



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                ****  PAGE  001  ****              08:17:59    08/25/86

SCROLL
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PRINT "          ***  GVESP.CMD                                         *** " END
PRINT "          ********************************************************** " END
PRINT "          ***                                                    *** " END
PRINT "          ***  DEPARTMENT OF CLINICAL NEUROPHYSIOLOGY            *** " END
PRINT "          ***  WESSEX NEUROLOGICAL CENTRE                        *** " END
PRINT "          ***  SOUTHAMPTON GENERAL HOSPITAL                      *** " END
PRINT "          ***                                                    *** " END
PRINT "          ********************************************************** " END
PRINT "          ********************************************************** " END
PRINT "          ***                                                    *** " END
PRINT "          ***  GOGGLE FLASH VISUAL EP                            *** " END
PRINT "          ***  CH 1 :- A1-LLL   **  CH 2 A2-RLL                  *** " END
PRINT "          ***  CH 3 :- T3.5-CZ  **  CH 4 T4.5-CZ                 *** " END
PRINT "          ***  CH 5 :- O1-C3    **  CH 6 OZ-CZ                   *** " END
PRINT "          ***  CH 7 :- O2-C4    **                               *** " END
PRINT "          ********************************************************** " END
PRINT "          ********************************************************** " END
INPUT "          ***  SENSITIVITY     :-          " TO SENS END
SET SYS :REM\CHN=2\CHN "2"=5\TRG=M\MST=20\TME=150\SWP "B"=500
TRG "2"=N\TME "2"=170\DLY "B"=0\ART=ON
BIND NULL GVP
SET STIM :RAT=4.7;DUR=100;GAT=0;MOD=0
SET AMP "1" :HBP=1500;LBP=5;CAL=0
SET AMP "2" :HBP=1500;LBP=5;CAL=0
SET AMP "3" :HBP=1500;LBP=30;CAL=0
SET AMP "4" :HBP=1500;LBP=30;CAL=0
SET AMP "5" :HBP=500;LBP=5;CAL=0
SET AMP "6" :HBP=500;LBP=5;CAL=0
SET AMP "7" :HBP=500;LBP=5;CAL=0
SET AMP "1" :SNS=200;NCH=0
SET AMP "2" :SNS=200;NCH=0
SET AMP "3" :SNS=^SENS;NCH=0
SET AMP "4" :SNS=^SENS;NCH=0
SET AMP "5" :SNS=^SENS;NCH=0
SET AMP "6" :SNS=^SENS;NCH=0
SET AMP "7" :SNS=^SENS;NCH=0
PRINT " ********************************************************************** " END
PRINT " ****                                                          **** " END
PRINT " ****          RT1     **     RT2     **     RTRPT           **** " END
PRINT " ****          LT1     **     LT2     **     LTRPT           **** " END
PRINT " ****                                                          **** " END
INPUT " ****  ENTER SEQUENCE REQUIRED  :-        " TO RESP END
          IF RESP = "RT1" THEN
SET GVP :MOD=3
SPLIT\GAIN=4
DSP A1 A2 A3 A4 A5 A6 A7\ZAP
AVE A1 A2 &AVE2 "3" A3-A7&\DATE
INPUT " *****  NAME    :-                  " TO NAME END
RMK A1=OD A1-LLL * ELECTRORETINOGRAM
RMK A2=OD A2-RLL * ^NAME
RMK A3=OD T3.5-CZ * VESP
RMK A3=OD T3.5-CZ * VESP\RMK A4=OD T4.5-CZ * ^NAME
RMK A5=OD O1-C3 * GOGGLE FVP
```

```
RMK A6=OD O2-C4 * ^NAME
RMK A7=OD OZ-CZ * GOGGLE FLASH VEP
DATE
PRINT " ***** SIMULTANEOUS GOGGLE FLASH ERG VEP VESP **** " END
            ENDIF
            IF RESP = "RT2" THEN
SET GVP :MOD=3
SPLIT\GAIN=4
DSP A3 A4 B3 B4\ZAP B1-B7
AVE B1 B2 &AVE2 "3" B3-B7&\DATE
OVR A3 B3\OVR A4 B4\BLC
RMK B1=OD A1-LLL * ERG 2\RMK B2=OD A2-RLL * ERG 2
RMK B3=OD T3.5-CZ * VESP 2\RMK B4=OD T4.5-CZ * VESP 2
RMK B5=OD O1-C3 * GVP 2\RMK B6=OD O2-C4 * GVP 2
RMK B7=OD OZ-CZ * GVP 2
PRINT " **** GOGGLE FLASH ERG VEP VESP ***** " END
            ENDIF
            IF RESP = "LT1" THEN
SET GVP :MOD=2
SPLIT\GAIN=4
DSP A1-A7\ZAP
AVE A1 A2 &AVE2 "3" A3-A7&\DATE
INPUT " **** NAME      :-          " TO NAME END
RMK A1=OS A1-LLL * ^NAME
RMK A2=OS A2-RLL * ELECTRORETINOGRAM
RMK A3=OS T3.5-CZ * ^NAME
RMK A4=OS T4.5-CZ * VESP
RMK A5=OS O1-C3 * ^NAME\RMK A6=OS O2-C4 * GOGGLE FVP
RMK A7=OS OZ-CZ * GVP
PRINT " **** GOGGLE FLASH VEP ERG VESP **** " END
            ENDIF
            IF RESP = "LT2" THEN
SET GVP :MOD=2
SPLIT\GAIN=4
DSP A3 A4 B3 B4\ZAP B1-B8
AVE B1 B2 &AVE2 "3" B3-B7&\DATE
RMK B1=OS A1-LLL * ERG 2\RMK B2=OS A2-RLL * ERG 2
RMK B3=OS T3.5-CZ * VESP 2\RMK B4=OS T4.5-CZ * VESP 2
RMK B5=OS O1-C3 * GVP 2\RMK B6=OS O2-C4 * GVP 2
RMK B7=OS OZ-CZ * GVP 2
PRINT " **** GOGGLE VEP ERG VESP **** " END
          ENDIF
          IF RESP = "RTRPT" THEN
SET GVP :MOD=3
SWP=100
SPLIT\GAIN=4
DSP A3 A4 B3 B4\BLC
AVE A1 A2 &AVE2 "3" A3-A7&\DATE
OVR A3 B3\OVR A4 B4\BLC
PRINT " **** GOGGLE VEP ERG VESP **** " END
WAIT AVE\WAIT AVE2
AVE B1 B2 &AVE2 "3" B3-B7&\DATE
PRINT " **** GOGGLE VEP ERG VESP **** " END
            ENDIF
            IF RESP = "LTRPT" THEN
```

```
SET GVP :MOD=2\SWP=100
SPLIT\GAIN=4
DSP A3 B3 A4 B4\BLC
AVE A1 A2 &AVE2 "3" AA7&\DATE
OVR A3 B3\OVR A4 B4\BLC
PRINT " ¥¥¥¥ GOGGLE VEP ERG VESP ¥¥¥¥ " END
WAIT AVE\WAIT AVE2
AVE B1 B2 &AVE2 "3" B3-B7&\BLC\DATE
PRINT " ¥¥¥¥ GOGGLE VEP ERG VESP ¥¥¥¥ " END
          ENDIF
```

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