The development of flash visual evoked potential techniques for the diagnosis of visual disorders with dense opacities of the optic media.

By

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SUMMARY

Visual evoked potentials (VEP)were recorded in a large normal population. Significant age differences were found, and the P2 component (latency 116 m.sec.) was the most consistent component of the VEP both between and within the individuals.

The validity of the normal VEP criteria were tested in two groups of patients with known visual field defects. One group with central lesions and hemianopia, and a second with senile macula degeneration. The VEP varied with the degree of visual impairment with low amplitudes, long latencies and no localization at either occiput being consistent with poor acuity. The P2 component appeared to be particularly effected by the loss of central retinal function.

Two prospective studies were carried out on patients with dense opacities of the optic media. One group of patients had unilateral longstanding cataracts, the second group had recently sustained severe eye injuries with penetration of the globe. The VEP was graded to predict a good visual recovery or no useful function remaining and the gradings were significantly correlated with the final visual outcome.

It was concluded that the flash VEP is particularly useful to monitor visual function with dense opacities of the optic media if there is damage to the central retina or visual pathways and cortex.

Key Words: VISUAL EVOKED POTENTIALS (VEP), NORMAL, ABNORMAL, FLASH, OPACITIES.

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CONTENTS

CHAPTER 1

Techniques of visual evoked potential recording.

Introduction

The work described in this thesis concerns the development of ideas and techniques over a six year period that were, and still are directed towards developing a clinical electrophysiological diagnostic service. The methods that have been used are confined first, by the facilities available within a hospital department, and more importantly, are restricted by the characteristics of a diverse clinical population. At worst this means that the system must try to cope with a possibly very young, totally uncooperative patient. The drugs that the patient is taking, his behaviour, complete information about his symptoms, and incorporation of repeat investigations, and clinical control groups, are often beyond the influence of the investigator.

Detailed studies of normal populations, where many of the intervening variables can be controlled, reveals that the pattern of the visual evoked potential (VEP) to flash stimulation varies considerably among individuals under similar experimental conditions. Further complications are that the VEP configuration is highly sensitive to changes in stimulation, and experimental and subjective conditions. Parameters such as stimulus size, intensity, colour and stimulation frequency; electrode position and electrode combination, background illumination, attention and arousal all effect the form of the VEP. There is little doubt that the sensitivity of visual potentials to intervening parameters, account for many of the discrepancies in reported attempts to describe the general pattern of the normal VEP. The problem of deciding whether a VEP is abnormal or normal is therefore very difficult. So far no well validated, quantitative technique has been proposed, where a given flash VEP can be reliably

labelled normal or abnormal. At best most methods can only detect gross alterations in wave form.

The approach and aim of the literature review is not a comprehensive survey of the vast literature on VEPs, but is a selective look at areas which the author believes to be important in clinical investigations. The stimulus parameters need to be selected on the basis of firstly clinical, and secondly physiological appropriateness. The norms and variability of the evoked potential features need to be specified, together with an understanding of just how important are the unwanted effects of spurious changes in subjective and environmental conditions. The VEP changes that can define pathological conditions need to be quantified. An understanding of the relationships of surface potentials with underlying physiology, anatomy and generator sites is only immediately important if it aids in the clarification of clinical findings.

The aim of the research and development of investigative techniques in clinical visual evoked potentials is to provide more data than are available from subjective tests, and to provide a reliable aid to eventual diagnosis. The second aim is to produce techniques that are easy to use, and are free from risk or patient discomfort.

1.1 Historical Review

The first record of the electrical activity of the brain was made by Caton in 1875. He managed to monitor both spontaneous brain activity, and potentials evoked by electrical stimulation, from two electrodes on the exposed cerebral cortex of animals. Half a century later, Hans Berger (1929)

discovered that brain activity could be recorded through the intact skull in man, the first electroencephalogram (EEG). Adrian and Matthews (1934) confirmed that the oscillations obtained by Berger came from the brain, and the field of EEG research developed rapidly with the growth and improvements in electronic technology. The importance of the EEG as a clinical tool was confirmed when distinct wave forms were clearly associated with epilepsy (Gibbs et al., 1935), and after Walter (1936) demonstrated that the EEG can help to localise brain lesions.

The recording of evoked potentials was not so easy, for in the majority of people the sensory responses to external stimuli are lost in the higher amplitudes of the outgoing EEG. Dawson (1947) was the first to suggest a way of detecting evoked potentials from scalp recordings. His method was based on the assumption that cortical evoked responses occurred at a fixed time after the stimulus, and that their wave form was relatively uniform, while the timing and frequency of the spontaneous EEG waves would be random in relation to the stumulus. Dawson (1951, 1954) displayed EEG traces during sensory stimulation on a cathode ray oscilloscope, and superimposed a number of these traces on a photographic record. The results showed that there were time coherent events occurring after the stimulus. Dawson subsequently devised an instrument for automatic summation of the EEG during stimulation to detect small potentials. Based on the same principles as superimposition, summation produced clearer results. As the EEG is sampled after each stimulus, the small time locked

potentials add together, while the random appearance of positive and negative phases of the background EEG tend to sum to zero. Commercially available special purpose computers were introduced at the beginning of the 1960's, which lead to an exponential growth in evoked potential research.

These special computers, for example, the Average Response Computer (ARC), the Medelec Averager and the Computer of Average Transients (CAT), have fixed programmes. That is, the desired analysis is wired into the control circuits, making the equipment reliable, efficient and easy to use. The EEG is periodically sampled and an analogue to digital conversion performed to generate a series of numerical values for the EEG potentials at regular points in time. These values are added to the corresponding previous sums, which are held in digital stores. The results are displayed either as the total sum of the EEG samples, with the amplitude of the waveforms depending on the number of EEG samples taken, or else an average is performed to render the amplitude independant of the number of sweeps or samples. General purpose computers are now being used more and more frequently for research and diagnosis. The greater storage capacity and flexibility of programming ensures more sophisticated data handling, and more channels for processing the EEG data.

1.2. Recording Procedures.

The configuration and interpretation of evoked potentials are both dependent on recording techniques. The size and linkage of the electrodes, their positions on the scalp, the sampling rate and data handling of the system,and the type

of stimulation, all these factors play a vital role in determining the form and significance of the evoked potential.

1.2.1. Stimulation Methods.

Probably the most widely used stimulus in flash evoked potential work is the Xenon flash of the stroboscope, which produces a very bright, short duration visual stimulus of approximately 10-15 μsecs. This popularity may be partly due to the easy availability of the equipment, rather than an intelligent guess about what the biological system is capable of handling.

The use that the stroboscope is put to are numerous. For example it has been used to stimulate the eyes directly (Ciganek, 1961, 1967, 1969; Rhodes et al. 1969; Callaway and Halliday, 1973; Ellingson, 1970), or else it has been reflected from a white, diffusing surface (Lewis and Beck, 1970; Schenkenberg and Dustman, 1970). The xenon flashes have been coloured with various colour filters (Eason et al. 1967; Behrman, 1969), and the size of the illuminated surface of the stroboscope has been reduced to produce small flashes with a reduced angle of view (Potts and Nagaya, 1965, 1969; Eason et al., 1967; Fishman and Copenhaver, 1967; Bourne et al., 1971). Geometric patterns have also been illuminated by stroboscopes (Harter and White, 1968; Russel and White, 1970; Yinon et al., 1974). In most cases measurements of intensity and colour are not specified, or else are given in terms which do not have any direct relationship with the light intensity reaching the eye. A maxwellian view eliminates part of this problem, since a lens or mirror throws an image of the light

source into the plane of the pupil of the subject's eye. Almost all the light enters the eye, and effective stimulation is therefore equal to the maximum theoretical luminance (Regan, 1972). There are, however, problems with this method, since even small eye and head movements immediately reduce the effectiveness of the light source. The main characteristic of the methods of stimulation that have been mentioned, is that the visual system is periodically given a sudden step input, which produces a "transient" evoked response.

In recent years it has been realized that a more appropriate method of producing visual evoked potentials is to excite the visual system with periodic changes of pattern, by either movement or appearance, where there is very little or no appreciable change in ambient intensity. Such forms of stimulation provide a better simulation of the usual visual effects on the eyes as they rapidly scan and fixate richly patterned environments, of fairly constant brightness. Such pattern VEPs are often reported to be larger than the flash evoked response (Jeffreys, 1969; Armington, Corwin and Massetta, 1971), and far more consistent (Jeffreys, 1971; Michael and Halliday, 1971; Regan, 1972; Halliday et al., 1977). Effective pattern stimulation is even more susceptible than flash stimulation to many behavioural changes, since the pattern must remain clearly in focus throughout the recording. Despite the wealth of papers reporting the usefulness of pattern stimulation as a clinical tool, there are surprisingly few accounts of the variation of the normal pattern VEP, with for example changes in focus and attention.

The interstimulus interval has a significant effect on the morphology of the VEP. This is particularly so in neonates, when stimulation rates as slow as 1 f/sec. may cause complete attenuation of the visual potentials, and much slower frequencies must be used to obtain a VEP (Hrbek et al., 1966). Induced rhythmic responses (to fast frequencies of stimulation) do not appear until the VEP had completely disappeared, suggesting that the two types of response may be unrelated (Regan,1972). Lehtonen (1973) found that the optimum frequency for transient evoked responses was no faster than 1 f/sec. If the stimulation rate was slowed from 2 to 1 flash/sec., there was a slight increase in amplitude of all components. In the mature brain, increasing the frequency of stimulation leads to an overlap of VEP components, until only two waves, generally reported to be early components (Ciganek, 1961), are left forming an apparent harmonic of the rate of stimulation. There is a transition to a rhythmic sinusoidal response around 10 f/sec. Kinney, McKay, Mensch and Luria (1973) found no difference between responses to 4 f/sec. compared with slower flash rates. Kitasato (1966) recorded responses which were similar to a single VEP up to 7 f/sec., with no interaction between components. Above this frequency, interaction produced additional sinusoids, which made the response different from either single or double flashes. Ciganek (1964) looked at the effects of the interstimulus intervals between pairs of stimuli. There was an absolute refactory period of 40 m.sec., when there was no difference between a single and paired stimulus response. There were two subsequent times of maximum facilitation at 100 m.sec. and 200 m.sec after the first stimulus, with incomplete subnormal periods inbetween. Li, Cullen and Jasper

(1956) recorded the same results in intra-cortical spike activity.

Depth studies in patients (Chatrian et al., 1960), showed that with increasing stimulation frequency, late components of the evoked potentials gradually disappeared, until simple oscillations appeared, which followed the frequency of stimulation. Response harmonics were usually recorded in the visual cortex, but were never seen in the auditory cortex. Uttal (1965) raised the possibility that part of the response mechanism to high stimulation rates lies in the peripheral nervous system. In the peripheral cutaneous fibres there was an overlying periodic oscillation of maxima and minima in spike amplitude. The period was approximately 100 m.sec., and was independant of stimulus intensity and interstimulus interval.

Steady state evoked potentials (SSEPs) are responses to fast stimulation rates which are frequency filtered using very narrow band filtering. According to those that have a wide experience of this evocation technique (Milner et al., 1972; Regan, 1972), the signal to noise ratio is superior to normal averaging techniques. The system is also less susceptible to artifacts and psychological states of the subject. As the variability is reduced compared with transient responses (Gastaut and Regis, 1964), the identification of an abnormal response should be easier, although there is very little information on this; the technique is fast, with potentials as small as 0.2 μV being precisely measured. The main problem is that an apriori prediction is made about the response of the system, in order to set up the filters, and any results that

occur outside this range are lost. Vaughan (1969) questioned the relationship between SSEPs, which appear similar to recruiting responses, and perception. He found flash rates of 10 c/sec. produced recruiting responses over a deafferent visual cortex as well as other regions of the brain. Transient evoked responses can not be predicted from steady state evoked potentials (Gastaut and Regis, 1965) and the two techniques probably give different insights into the CNS.

1.2.2 Electrodes and their Placement.

There are almost as many recording sites on the skull for VEP investigations are there are investigators. Many use the International 10-20 system of electrode placement (Jasper, 1958), which standardizes electrode positions, and is independant of head size. Other workers quote millimetre distances generally referenced to the inion and midline. The great majority record over the occiputs where the largest amplitude and clearest responses occur (Kooi and Bagchi, 1964; Remond, 1969; McKay and Kinney, 1976).

There are two types of electrode linkage. These are known as monopolar and bipolar recordings. In monopolar recording the active lead is connected to Grid 1 of the amplifier, and the second, indifferent reference lead to Grid 11. The great problem with the monopolar recording of cortical evoked potentials is that it can not be assumed that the second electrode is unaffected by the source generator. Cranial and extracranial time locked activity has been picked up from standard reference sites (Kooi and Bagchi, 1964; Prichard, Chimienti and Galambos, 1965; Jeffreys, 1977). Frequently

used reference sites are the ear-lobe (Eason et al., 1967 ; Schenkenberg and Dustman, 1970), the nose (Vaughan 1969), the chin (Creutzfeldt and Kuhnt, 1967) the mastoid (Regan and Cartwright, 1970) and a non-cephalic reference (Kooi et al., 1972; Lehtonen, 1973; Peacock and Conroy, 1974). The vertex position is contraindicated both as a reference point or in a bipolar linkage (Gastaut and Regis, 1965), since it is an active source of visual evoked potentials (Vaughan, 1969, Lehtonen, 1973).

With bipolar electrode linkages the resulting electrophysiological signal is the difference in voltage between the two electrode sites. If similar signals arrive in phase they tend to cancel each other out, which is often a convenient method of eliminating undesirable potentials. Bipolar recordings can also be used to improve the detection of differences between the potentials emanating from two close points (Kooi, 1971; Thompson and Patterson, 1974).

1.3. The Limitations of Averaging Techniques.

If the signal is stable and timelocked, and the background EEG "Noise" is random, the signal to noise ratio during averaging will improve as the square root of the number of signals sampled. Thus the improvement in signal strength is relatively greater for a small number of samples. There is also less of a problem of changing conditions within the brain with a reduced sampling time.

The final averaged VEP is unlikely to exactly reproduce 'real' brain events. The first assumption that the response mechanism

is stable can not be applied to a biological system, and there are clear variations from time to time of the amplitude, polarity, duration and latency of cortical evoked sensory components, which are lost in an average (Thompson and Patterson, 1974). Thus, for example, a high frequency wave with a variable onset latency will be averaged as a slow duration component. Brazier (1964, 1969) points out that hidden within the average is a trend of change, with a gradual decrease in the responsiveness of the system during repetitive, monotonous stimulation. Part of the effect is peripheral, through pupillary changes and corticofugal influences. The electroretinogram (ERG) to the first flash is of greater amplitude than any subsequent retinal potential. There is also central inhibition, with the failure of late components to be recorded serially from the visual cortex of the cat. Brazier also points out that non directional variability, which may be significant, is also lost.

Some attempts have been made to improve upon the insensitivity of measuring a mean, averaged response. The EEG and VEP can be subjected to a fast frequency analysis during stimulation, which provides a much speedier recording technique (Regan, 1966a, 1966b, 1972; Fenwick et al., 1969; Sayers et al., 1972). Multivariate analysis tackles the problem of computing variability within components in order to detect possible significant shifts in latency (Regan, 1972). Woody, (1967) detected the visual potential by progressively developing descriptive criteria of the potential to form a template which then scans the data sample after the stimulus in order to detect the presence of a single visual potential. These techniques are not yet widely used, and usually require sophisticated

computer facilities.

The second assumption of signal averaging, that the background noise of the EEG is random in relation to the signal, is doubtful. Perry and Childers (1969) found that after summation, the signal to noise ratio improved by a factor which varied from 2:1 to 4:1 depending on the background EEG. Galbraith (1967) showed that the frequencies of brain waves in the cortex and subcortically within the thalamus, hippocampus and reticular formation, both before and during visual stimulation had a marked influence on the visual response. During depth recordings in man, the amplitude of the VEP was positively correlated with the amplitude of the EEG (Petrek et al., 1968). Remond and Lésèvre (1967) drew attention to the influence of rhythmic alpha activity and other EEG frequencies upon evoked potentials. If the rhythms appear early they can mask the response, or there may be an initial suppression with later time locking to form a simple after discharge. Much slower electrical changes within the cortex, not usually recorded, can also have a large effect on the morphology of the VEP. Steady negative potentials can alter the size of positive and negative components and may significantly shorten latencies (McAdam, 1969; Fromm and Glass, 1970). Some idea of EEG variance can be estimated in a no signal condition, but sensory stimulation may alter the EEG in an inconstant manner, varying from time to time and subject to subject.

Some workers have suggested that the electrophysiological response of the visual system is as well or better described by the characteristics of the EEG rather than an averaged

VEP during visual stimulation. The VEP is therefore not an independant phenomenon buried in EEG "noise", but part of the same process. Fenwick, Dollimore and Walker, (1969), constructed an autoregressive model of the EEG which retains phase and spectral information. The auto regressive coefficients act upon a random input like a narrow band filter to regenerate the EEG. The impulse function of the model in the eyes open condition produces a form of VEP which the authors claim, fits closely with the averaged pattern VEP recorded from the same electrodes. The model derived from an eyes closed record can predict the averaged VEP to flash. Sayers, Beagley and Henshall (1974) found that the average power in the post-stimulus average was not significantly different from the pre-stimulus, no signal condition. These authors did in fact look at a low intensity 30dB auditory stimulus, which generally produces responses very close to the noise level of the system. These findings therefore suggest the possibility that the evoked response represents some reorganization of the pre-existing spontaneous activity. Thus effective stimuli synchronise or control the phase of spectral components of the EEG. If true, this would make the notion of signal to noise ratios inapplicable, however the appearance of large, clear VEPs in the EEG traces of some neonates and old people, which are clearly different from the EEG, add some support to the principles of evoked potential averaging.

1.4. Problems with Artifacts.

The final problem of averaging techniques is that the potential changes recorded by the system may not be of cerebral origin.

These 'artifacts' can be produced by electrical or mechanical faults, or arise as extracerebral potentials from the subject. Their amplitude may be so large that the evoked potential is swamped, or else they may be associated with the stimulus, but not be of cortical origin.

The most notorious artifact is the myogenic response which originates in the groups of cranial musculature around the inion, temporal and frontal regions (Bickford, 1964; Bickford et al., 1964; Bickford, 1969; Picton et al., 1974). The latency of onset of the muscle potentials is 8-12 m.sec., which is a much shorter latency than the VEP, but early and middle components of the averaged visual evoked potential, as late as 150 m.sec., can be significantly effected. A lower stimulus intensity than that used by Bickford, and careful placement of electrodes away from muscle insertion points, can eliminate the artifact.

The eyes can also be a source of artifact, since the potential between the front and back of the eyeball is many times larger than EEG potentials. The electro-oculogram (EOG) is maximal frontally, and may still have amplitudes of 20 μV at the vertex (Vaughan, 1969). During a recording session there may be small eye movements or eye closures to each light stimulus, which can often be picked up in the occipital leads, but it is a slower response than the VEP, and only rarely contaminates the late components of the VEP (Harding, 1974). Jonkman (1967) found that the peak EOG amplitude occurred at 150 m.sec., and suggested that this potential may effect VEP records if the subject blinked at the light flash. Eisengart and Symmes (1971) recording from young children, found that the average probability

of reflex blinking to a moderately intense flash was 0.62, with a significant trend to increased blinking during continued testing. When the authors segregated VEPs with and without eye movements, a substantial difference was demonstrated in all locations as far back as the occipital area. Blinking resulted in a positive wave around 200 m.sec. which enhanced the trials in which eye movements occurred. Artifacts can be detected by plotting the topographic distribution of the potentials recorded, or trials when eye movements are detected can be eliminated from the average.

Another problem of eye movements is whether stimulation can be effective during the actual movement, when perceptual blanking is said to occur. Visual thresholds increase during a saccade and Barlow and Ciganek (1969), and Ebersole and Galambos (1969), report a depression of the VEP. Gross, Vaughan and Valenstein (1967), and Chase and Kalil (1972) found that only pattern responses were effected by eye movements. Eye movement artifact can significantly contaminate the VEP at high stimulus intensities (Rietveld et al., 1966), and Castellini (1974) found the source of the high variability of his pattern evoked potentials was wandering gaze. The ability to maintain fixation for a sustained period is vital during pattern stimulation and is also important if very small stimuli are used.

Pupillary changes either during attention or habituation is said to have an effect on the cortical response (Bergamini and Bergamasco, 1965), although this is not always found (Kooi and Bagchi, 1964). The ERG may, of course, influence a reference electrode if placed on the nose or frontal areas of the scalp.

1.5 The Relationship of the VEP to cortical events

With so many technical problems, although many can be avoided by careful experimental controls, the question must arise as to whether the averaged VEP bears any resemblance to the electrophysiological events within the brain.

Visual activation of the cortex starts in the fourth layer with the Golgi type 11 cells, and spreads upwards and then finally down to layers V and V1 involving the large pyramid cells (Bishop and Clare, 1952; Bergamini and Bergamasco, 1967). The resulting surface potentials over the striate cortex are similar to reported scalp recordings in both animals and man (Chartrian et al., 1960; Cooper et al., 1966; Kelly et al., 1965; Heath and Galbraith, 1966; Hardin and Castelluci, 1970). The scalp response is attenuated; the ratio of 1:3 to 1:4 is the generally accepted voltage drop of cortical activity at the surface. However, the over-riding consideration is the nature of the voltage source, particularly its orientation and extent, and measurement has revealed ratios of voltage differences as various as less than 1:2 to 1:50 (Kooi, 1971).

Early workers in brain physiology, believing that the formation of action potentials in a neuron was the only measure of excitation, could find no obvious relationship between cell spiking and surface potentials (Li et al., 1956; Purpura, 1959; Amassian et al., 1964). Creutzfeldt, Watanabe and Lux (1966) and Creutzfeldt and Kuhnt, (1967) summarised the findings by declaring that slow surface potentials were unrelated to cell firing rates, but did reflect the summated post synaptic potentials

of the 'average' cortical neuron. Synchronized excitatory potentials resulted in the formation of a surface negative, while inhibitory potentials produced a surface positive wave. Many authors agreed that surface potentials reflected the summations of slow synaptic potentials of the neuronal population (Chang, 1959; Elul, 1968; John and Morgades, 1969; Thompson et al., 1969), although there was some dispute as to whether depolarization produced surface negative or positive potentials. Part of this dispute can be answered by looking at the effect that the depth of the potential sources have, for example, superficial hyperpolarization can produce the same results as deep depolarization.

Humphrey (1968) pointed out that the field of a cell discharge falls off extremely rapidly outside the cell body, and that only post-synaptic potentials can have any widespread influence. However improved techniques of analysis have produced some impressive correlations between single cell firing and focal evoked potentials. Fox and O'Brien (1965) produced a firing rate distribution of single cells within the striate cortex, which fired to a flash presented many thousands of times. Given enough stimulation a single cell could generate a frequency distribution which duplicated the entire evoked potential at the surface, even for components as late as 500 m.sec. Thus the VEP appeared to reflect the probability of firing of any single visual cell which always responded to visual stimulation. Vaughan (1969) described similar findings, but suggested that other less common post-stimulus histograms of cell spiking have also been recorded. Some cells may show a decrease in firing rate over the entire time course of the

evoked potential. Another cell may follow only one deflection of the surface response, while a third may appear shifted in phase and be more closely related to the slope or rate of change of polarity. Fromm and Bond (1967) and Fromm and Glass (1970) found that the cell firing rate correlated well with the evoked potential if the steady potential was about 1. 2 μV. If the cortex became more negative, both the firing patterns and evoked potentials were effected, and the relationship between the two became disassociated. Creutzfeldt, Rosina, Ito and Probst (1969) suggested that different neuron populations within the visual cortex correlate differently with the surface potential. Geniculo-cortical 'off' fibres are inhibited during the first 40 to 90 m.sec., while 'on' fibre excitation coincides with the first positive surface deflection. In the striate cortex, 33% of the cells were primarily excitated, followed by a period of inhibition. The remaining 66% of neurones showed long lasting inhibition, briefly interrupted by an excitatory burst.

The longstanding argument about whether post-synaptic potentials or the action potentials of cortical neurones contribute to surface potentials is largely irrelevant (Uttal, 1965). Slow inhibitory and excitatory potentials must be related to the cell spikes, since they are the precursers of all cell firing, and the two approaches are just a different expression of the same information. Thus the evoked potential represents some form of summation of both spike and slow potential activity.

1.6. Summary

Critics argue that stimuli do not naturally occur as punctate,

discrete events, which are continuously repeated at random or regular intervals for prolonged periods. Evolution has designed a brain which reduces the effectiveness of this type of redundant, low information stimulation. Therefore evoked potential studies reflect a view of brain function which is badly distorted by artificial, unnatural experimental situations. This may concern researchers who are attempting to build an electrophysiological model which accurately reflects perceptual behaviour. The demands of clinical research are far less stringent, they have to be, when fewer controls can be applied. Whatever the method of stimulation, however the VEP is recorded, whatever the state of the subject, the recorded response, if it is to be useful clinically, must reliably reflect the functional state of the visual input system.

CHAPTER 2

The Organization of the visual system.

2.1. Receptor Organization

The receptor layer of the eye is composed of a complex mosaic of rods and cones. At the centre of the eye, lying on the principle axis of the lens, is the fovea centralis or foveola (terms after Polyak, 1957), which is a very small area of retina subtending approximately 1^{o} 20' of visual view, and containing only densely packed, narrow cone receptors, which are not overlayed with the optically distorting network of neural elements, nor with the fine branches of the blood capillary system. Here the receptor connections with the ganglion cells, which output visual information to the optic nerve, are monosynaptic, which means that there must be very little data reduction from this point of the retina. The foveola lies at the very centre of the foveal pit (the fovea subtends approximately 5^{o} of visual view). This latter area contains approximately 100,000 cones and about half as many rod receptors. In all parts of the retina outside the central foveola, rods and cones share a common pathway to the CNS, interacting together through the rich connecting networks of horizontal cells, amacrine cells and corticofugal inputs. Outside the fovea lies the macula (subtending a visual angle of approximately 20^{o}) and in this area the number of cone receptors per unit area is falling, while there is an increasing proportion of rod receptors, which have a maximum density at about 4 mm from the fovea. Graham (1965) stated that there are about 100,000 private, that is single receptor channels, linking each receptor with the brain within the foveola, and about 50% of all ganglia lie within the macula area. This represents a large loading of receptor information

from the central area of the retina. There are fewer output channels for the larger remaining area of the peripheral retina, which necessitates some data reduction within the periphery of the eye. At the edge of the macula the ratio of rods to cones is about 3 or 4:1, and this proportion remains constant to the edge of the retina, while the number of ganglion cells serving each group of receptors gradually declines. Thus, the organization of the periphery becomes more diffuse with large polysynaptic fields. Visual acuity changes as a function of angle of view, thus if foveal acuity is equal to unity, at 5^{o}, the acuity is only about a quarter of that found at the fovea. The fall in visual acuity correlates with the fall in the density of the cone distribution, and with the increasing diffusion of the ganglia connections. The visual acuity in the dark adapted eye with scotopic luminous intensities and parafoveal vision, is only a small fraction of that obtained in photopic conditions at the centre of fixation.

2.2 Visual pathways

In the monkey each optic nerve contains a million nerve fibres, and in man the number of visual channels is believed to be of the same order (Davson and Graham, 1977). Thus, about 38% of all sensory fibres entering the CNS carry visual information, which underlines the obvious importance and dominance of vision over the other sensory functions in man and primates. In cats, the other species most commonly studied in vision physiology, the optic nerve has a very much reduced input capacity, with only approximately 119,000 fibres within each optic nerve (Jung, 1973). This suggests more retinal preprocessing

or different, and perhaps more limited central processes.

The chiasma of the optic nerve is unique among the sensory modalities, and is the point where half of the output information from one eye crosses to the contralateral optic tract. In cats and monkeys 50% of all fibres cross, while in man it is believed that there are a greater number of fibres crossing, because of the larger area of the nasal portion of the retina. Adler, (1959) quotes that 70% of the fibres decussate in man. The strict topographical organization of the retina, with central and peripheral regions, right and left visual fields, and upper and lower portions of the retina, is strictly maintained within the optic nerve and throughout the entire primary visual system. Thus, at the chiasma it is the nasal portion of each retina that decussates, dividing strictly along the vertical meridian of the eye, which runs perpendicular through the foveola. Patients with completely isolated right and left hemispheres after total surgical transection of the forebrain commissures, show no overlap at all of the visual fields across the vertical meridian (Sperry, 1970; Trevarthen and Sperry, 1973). Stone (1966) found that the vertical meridian in the cat is not a distinct boundary, but a strip approximately 0.9^{o} wide, with the neurons from within this area sometimes crossing, while others remained on the ipsilateral side. Whether this applies in man is doubtful (Jung, 1973), but if it did, it could involve a significant proportion of the central cones, which are packed so densely into the foveala. The majority of optic nerve fibres in the cat, monkey and man, terminate in the lateral

geniculate nucleus (LGN) of the thalamus, although a few fine fibres continue beyond to enter the pregeniculate grey, and pretectal nuclei, and the superior colliculi of the midbrain. The thickest fibres enter the LGN ventrally, and are all decussate, coming from the contralateral monocular retina which has no binocular view.

The rest of the fibres from the binocular portions of the homonymous half fields of both retinas, are distributed according to their retinal spacial relationships to the various coronal cross sections and levels of the LGN. The LGN is thus a '3D' map of the retina. Anteriorly, near the hilum, where most of the larger fibres enter, only a small segment of the nucleus receives central retinal inputs, and most of the area is devoted to peripheral retinal information. As you move more posteriorly (dorsally) through the LGN until the upper extremity is reached, there is an increasing proportion of the fine input fibres which are more likely to originate from within the macula. There is therefore an increasing volume of the posterior nucleus which is dealing with the inflow of information from the central retina, and the majority of foveal fibres are restricted to the posterior quarter of the LGN. Superimposed on the topographical arrangement is a second level of organization, with the LGN divided into separate layers. In most animals the entire nucleus in composed of four layers. Only in man and primates are there six layers. These additional layers occur at the extreme posterior end of the nucleus where the central retinal inputs terminate. The crossed and uncrossed fibres of each optic nerve go to one of the separate layers (Polyak, 1957)

so that the right and left homonymous retinal points appear to be dealt with in distinct and separate areas.

The relation between the right and left field laminae is far from clear. Rushton (1961) believed their mutual effect was inhibitory not additive. The arrangement certainly brings close together the ipsilateral and contralateral corresponding retinal points. Polyak (1957) suggested that although this close proximity is maintained throughout the optic tract and LGN, there is not yet any merging of the inputs from the two fields into a single binocular functional unit. This does not in fact occur until the level of the cortex. How true this isolation of the fields is at this level of the visual system, has not yet been satisfactorily determined. Glickstein(1969) found that the majority of the neurons within the main laminae of the cat's LGN receive binocular inputs, and Richard (1968) also suggests some interaction of the two eyes at this level, at least in the cat, (See section 3.3.1.).

Each optic tract terminates on approximately six cells within the LGN, and there is no overlap of inputs or outputs in the monkey, so that highly precise interconnections are maintained at this junction in the input pathways (Jung, 1973).

2.3. The primary visual cortex

From the LGN all the fibres form the optic radiations, which fan outwards and pass posteriorly to terminate in layer IV of the striate cortex, also named area 17 (Brodman,1909) or visual area 1 (Hubel and Wiesel, 1965). This primary sensory projection area lies at the occipital pole.

Retinal topography is still precisely maintained, with each quadrant of the retina represented by the respective quadrant of area 17, intercepting at the calcarine and longitudinal fissures. The horizontal meridian lies within the calcarine fissure. The vertical meridian lies on the medial surfaces of the two hemispheres. In man the calcarine fissure is very similar to the monkey, and is formed by the fusion of the medial and lateral calcarine fissures. Its configuration varies widely between individuals and between hemispheres. It is rarely a straight horizontal furrow running from the isthmal region to the occipital pole. It generally curves, arches and winds, and posteriorly may often be forked or fall short of the pole, or it may stretch for a shorter or longer distance out over the lateral surfaces of the occipital lobe. In primitive mammals more than 50% of the striate cortex is spread across the exposed lateral surfaces of the brain. In monkeys the gyri deepen and lengthen to enfold much of the primary receiving area, but still the posterior third of the visual projection area is accessable on the lateral side of the hemisphere. In man the folding of the cortex is complete, so that very little of the striate lies outside the intucking of the calcarine fissure. The spacial relations of the central and peripheral portions of the retina, and of the upper and lower fields, are preserved in the striate cortex. The fovea and foveala terminate in the most posterior portions of the visual cortex, at or close to, the occipital poles. The extra foveal and extra areal retinal fibres arrive more anteriorly, tucked deeper down onto the medial surface, while the peripheral monocular portion of each eye, enters

the striate at the most anterior and inaccessable point, close to the lateral ventricles and the splenium of the corpus callosum.

In some human brains a visual operculum, similar to the exposed striate of primate brains, is present. This "primitive" organization is not associated with either primitive ethnic groups or individuals. In such brains the striate cortex may spread laterally to a position approximating to just beneath the posterior temporal scalp electrodes of Jasper's (1958) international 10/20 electrode system (calculations after Polyak, 1957). Between this extreme and the other, where no striate is present at all on the lateral surface, or even within several millimetres of the occipital pole, is a whole range of visual anatomy, that varies widely between individuals and between hemispheres. Generally, on average, only approximately the central 1 to 2^{o} of vision is exposed on the lateral surface of the human brain, and is immediately accessable to scalp recording electrodes.

Usually a larger area of the striate spreads out over the lower lingual lip of the calcarine fissure compared with the upper, cuneal lip, and when the striate lies on the lateral surface it is often unequal, and there is more frequently a larger area over the left hemisphere compared with the right (Polyak, 1957).

The linear extent of the striate cortex to which each degree of retina projects is termed the cortical magnification factor. The magnification factor is largest for the central foveal region of the retina, and decreases with increasing

retinal eccentricity. That is a far larger area of the striate cortex is involved in the primary processing of the central 2^{o} of vision, and progressively smaller areas of cortex receive increasingly peripheral inputs. Rolls and Cowey (1974) using implanted electrodes, related the cortical magnification factor to visual activity in man. From Table 1 it can be seen that the reciprocal of the cortical magnification is directly proportional to visual acuity, and the minimal angle of resolution at each retinal point, is represented by a constant cortical strip.

2.4. Visual association areas

Surrounding the primary sensory area are the visual association areas 18 and 19 (Brodman, 1909) , or visual areas II and III (Hubel and Wiesel, 1965). These two adjacent cyto-architectural fields maintain the organization laid down within the striate cortex, with the contralateral half of the visual field orderly and continuously projected over each hemisphere, with two reversals in representation. At the boundary between 17 and 18 is the map of the area around the vertical meridian of the retina. In the more anterior portions of 18 are the peripheral maps. At the border between 18 and 19 the peripheral maps are in juxta position, while further into area 19, are central retinal projections.

Upper and lower fields of the extrastriate cortex are ordered above and below the calcarine fissure, but the anterior-posterior arrangement of the extrastriate is asymmetrical (Zeki, 1974). Above the fissure the lower visual field lies chiefly on the upper complexity of the lobes in close proximity

Eccentricity in degrees	0	1	3	5	7	10	15	20	30	40	60	70
Magnification factor mm/degree	15.1	8.3	4.16	3.08	2.1	1.75	1.16	0.82	0.49	0.34	0.22	0.16

TABLE 1

The Cortical magnification factor: its relation to visual actuity.

Adapted from Rolls and Cowey (1974).

to scalp electrodes. Below the fissure a substantial portion of the upper visual field lies tucked away from the surface on the underside of the lobes above the cerebellum.

2.5. Cortical conncections

Intracortical connections are not well developed within area 17, and strychnine spikes remain very localised, except for some spread at the boundary of the striate over into area 18, where there are very short fibre tracks which involve only the boundaries of the two cortical areas. These areas represent approximately 1^{o} of central visual view (Regan, 1972). There are also reported to be some longer connecting pathways between regions of 17 and area 19, (Pollen and Ronner, 1975), although these direct links are not completely confirmed (Poggio, 1968).

Interconnections within area 18 are extensive, and local application of strychnine leads to widespread activation within the rest of 18, within area 19, within the temporal convolutions, and within area 18 of the contralateral hemisphere. In a narrow band of area 18 representing the section of retina bounding the vertical meridian are transcallosal connections with the corresponding positions of 18 in the opposite hemisphere (see section 3.3.1.).

In area 19, strychnine only activates tissue in the close vicinity of the application, and initiates a suppression of electrical activity, which begins close to the strychnine, and sweeps across the entire hemisphere. There is no evidence of callosal connections, or any extensive cortico-cortical connections within 19, and the chief projections of area 19

may be to deeper structures.

Cragg (1969)suggested that in the cat the LGN projects to both 17 and 18, but in monkeys and man there is no suggestion that the LGN projects outside the striate cortex (Polyak 1957). The pulvinar nucleus of the dorsal thalamus projects to all the visual cortex surrounding the striate, and compared with the cat,shows a large increase in size in the monkey. It receives fibres from the occipital cortex and the superior colliculi.

Ablation of area 17 in man results in irrepairable blindness, although there is some recent evidence that with this damage, an individual's guesses of whether a light is being flashed into the right or left visual field, is far better than the chance level (Blakemore, 1977). Visual field defects occur when corresponding striate areas are destroyed. Monkeys and cats retain some light and dark perception, and also possibly gross movement. When areas 17, 18 and 19 of the visual cortex of the monkey are destroyed, vision is entirely lost, leaving only pupillary and blink reflexes mediated by sub-cortical pretectal pathways. Bilateral removal of 18 and 19 results in a disturbance of spacial judgement and confusion of moving objects, while visual recognition responses remain intact. With inferiotemporal cortical lesions monkeys loose the ability to recognize and detect the meaning and significance of objects (Galun et al., 1975).

2.6. Accessory visual systems

The question has often arisen of other systems being concerned

with visual perception, especially as animals and even primates maintain light-dark discrimination after the removal of the striate cortex. It is known that a considerable number of fibres reach the mid-brain in a cat. Less are found in monkeys. Some of the very fine optic tract fibres, probably from central retinal areas, bipass the LGN and enter the neighbouring pre-geniculate grey nucleus. From there they pass to the superior colliculi of the mid-brain where the paired right and left colliculi receive the same contralateral visual input as the right and left cortices. The difference is that there is no recrossing of fibres that occurs in the forebrain commissures of the cortex. There are also connections between the optic tract and the tegmental region, and the pretectal nucleus. The superior colliculi also receive corticofugal inputs, and information from the ocular motor pathways and the somesthesic, vestibular, and auditory systems. In turn the superior colliculi project to the cortex via the pulvinar nucleus. The mid-brain area is as well developed in monkeys as in the cat and presents an "open and noisy" multi-input system, which contrasts with the closed, precisely defined organization of the primary visual system. In spite of increased cortical dominance in man the midbrain arrangement is very similar (Polyak, 1957).

Further visual connections have been hypothesised, but as yet not established. Bignall (1968) suggests a small fibre system from the retina direct to the association cortex, independent of the primary visual system. There is no anatomical evidence for such an arrangement (Polyak, 1957). However, Dubner and Brown, (1968) found that two thirds of the cells in association areas anterior to the cat's visual cortex responded both to

diffuse stimuli, and to restrictive line stimuli such as slits, bars, etc. The majority of these cells responded to binocular stimulation when corresponding retinal areas were stimulated, and also responded to sound. Lesions within the medial thalamus had no significant effect, but the responses did depend upon the functioning of the primary visual system. Bignall, Imbert and Buser (1969) also recorded visual responses in anterior areas, which were independent of LGN. When the primary visual cortex was removed the responses disappeared in 50% of the cat preparations, but were still present in the remainder. These findings certainly suggest that there are extensive projections from parts of the visual cortex to most of the association cortex and the implications of additional pathways does not necessarily follow from the data. Pasik and Pasik (1973) found that monkeys were still capable of discriminating between light and dark without the striate cortex, and also with additional lesions in the temporal lobes, hippocampus, pulvinars, superior colliculi and medial pretectum. Only when lesions were made in the accessory optic tract to subcortical areas was discrimination lost. This visual pathway terminates in a nucleus immediately ventral to the inferior colliculi, which is equivalent to the nucleus paralemnicalis in man, and the authors suggested that this system may be involved in light perception in sub-human species.

2.7. Summary

Physiological evidence suggests that the visual system of the cat, in certain aspects of its anatomy and function, is fundamentally

different from higher primates and man, and it may be an oversimplification to apply models of vision derived from research on cats, as the functional mechanism in man.

It is far from certain that accessory systems do partake in the visual perception of animals. In man these suggestions are even more doubtful, and it is generally believed that only the primary visual cortex can accomplish the first essential steps in the perceptual processing of both flash and patterned stimulation. Cortical responses to all types of visual stimulus depend on the integrity of the primary processing areas. The classical maps of the visual system constructed from post-mortem results in man, and from animal studies, have been confirmed in electric stimulation studies on patients during brain operations (Brindley and Lewin, 1968). Some of the findings, however, do not agree with normally experienced perceptual phenomenon. Unexpectedly, only cortical phosphenes were evoked and patterns were never seen. Also, the authors reported that they could find no flicker fusion for the cortical phosphenes, even when the frequency of stimulation was as high as hundreds of stimuli per second.

There is evidence of wide individual differences in the cortical anatomy of the visual projection areas (Polyak, 1957) which may contribute both to large individual differences in the distribution of the scalp VEP and also to variations in its form at different recording sites. Secondly, the widespread nature of many of the components of the scalp recorded VEP is consistent with the far ranging activity generated from within area 18 of the visual cortex. However, the exact relationship between scalp recordings and events within the visual processing areas

is yet to be discovered (Jeffreys, 1977).

The VEP is more likely to relate to central visual functioning, since it is the centre of the retina which projects to the most accessible occipital pole regions of the cortex, and which also has a larger cortical representation area than the more peripheral retina. This certainly makes the VEP a very useful clinical measure, since in terms of the welfare of the patient it is central visual function, that is potential visual acuity, that is of paramount importance. There is also the implication that when no visual potential can be recorded to visual stimulation, this would not necessarily be consistent with complete blindness, and peripheral vision, maintaining some perception of light, may still be functioning, but projecting to deep, inaccessible cortical areas away from the scalp electrodes.

CHAPTER 3

A review of the characteristics of the visual evoked potential to diffuse flash stimulation in the normal population

3.1. The Adult VEP to Diffuse Light Stimuli.

Despite the problem of artifact contamination, and the limitations of the techniques that are at present available to record small cortical potentials, consistent VEPs have been reported from many laboratories to diffuse and structured light sources. As yet a report has not been read by the author, of a total failure to record a VEP, although at times the amplitudes may be very low (less than 5μV). The wave form is often improved by pattern rather than diffused light stimulation (See section 5.3.3.).

3.1.1. Primary and Secondary Components of the VEP

The literature presents a bewildering variety of wave forms of the VEP which is confused by the different nomenclature applied to the various components of the averaged potentials. When transient responses are evoked, the whole shape of cortical potential depends very much on each individual laboratory technique. The type of stimulus used (stroboscopic flash, tachistoscope, Maxwellian view lens system), its duration and colour, the size of the stimulus field and the relative changes in intensity etc., all effect the VEP (see section 1.2.1.). The position of the electrodes and how they are linked to the amplifiers are also important (See section 1.2.2. and 3.2.). Although most authors have developed their own methods of obtaining a VEP, it is sometimes surprising and gratifying that there are many common features in their reported findings. Some of the first papers in the early 1960's provided detailed information on

normative data in the young adult population, which has been continually referred to and generally supported in subsequent years, using improved methods of stimulus presentation and recording. Ciganek (1961) recorded the midline response between O_z and P_z (international 10-20 system of electrode placement) in 55 subjects, and reported a clear wave form common to the group which consisted of a complex of seven alternating positive and negative peaks or components. The first component occurred around 39 m.sec. which he named wave 1, and the final wave (wave V11) occurred after 150 m.sec. This last wave he believed was the first portion of the rhythmic after discharge. The most prominent component was a positive going triphasic wave peaking just before and after 100 m.sec. His later work (Cignanek, 1965; 1969) confirmed the general wave form, although the mean latencies and nomenclature had changed. Ciganek found that the early waves 1 to 111, which occurred between 30 and 70 m.sec. were far less variable than the later waves. They remained unaltered in sleep, and when the flash rate was increased up to 10 f.sec. This led him to suggest that these early components were what he termed the primary response, arising from area 17 of the occipital cortex, while all activity later than wave 1V, at around 95 m.sec. was the so called secondary response, which reflected the activation of non specific diffuse activating pathways. In one paper (Ciganek, 1965) he claimed to have recorded similar potentials for both auditory and visual stimuli from the same mid-line electrodes. This led him to suspect his original primary and secondary subdivision of the response, and to wonder whether the whole visual potential recorded from the scalp might be entirely from association areas.

VEPs that have been recorded from cortical and subcortical sites in monkeys and cats, do suggest that there are some much earlier potentials in the visual cortex than Ciganek recorded from the scalp. Brazier (1960) recorded the onset of the VEP at 20 m.sec., while Chang (1959), when stimulating the optic nerve of the cat, found that the first cortical potentials occurred around 8 m.sec. His technique avoided the long delay of retinal transmission times. Calculations for visual pathway transmission delays vary from 15-26 m.sec. (Ogden and Miller, 1966; Remond and Leserve, 1967; Morrell, 1967). Since several authors including Ciganek have recorded initial components occurring between 25-30 m.sec. after stimulus (Cobb and Dawson, 1965; Gastaut and Regis, 1965; Ciganek, 1969), it does seem possible that the very early components that can be picked up from the scalp may reflect the synchronised arrival of optic radiation impulses within the occipital lobes. More often than not these initial waves are not recorded at all from the scalp, and even authors who have obtained them (Gastaut and Regis, 1964; 1965) report that they can only be seen in less than 20% of their normal population.

The question of the origin of the various parts of the VEP is far from being solved, even in terms of specific visual function and non-specific diffuse activation of the cortex. The majority of opinion follows Ciganek's early proposals in his paper of 1965, that the primary evoked potential which occurs approximately within the first 100 m.sec., and may or may not include the prominent positive component around 100 m.sec., reflects the activity of some part of the visual cortex. The succeeding secondary

response reflects the behaviour of pathways which project to the association areas (Van Balen and Henkes, 1960; Rietveld, 1962; Contamini and Cathala, 1964; Katzman, 1964; Kooi and Bagchi, 1964; Morocutti et. al. 1964; Jeffreys and Axford, 1972a, 1972b).

The reason for this distinction is mainly that the early components have a fairly stable latency distribution both in terms of subject and population variability, and have been reported to change very little with changing levels of arousal, frequency of stimulus, and other environmental and subjective changes. Jeffreys and Axford (1972a, 1972b) suggested that their VEP component at 80 m.sec. arose from the striate cortex, and received its major contribution from the 2 to 6^{o} area of the central retina. The following component at 110 m.sec. also arose from the primary visual system, and was they suggested of extrastriate origin with the main retinal contribution arising from the central 1^{o} of vision. Reitveld (1962) concluded that the same negative and positive components up to about 110 m.sec. were evoked after excitation of the central 2^{o} of retina, while all the later components were extrafoveal. He thus concluded that the entire VEP complex is of primary visual origin. Gastaut and Regis (1964, 1965) agreed that both early and late waves reflected primary visual processing. Their central positive component, called by the authors wave V, was usually triphasic. The first portion Va was largest when a bright light stimulated the retina, and they suggested that the component reflected the photopic, cone system. The amplitude of the later positive deflection Vc, at 160 - 180 m.sec. was significantly increased in amplitude

after dark adaptation and when the eyes were closed. This wave therefore possibly represented the scotopic mechanism which dominates in low illumination levels. Van Balen and Henkes (1960) found a similar triphasic complex around 100 m.sec., and suggested that the first positive reflected activity of the foveal retina, while the second positive at around 140 m.sec. arose from peripheral retinal inputs.

In contrast to these workers Katzman (1964), Morocutti, Sommer-Smith, and Creutzfeldt (1964) and Contamini and Cathala (1964) found that the later waves of the VEP were widespread and resembled the vertex response which was very similar for all sense modalities. They therefore concluded that this portion of the VEP was a non-specific response (See section 3.2.). Creutzfeldt and Kuhnt (1967) went even further and proposed that any sub-division of the wave forms before 90 m.sec. into separate early components, was artificial as the components were always very small and highly variable. They found that the whole VEP was recorded over a wide area of the posterior cortex, with some of the later components after 150 m.sec. being of shorter latency and of greater amplitude at the vertex.

3.1.2. Details of the VEP morphology

In spite of problems about the origins of the VEP there is some agreement about the general wave form. Gastaut and Regis (1964, 1965) reported very similar potentials to those of Ciganek with a prominent triphasic positive (wave V)occurring between 130 - 160 m.sec. This component together with the adjacent negative

peaks (waves III and VI) were always recorded. Vaughan and Katzman (1964) agreed with the consistent appearance of these "central" components, that generally occur between 75 and 130 m.sec. In fact components occurring within this time are reported by the majority of authors, sometimes as the only identifiable parts of the VEP, even in a large population. Thus for both monopolar and bipolar electrode recordings, provided the occipital electrode, that presumably lies over the active source, is grid 1 of the electrode linkage, a central negative-positive-negative complex is always recorded. The range of the means sited in the literature for each component shows that the first negative, (termed by the author N_2 after Harding, 1974) has been found between 55-100 m.sec., the positive component (author's nomenclature P2) occurs between 90 and 135 m.sec., and the second negative (author's nomenclature N3) is seen between 120-175 m.sec. (Ciganek, 1961, 1969; Rietveld , 1962; Gastaut and Regis, 1964, 1965; Kooi and Bagchi, 1964; Werre and Smith, 1964; Creutzveldt and Kuhnt, 1967; Potts et. al., 1968; Dustman and Beck, 1969; Jeffreys and Axford, 1972a, 1972b; Kakigi et. al., 1972; Lehtonen, 1973). A few authors (Van Balen and Henkes, 1960; Chalk and Ertl, 1965; Eason et. al, 1967) reported a negative component occurring between 110-150 m.sec. which was always clear and appeared to be the most consistent component both between and within subjects. Their results appear to be of opposite polarity when compared with the findings of many authors. It is often very difficult to determine whether this finding is due simply to an inversion of the usual polarities by, for example, a different combination of electrodes, or whether there is some fundamental difference in the type of stimulus used; the former is usually suspected.

Occasionally the stable "central" portion of the VEP has been reported as absent or very different compared with the general findings of the normal population (Ellingson et. al., 1973). This may be because the length of the analysis time was too short to include components after 100 m.sec. (Cobb and Dawson, 1960) or, the flash frequency may have been too high for a complete evoked potential to be recorded. Other reasons why there are large differences in the reported VEP still wait to be resolved. There is the hope that more standardisation between laboratories and more information and a better understanding of the many techniques used, will throw some light upon these problems.

3.1.3. Lambda waves and the VEP

Many authors have in particular mentioned the prominance and stability of the central positive component (P_2) and its very nature raises the question of whether it or any other part of the VEP is related to the lambda response. This response is a large monophasic occipitally positive potential, which can be seen in the raw EEG when the subject is visually scanning a field rich in high contrast boundaries. The lambda wave completely attenuates if the field is unstructured, when the illumination is very low, or when the eyes are closed. Gastaut and Regis (1965) and others have suggested that the lambda wave represents some mechanism of perceptual blocking during the eye movements to prevent the blurring of the image. Scott and Bickford (1968) and Barlow and Ciganek (1969) pointed out that the saccadic eye movements are generally completed before the peak of the lambda response, and it seems likely as Vaughan, Costa and Ritter

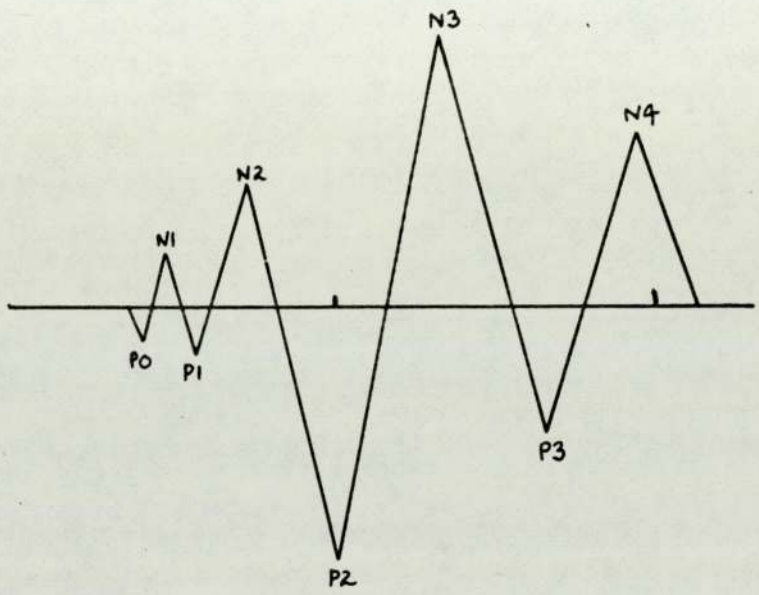
(1968) suggested that there is suppression during the saccad, and that the lambda wave is the result of disinhibition at the termination of the eye movement. That is, the lambda wave is an evoked potential, not elicited by an external stimulus, but by an internal change in excitability within the nervous system, which is time-locked to an observable event, the saccad. Kurtzberg and Vaughan (1973) and Armington (1974) reported that the lambda wave was identical in both form and latency to the evoked potential obtained to pattern movement, which is a large monophasic positive at 100 m.sec. Gastaut and Regis (1964) also found that the lambda wave clearly coincided with their Va component (P_2), when the averager was triggered by saccadic eye movements.

3.1.4. Summary

It is very difficult to summarise all the data that has been produced on the morphology of the VEP. However, Dustman and Beck (1969) provided an idealised VEP recorded from the occipital region, which probably provides the best description of both the data in the literature, and also of the results obtained from the research in the Neuropsychology Unit. Their terminology of N1, P1, N2 up to N4 for all the alternating negative and positive components was adopted by the Neuropsychology Unit as the best system for labelling the successive waves, which immediately makes the polarity of the VEP components apparent (See Fig. 1, page 43).

Gastaut and Regis (1965) report that the VEP obtained from an individual, provided that the individual is an adult, is reproducible

FIG 1. THE IDEAL FLASH VEP



Authors VEP Nomenclature

Thompson (Harding 1974)	P0	N1	P1	N2	P2	N3	P3	N4
Schenkenberg (1970)	P1	N1	P2	N2	P3	N3	P4	N4
Gastaut-Regis (1964) Ciganek (1969)	I	II	III	IV	Va	Vb	Vc	VI
Ciganek (1961) Jonkman (1967)		I	II	III	IV	V	VI	VII

from day to day, from month to month, and from year to year, a "thumbprint" of brain activity. Differences between individuals are enormous, even when the same techniques are used for recording the VEP.

3.2. Topography of VEP

Compared with all the information collected on the VEP correlates of subjective and environmental changes, there has not been a great deal of detailed research on the distribution of visual potentials over the scalp, and how these results correspond with the anatomy of the underlying brain areas. Many questions still await an adequate answer. For example, does foveal and peripheral retinal stimulation which excites different areas of the cortex produce VEPs that are accessable to scalp electrodes? Does a response evoked by pattern stimulation result in the same topography as a response to a diffused light source, and are any differences in distribution only a result of the problem of discrete retinal stimulation with light flashes. This topographical approach is adopted even less frequently within the clinical field, and little is known of the distribution of visual potentials over the scalp in patients with visual field defects, amblyopia,etc. (See Chapter 6, page 106). Information is more often than not collected from one, or perhaps two channels of the EEG, with the electrodes placed somewhere over the primary visual projection areas.

Gastaut and Regis (1965) and Bickford (1964, 1969) have clearly demonstrated the need for care to be taken when mapping VEP distributions, because of the problems of non-cortical contamination, which present a serious hazard at recording points near muscle

groups and close to the eyes (See section (1.4.). The results of VEP mapping over the scalp seem to fall into two general groups. The potentials have either been found posteriorly over the primary sensory projection areas, or the evoked potentials are diffusely distributed and recorded from most areas of the scalp,with sources remote from the visual areas.

3.2.1. Localized VEP distributions.

Gastaut and Regis (1965) found that the VEP was well developed at the inion, and remained at maximum amplitude within a 3 cm. semi-circle anterior to the inion. There was a progressive attenuation of amplitude in all directions away from the inion in more frontal derivations along the mid-line electrodes. The visual potential disappeared at the vertex, to be replaced by a large amplitude 'artifact' which was maximal in the frontal and periorbital regions. The first wave of the response, around 35 m.sec., could be recorded over the entire occipital cortex while later waves (111, 1V and V1) which occur up to 120 m.sec. after the stimulus also appeared in the secondary visual areas of the parietal and temporal lobes as well as the occiput.

Other authors have also found a clear localization of the VEP around the occiput. Kooi, Tucker, Danial and Marshall (1972) used various sized targets from 1^{o} to 36^{o}, and found that all the stimuli produced similar distributions, with the visual potentials gradually declining in amplitude with increasing distance away from the occiputs. There was a dramatic fall in amplitude in positions posterior to the inion. The voltages in the post-temporal areas were minute, and the evoked potential did not spread any further laterally.

They found a great deal of individual variation in the VEP distribution, and only subjects with a large response at the inion had a clear distribution over the posterior parts of the head. Vanzulli et. al., (1966); Werre and Smith, (1964) and Morrell and Morrell (1966) all found the shortest latencies and the most complex VEP wave form at the occipital pole, near the posterior mid-line position, and this was particularly so for components within the first 100 m.sec. Vanzulli, Bogacz, Handler and Garcia-Austt (1966) recorded 20 to 30 m.sec. delays for components within the parietal and central areas, and even longer latencies were seen temporally. The maximum amplitudes occurred in the area between O1 and O2, and very small visual responses were recorded as far forward as the frontal regions and the mastoid.

Jeffreys and Axford (1971, 1972a, 1972b) used multi-channelled recordings for their VEP's and have found some interesting topographical differences with the various stimuli that they presented. The potentials were larger and clearer when pattern stimuli were used, with no significant change in intensity. The three major components were C1 at 80 m.sec., C11 at 100 m.sec. and C111 around 160 m.sec. Along the longitudinal axis passing through the mid-line the C11 component was maximal 5 to 10 cm. anterior to the inion for upper field stimulation. It was more posterior, around 2.5 to 5 cms. in front of the inion, for lower field stimulation. The amplitude distribution declined symmetrically in both anterior and posterior directions for the upper field, while there was a rapid attenuation posteriorly and a very gradual decline in anterior derivations for the lower retinal field. With pattern stimulation the components of the VEP produced after upper-field stimulation

were phase reversed compared with the lower field and this polarity reversal occurred around the position of the calcarine fissure. Jeffreys suggested that of the evoked potential components only C1 has its source location in the striate cortex on the floor and roof of the calcarine fissure. The distribution results of the second component were better explained as deriving from extra-striate areas of the upper and under surfaces of the occipital lobes associated with the lower and upper fields respectively. The transverse distributions of upper and lower fields were similar, and were maximal over the mid-line, with asymmetrical attenuation in the left and right hemispheres to very small potentials in the posterior-temporal regions. When left or right fields were stimulated by patterns the maximal response was obtained in the contralateral hemisphere with the largest amplitude occurring in the lateral parietal and posterior temporal regions. Generally, whole field pattern stimulation was very similar to the sum of the two half field contributions. Diffuse light flashes produced less distinct, lower amplitude evoked potentials, with a more widespread distribution. There was no phase reversal of any component when different retinal areas were stimulated, and maximum values occurred in more anterior locations compared with pattern responses. The largest response occurred in an area approximately 10 to 20 cms. anterior to the inion. No simple relation was found between the whole field and part field stimulation.

Michael and Halliday (1971) used similar patterns to evoke scalp potentials. The VEPs were of similar form. Maximum amplitudes occurred in the region 5 to 7.5 cms. anterior to the inion, and the authors therefore concluded that the origin of the generators

of the pattern potentials are not within the striate cortex.

Rietveld et. al., (1965) also used similar techniques of upper and lower field stimulation, but the only differences they found were some shifts of latency of the recorded components. Jeffreys and Axford (1972a) stated that the polarity reversal across the calcarine fissure was not always found, and this may be partly due to the huge individual differences in the detailed anatomy of the striate cortex around the calcarine fissure and on the lateral surfaces of the hemispheres.

3.2.2. Widespread VEP distributions

A secondary source of the scalp VEP is often, although not invariably reported to occur around the vertex position. Vaughan (1969) using monopolar recordings referenced to the tip of the nose, produced amplitude distribution maps of a late P200 component. This was maximal over the occipital regions, and Vaughan suggested that the position of the calcarine fissure could be successfully located by plotting the amplitude distribution of this reliable component. A second peak amplitude was found over the vertex position. He suggested that his late occipital component was similar, but not identical to the vertex response, and could find no constant relationship between the amplitudes of the two areas. Kooi and Bagchi (1964) could also find no relationship between the vertex and occipital response, and the major portion of their VEP's occurred maximally either in the parietal or occipital regions. Lehtonen (1973) found that the response produced at the vertex to visual stimulation had a simple biphasic waveform with a negative component occurring between 110 and 117 m.sec., and a positive

at 160 - 250 m.sec. The response appeared to behave differently from the faster occipital potential when various stimulus parameters, such as repetition rate, were altered, which suggested a different neurophysiological origin for the two wave forms. Creutzfeldt and Kuhnt (1967) using flashes to evoke scalp potentials found a very widespread distribution of all the components which occurred between 75 and 250 m.sec. They found that particular components (for example a negative at 150 m.sec) were often of shorter latency in central and pre-central regions and maximum amplitudes were often recorded some distance from the occipital cortex. The authors therefore believed that the entire evoked response must have been non-specific, although they gave no reassurances that non-cortical contamination had been reliably eliminated from their records.

3.2.3. Hemispheric differences

Some attention has been paid to differences in the VEP arising from the two hemispheres. Some of these results are discussed in the section which reviews the effects of presentation of meaningful stimuli (See section 4.3.). Gastaut and Regis (1966), Dustman and Beck (1969) and Kooi, Tucker, Danial and Marshall (1972) found that when presenting simple patterns or diffuse flashes, if the field was large and viewed centrally, then the VEP was symmetrical and synchronous between the two hemispheres. Harmony et. al., (1973) found that 90% of all the VEP's recorded from 139 subjects showed less than a 40% difference in amplitude. This result was obtained by comparing hemispheric differences within the occipital, parietal and temporal regions. The appearance of unilateral peaks occurred

in 5% of the population, and these asymmetric components generally occurred within the first 50 m.sec. Latency differences for all the components did not generally exceed 5 m.sec. In contrast Schenkenberg and Dustman (1971) suggested a constant trend of larger VEP's in the right hemisphere compared with the left for the portion of the response occurring between 100 - 200 m.sec. They made no comment on the handedness or cerebral dominance of their subjects. Eason, Oden and White (1967) reported that left handed subjects had greater amplitude evoked potentials over the right occipital lobe, and this was true for all the retinal locations stimulated. Right handed subjects, however, showed no consistent differences between the two hemispheres.

3.3. Age Variations and the VEP

3.3.1. Maturation of the visual system

The eyes of an infant are relatively well developed, and vision advances rapidly compared with other processes within the body. Most binocular reflexes, fixation and conjugate eye movements are well established, and visual acuity of a reasonable degree is accomplished before the child begins to crawl, walk or talk. At birth there is an average state of hypermetropia of about 6/150 at birth, progressing to 6/6 at around five years old. The ability to fixate is present to a limited extent at birth and this develops to become an established reflex by about six months, when the fovea is fully differentiated. The eye movements of the neonate are often conjugate, and generally become increasingly accurate, again probably dependent upon the development of foveal

vision. Most of the binocular reflexes develop simultaneously and are established by the age of six months, although they may be extinguished fairly readily through disuse. Fusion, however, is not fully developed until the age of about five years, and this is probably associated with the final stages of development of visual acuity. The binocular reflexes continue to be reinforced and therefore become more firmly established until they are permanent at around eight years. It is also at this stage that the eye reaches adult dimensions.

It is believed that an infant can see from the moment of birth, and can perceive brightness, forms, patterns and probably colour. At first only gross discrimination is possible, and only large differences in stimulus quality are detected.

Developmental changes within the CNS have been investigated mainly in animal work, but similar evoked potential findings indicate that there may well be parallel processes in the maturing brain of many mammalian species, and in man. Axodentritic synapses are seen within the cortex of a new born kitten, and these continue to develop and elaborate throughout the first three weeks of life. Axosomatic connections are rarely seen until after the first post-natal week and connection with the diffuse thalamic projection system is late to develop. Intracortical excitatory post synaptic potentials have been recorded by Purpura and McMurty (1965), and they appear to have much longer latencies, and slower rise times than the excitatory post synaptic potentials in the adult brain, and they also obtain far greater amplitudes. Inhibitory post synaptic potentials are also recorded from birth, and show the same general characteristic of slow latencies and rise times.

Within the human brain myelination of nerve fibres begins around the sixth month of foetal development, but progress is slow, and only the basal ganglia and the fibres ascending from the spinal cord are sheathed at birth. In fact myelination is essentially a post-natal process, with the primary sensory and motor systems being the first to acquire their myelin insulation. Keeney (1966) found a seven fold increase in the maximum conduction velocities of callosal fibres when myelination was complete in the young kitten.

3.3.2. Developmental changes and the VEP

Since the neural networks of the cortex, and the input pathways are very immature at birth, and for some period afterwards, it would follow that the visual evoked potential should monitor at least some aspects of brain maturation, as does the background EEG. There is plenty of information on premature babies and neonates, and most of the data is in good agreement (Ellingson, 1961, 1964; Ferris, et al., 1967; Ellingson, Umezaki and Morrell, 1970; Lathrop, Danasey and Nelson, 1973; Hrbek et. al., 1973). In the premature, only a surface negative wave can be recorded to diffuse light flashes, and this simple wave is of high amplitude and very long latency, occurring between 200 and 219 m.sec. after the flash. In older prematures and neonates the evoked response has a simple biphasic form, with an initial positive wave around 187 to 189 m.sec., followed by a negative component.

During the proceeding months, the latencies gradually decreased with a sudden acceleration in the process around the fourth to fifth week (Ellingson, 1964), which corresponds with a rapid increase

in body weight. The rate of decrease of latency then begins to fall off, and to become a shallow slope by about twelve months of age. Zetterstom (1955) studied changes in the ERG and suggested that the retina contributed less than one fifth of the difference seen in the latencies of infants compared with adults, which suggests that the majority of the delay occurs during central processing.

Concommitant with the latency changes, the wave form slowly becomes more complex, with the appearance of additional components. The amplitude of the VEP is generally large, with the main components often approaching 50 μv, and Ellingson (1964) reported that the potential can be clearly seen without averaging techniques in 50% of young infants. These amplitude findings may be due in part to extracranial effects, such as skull thickness, scalp impedance , pupil reflex and refraction differences in infants (Dustman and Beck, 1969).

The evoked responses of young children appear to be far more variable than those of adults (Hrbek and Mares, 1964; Harter and Suitt, 1970; Callaway and Halliday, 1973). The very rapid habituation and high fatiguability of the young visual system, makes the repetitive flashing needed for the averaging technique often a doubtful means of obtaining visual potentials. This fatiguability is particularly apparent as the flash rate is increased, and Ellingson (1964) suggested that rates faster than 1 flash every 3 seconds produces a significant decrement in the amplitude potential, with no response recordable at high flash rates.

The topography of the VEP reflects the limited synaptic development of the cortex, especially of the diffuse association network of

the young brain. Ellingson (1964), found no response outside the occipital cortex until the third month of life, and the distribution of potentials did not resemble the adult topography until the second or third year. Creutzfeldt and Kuhnt (1967) did not find VEP's in the association areas until even later, around nine months of age. Only a few of the one to two years olds had VEPs in the parietal and central areas, and the association responses were not found regularly until about the fifth year of life.

There is far less information on the older infant and child, and inevitably there is a wide variation in the suggested age at which the VEP closely resembles the adult form. Gastaut and Regis (1965) found that the VEP was complete by the end of the first year. Ellingson (1964) suggested that three to four year olds have VEP's which were very similar to adults. Creutzfeldt and Kuhnt (1967) found that the definitive adult form was not seen until the sixth year of life. Dustman and his co-workers (Dustman and Beck, 1969; Rhodes, Dustman and Beck, 1969; Schenkenberg and Dustman, 1970, 1971) have provided the only significant data on the changes in the VEP that occur throughout childhood and adolescence until the final stable adult VEP emerges around the age of eighteen years. There was a gradual, very slight decrease in latency of the later portions of the visual responses (100 to 200 m.sec.) throughout these years, while the latency of the early primary response was fairly stable after the fourth year. There was a gradual decline in the amplitude during infancy, with a sudden dramatic increase in the amplitude of the secondary response in the five to six year old group of children. There was then a further decline in the amplitude of components, until a secondary smaller peak in amplitude occurred in the fourteen to fifteen

year old group. After this the VEP amplitude stabilised to become the adult wave form.

In terms of topography there was little correlation between the occipital and parietal responses in the four to six year old group compared with the young adults who showed very similar wave forms in the parietal and occipital regions of the scalp. The responses from the right and left occipital lobes were very similar in the young children (0 to 4 year olds), and this close relationship gradually declined over the years. Thus, there was an increasing difference between the two hemispheres, mainly seen in the later components, which the authors attributed to some intelligence factors. The children who performed poorly in the WISC intelligence test, retained the infants' pattern of similar responses from the two occiputs.

3.3.3. Senescence and the visual system.

Compared with the research work on children and young adults, comparatively little attention has been paid to any possible VEP changes as the processes of ageing and senescence slowly change the properties and environment of the brain and body. The implicit assumption appears to be that there is little significant change in the VEP once the stable adult form is established. Yet, some of the ageing effects within the brain and the eye are quite dramatic, and since many clinical problems, such as cataracts, macular degeneration, vitreal tears, glaucoma etc. are prevalent in the older population, it is as important as in the young group, to carefully establish the normal range of VEP variation in the healthy old system.

Ageing at the receptor level generally involves the accessory structures of the eye (Magladery, 1959). There is a fatty invasion of the cornea, sclera and conjunctiva, which leads to the increased rigidity of these structures. The iris thins, becomes more rigid and tends to loose its pigment, while there is a diminution of the pupil area. The lens decreases in axial length. The retina itself, and the vitreous and aqueous humours are believed to be relatively free from senile change although there is often difficulty in distinguishing between minor, initial pathological degeneration, and possibly normal senescence. There is probably some accumulation of corpuscular or filiform agglomerations in the vitreous humor, and vacuoles may appear at the edge of the retina.

All these ageing processes of the eye result in a reduction in the power of accommodation and reduced acuity in the old. Because of the yellowish fatty deposits in the transmitting structures, colour vision is effected, mainly in the blue-violet part of the spectrum. There is some restriction of the visual field and much more light is scattered as it passes through the old eye, so that the ageing retina receives only a third of the amount of light that the young retina does. It follows that there is a reduction in the amplitude of the ERG.

Some of the ageing processes of the sensory systems begin very early in life, although this early detection is, in part,due to the greater sensitivity of the available psychophysical tests of sensory perception. Accommodation begins to decline in the

young adult, and has often reached a minimum value by the age of fifty years. The decline in the rate of dark adaptation, and the lowering of the CFF level is linear after the first twenty years of life. Nerve conduction velocity drops after thirty years and the maximum oxygen uptake falls by 5 to 10%.

Within the brain itself ageing results in a reduction of brain weight, oxygen comsumption and neuron density, with increasing amounts of DNA and water content (Gaitz, 1972). These effects may begin between twenty five and forty five years of age, but there is a sudden rapid acceleration in ageing processes around seventy years, which is considered by some to be the beginning of senescence. The problems of tissue perfusion increase as the blood pressure drops in relation to vascular resistance (Obrist, 1954). The decreasing blood flow leads to ischaemic hypoxia and diffuse degenerative changes, with the borderline between ageing and pathological processes a very difficult one to identify. There is a decrease in endocrine secretory activity within the brain. There is also a decrease in the reactive capacity of the body tissues so that higher hormone levels are needed to provoke a reaction. These two factors result in the fact that CNS shifts in homeostatic control, may often fail to be reflected in the periphery. The body is less adaptable when old (Frolkis, 1968).

The EEG shows only small changes during normal ageing processes. The amplitude and amount of alpha activity is reduced compared with a young population, and beta activity is more prominant (Obrist and Booth, 1965; Straumanis et al., 1965; Otomo, 1966). There is a slower mean alpha frequency in the older population,

which is significant after the seventh decade. By the eighth decade there was a further significant fall in the alpha frequency.

3.3.4. Ageing changes and the VEP.

In the few VEP studies that have been carried out on an older population only Lago and Daniel (1970) have reported complete medical screening, and they made no special mention of checks of the visual fields and acuity. Most authors only report on I.Q. results and clinical history. There is always therefore the problem of the greater probability of subjects within the older age group presenting abnormal symptoms either of the visual system itself, or of degenerative changes within the central nervous system compared with any other age group. Lago and Daniel (1970) found no significant difference in the occipital evoked response to flashed compared with other adult groups, and the P_2 component was still the clearest and most dependable landmark. Schenkenberg, Dustman and Beck (1972) found that the auditory evoked response was stable throughout life, but that the visual evoked response showed increases in the latency of the components in the normal elderly (mean age 72.1 years). In another paper (Schenkenberg and Dustman, 1971), they suggested the latency of the early portion of the VEP was fairly stable, and that it was the later components from 100 - 200 m.sec. which were significantly later in the elderly.

Shagass (1966) reported an increase of both latency and amplitude of the visual evoked potential and the somatosensory evoked potential in the elderly. Dustman and Beck (1969) and Schenkenberg

and Dustman (1971) gave more detailed changes of the VEP amplitude. They reported a significant increase in the amplitude of the early components which occurred between 0 and 125 m.sec. in their fifty eight to eighty one year old age group, with also a dramatic reduction in amplitude of the later portion of the VEP which occurred after 200 m.sec.

3.4. VEP and binocular vision

3.4.1. Binocular physiology

The most characteristic feature of our visual input is that it is sharply and precisely divided into right and left sides. The isolation of information from the right and left visual fields is probably maintained until the cortex is reached, yet the world is perceived as a continuous panorama. The most peripheral scenes are viewed monocularly; the central 120^{o} is seen by both eyes, with approximately the middle 40^{o} also represented in both hemispheres.

When the two eyes are directed towards a point of interest, two slightly different images fall upon the retinas, which somehow are combined within the visual system to produce a '3D' impression. This experience of depth is unique and personal. In a survey of 150 normal subjects, Julesz (1960) found that 4% of his sample had no stereopsis or sensation of depth, and 10% had great difficulty and gave incorrect reports of apparent depth. Abnormal binocular movement probably leads to abnormal interactions within the visual system, so that perhaps even slight misalignment of the eyes will cause the stereoscopic mechanism to degenerate. This may explain Julesz's findings, since the incidence of squint in adults is

reported to vary between 2 and 9% of the population.

Somehow the visual system must combine the inputs from the two eyes. If the images are similar in form and size, and lie at corresponding retinal positions, then one object will be perceived. Fusion still occurs even when the two images are not exactly on corresponding retinal positions, so long as they lie within "Panum's Fusional Areas". These areas are approximately 6 to 8' of arc within the central 2^{o}, and increase in size towards the periphery (Graham, 1965). One subjective image or direction results if the fusion of the two images occurs. This is either a compromise between the two principle visual directions, or else the perceived direction corresponds with the dominant eye.

Retinal disparities along the horizontal meridian are the basis of depth perception, and approximately 1^{o} of horizontal variance is needed in man for stereopsis (Hubel and Wiesel, 1967). As the disparity of the images increases beyond the fusional areas, debilitating diplopia is experienced. There is also a minimum visual angle when no stereopsis is perceived, which corresponds to an object about a quarter of a mile away.

Generally, stereoptic acuity is related to monocular acuity, although some individuals with good vision have no stereopsis. Stereopsis occurs over the entire field, and has been demonstrated in low illumination involving only the rod system. Stereopsis varies with the duration of the stimuli, with maximum acuity occurring for stimuli lasting 2 to 3 seconds. Less than a 0.2 seconds stimulus presentation results in acuity decreasing by a factor of four or

five from the maximum level. Stereopsis is the primary property of the binocular system. There is no superiority of acuity compared with monocular viewing, and the sensation of brightness is only very slightly enhanced.

As yet, it is far from clear how stereopsis and the compulsion for fusion are related (Jung, 1973). Most theories support the idea that fusion of the inputs from the two eyes occurs in the cortex, since ipsilateral and contralateral visual inputs to the lateral geniculate nucleus appear anatomically segregated into separate layers. Within the cat's brain part of the initial process of binocular interaction may occur within this thalamic nucleus. Fukada and Saito (1972), Singer (1973) and Hubel and Weisel (1962) have all recorded units which are binocularly driven in cats. Richards (1968) hypothesized some binocular interaction within the LGN, so that visual space can be remapped, and apparent distance preserved as images move laterally across the retina during convergence and accomodation.

Within the striate cortex of the cat, 84% of the cells are influenced by both eyes. More neurons are dominated by the contralateral eye, than are influenced equally by both eyes, and a minority of cells were most effected by the ipsilateral eye (Hubel and Wiesel, 1962; Burns and Pritchard, 1968). Joshua and Bishop (1970) found 73% of the cells were binocular, but they did not find the tendency of the contralateral eye to dominate the responses. Some neurons fired only when both the corresponding retinal positions were stimulated, and remained silent during monocular stimulation. If there was a dominant eye, the receptive field was larger compared

with that of the non-dominant eye. Hubel and Wiesel (1967), Barlow, Blakemore and Pettigrew (1967) and Pettigrew, Nikara and Bishop (1968) all found some binocular units which were sensitive to horizontal disparities, getting a maximum response when there was approximately 1 to 2^{o} of horizontal variance between the points of retinal stimulation (Hubel and Wiesel,1967). When the receptive fields of the binocular units were optimally superimposed, the neuron response was greater than the sum of the two separate monocular responses (Burns and Pritchard, 1968; Joshua and Bishop, 1970). This behaviour was only seen in the simple type of neurons, and the maximal response very rapidly declined as the stimuli moved away from the optimum position. A few of the binocular neurons responded only if the optimum stimulus was moving backward and forward in space. That is, the cell response was to changing retinal disparity (Pettigrew, 1973).

In contrast to the cat, which is so often used as an experimental model, Poggio (1968) concluded that the convergence of inputs from the two eyes is rarely found in the striate cortex of primates and not seen in the thalamus. The majority of recorded cells were monocularly driven, with a greater number being effected by the contralateral eye. Hubel and Wiesel's findings (1968) were similar, with most neurons in area 17 being monocular, though there was a tendency for more cells to be effected by both eyes away from layer 4.

All agreed that orientation or pattern sensitivity and binocular convergence appear to be organized along different dimensions.

In the circumstriate cortex of the cat, most of the cells were driven by both eyes, with the optimum stimulus for each eye having the same character, size, orientation and position. Both eyes gave a greater response than one eye alone. In areas 18 and 19 of the monkey, the organization of binocular convergence and dominance appeared to be closer to that of the cat's striate cortex. Bough (1970) has shown that monkeys have the ability to distinguish objects at different apparent distances in the absence of monocular cues. That is, monkeys possess stereopic vision. Hubel and Wiesel (1970) found that 57% of their recorded cells in area 18 were binocular and of these 43% were binocular depth cells, and produced very little response to monocular stimulation. The disparity range that each cell was sensitive to was very small. The effective displacement was always at right angles to the plane of stimulus orientation. There was an increasing proportion of depth cells in areas representing increasingly distant points from the vertical meridian.

There are some wide differences between the system in a cat's brain compared with monkeys, which immediately raises the question of how precise a model of human binocular vision and visual processing can be constructed from feline and primate research, especially with the unique feature in man of unilateral specialization of function.

A structure vital in preserving the integrity of the visual world, is the forebrain commisure system. Visual information is exchanged between two hemispheres of the cat via the posterior half to two thirds of the corpus callosum. In the chimpanzee only the

splenium and anterior commisures are involved. There is a strict localization of function within the forebrain commisure for each sense modality, while within each functional sector there appears to be remarkable equipotentiality. All the primary sensory projection areas are free from commisural connections, and this is particularly so for striate cortex, where there is no communication between the right and left hemispheres in man, monkey and the cat. Lower down the phylogenetic scale there is increasing penetration of the primary sensory areas. Only area 18 is connected by commisural fibres with the opposite hemisphere. Diffuse stimuli produce no response from the fibres of the corpus callosum in the cat (Hubel and Wiesel, 1967; Berlucchi and Rizzolatti, 1972) and the properties of fibre activation correspond closely to the simple, complex and hypercomplex neurons described by Hubel and Wiesel in the visual cortex (1962, 1965). Without exception all the corpus callosum fibres were binocularly driven, and all had receptive fields in contact with, or very close to, the vertical meridian. About half the fields lay within the foveala, the rest were directly above or below (Hubel and Wiesel, 1967). Most of the fields were less than 1° although a few fibres did show an unusual expansion of the general field size, of up to 20°.

Corpus callosal transmission is very rapid, with at most a 2.5 to 3.5 m.sec. delay compared with direct evoked potentials. The shape of the callosal evoked potential is strictly similar to a potential generated directly on the same cortical patch, but there is a faster rate of decay as the stimulus repetition rate increases from one up to three or four flashes per second (Choudbury et. al.,

1965). In cats only the transfer of information on brightness and flicker can occur without the corpus callosum intact. In monkeys brightness data may still be transferred when the splenium is sectioned (Myers, 1972).

Jung (1973) suggests that there is no visual transfer from the right to the left hemisphere in sectioned patients, when the stimuli are complex and stationary. Some patients can perform very good peripheral matching of two stimuli, if they are comparing relative motion, size or position by making reports either verbally or with hand movements (Trevarthon and Sperry, 1973). In normal individuals, observation with one eye of various stimuli produces an after image when stimulation ceases. The response is strong in the adapted eye, and there is also a response in the other eye. That is introcular transfer of after effects can occur (Ware and Mitchell, 1974). No transfer could be demonstrated in stereoblind subjects, and the authors suggest that this may be because there are no binocular neurons in the stereoblind.

3.4.2. The binocular and monocular VEP.

The reports of comparisons of visual evoked responses between binocular and monocular conditions are conflicting. With monocular presentation, Groth, Weled and Batkin (1970) found greater amplitudes in the contralateral hemisphere in infants and neonates, but there was no significant difference in adults, although the results tended to be in the same direction. Lehman and Fender (1967) also reported greater amplitudes in the contralateral hemisphere.

Ciganek (1970) found a large (100%) increase in the VEP amplitude

when low intensity stimuli were presented binocularly, compared with monocular viewing, while high intensity stimuli generally showed only slight summation effects for the binocular condition. Bartlett, Eason and White (1968) also found a significant increase in amplitude, but only when a red or blue light was viewed binocularly. Perry, Childers and McCoy (1968) found a 31 to 43% increase in response amplitude for binocular stimulation, with the amplitude of the activity depending on the scalp location. Gouras and Link (1966) and Cobb, Ettlinger and Morton (1967), recording steady state evoked potentials, found that binocular responses were twice the size of the monocular response. In contrast Vaughan (1966) Kooi (1971) and Martin (1970) found no such clear relationship in their normal groups. Campbell and Green (1965) and White and Bonelli (1970) only found binocular summation compared with monocular stimulation when pattern stimuli were clearly in focus, and the effect was enhanced by increasing the contour density. Similar effects have been reported with pattern stimuli (Harter et. al., 1974), and the authors suggested that components between 100 and 150 m.sec. were always of higher amplitude in the binocular condition. Only Jeffreys and Axford (1972a, 1972b) reported any data on latencies, and they found an increase in their main C1 and C2 components of the order of 20 m.sec. with monocular viewing.

Few reports have suggested any differences between the two monocular responses that may relate to eye dominance. Martin (1970) found no significant difference between right and left eye stimulation in his small sample of adults. Perry, Childers and McCoy (1968) found a large asymmetry in the response from one eye compared with the other in 10% of their normal sample. Amplitude differences

were as great as those reported in unilateral eye disease, (Copenhaver and Perry, 1964), even though visual acuity and stereopsis were normal.

Most workers have used conditions of fusion and rivalry to determine monocular interaction and relative dominance. When 'line' patterns of different orientations were presented to each eye, Cobb et. al., (1967) found a significant reduction in the amplitude of the steady state evoked potential from the suppressed eye, with no change occurring for the dominant eye. Tsutsui and Regan (1968) and Kawasaki et. al., (1970) used similar patterns which could be rotated until bonocular fusion was broken. A late occipital positive occurring between 270-300 m.sec. appeared to be specific to binocular fusion, since it was absent in conditions of binocular rivalry. The degree of suppression of the positive component was not related to the difference in the angle of rotation of the two patterns, but only to whether the patterns subjectively appeared to be fused or not. Harter et. al., (1974) also found that late components between 200 and 250 m.sec. were suppressed during dichoptic viewing and were enhanced by dioptic viewing. Lehman and Fender (1967) and Wooten(1972) have looked at the effects of presenting two totally different stimuli to each eye, where fusion was at no time possible. They found an increasing reduction in the evoked potential amplitude, as the 'visual information load' was increased in the other eye. Visual loading varied from darkness to diffused light, crosses and grids. There are technical problems in recording evoked potential correlates of stereopsis, since the stimulus duration needs to be longer than generally used in evoked response work, that is, of the order of two to three seconds for

maximum stereopic acuity (Martin, 1970). Regan and Spekreisje (1970) produced a percept of depth using random dot patterns, and recorded a prominant positive wave peaking around 160 m.sec. with each change in perceived depth as the patterns moved. Florentini and Maffei (1973) found increases in the amplitude of the visual potentials with increasing retinal disparity of the patterns which correlated with increasing subjective percepts of depth.

Despite some contradictions in literature, it seems probable that the visual evoked potential is reflecting some initial stages in visual processing, that involve the combination and interaction of inputs from the two eyes and two fields of view. How this interaction is related to stereopsis or fusion is yet to be answered.

3.5. Summary

Many factors must be taken into account when attempting to interpret the flash VEP. There are consistent changes in the response morphology depending on the age of the subject, with much larger variations acceptable in the young population than can be applied to the normal response of an adult. The waveform of the visual potential changes at different locations on the scalp. The largest and clearest responses are recorded over the occipital poles, and it would appear that the distribution of the VEP over the primary visual and association areas may supply useful information about the underlying visual anatomy. The form of the visual potential is altered by binocular or monocular stimulation, and these effects must be understood if unilateral pathology of the eye or visual field defects are tested with monocular stimulation. It is possible that the interaction of the two eyes and of the two visual fields can

be monitored by the VEP, which therefore may aid the understanding of binocular vision and of the abnormalities that can develop in pattern and depth perception.

CHAPTER 4

The effects of changes in subjective parameters on the flash VEP.

4.1. Introduction

One of the problems inherent in the recording of evoked potentials from the scalp, is that in order to obtain a clear response a large number of stimuli must be presented for each average. The mode for the number of repetitions lies between 25 and 100 stimuli; very few authors use any less, and some, present up to 500 stimuli for each averaged evoked response. Further, if the response is of low amplitude or rather variable in latency, the tendency is for more stimulus presentations to be given in an attempt to improve the signal to noise characteristics of the final trace.

During the recording of the VEP well established changes occur in the brain's responsivity to monotonous stimulation. That is habituation occurs. There may also be changes in the behaviour of the subject. For example, there may be a shift in attention, a change in the level of arousal, visual fatigue, changes in perceptual set, etc. The question arises as to whether such changes have a significant effect on the evoked response, and therefore need to be carefully controlled, and whether the effects are similar and therefore predictable in different patient populations, such as in young children who are sent for electrophysiological assessment.

4.2. Habituation within the Central Nervous System.

No organism produces a stereotyped response to repetitive stimulation, and generally there is a diminution in response size as stimulation proceeds. Even the simple neural nets of Aplysia show a reduction in amplitude of the excitatory postsynaptic potentials during

a monotonous train of stimuli, the amplitude being restored by a novel stimulus (Bruner and Tauc, 1966). Depth studies in aminals and man show more complicated changes. Marsh and Worden (1964) looked at acoustic habituation in the cat, and suggested that the attenuation of evoked potentials only occurred in the cortex, with no corresponding change at lower levels. Over six hours of stimulation there was a consistent progressive reduction in amplitude to about 78% of the initial amplitude values. The authorsalso suggested that the evoked potential amplitude correlated directly with the state of EEG synchronization regardless of how it was produced. In monkeys, Grandstaff and Pribram (1972) found a significant decrement in primary components of the flash response in the optic nerve and LGN, but less than 50% of the striate cortical leads showed the same decrease in amplitude. The cortical responses were highly variable and showed increases, decreases or no change in amplitude. The results were more closely associated with the changes in the background EEG than with habituation. A dishabituating stimulus produced consistent reductions in evoked potential amplitude in the cortex, but no clear pattern was seen in the optic nerve or LGN, again a result best explained by changes in the EEG. Brazier (1967) found that habituation developed in the structures concerned with the non-specific sensory systems, and therefore in the cortex the most marked effects occurred in the later components of the sensory potentials. Only non-specific thalamic nuclei showed a gradual reduction in amplitude, with no habituation occurring in the LGN.

Depth recordings in man (Guerro-Figueroa and Heath, 1964) showed a gradual reduction of both the primary and secondary components

to continuous flash stimulation in the reticular formation and cortex, suggesting that possibly greater habituation effects occur in man than are recorded in lower species.

Ritter, Vaughan and Coster (1968) found a rapid reduction in the amplitude of the scalp response of normal subjects over the first four click presentations. By the fourth stimulus, the decline had stabilized to around 50% of the first response. A change in the frequency of the stimulus did not restore the initial amplitude. Interstimulus intervals of longer than ten seconds did not produce such a dramatic habituation of the scalp response. Bogactz, Vanzulli, Handler and Garcia-Austt (1960) also reported a significant, progressive decrease in the response amplitude to constant flicker stimulation.

There is some controversy as to whether habituation is peripheral and therefore easily controlled experimentally, or central. Pagni, (1964); Bergamini, Bergamasco, Mombelli and Gandiglio, (1965); and Bergamini and Bergamasco, (1967) believed that visual habituation was due to myosis of the pupil during prolonged stimulation. Pupil constriction increased the latency and reduced the amplitude of the VEP, and elimination of the pupils' responsiveness reduced habituation changes (Bergamini et al., 1965). Other authors disagreed (Perry and Copenhaver, 1965; Fleming, 1969) since they could find no satisfactory evidence that pupil fluctuations correlated with amplitude changes in the VEP. Brazier (1969) believed that both peripheral and central mechanisms were involved, as had been suggested by Hernandez-Peon et. al (1957).

Perry and Childers (1969) suggested that habituation effects could be reduced by frequent rest periods, by counter-balancing stimuli, and by using random interstimulus intervals. The last suggestion was found to be ineffective, when recording responses to monotonous stimulation in various brain sites (Simmonds et. al., 1966; Baumann et. al., 1968). Garcia-Austt, Bogactz and Vanzulli (1964) found less habituation with very irregular stimulation, but the effect still occurred.

Shagass (1972) found that the magnitide of change of the averaged potentials in adults over an experimental period was usually small. However he suggested that there may be a difference in susceptibility to habituation in adults and children. Shagass and Schwartz (1965) showed greater habituation effects in psychiatric patients compared with normal controls. Ellingson (1970) and Ellingson, Lathrop, Danaby and Nelson (1973) recorded far larger variations in the VEPs of neonates and infants compared with adults,and Pampiglione (1967) warned of the highly variable responses in children. He found that conditions such as alertness, attention and adaptation phenomena seemed to be much more short lived in children than in adults, and had a greater effect on the final results. The question of whether prolonged stimulation has a more or less pronounced effect on patients and children compared with a normal adult group is yet to be conclusively answered.

4.3. Changes in attention and the VEP.

It is generally agreed that habituation is a gradual and inevitable adaptation of the CNS to monotonous stimulation. Imposed upon this trend are the additional effects of attention and distraction,

and changes in arousal or activation.

Depth recordings in animals suggest that when attention is being paid to the stimulus, there is an increase in the amplitude of responses in the primary sensory regions (Thompson and Shaw, 1965). Similar findings have been seen during attention and increased arousal after reticular formation stimulation (Hernandez-Peon et. al., 1957). Thompson, Denny and Smith (1966) suggested that attention effects can only be simulated by electrical stimulation of the frontal lobes, which produced an enhancement of the late potentials of the primary visual cortex response, with a concommitant decrease in the amplitude of potentials in association areas. He suggested that the two results reflected the activity of separate systems. During depth studies in man, Guerrero-Figueroa and Heath (1964) found a reduction of the secondary components in the striate cortex after thalamic stimulation during distraction, while after peripheral stimulation, both primary and secondary components were attentuated during distraction.

In normal subjects, counting has often been used to maintain attention to a particular stimulus, and the findings are equivocal, (Van et al,1962; Garcia-Austt, 1963; Spong, et. al., 1965). Spong, Haider and Lindsley (1965) suggested that this may be because the task of counting itself introduces some distraction. Garcia-Austt et. al., (1964) suggested that only in habituated subjects does attention produce an increase in the amplitude of cortical evoked potentials, while in the aroused, non habituated subject both attention and distraction decreased the amplitude of the response. When a subject is responding to a stimulus in a simple reaction

time experiment, one may assume that the act of responding requires some attention to the stimulus, and that faster reaction times reflect greater attention to the event of the preceeding stimulus. Many authors found significant negative correlations between VEP amplitudes and reaction times, (Larsson, 1960; Haider, Spong and Lindsley, 1964; Donchin and Lindsley, 1965; Morrell and Morrell, 1966; Wilkinson and Morlock, 1967; Kopell et. al., 1969; Bostock and Jarvis, 1970). The detailed changes of amplitude varied between the experimental conditions and authors. Some authors reported an overall increase of all the components present in the evoked potential, which was more often than not recorded from the vertex (Larsson, 1960; Haider et al. 1974; Eason and Harter, 1969; Eason, Harter and White, 1969; Kopell et. al., 1969). Others found that the amplitude changes were more specific and occurred in the later, secondary components. Morrell and Morrell (1966) found that a significant amplitude increase in the components after 100 m.sec was associated with faster reaction times. Donchin and Lindsley (1965) recorded the largest amplitude changes during fast reaction times in a component between 160 and 200 m.sec. The polarity was uncertain, but its amplitude and distribution suggested that the component might have reflected the non-specific effects of cortical excitability. Other authors (Wilkinson, Morlock and Williams, 1966; Wilkinson, 1967; Wilkinson and Morlock, 1967; Bostock and Jarvis, 1970) attributed a late component (termed N_2) around 250 m.sec. with the property of reflecting cortical arousal. They found a decrease in the amplitude of N_2 during increased reaction times, and a decreased amplitude of N_2 for missed signals in an auditory vigilance task. Other late components

around 300 m.sec. also reflected attentional changes during reaction time experiments. Dustman and Beck (1965) reported that latency changes were recorded over the primary sensory projection area. A positive wave at 57 m.sec. was particularly effected (showing a positive correlation), and the authors believed that this wave represented the surface event of the interaction of the incoming afferents and the fluctuating cortical excitability cycle which is reflected in the activity of the alpha rhythm. They found amplitude changes which correlated with attention at the distant electrode site of the vertex. Ciganek (1967) reported highly variable findings in his attempts to manipulate subjects' attention and distraction. He found that there was a general increase in the amplitude of components with attention, although the opposite result was only just less frequent. The degree of change of amplitude was different for different components. The greatest change occurred in an early component at 60 m.sec., and wave V increased with distraction.

Similar findings are reported during vigilance tasks, with larger cortical potentials to detected signals compared with missed signals (Haider, Spong and Lindsley, 1965; Ritter and Vaughan, 1969). There was also a gradual fluctuating decline in the VEP amplitude from 13 to 10 μv over the vigilance session, which correlated with a drop in the detection rate from 80 to 50% of the signals. Latencies also increased from 155 to 165 m.sec. (Haider, Spong and Lindsley, 1965). There was a significant amplitude increase in a late positive component (300 to 500 m.sec.) for detected signals at both the vertex and occiput, in visual and auditory vigilance tasks (Ritter and Vaughan, 1969). This late positive was present

for all the stimuli at the beginning of an easy task, and remained throughout a very difficult discimination task. The same late positive appeared for unpredicted changes in the stimulus. They suggested that the component may represent some part of the comparator mechanism that operates with the orienting response, and is associated with the cognitive evaluation of stimulus significance.

There is some agreement that attentional processes usually enhance the amplitude of late components of cortical potentials. Näätanen (1967) suggested that this only happens in a discrimination task, when the stimuli are regular and easily anticipated. When the stimuli are random and not predictable, there are no differences in amplitude between the relevant and irrelevant stimulus responses even though performance is good. That is an increase in the amplitude of a response to an attended stimulus represents anticipatory and preparatory arousal before the stimulus. Chapman (1966) instructed his subjects to solve problems that required close attention to some displayed numbers while others were ignored. Pupil size and accommodation were controlled. The main VEP components were always larger for the attended stimuli, and these effects did not depend on any anticipation of the stimulus, or of the different physical characters of relevant and irrelevant stimuli. Eason and Harter (1969) looked specifically at the interaction of arousal and attention. Arousal was manipulated by applying electric shocks during a visual discrimination task, which used dim flashes in the right and left visual fields. They reported a larger visual evoked potential to the relevant stimulus, and this increase in amplitude was magnified during the electric shock when presumably arousal was higher. Amplitude changes were therefore primarily related

to attention, and to a lesser extent to the arousal levels of the subject.

4.4. Meaning, information and the VEP.

In an attempt to sort out some of the conflicting evidence about the effects of attention of the VEP better specification and control is needed of the actual psychological states evoked within the experimental conditions. Also attention must be paid as to whether attitudes and percepts are uniform throughout a group of subjects or whether there are large differences between individuals. There is a further problem that needs to be considered, even when only dealing with changes in the physical parameters of a stimulus. Identical stimulus states may produce different percepts in different individuals, for example, a double flash may 'look longer', 'look double' or 'have a different colour'. Is this source of variation important, or can it be ignored?

When investigating the effects of meaningful stimuli, the problem of accumulating trials is even more serious than when trying to maintain attention and interest across subjects. The surest way of destroying the meaning of a word is to repeat it, and authors must guarantee meaningfulness at each presentation, and preferably the same meaning. Practically no attempt has been made to ensure this. Looking at the difference in brain potentials evoked to words, and comparing the results with responses to nonsense syllables, is one way of attempting to record some electrophysiological correlate of perceived meaning. This has mainly been done using auditory evoked responses (Sharrad, 1969; Roth, et. al., 1970; Cohn, 1971; Wood, et. al., 1971; Matsumiya et, al., 1972; Worden et. al.,

1972), but visual presentations have also been used. Buchsbaum and Fedio (1969, 1970) presented words, nonsence syllables, geometric and random patterns, all constructed from the same number of light dots, to the right and left visual fields. Significant differences were found in the late portion of the occipital response (after 300 m.sec.) to words compared with the other conditions. This was true for both hemispheres, but there were greater differences within the left hemisphere. Weinberg and Cole (1968) investigated the emotional overtones of meaning by using taboo and neutral words, letters and a blank field. The only clear differences they could record were between the first three conditions and the blank flash. Shelburne (1972, 1973) used a different method, with the letters being presented separately to form either a three lettered word or nonsense syllable, with a response required to the word. Either the first or third syllable was altered, e.g. CAT, CAC, ZAT. No overall difference was found between the meaningful or non meaningful stimuli. However if the first syllable was altered a large, late positive between 160 and 300 m.sec. appeared, compared with the other two syllables. The same change in the late positive occurred at 450 to 590 m.sec. to the third syllable, when that syllable was altered. Similar results were found in children between the age of 8 and 12 years (Shelburne, 1973), however compared with the adult population the results were highly variable, and some children performed badly. Also the children had little control over their eye movements, which generally consisted of blinking mainly to the first syllable presented. The vertical eye movements increased the amplitude of a positive at 170 to 250 m.sec in the vertex and parietal leads. Symmes and Eisengert

(1971) also used children and compared the occipital responses to pictures and blank flashes. There was some increase in amplitudes very late in the response (around 512 to 532 m.sec.), but the results were highly variable and no significant difference was seen between the classes of stimuli. Complex patterns were also used by Lifshitz (1966) to investigate the difference between meaning, emotional content and abstract patterns. Defocusing the pictures produced responses similar to a blank flash response with the loss of a late positive component between 250 and 400 m.sec. The change to pattern was maximal at the vertex, and a larger increase in the amplitude of the late positive wave occurred when pictures were viewed compared with letters and patterns. No difference was obtained between the three classes of picture stimuli which were attempting to evoke neutral, unpleasant and pleasing emotional responses. This finding was not surprising as there was no control of the physical characteristics of the stimuli, and no report on the reactions of each subject. Sandler and Schwartz (1971) overcame the problem of changing meaning without changing the physical characteristics of the stimulus by using ambiguous figures. The most interesting results were obtained from a random dot pattern as it was perceived initially in all subjects, and the perception of a figure within the dot pattern. A significant increase in the amplitude of most of the major components of the VEP occurred to the meaningful pattern. The difference was not an order effect and was not altered by changing the visual angle of the stimulus or lowering the intensity.

The changes in the late components of the VEP usually a positive component, are believed to reflect the significance of the stimulus

to the subject (Sutton, Braren and Zubing, 1965; Sutton, Tueting and Zubin, 1967; Sutton, 1969). In experiments where the subject had to predict what type of stimulus would come next, no late positive at 300 m.sec. (called the P300) was recorded when the subject was certain. The amplitude of the P300 depended on the stimulus probabilities, sequential probabilities, the sequence of correct and incorrect guesses, the pay off structure of the experiment, and on the physical parameters of the stimulus alternatives. These findings were most significant in the central regions of the scalp, but were still seen in more posterior locations.

Several questions remain unanswered from this research. Are content changes different from emotional and attentional changes, or are we still looking at attentional processes? Does the change in the evoked potential reflect information processes used by the CNS and is therefore closely associated with behaviour, or is it not directly involved and therefore only occassionally a relevant sign. How does each individual approach a task? Training, cooperation and understanding are often needed, especially in more complicated experimental situations, and you cannot rely on each normal cooperative adult to attend or recognise a repetitive stimulus consistently, therefore how would different patients with a wide variety of emotional and physical problems approach the task? The difficulties are even greater when children are involved. The problem is not finding behavioural correlates of evoked potentials, but of finding too many. Fatigue, attention and habituation can be controlled by careful counterbalancing of experimental design. This is not always feasible in a clinical investigation where the questions are constantly changing, and therefore must be managed in a different

way, perhaps by continuously monitoring the changes in the background EEG, and by recording large amplitude VEPs using supra-threshold stimuli.

CHAPTER 5

The effects of changes in stimulus parameters on the flash VEP.

5.1. Introduction.

Many of the changes in stimulus parameters are clearly perceived and consistently reported by subjects, and if the recorded scalp potentials are related to the internal event, the perceived phenomenon, then there must be changes in these potentials, which coincide with at least the most dramatic changes in stimulus characteristics. One question is, are there clear and reliable electrophysiological correlates of perception, and do they relate to the underlying physiological processes. A second question is what are the most effective ways of stimulating the visual system in order to obtain the most consistent and reliable VEP signs of visual function. That is the range of inter and intraindividual variations within one group should be as small as possible. Such questions need to be asked as how effective is an increase in the intensity or duration of a light flash in order to obtain reliable results, is information gained or lost? At what light intensity are most of the main components of the VEP clearly seen in most individuals? In this second approach the exact relationship between the brain and scalp potential is not of primary importance, only the development of a range of stimulus potentiators, which are effective in eliciting a consistent response in a large majority of a normal population, and which can be easily and usefully applied to new populations such as a clinical group.

5.2. The response to visual stimulation within the CNS.

The visual system is a very sensitive and versatile receiver of intensity, responding to intensities so low that only one quantum of light is striking one receptor, and with a dynamic

range of 140dB before damage occurs. At the retinal level the rods respond to low intensity information, with the rods and cones interacting as the brightness increases, until only the cones respond at high intensities (Davson&Graham 1977).Gouras and Link, (1966) measured the latency of activation in the ganglia cells of the monkey, and were able to differentiate rod and cone inputs by using latency criteria. Both the rod and cone latencies became slower with the increasing luminance of the test stimulus, the cone input always being faster by some 30 m.sec. than the rod system.

At the level of the LGN, De Valois (1972), found that about one third of the cells were spectrally insensitive, and responded to all wave lengths. They reacted to changes in light intensity by increasing their firing rate as the light became bright, and decreasing their firing with a lowering of intensity. The remaining two thirds of the cells only responded to a particular colour. The author suggested that all LGN cells carry some intensity information, but that there were separate pathways for intensity and colour. Chang (1952) found an increase in the amplitude of evoked potentials in the LGN and in the striate cortex of the cat when there was an increase in the intensity of diffuse illumination of the retina.

According to Hubel and Wiesel (1962, 1965) and Hubel (1971) the biological importance of coding brightness changes is far less significant than the processing of information on the position and velocity of detailed patterned images. During the depth recording of single cells in the cat's visual system they have

accumulated substantial evidence that a diffuse stimulus flashed onto the retinal failed to effect many of the neurons recorded in areas 17, 18 and 19 of the cat's visual system. Bright or dark lines or edges were the most effective stimuli. At various precise orientations on the retina these stimuli would excite specific 'simple' cortical cells, which formed 77% of the cell sample of the striate cortex and were believed to represent the first or early stages of cortical pattern analysis. More complicated pattern neurons were found in areas 18 and 19.

Hubel and Wiesel (1968) found a similar type of organization within the monkey's visual system. Cortical cells still responded only to small, discrete stimuli, preferably lines and edges at a particular orientation. The main differences between the two species was that in the more highly evolved animal there were firstly fewer simple cells in the striate cortex, that is the majority of cells required a moving stimulus to initiate a response. Secondly, the average field size was much smaller than in cats, although the authors suggested that it was not the field size but the width of the optionally shaped stimulus, that related to the visual acuity. There were also cortical cells which responded to colour in the monkey, but the number of cells which were spectrally sensitive were disappointingly few in number and were mainly of simple cell organization. Hubel and Wiesel concluded that the primary function of the striate cortex (and probably the surrounding association areas) was contour analysis.

Many authors agreed with these basic findings, both in cats (Dreher, 1972; Frumkes, Battesby and Storek, 1972; Fukada and

Saito, 1972), and monkeys (Wurtz, 1968a, 1968b, Dow and Gouras, 1973). Wurtz (1968a) pointed out that in monkeys who are awake and active rather than anaesthetised, the majority of units would fire to stationary stimuli. This was probably because physiological nystagmus made any movement of the stimulus unnecessary to fire a cortical cell.

There is not such complete agreement about the total ineffectiveness of diffuse unstructured light stimuli in activating the cortex. Dubner and Brown (1968) found no cell in the primary visual and association areas of the cat that responded to a restricted light stimulus such as a line, that did not also respond to diffuse light. Further if they produced a transient depression of activity in area 17 by applying a dilute solution of potassium chloride, the cells failed to respond to contours, but still fired to a diffuse flash for some time afterwards. Spinelli, Pribram and Bridgeman (1970) found a complex organisation in the monkey's striate cortex. Thirty seven per cent of their cell sample appeared to be typical of Hubel and Wiesel's recordings of line and edge detectors. A large number (26%) of the neurons had a much simpler organisation, with circular receptive fields similar to the LGN and ganglia retinal fields, which were not particularly sensitive to any direction or orientation. Six per cent of the cells responded maximally to a diffuse stimulus, which was a significant reduction compared with the cat's cortex, where the authors found that 75% of the neurons responded to unstructured light stimuli. Compared with lower species Spinelli and his co-authors generally found a far larger number of unidentified cell types in the monkey, that is the optimum stimulus was not found. Also there was greater

variation in the type of stimulus that was effective, with neurons responding to such parameters as total illumination of the retina, or any form of stimulus as long as it moved. Cell firing patterns were also more variable, and the authors stated that there was less specification than for example in the cat's brain which ultimately meant far greater flexibility and reliability in the visual system, which may rely for perception on the pattern of response of a very large area of the visual cortex, rather than the more discrete columns of Hubel and Wiesel.

5.3. VEP correlates of stimulus parameters.

It is apparent that the procedure used to stimulate the eyes is as important as the collection and analysis of the data, and we need to select stimuli and alter their parameters on the basis of their appropriateness to what is known of the functional organization of the brain. Much of the animal research suggests that spatial structure and motion are the most biologically important types of information, but there is also some evidence that unstructured diffuse light is not entirely inappropriate in certain conditions.

5.3.1. The VEP and changes in light intensity.

Comparisons between different papers reporting on the effects of stimulus intensity on the VEP, are always made singularly difficult by the lack of any standardization of techniques between the laboratories. Specification of units of intensity vary widely for example, nit seconds, candellas/sq. metre, trollands, etc., and also factors such as the colour and duration of the stimulus, and the angle of subtense and distance of the light, probably have important effects on the VEP.

The majority of authors find that the components of the VEP increase in amplitude with increasing brightness of the stimulus. At high intensities there is often a saturation effect, with no further increase in amplitude as the intensity increases, and there is sometimes even a reduction in amplitude at or before the highest light intensities that are safe to use. This flattening of the amplitude curve generally occurs around 3 log units above threshold, although there is considerable individual variation (Vaughan and Hull, 1965; Shipley, Wayne-Jones and Fry, 1966; Vaughan, 1966; Kopell, Wittner and Warrick, 1969; Armington, Corwin and Marsetta, 1971; Uenoyama, 1971). The saturation phenomenon is also seen in SSEP's. If the modulation depth or percentage change of a repetitive stimulus is increased from zero while keeping the mean stimulus luminance constant, then the amplitude of the steady state potential is approximately proportional to the modulation depth. At about 30 percent change in depth the SSEP amplitude reaches a maximum level, and may diminish at higher modulation depths (Van der Tweel and Sprekreijse, 1966; Sprekreijse, 1966). Kopell, Wittner and Warrick, 1969) only recorded significant changes in the amplitude of components to changing light intensity, when the subjects did not attend to the stimulus. When attention was high the VEP amplitudes were already maximum, and increasing the light intensity did not produce any further change.

Most authors do not find any change in wave form consistent with intensity changes. However, Vaughan and Hull (1965) recorded a more complicated VEP at higher intensities, with seven to eight peaks. With a drop in intensity the number of waves was reduced, and some components (a positive wave at 100 m.sec.) increased

in amplitude, while others became smaller (a negative wave at 75 m. sec.).

There is some suggestion that the latencies of VEP components vary consistently with intensity changes, although the degree of change is smaller than in the amplitude dimension. There is general agreement that brighter lights produce a decrease in the latency of most components (Tepas and Armington, 1962; Wicke, Donchin and Lindsley, 1964; Vaughan and Hull, 1965; Shipley et al., 1966; May, Furbes and Piantanida, 1971), and that this effect may be more marked for early components within the first 100 m.sec. (Cobb and Dawson, 1960). Spehlmann (1965) found no significant difference in the VEP at different light intensities, and suggested that the changes were minute compared with pattern effects.

As yet no one has produced clear evidence of a consistant relationship between the VEP and changes in subjective brightness above threshold. One of the problems here is that there is a shift from the photopic cone system at high intensities, to the rod system at low levels of illumination. This change to scotopic vision results in a sudden large increase in the latency of the VEP (Vaughan and Hull, 1965; Vaughan, 1966). The waveform also changes, which makes identification of the components a problem. Huber and Adachi-Usami (1972) pointed out that the VEP at low illumination levels is entirely lost, unless some twelve to fourteen minutes is allowed for dark adaptation, after which the response was clearly seen. Little attention has been paid to the threshold of the VEP, and its relation to perceptual thresholds. Devoe, Ripps and Vaughan (1968) used graphical extrapolation to find that in the two subjects

tested, the VEP amplitudes approached zero at a point which coincided with subjective thresholds. They used the latency of 'P_1' (a positive component at 100 m.sec.) as an index of luminous efficiency, and this measure coincided with changes in subjective brightness over the luminance range.

Compared with the use of auditory evoked potentials in the assessment of auditory thresholds, information on visual thresholds is not useful clinically, and since threshold VEPs are of low amplitude suprathreshold flash intensities are indicated for clinical work.

5.3.2. The effects of stimulus duration.

There has been very little work on the possible effects of the duration of the stimulus on the waveform of the VEP, even though it has been known for a long time that many neuronal elements within the visual system respond differently to either the onset or cessation of stimulation. This lack of interest is partly historical, since a large majority of researchers use readily available stroboscope lamps, which have a brief pulse duration of 10 to 40 μsecs. The probable interaction of 'on' and 'off' responses, and the possible difference in behaviour of these two elements of the brain potential to changing stimulus parameters is largely ignored. Harter (1971) using a 600 m.sec. light stimulus recorded clearly separated 'on' and 'off' responses, which were of similar, rather simple wave form. The 'on' potential was the larger, with a surface negative at 90 to 100 m.sec., followed by a positive wave at 180 m.sec. The 'off' response had the same latencies, with the positive wave of lower amplitude and longer duration. When pattern stimuli were presented, the most effective stimulus

in terms of producing the maximum increase in amplitude, was different for the 'on' and 'off' portions. Defocusing reduced the amplitude of both responses, the 'on' being the more effected. Nash and Fleming (1970) recorded different results when they used a 500 m.sec and a 700 m.sec. stimulus. They described their VEP as having a typical wave form similar to Dustman and Beck (1969). The most reliable components were a negative wave at 160 m.sec. and a positive wave at 235 m.sec., the surface negative potential being the major component of the 'on' response, and the positive being the largest component of the 'off' response. Nash and Fleming found that the 'off' response was only clear for patterned stimulation and was less marked with diffused light stimuli.

5.3.3. Pattern stimulation.

The most common geometric patterns used in visual evoked potential research are those that are easy to quantify in terms of the size of pattern elements, element density, contrast etc., that is black and white grids, checkerboards and gratings. The patterns can be presented for a very brief period of time by illuminating them with a flash of light generally from a stroboscope ('flashed' pattern). Another method of presentation is pattern appearance or disappearance with no concommitant intensity variation. With pattern appearance there is a major positive deflection at 100 to 120 m.sec. at the inion, which is of opposite polarity for pattern disappearance (Mackay and Jeffreys, 1971). A third means of evoking responses to a patterned stimulus is by using a regularly occurring pattern design, where the symmetrical black and white portions can be reversed either by alternately presenting two

superimposed patterns, or by moving the pattern the distance of one pattern element using a rotating mirror. A response occurs to the pattern reversal which has a simple wave form similar to that produced by pattern appearance or disappearance. This response is very stable with little inter or intraindividual variation (Desmedt,1977), and it also follows the rate of stimulus reversals up to approximately forty reversals/min.(May, Furbes and Piantanida, 1971; Regan, 1972). The effect of the motion of the pattern in pattern reversal does not appear to contribute significantly to the pattern VEP(Regan and Sprekreijse, 1970).

The general findings for the flashed pattern responses are more complicated. The VEP is larger and clearer than the response to a diffuse light even when the overall intensity is reduced. Uenoyama (1971) found that in a few of his subjects a VEP could only be recorded to pattern and no potentials were apparently evoked to a plain flash. The visual responses are generally recorded from the occipital regions, and most of the differences in the pattern response, although varying in polarity and latency between authors, occur after 100 m.sec., and commonly involve late predominantly positive components. These waves were believed by Brazier (1967) to be diffuse and non-specific components. With flashed on patterns some authors found that a negative component occurring between 90 and 130 m.sec. (the occipital lead does appear to be Grid 1 in most instances), and a positive wave at 170 to 235 m.sec., both increased in amplitude during pattern stimulation and varied consistently with changes in pattern parameters (Harter and White, 1968; White, 1968; Nash and Fleming, 1970; Russel and White, 1970;

Harter and Salmon, 1971; Uenoyama, 1971). The positive component often occurred later, between 200 and 250 m.sec., and produced the only significant changes (Sphelman, 1965; Kinney , McKay, Mensch and Luria, 1973). Rietveld (1962) suggested that the presentation of a flashed checkerboard pattern produced a reversal in polarity compared with a simple diffuse light. However, these findings have been criticised by Nash and Fleming (1970), who pointed out that his results were inconsistent in different publications.

It is not certain whether the effect of the flash and the pattern interact in a linear or non-linear fashion. This relationship may be linear over a restricted range of stimulus patterns and intensities, and it was suggested by Kinney et al. (1972), that since the configuration of pattern responses is so markedly different from flash responses, a method of subtraction of one from the other aids analysis. The authors found that the wide individual differences tended to disappear, and the "real" pattern response emerged in all the subjects with a 'peak' at 100 to 130 m.sec., followed by a 'trough' at 200 to 250 m.sec. (the polarity of the waves was not clear). There is certainly a problem when analysing the pattern responses. Some authors suggested that individual components responded differently to the pattern and that there was no overall increase or decrease in the total wave form (Huber and Adachi-Usami, 1972). Negative and positive waves must, therefore, be measured separately, and peak to peak calculations or total wave excursion may obliterate any individual changes. This immediately raises the difficulties of calculating the zero or baseline levels of an averaged trace.

There are some consistent changes reported in the behaviour of the most pattern sensitive components of the VEP when different patterns are presented. One of the most important parameters is contour density or the size and frequency of distribution of the pattern elements. Increasing contour density is paralleled by a linear increase in the amplitude of the VEP components particularly the latter portions of the response. This relationship holds for changes in element size from 10' of arc, up to large patterns of one to two degrees of arc. Maximum amplitudes are recorded for 10' element sizes (White, 1968; Russel and White, 1970; White and Bartlett, 1970; Harter, 1971; Regan and Richards, 1971; Huber and Adachi-Usami, 1972; Regan, 1972). Very occasionally slightly smaller patterns produce the largest response (Harter, 1971; Uenoyama, 1971), but generally there is a sharp drop in amplitude as the size of the patterns approaches the limits of the visual resolution of the eye. Some authors (Sprekreijse, 1966; Harter, 1971, May, Forbes and Plantanida, 1971) recorded the largest cortical potentials for pattern sizes between 11' and 30' of arc. It is interesting to note that Hubel and Weisel (1962) found that the optimal size for LGN neurons lay between 7 and 30' of arc when the central retina was stimulated, and that similar stimuli produced the best results in the simple cortical cells of area 17 of the cat. With increasing eccentricity of stimulation larger patterns were necessary to produce the maximum response, following the trend of increasing receptive field size of the more peripherally located input channels. Huber and Adachi-Usami (1972) found that 10' pattern elements were best for fovea stimulation; Harter (1971) recorded a maximum foveal response

for 10 to 30' pattern sizes, and there was agreement that patterns smaller than 15' of arc provided a good indication of a purely foveal response, especially in conditions where the light intensity is constant. A pattern size somewhere between 30 and 60' of arc, provided the best extra foveal stimulation evoking maximum responses from an area of some 4.5 to 7.5^{o} eccentricity. Eason, White and Bartlett (1970) found that the check size which produced the largest VEP differed for upper and lower field stimulation. Checks of 10' subtense were optimal for the upper field, whereas 40' checks were best for the lower field. The authors speculated that these differences may have reflected differences in cortical receptive field sizes.

Other stimulus parameters have been looked at in less detail. Contrast is important. Increasing the contrast of black and white patterns will produce a linear increase in the amplitude of the VEP components (Nash and Fleming, 1970; Uenoyama, 1971). The number of intersections may also influence the effectiveness of the stimulus with grids generally producing larger responses than lines, gratings, radial lines and concentric circles (Harter, 1971; Armington, Corwin and Marsetta, 1971). The most effective stimulus of all is the high contrast checkerboard pattern (Harter and White, 1968; White, 1968).

Some analysis of the different component contributions in pattern stimulation can be carried out by looking at the effects of blurring the image either with lenses in front of the eyes, or by defocusing the image on a screen. Both transient responses and SSEPs to small patterns (10 to 30' of arc) are very sensitive to loss of resolution, compared with responses to the larger

patterns (40' of arc and greater), although the amount of defocusing necessary to produce a significant change in the pattern VEP varies greatly with the method of stimulus presentation. With flashed patterns Harter and White (1968) and Harter (1971) found that only the amplitude of two components of the VEP (a negative at 90 m.sec., and a positive at 180 to 200 m.sec) changed as the pattern was blurred. When a 12' check pattern was gradually defocused by placing a series of lenses in front of the subjects' eyes, there was a fairly linear decrease in amplitude with increasing power of the lens, until the components were lost in the 'noise' levels of the system. During the conditions of maximum sensitivity to blurring that is the smallest patterns were viewed, there was a 25% drop in amplitude of the two components between 0 and +3 dioptres of defocus, and then a more gradual decline with more powerful lenses. Responses to larger checks subtending 40' of arc did not show any significant change when the pattern was viewed through the same lenses. Russel and White (1970) found that no size of checkerboard (the sizes tested ranged from 10' to 120' of arc) produced a clear pattern VEP when viewed through a +5 dioptre lens, and the VEP was the same as a response to a plain flash. A slightly weaker +3 dioptre lens did not effect the larger patterns between 60 and 120' of arc, while the effects of smaller patterns (5 to 40' of arc) were completely lost.

Similar results have been reported for SSEP amplitude when fine patterns were blurred. Behrman, Nissin and Arden (1972) found a 50% reduction in amplitude when a 20' pattern was reviewed

through a positive or negative two dioptre lens. Regan and Richards (1971) produced a similar reduction in the amplitude of the SSEP to a 12' pattern with only one dioptre change in focus. Van der Tweel, Regan and Sprekreijse (1970) found that 1 to 3 dioptres lenses resulted in a 50% reduction in amplitude. The findings seem to suggest that the SSEP is more sensitive to a slight blurring of a pattern than the flashed pattern VEP, which is confounded by changes in intensity as well as pattern, and the effects may well summate in a non-linear fashion. It follows that the VEP to pure pattern stimulation with no intensity change is also particularly sensitive to small changes in the focus of the image particularly when small patterns are viewed (Regan, 1972).

The effect of presenting patterns that are meaningful to the subject are mentioned elsewhere (Chapter 4, section 4.3.). As with abstract geometric patterns, a change in amplitude of particular late components is the most consistent finding, with the late positive component between 190 and 280 m.sec., increasing in amplitude when the potentials are compared with responses to unstructured stimuli. Lifshitz (1966) and Buchsbaum and Fedio (1969, 1970) suggested that the amplitude changes were far greater when the pattern was meaningful, whether it was a complex picture or symbols and words. The problem is, however, that there is often more complexity of colour, contour, and contrast in the meaningful stimuli which may be the primary cause of the larger changes. There was usually no mention of any control of fixation of gaze which is likely to differ with the different classes of stimuli. Garcia Austt and Vanzulli (1970) attempted some degree

of control over these factors by using ambiguous figures and claimed that the wave form changes of the VEP were related to perception and not to changes in the stimulus parameters. They warned that perceptual set and the type of task to be accomplished by the individual have strong influences on the final response shape.

It should be mentioned that clear changes to flashed pattern are not always found. This was particularly pointed out by Dawson, Perry and Childers (1972) when 25% of their subjects showed no difference between a flash presented pattern response and a diffuse flash response, even though all had $^{6}/_{6}$ vision. In the remaining 'pattern sensitive' people, they did not find a simple relationship between the amount of blurring of the pattern using various lenses, with some of the subjects displaying different peaks and troughs in the response at different lens powers. This may have been partly due to the different refractive errors of the subjects, but the authors suggested that the pattern response was very labile, even though a cycloplegic was used to eliminate small changes in accommodation during the accumulation of an evoked response. John, Herrington and Sutton (1967) found that 40% of their subjects showed no consistency with flashed patterns, and 20% of Spehlmann's subjects(1965) showed no significant difference between flash and flashed pattern. Certainly there are huge individual differences in wave-form and White & Bonelli(1970), and Kinney, et al., (1972) were unable to find any clear differences in wave form to different geometric patterns because of such large variations in both amplitude and latency measurements. Spehlmann(1965) in fact suggested that the changes in the late

components of the VEP to flashed pattern stimuli may not reflect processes of pattern analysis, but reflect instead attentional changes with a more intrinsically interesting stimulus.

From a review of the literature it is clear, that a pattern, especially fine patterns which are stimulating the foveal area of the retina, must be clearly focused on the retina, and this makes any work with groups other than cooperative older children and adults very difficult indeed.

5.4. Eye movement problems.

5.4.1. The structure of the eye.

The retina is a highly heterogeneous structure, with an increasing number of both receptor and other retinal cells towards the visual fixation point at the centre of the eye (section 2.2.). The retinal topography is maintained throughout the visual system, and one of the most striking characteristics is the relative magnification of the fovea compared with the rest of the retina, at successive levels in the CNS. Less than 0.007% of retinal receptor elements are within the fovea, which suggests that the ERG is of little use in assessing central retinal function. At the cortex the numerical disadvantage of the fovea has been improved by a factor of 1,000 times, with 7.5% of the striate cortex representing the fovea, and as already mentioned (Section 2.3.) this portion of the visual cortex is most accessible to scalp electrodes. This suggests that the cortical evoked potential may be a useful sign of central retinal function and hence correlate with the potential visual acuity of the eye.

5.4.2. The VEP and central and peripheral retinal function.

What is known of the underlying visual physiology raises general questions. Does the visual evoked potential recorded from the scalp reflect mainly foveal activity, no matter how large an area of the retina is stimulated? At high ambient light intensities does the VEP reflect only cone function? Could VEPs evoked by small discrete points of light contribute any useful information about central and peripheral function? These questions are important since a decision must be made between either using small light sources, which require the subjects to continuously maintain fixation often over quite prolonged periods while the evoked response record is accumulating, or else using diffuse whole field stimulation, where eye and head movements have less influence on the final results.

Most authors who have used small point stimuli, report their findings for cooperative adults. De Voe, Ripps and Vaughan (1968) used 1^{o} flash stimulus, and found that if it was presented 5^{o} eccentrically, the amplitude of the VEP was reduced to the ongoing noise levels. When the light intensities were kept constant, and the size of stimulus increased from 10' to whole field stimulation, the maximum responses and shortest latencies were recorded for a 2^{o} 40' light spot. Eason, Oden and White (1967) only reported on the latencies of the VEP as amplitudes were too variable to be analysed. They found increasing latencies as a 1^{o} light spot was moved from the visual axis to a position 5^{o} away from the centre. The latencies were then stable until some 20^{o} from the retinal centre, when there was a further continuous

increase in latencies towards the periphery. Although Eason, Oden & White (1967) used a similar 1^{o} stimulus just above the threshold intensity, their results differed from others in that between 0 and 15^{o} there was no change in VEP amplitudes. At 20^{o} from the centre of the retina, the amplitudes were one third of the central responses, and remained stable with further increases of eccentricity of the stimulus. The responses of the nasal retina were always of lower amplitude. Ohba (1967) reported no response plateaux but a gradual decline in the amplitude and increase in the latency of the VEP to a 1^{o} white light stimulus, at points of increasing eccentricity on the retina. Potts and Nagaya (1965, 1969) used an even smaller stimulus of 0.06^{o}, and found a very sharp drop in amplitude at 1^{o} from the centre of the retina when evoked responses could no longer be recorded. Although they found a high correlation between recorded responses and subjective perceptual acuity, they reported that attention, and a sharply focused retinal image were very important for good results. The larger stimuli used by Copenhaver and Perry (1964) of 2.5^{o} did not avoid a 50% reduction in VEP amplitudes when the stimulus was 2.5^{o} from the foveal centre, and at 30^{o} no response could be detected. In pattern reversal stimulation, where the pattern elements subtend small visual angles, and therefore only effectively stimulate central retinal areas, Cobb, Morton and Ettlinger (1967) found that the evoked response was drastically reduced if the edge of the target was fixated, and was not present if the subject's eyes were only a few degrees either side of the stimulus field.

The yellowness of the macula is due to the presence of carotenoids, identical to iodopsin. The function of these pigments is believed

to be the filtering out of much of the blue segment of the visual spectrum, thus protecting the low threshold rods in the central area (Polyak 1957). With this in mind colour stimulation, together with high and low light intensities, have occasionally been used in an attempt to separate the rod and cone contributions to the VEP. Eason, Oden and White (1967) found the largest response to a red light spot occurred between 0 and 10°, and no response was recorded more peripherally than 20° from the foveal centre. A blue light produced much smaller responses, with a much flatter amplitude distribution out to 30° from the centre. Potts and Nagaya (1969) found that a 0.06° red stimulus produced visual potentials that correlated well with the known presence or absence of central function in normal and abnormal eyes. A white light of similar size was ineffective. Clynes and Kohn (1967) found whole field stimulation with low intensity blue light produced a small late response between 150 and 250 m.sec. Increasing the light intensity by a factor of one hundred, did not change the amplitude, which suggested this response may be primarily a sign of either peripheral or rod function. The response to red light was much more distinctive and at low intensity the early portion of the response disappeared, while late components after 200 m.sec. were more marked. Small green and red dots subtending a 9' visual angle, produced simpler responses for central fixation. If the small light sources were moved to a position 10° lateral to the centre, the green response disappeared and the red response was small and of longer latency. Adams, Arden and Behrman (1969) by presenting very low intensity blue-green light flashes to a dark adapted eye, believed that they could record a cortical response that truely reflected rod function. No details were given of the

VEP morphology, as there were large variations between subjects from day to day. The authors suggested that intense white flashes reflected the photopic mechanism. De Voe, Ripps and Vaughan (1968) similarly suggested that because of the organization of the visual system, the VEP to bright light was derived from the cone-foveal system.

There is some evidence that optic fibres subserving rods and cones, transmit only cone information when the light intensity exceeds a certain threshold. The mechanism for this may be through the horizontal cells, whose dendrites relate only to the cones, and which are believed to have inhibitory effects on more or less distant rods and cones (Polyak, 1957). Wooten (1972) also agreed that the responses to bright flashes are probably photopic and principally arising from the centre of the retina. With a 5^{o} stimulus and central fixation, clear responses were evoked with a maximum deflection of 11 μv at 150 m.sec. In scotopic conditions of low illumination and dark adaptation, the evoked response was of extremely low amplitude (3μv) with the latency of the first peak occurring between 225 and 325 m.sec; which was not a significant contribution to most visual evoked potentials evoked by bright stroboscopic flashes. Kooi, Tucker, Danial and Marshall (1972) disagreed that there is no peripheral contribution with whole field stimulation; they could not say whether both rod and cone activity were contributing to the response. Central stimulation produced an early negative between 40 and 80 m.sec. which was localized in the occiput, while peripheral stimulation gave a widespread early negative, which was less pronounced in the occiput.

The use of small light stimuli seems to have presented the researchers with problems in the few papers that report its use. Fishman and Copenhaver (1967) found that it was impossible to demonstrate foveal activity behind opacities with restricted light stimulation and recommended at least a 10^{o} light source, since smaller stimuli were too difficult to fixate. Copenhaver and Perry (1964) could not draw any conclusions about the relationship of the size of the VEP to a 2.5^{o} stimulus and visual acuity in patients. Potts and Nagaya (1965, 1969) reported great success in differentiating amblyopic and normal eyes using a 0.06^{o} red stimulus. They stated however that the subjects were adult and very cooperative. The authors are developing a hand held stimulus generator so that they can ensure that the light falls on the central fovea in more difficult patients or in those who are unable to maintain fixation. They have not yet reported any successful findings.

The detailed results of restricted light stimulation of different parts of the retina are inconsistent. This may be partly due to the poor control of entopic stray light, to changes in light intensity with different size sources, and to the possible failure on the part of the subjects to maintain a constant fixation throughout up to six hundred stimulus presentations. There is general agreement however, that if a small light source fails to stimulate the foveal region, there is a marked reduction in amplitude. In situations where the background noise levels of the EEG activity and non cortical artifacts may be high, as is found in a tense patient or an active child, any reduction in the amplitude of the VEP means that the response becomes more difficult to identify.

In most reports on patients and children where careful ocular control is difficult or impossible, whole field stimulation has been used with some success (Vaughan and Katzman, 1964; Dustman and Beck, 1969; Lombrosso, Duffy and Robb, 1969; Lewis and Beck, 1970; Umezaki and Morrell, 1970; Schenkenberg and Dustman, 1971; Callaway and Halliday, 1973; Tsutsui, Nakamura, Takenaka and Fukai 1973).

Discrete retinal stimulation could provide more information about retinal pathology and minor visual field defects. The easiest way to accomplish this is by using pattern stimulation where there is no change in light intensity. However only cooperative patients with reasonable visual acuity can be tested with this method. If small light sources are used to stimulate the eyes the problems of light scatter during each flash are unsurmountable, although the use of high intensity background illumination can provide a partial solution. There is also a need for sophisticated equipment to adjust the position of the stimuli and compensate for any eye movements in uncooperative individuals and in those who cannot fixate, and unless responses recorded while the eye is moving can be rejected, whole field flash stimulation is the best compromise. This is particularly the case in patients where gross eye movement and head movements are fairly continuous.

CHAPTER 6

The clinical application of the flash visual evoked potential.

6.1. Introduction

It is still not certain just how closely either the pattern or flash potential reflects visual processing. Even when attentive, cooperative, young adults are used as subjects, the results can often be inconclusive because of the very high variability between individuals. Doubts are, therefore, raised as to whether evoked potential recordings are at all worth while as an aid to diagnosis in the far more difficult clinical situation, where during the recording eye movements may be continuous or uncontrollable, central fixation impossible, the patients tense or uncooperative and accurate electrode placement difficult.

Despite the present lack of knowledge evoked potentials can provide a valuable contribution. Firstly, there is the problem of the significant species differences in organization and functioning of the visual system, and the questionable validity of applying animal experimental models to man. The clinical situation provides a useful basis for evaluating the hypothetical models constructed from animal work and normal research. There are always limitations on how useful clinical interpretation can be, since it is never, or rarely, the case that a complete understanding of the underlying pathology is obtained. Yet investigations of clinical manifestations and the underlying pathology remain the principle way of disclosing the intrinsic organisation in man.

On a more applied medical basis, the second justification for evoked potential studies in patients is that evoked response techniques may be able to supplement standard diagnostic practices. Reliable recordings of cortical evoked potentials involve the

meticulous application of fairly rigorous techniques. Expensive equipment is usually needed, and with the present methods of analysis, the recording time can be long and tedious. Because of these practical difficulties and the present state of the art of evoked potential interpretation, the standard diagnostic practices which require some recognisable behavioural or verbal response from the patient during testing, and keen observation by the diagnostician are far superior, being quicker and more accurate.

There are, however, situations where standard diagnostic techniques fail. This is usually, when the patient is unable to, or refuses, to communicate any information, or when the clinician fails to observe any symptoms. This situation often arises in neonates and young infants, whose behaviour is often too diffuse to be clearly recognised as a specific response. Children with brain damage often involving motor disorders and failure of verbal communication, and behaviour disorders in general, usually present similar problems of diagnosis to the clinician. In adults difficulties can arise in cases where the symptoms are probably of psychogenic origin, where the patient in unconscious or when a disease may be obscured by other symptoms as in the nature of a retina behind a dense cataract.

6.2. Visual field defects

6.2.1. Etiology

Because of the precise anatomical organisation of the visual system, when any part of the input pathways is damaged, there is a predictable corresponding area of visual loss. This loss

of function can be a total blindness or a partial loss of pattern or colour descrimination. Sometimes the impairment is so slight, that the defect goes unnoticed by the patient.

To a certain extent the type of field defect depends at what level the damage occurs within the visual system. At the retina the principal defects are amaurosis (blindness in one eye) or a scotoma which can be central, sector or annular in form. The pathology is typically unilateral or incongruous, even if both retinas or optic nerves are involved. Because of the position of the fovea, temporal to the blind spot, the temporal retinal bundles are not arranged radially, as in the nasal retina, but come together as sweeping tracts above and below the fovea. Therefore, lesions at these points near the centre may involve more than the immediate retina, forming an annular or ring scotoma, generally ending at the blind spot. This type of visual defect is characteristic of glaucoma.

Because of the small size and compact nature of the optic nerve, any pathology of this part of the system tends to produce very global symptoms. Enveloping tumours and inflamatory and toxic processes will first effect superficial areas of the nerve, impairing peripheral vision, with a gradual contraction of the fields as central vision becomes involved. Peripheral lesions are generally the result of trauma, infections, pathology of the eye or some toxic agent.

At the chiasma, foveal representation runs along the posterior margins, resulting in frequent bitemporal, central and paracentral

scotomas, when damage occurs at the chiasma. Pathology is commonly caused by pituitary or hypothalmic tumours , and only 50% of lesions result in optic atrophy (Polyak,1957). Nasal hemianopia is rare, and caused by the bilateral interruption of the blood supply.

Lesions above the chiasma are easy to distinguish from pre-chiasmal lesions, because the right and left tracts become quite widely separated, and often damage to one side does not involve inputs on the other side of the brain. Characteristically there is a symmetrical visual field defect contralateral to the side of the pathology. The optic tract is much more widely spread than the optic nerve, and more selective damage can occur, although the defects rarely exhibit straight boundaries, unless there is a total loss.

Within the lateral geniculate nucleus small isolated injuries involving one sector are very rare, and injury generally results in large losses.

Within the optic radiations and the striate cortex the inputs from the right and left eyes are now intimately mingled, and any field defect is congruous in shape, size and location. There is also a dispersion of the channels from the various retinal regions, and therefore, a far greater probability that small lesions will produce small discrete field defects. Some damage may be so localised that the visual impairment is too elusive to be determined by standard perimetry, and is manifest by such decreases in function as either a drop in the visual acuity (amblyopia) a blurring of objects or a dimming of colour vision. Central lesions

are generally the result of a haemorrhage or embolism, arterial sclerosis, spastic ischaemia, infectious diseases, tumour or trauma.

When a central lesions results in a loss of vision in corresponding areas of both halves of one visual field, the visual defect is termed homonymous hemianopia. There are two basic types. A field defect which extends to the vertical meridian (complete homonymous hemianopia) is frequently the result of a total optic tract lesion in or near the internal capsule, and other sensory and motor systems may also be involved. It is rarely the result of damage to the widespread optic radiations and striate cortex. The second form of field defect with central lesions is incomplete homonymous hemianopia, which occurs quite frequently. Here there is central sparing, which does not usually extend more than one half to three degrees beyond fixation. In a few cases there can be up to seven or eight degrees of sparing, which is always congruous (Polyak, 1957). This frequent presentation of central sparing has raised the question of how this can occur. Amongst the explanations are the existence of bilateral foveal connections, bilateral representation in the striate cortex with inputs from both the lateral geniculate nuclei, or, asymmetric division of decussating and non-decussating fibres. The most likely explanation is that the striate cortex at the occipital pole receives a multiple arterial supply, so that any arterial catastrophy will not eliminate the support system to cortical areas dealing with central vision, although more peripheral representation will suffer (Polyak, 1957). There are two problems with homonymous hemianopia, the first is that the boundaries of the defect do not have a clear cut-off

point between sight and blindness, but there is a transition zone with reduced vision. The second problem is that patients with total homonymous hemianopia often displace their point of fixation, which makes standard perimetry difficult.

Partial or total blindness occurs in man after damage to the visual pathways and the striate cortex. Higher order disturbances in areas 18 and 19 do not produce visual field defects, but since these areas maintain the topographical representation of the retina, discrete damage may cause visual agnosia or colour loss within some corresponding parts of the visual field. There is no loss of visual acuity.

6.2.2. The flash VEP and visual field defects.

The use of animal models in monitoring scalp VEP changes in gross field defects has failed to clarify the findings that could be expected or have been reported in man. Jacobson, Hirose and Suzuki (1968) recorded no VEP from the cats cortex to left eye stimulation after transection of the left optic nerve, while no cortical response was elicited in the contralateral cortex following chiasmal damage. On the contrary Frommer, Galambos and Norton (1968) found that the cortical potentials were only minimally effected after lesioning up to 90% of the optic tract, and suggested that the organisation of the retina with no foveal region meant that a normal VEP could be supported by very few fibres in the cat. Vaughan and Gross (1969) worked with primates and found support for their clinical studies by recording a reduction in the flash VEP of 50 to 75% over the damaged occipital area, while anteriorly the response was bilateral. Cohn (1969) was discouraged after producing homonymous

hemianopia in twelve monkeys and suggested that the flash VEP was nonspecific, bore no fixed relationship to the classical pathways and had therefore only very limited value in mapping visual field defects. He had recorded significant asymmetries shortly after surgery, but in time the VEP had showed an almost complete recovery. The unsatisfactory results may have been more a reflection of his limited recording technique, rather than the cortical potentials themselves.

The first attempts to use electrophysiological recordings for assessing visual field defects in man looked at the effects of photic driving on the EEG. Woolfe (1942) could produce photic driving in the monkey about 75% of the time. When the macula was destroyed photic driving was obtained on only 35% of the occasions. Weil and Nosik (1952) and Grader and Heller (1964) have used similar techniques with patients, and reported reduced photic driving and less alpha blocking when the damaged part of the visual system was stimulated. The authors failed to quantify the differences, and did not mention such problems as the rapid habituation of the alpha blocking response, the possibility of the alpha rhythm being absent or very reduced in the normal EEG, and the failure of many normal eyes to produce clear photic driving.

The VEP has been almost universally acclaimed as providing valuable information in cases where blindness is suspected but cannot be confirmed, as can occur in very young children or when the symptoms are believed to be psychogenic rather than neurological (Barnet, 1971; Duchowny, Weiss, Majlessi, Barnet, 1974; Abraham, Melamed, Lacy, 1975; Kooi, Yamada, Marshell, 1975; Harding, 1977).

If no response or only a minimal potential can be evoked to bright light flashes then the patient is cortically blind.

Better reliability was found in the cortical evoked potential compared with EEG activity when Vaughan, Katzman and Taylor (1963) produced the first results on the diagnostic value of the flash VEP in visual field defects. They looked at 30 patients with homonymous hemianopia, together with normal controls and patient controls with unilateral lesions but with no visual field defect. Recording from O1 and O2 (International 10-20 system, Jasper, 1958) their normal primary evoked response to high intensity flash stimulation consisted of wave 1 (negative component at 35 to 40 m.sec.),wave 2 (a positive at 45 to 55 m.sec.) and wave 3 (a negative at 60 to 65 m.sec.). In the normal controls the primary visual response was fairly symmetrical. There was some variation of the VEP within the clinical control group; wave 1 was absent either bilaterally or unilaterally in 33% of the subjects, while waves 2 and 3 were missing in one individual. In patients with homonymous hemianopia, wave 1 was absent on the normal side in 25%, and waves 2 and 3 in 20% of the group. In the brain damaged control group wave 2 was significantly reduced on the damaged side, while all three waves showed an even greater reduction in hemianopia. Similar results were found for the latency of the components, which were significantly delayed on the damaged side in both groups of patients, but particularly in the hemianopic group. The authors suggested that if the asymmetry in the amplitude of the VEP was greater than 50% this would distinguish between homonymous hemianopia and normal vision at the 1% confidence level. Sixty four per cent of hemianopic patients showed a greater

than 50% asymmetry between the VEP in the right and left hemispheres, but the authors noted that some patients with dense hemianopia failed to reach the criteria. They also pointed out that for accurate assessment the placement and impedance values of the electrodes were very important. The reference electrode in their monopolar linkage remained an underlying problem, and attention and arousal may have presented intervening variables. In the following year (Vaughan and Katzman, 1964) additional patient material confirmed the 50% asymmetry criterion, and they suggested that wave 2 was the most reliable component, as the remaining parts of the primary response were sometimes absent or very variable in the normal population. Later portions of the VEP often remained unaltered with field defects. Barlow (1960) had previously reported that only the late portions of the visual response were effected on the pathological side. A similar percentage of patients with homonymous hemianopia as was found in the previous study, presented greater than 50% reduction on the damaged side, but those patients with significant central sparing (10^{o} or more) did not differ significantly from normal.

After such hopeful beginnings other results have been disappointing. Cohn (1963) and Jacobson, Hirose and Suzuki, (1968) did find a significant reduction in the amplitude of the VEP components when the visual field defect spread as far as the vertical meridian. If there was any central sparing, waves 1, 2 and 3 could be normal, reduced, delayed or absent (Jacobson, Hirose and Suzuki, 1968). Gastaut and Regis (1965) found it impossible to confirm Vaughan and Katzman's results (1963, 1964), because one or more of the important components of the evoked potential were missing in 80%

of their normal groups, and they could not accept the vertex reference position. Gastaut and Regis found that the greatest change occurred much later in wave V (a positive at 110 to 120 m.sec.),and in the after discharge,both of which were significantly reduced over the hemisphere contralateral to the visual defect. High frequency flicker evoked responses were a better indicator of visual pathology, as normal subjects showed less hemispheric variation to this form of stimulation with no more than 17.5% difference between the right and left hemispheres. Oosterhuis, Ponsen, Jonkman and Magnus (1969) found that abnormality in waves 1 and 2(i.e. greater than 50% asymmetry) did not necessarily correlate with visual pathology, and they believed that wave 3 was a better indicator of visual impairment. As much asymmetry was found in patient controls with unilateral lesions as with homonymous hemianopia by Jonkman (1967),and asymmetry of the primary response was always associated with an asymmetry of the secondary response,particularly if the midline was displaced. Both portions of the VEP were reduced when lesions occurred in the parieto-occipital area of the brain,or in the visual pathways. The VEP was also seldom symmetrical if there were focal abnormalities in the EEG. He suggested that because of the severe limitations on its usefulness and the elaborate techniques that were used,cortical potentials were not suitable for routine clinics. Kooi (1965)did not believe that the criterion of amplitude asymmetry was at all useful,and found occasionally that there was an ever larger response on the pathological side in hemianopic patients. Peak latency times were more reliable,with longer latencies always occurring in the hemisphere contralateral to the field loss. Creutzfeldt and Kuhnt (1967)doubted the diagnostic value of evoked potentials,for the only times they found a large reduction, or a disappearance of the VEP after damage to the visual system,was

when there were clear changes in the EEG. When there was no EEG asymmetry there was no significant difference between the evoked potentials from the two hemispheres.

Crighell and Botez (1966) reported the flash VEP findings in patients with unilateral occipital ablations. The majority showed a significant reduction in the whole response over the damaged side,but a few had larger responses that they suggested was evidence of "deviation" in the function of the cortex. The recordings were however bipolar with the inion as one of the electrode positions. Perhaps a less exotic explanation might have been that the larger potential differences recorded were due to a reduction in the response from the parietal region of the damaged hemisphere. Lehmann,Kavanagh and Fender (1969) used bipolar linkages and recorded from electrode chains across the back of the head. They looked at one patient with a split chiasma, which resulted in clear bitemporal hemianopia up to the vertical meridian. With monocular stimulation the contralateral evoked potential was very similar to the ipsilateral side. The latencies were the same,and the amplitude was only slightly reduced. The authors found, however,that the primary evoked response reversed polarity in the contralateral hemisphere,while the secondary response was the same polarity for the right and left hemisphere. The head is a good, homogenous,linear conducting medium,and the evoked potential from the activity of one source can occur over a wide area. The primary response (0 to 160 m.sec.)that Lehmann recorded was probably from a single source in the ipsilateral cortex,while the secondary portion (180 to 250 m.sec)had a multi source origin. Kooi,Yamada and Marshall (1975) pointed out the difficulties that are involved in attempting to monitor asymmetries in visual function when the two visual cortices,especially those areas representing the maculae, are medially placed.

Potentials recorded over the involved hemisphere may well be generated in the opposite cortex. In an attempt to avoid these difficulties they mapped the evoked potential distribution over the scalp in one patient with bitemporal hemionopia. Normal distributions were symmetrical with the peak amplitude of waves 1 and 2 (a negative at 35 m.sec. and positive at 50 to 80 m.sec.) occurring over the mid-occipital region, while wave 3 (a negative at 80 to 90 m.sec.) had a maximal amplitude more anteriorly and laterally. In the patient, waves 1 to 4 (0 to 130 m.sec.) arose only in the ipsilateral cortex, but it was not possible to say whether the source was striate or parastriate. Later waves were widespread and symmetrical, and probably non-specific. A surface negative occurred on the side opposite to the primary visual input, in conjunction with the ipsilateral wave 2, which the authors suggested was a potential mediated by commisural structures. Harris and Bickford (1967) also looked at spatial maps of the visual evoked potential. Compared with the normal population, homonymous hemianopics produced very asymmetrical distributions with a large positive peak moving across from the intact to the blind hemisphere.

These are the only two studies reporting useful topographical information in visual field defects, and the majority of later papers have failed to clarify the typical VEP changes in gross field defects. The papers were frequently case study reports which have minimal validity when attempting to identify visual pathology in other patients, or else the normal criteria were not quantified, or clinical control groups were not used to ensure that the changes recorded in the VEP were not the effect of some

other clinical condition unrelated to the visual disorder (Saletu, Itil and Saletu, 1971; Cohn, 1973; Duchowny, Weiss, Majlessi, Barnet, 1974; Pouliquen et. al., 1974; Howe, Harcourt, 1976; Babel, Stangos, Korol, Spiritus, 1977). Cohn (1973) reported that asymmetries of more than two millimetres between the two hemispheres was significant, which raised some doubts as to the calibration of his recording system. Howe and Harcourt (1976) were among the few to quantify their results, with criteria for abnormal hemispheric responses based beyond three standard deviations of normal amplitude and latency hemispheric ratios. Only the primary portion of the VEP was measured although it was not stated which components were used. Complete homonymous hemianopia was identified in 83% of patients with cardiovascular accidents, and in 86% of those with space occupying lesions. Only 60 to 66% of those with macula sparing were clearly identified as abnormal. Such findings are an improvement on the early correlations of Vaughan and Katzman (1964).

The use of patterned stimulation rather than flash in the assessment of field defects means that the closer control of the stimulus parameters can provide more consistent findings particularly where there are subtle visual disturbances (Bodis-Wollner, Hendley, Atkin, 1977). One drawback is that cooperation and adequate refraction is needed to view the stimulus, and in these cases standard perimetry is feasible and produces better results. Wildberger, Van Lith, Wijngaarde and Mah (1976) used full field, pattern reversal stimulation in patients with hemianopia (the pattern size was half a degree) and their results showed no improvement

over flash stimulation with only three of the six patients with cortical lesions displaying a significant asymmetry (greater than 50%). Bitemporal hemianopia resulting after optic nerve damage at the chiasma, produced very significant general disturbances which obscured the changes related to the primary field defect. There is in fact some debate as to whether the ipsilateral or the contralateral pattern response is more abnormal in hemianopia, and factors such as pattern and field size and bipolar or monopolar electrode linkages are important (Barrett, Blumhart, Halliday and Kriss, 1976a, 1976b; Shagass, Amedio and Roemer, 1976; Holder, 1978). Barrett et. al. (1976) used a 50' check size which maximally stimulates parafoveal vision which projects on the medial surfaces of the occipital lobe. Such a source is best viewed by ipsilateral electodes. Halliday, et. al. (1976) reported that delayed pattern VEPs were frequently recorded with chiasmal compression and hemispheric asymmetries were a key feature, although the direction of the asymmetry was not always associated with the visual field defect.

The foveal contribution to the scalp evoked potential is overwhelming with the entire response arising within the central 2 to 8^{o} in conditions of high illumination (Van Balen and Henkes, 1960, Potts and Nagaya, 1965; Vaughan, 1966; Armington, 1968, 1977; Kooi et. al., 1972). Thus it is likely that the VEP is more sensitive to central macula degeneration and shows very little change in cases of peripheral degeneration. Not a great deal of work has been produced on flash evoked potential correlates of small areal defects, possibly because of the difficulties in stimulating specific retinal points in patients, and also possibly because of the lack of consistent success with VEP predictors in gross field defects.

In retinitis pigmentosa the VEP shows no changes until the late stages of the disease, and in cases where no ERG is recorded the visual response may be normal, delayed or absent (Jacobsen, Hirose, Suzuki, 1968; Muller, 1968; Borda, 1977; Sandberg, Berson and Ariel, 1977).

Copenhaver and Beinhocker (1963) detected significant reductions in the amplitude of the VEP within retinal areas with small scars when using a low intensity stroboscopic flash subtending 1.25^{o} or 2.5^{o} of field. Best results were obtained within the macula, and no response was elicited when the blind spot was stimulated, indicating that there were no problems with light scatter. Larger stimuli produced a normal response and the authors reported very high variability in some of the recordings which were attributed to head movements and unsteady fixation. They also mentioned that the technique was very fatiguing, and was not feasible in a number of patients who had been insufficiently cooperative. Fishman and Copenhaver (1967) stimulated central vision with a confined light source from an ophthalmoscope introduced by direct observation of the retina. Using a 3^{o} light source, patients with macula lesions were significantly different from normal controls with a reduction of the evoked potential amplitude to about 33 to 50% of normal. When the 12^{o} light source was used most of the differences were lost.

Most successful reports in cases of macula degeneration used small light sources between 1.5^{o} and 8^{o} of field (Potts and Nagaya, 1965; Van Balen, Dernier van de Gon and Hellendom, 1966; de Haas, 1972; Babel et. al., 1977; Sandberg, Berson and Ariel, 1977)

with no recordable cortical potentials when vision was less than 6/60. Muller (1968) found that the large positive component with a latency of approximately 100 to 120 m.sec., was selectively reduced in macula degeneration. Van Balen et. al., (1966) pointed out that although small light sources evoked significant VEP abnormalities in dense scotomas, the technique failed to detect early degenerative stages, diffuse retinal degeneration where the periphery was altered as well, or where macula function was altered but not destroyed.

Pattern stimulation has also been used very successfully in retinal pathology (Sokol, 1972; Orpin, Orpin and McCulloch, 1974), although acuity needs to be 20/80 or better, and patients with cataracts had to be excluded (Cappin and Nissim, 1975).

Very little work has been done using the flash VEP to assess visual function in dense opacities of the media, although in such cases the retina is often obscured from view and visual capabilities are in doubt. The ERG is frequently monitored in such conditions, and the corneal opacities have markedly little effect on the retinal response (Galloway, 1975) which could certainly mean that flash VEPs are feasible. Only one study has been found in the literature,Fricker (1971) used steady state evoked potentials to assess vision behind unilateral cataracts, using the patients as their own controls. The author looked at the amplitude and phase relation of the evoked potential at different frequencies of stimulation. Good vision produced a linear phase/frequency plot, and the amplitude was greater than " - 15dB with respect to 1 μv". In a control patient group with macula defects, but

with no cataracts, the evoked potential was of lower amplitude, with a sudden reduction to noise levels at high frequency stimulation, and the phase/frequency relation was non-linear. Using these criteria, 28% of the cataract patients who were predicted to have good vision, had low visual acuity postoperatively. All these patients had retinal damage, such as, macula lesions, extensive diabetic retinography, severe glaucoma, etc. Twenty-four percent of the patients who were predicted as having poor sight, had good vision postoperatively. The patients included senile cataracts, a dislocated lens and trauma cases. The author suggested that the greatest problem is the huge variation in the evoked potential recording due to the low amplitude of the evoked potentials, and the delays and interaction with the central nervous system and EEG. Arden and Sheoney (1977) have attempted to assess visual function behind opacities using a new method of laser interferometry. Subjective responses to the interference patterns are unreliable since aberrations in the eye can cause the fringes to appear broken and fine fringes can be severely masked. The patients were stimulated with a two cycles per degree pattern at 8 Hz., and a response was abnormal if it was absent or very much smaller than the other eye. The first studies have been case reports and this technique awaits validation.

6.3. General clinical applications of the VEP.

The flash VEP and ERG have been reported to be useful in monitoring cerebral function in comatose patients, and the cortical response can be a more sensitive indicator of CNS stress than the EEG (Bergamini and Bergamasco, 1967; Arfel, Albe-Fessard and Walter,

1968; Walter and Arfel, 1972; Adler, Kacer, and Mensikova, 1975; Reilly, Kondo, Brunberg and Doty, 1978) although the prognostic and diagnostic value of the VEP is still in doubt as the main changes in the cortical potentials closely parallel the ongoing clinical condition (Feinsod, 1976; Ommaya, 1976). Feinsod and Auerback (1973) suggested that the flash VEP can provide important information in unconscious or confused patients after injuries where damage to the optic nerve can be sustained even without fractures traversing the optic foramen or without tearing of the sheaths of the effected nerves.

Flash VEPs and ERG provide valuable monitoring in progressive metabolic storage diseases in childhood where the outcome is hopeless (Harden and Pampiglione, 1972, 1977). More information is obtained in serial testing and the evolution of parameters which are characteristic of each storage disease. Early electro-diagnosis is possible and important for prognostic and genetic considerations. Only flash stimulation is possible in these patients and by monitoring the ERG, VEP and EEG, an opportunity is gained to study the progressive involvement of the retina, pathways and maturing brain.

The success of the pattern VEP in detecting demylenating lesions within the visual pathways particularly in multiple sclerosis is indisputable (McAlpine, Lumsden and Acheson, 1965; Halliday, McDonald and Mushin, 1972, 1973, 1974, 1977; Wybar, 1972; Cook and Arden, 1977; Lehmann et. al., 1969; Regan, Milner and Heron, 1977; Duwaer and Spekreijse, 1978; Persson and Sachs, 1978) and the criteria of abnormal and normal responses are thoroughly researched. There is some variation in the reported success rate

in detecting abnormal pattern responses in definite and probable cases of multiple sclerosis (between 67% and 96% correctly identified) and the large delays recorded in the response are not specific to the plaque formation in multiple sclerosis but can occur with optic nerve compression, nutritional and toxic amblyopias, ischaemic atrophy etc. (Asselman, Chadwick and Marsden, 1975). Ellenberger and Zeigler (1977) and Feinsod et. al., (1977) found that the flash VEP was also a sensitive and reliable indicator of the presence of multiple sclerosis and was particularly useful in the acute stages of optic neuritis when visual acuity is severely impaired.

The VEP has been extensively reported in amblyopia which is a common condition where impairment of pattern vision cannot be corrected by changes in the visual optics, and where there is no definite retinal or central lesion. Spekreijse et. al., (1972) suggested that amblyopia is found in 3% of the adult "non-clinical" population. Graham(1975) quoted that 1 to 2% of children suffer from some amblyopic defect.

The most important concept in understanding the mechanism of amblyopia is the importance of the critical period, when the brain of the newborn is going through a very active period of growth and differentiation, and therefore has a high degree of plasticity. During this time the environment can exert its greatest effect on brain development.

A loss of visual acuity can occur for a number of reasons. It can be caused by direct trauma to the system, such as toxic agents and visual function is reduced, but not abolished. It may be of so called "psychogenic origin", where the patients history

suggests no underlying developmental or organic causes, and standard diagnostic tests may reveal variable and unconvincing responses. There may also be some indication of environmental stresses, and personality problems which may support a withdrawal of visual contact. A large percentage of cases of amblyopia are due to aberrant developmental processes. If a young child has a very high refractive error, which is not corrected at an early age, no clear image is focused upon the macula and an irrepairable loss of visual acuity occurs. Similarly, if pattern stimulation is effectively removed by some congenital defect such as cataracts, lens abnormalities etc., or after some birth trauma, amblyopia will result. The final largest group of ambylopics occurs when there is ocular motor imbalance. In the normal visual system it is amazing how precisely these two bilateral organs are aligned. If, however, one eye develops a divergent or convergent squint, suppression amblyopia may occur to a varying degree.

There is a finite time in the maturing visual system when correction of the light focusing abnormalities will reverse the process of poor acuity, and pattern perception will begin to improve. This period of readjustment is far longer in man than in animals and can occur up to the age of about 7 years (Crews, 1974). After this time no treatment will produce any clinical improvement.

Many authors have found no significant difference in the VEP to unstructured light flashes in the amblyopic eye (Fishman and Copenhaver, 1967; Lombroso, Duffy and Robb, 1969; Bourassa, Singer, Mills, Lynch and Groesbeck, 1971; Spekreijse, Khoe and Van der Tweel, 1972). Alternatively, the VEP may be reduced in amplitude,

changed in form or delayed (Van Balen and Henkes, 1962; Hata, 1966; Nawratzki, 1966). Whether the evoked response differences can be obtained from an amblyopic eye may depend on several factors. Firstly, the site of the scalp recording may be important, Lombroso, Duffy and Robb (1969) found significant changes in only one small group of amblyopics after careful mapping of the visual cortices. It may also depend on the method of flash stimulation. Potts and Nagaya (1969) used a very small red flash (0.06^{o} visual view) to stimulate only the central retina, and there was a diminished or absent response from the amblyopic eye. An increase in the stimulus size to 0.6^{o} subtense eliminated any differences between the amblyopic and normal eye.

Another factor which may play an important part in the VEP findings in amblyopia is the underlying clinical history of the pattern impairment. In Hata's group of amblyopes (1966) visual potentials from patients with stabismic amblyopia were not significantly different from normal. Anisometropic amblyopia produced a significant reduction in a particular "b" component around 100 m.sec. Tsutsui, Nakamura, Takenaka and Fukai (1973) studied 93 patients who had monocular visual impairment due to either stimulus deprivation (cataracts), stabismus, enisometropia or ametropia. The most dramatic findings was an absent response to either pattern or low intensity flashes which was seen most commonly in the stimulus deprivation group (33%), and no response was also seen in 8% of those with strabismic amblyopia.

Far greater differences are apparent in the evoked potential when various patterns are presented to the amblyopic eye, rather

than light flashes. The visual potential is usually of lower amplitude, and less complicated waveform compared with the normal eye or, is no different in form to a flash VEP, if the pattern is presented as pattern appearance and disappearance with a change in intensity (Spekreijse et. al., 1972; Tsutsui, Nakamura, Takenaka, and Fukai, 1973; Yinon, Jakobovitz and Auerback, 1974). The degree of difference compared with the normal eye depends on the amount of impairment of visual acuity, and the results are the same as the effects of defocusing during pattern presentation (Eason, et. al., 1970).

When pattern reversal is used to stimulate amblyopic eyes the cortical responses are of very low amplitude or absent depending on the pattern size and the degree of visual impairment (Behrman, 1969; Behrman and Levy, 1975).

6.4. Summary.

Many hopeful reports have raised the possibility that the flash VEP can be used as an indicator of underlying visual pathology, but no results as yet have managed to withstand replications in different laboratories with similar or different stimulation and recording techniques. The reported testing procedure is often too demanding and exhausting to be useful in a standard clinical situation, or else the results prove too variable to be completely relied upon.

One of the greatest problems in all cases of visual field defects is the medial placement of the visual cortices, particularly the areas of foveal representation, and frequently a normal visual potential is consistently recorded over the involved

hemisphere. The further away the second or reference electrode is moved the greater the problem. Multichannel mapping of visual potential generators in normals and patients with visual defects may solve some of these difficulties.

Another, perpetual problem is the interaction between the unwanted "noise" of the background EEG and the configuration of the VEP. Even in patients with no suspected brain damage there may often be far more cortical artifacts, greater variability in the EEG, and perhaps more rhythmic alpha and theta activity than in normal control groups. This is because of the very fact that patients are often unwell, or may have reduced visual acuity or are merely anxious about their symptoms. Thus the initial signal to noise situation is far less satisfactory than in the laboratory situation, where subjects are healthy, alert, and frequently used to the experimental environment. These problems are greatly increased in patients with central neurological signs which may or may not be related to the visual impairment. These abnormalities may result in an EEG with continuous or occasional high voltage slow waves or epileptogenic activity, which may obscure or transform the VEP which is recorded during such activity.

Finally, in many clinical cases pattern presentation, preferably without changes in stimulus intensity, provides a much more elegant method for testing changes in visual acuity and correct visual functioning generally. The pattern elements must be small (10 to 20' of arc) to adequately stimulate the foveal areas and avoid luminance effects that larger patterns produce, and there is a constant problem of maintaining fixation for the period of the

accumulation of the evoked potential, which is fatiguing for any subject. Patients, especially the young and ill, may not keep the pattern in focus, or even within the centre of gaze, and any lapse will confound the results. Simple problems of accommodation and inattention may so easily be misinterpreted as reduced visual function or pattern impairment. Such difficulties have been recognised by Regan and Milner, (1978). If VEP techniques are to be useful as a clinical diagnostic tool, more reliable results must be obtained with techniques which are practical in the most difficult clinical situations.

CHAPTER 7

The flash VEP in the normal population, and the development of criteria to distinguish between normal and abnormal VEPs

The work described in this dissertation concerns the development of VEP techniques that would be suitable and reliable in clinical diagnosis. One of the primary advantages that electrophysiological recording provides, which is so important in clinical work, is that consistent results can be obtained with very little, or no cooperation from the individual being investigated. The VEP provides the most valuable information where standard diagnostic tests fail, and almost by definition this involves working with difficult patients. It was anticipated that referals to an electrodiagnostic clinic would include infants, brain damaged children with communication problems and behaviour disorders, adults with dense opacities of the optic media which prevent the assessment of visual function with standard procedures, individuals with visual disturbances that are suspected to be non-organic, comatose patients and many others. With such patients as these, cooperation could not be relied upon, attention and arousal would be difficult to control, and eye fixation and maintainence of accommodation difficult or impossible. Although many have reported that patterns are physiologically a more suitable method of stimulating the visual system (Hubel and Wiesel, 1962, 1965, 1968; Dreher, 1972), and at least in a normal population elicit far more consistent VEPs (Michael and Halliday, 1971; White, 1974), it is not a suitable form of stimulus with difficult patients or where there are eye opacities, and flash stimulation is the only practical method of stimulating the eyes and getting some information about visual function. Apart from being the most suitable stimulus in some clinical situations

flash stimulation is very quick and easy to use; an important factor in a diagnostic setting. The eye can be flooded with the light of high intensity flashes generated by a stroboscope, and even if the patient is not looking directly at the lamp, entopic scatter ensures that most of the retina is adequately stimulated. There is also very little change in the VEPs as the distance of the stroboscope varies, at least between 15 and 50 centimetres from the subject's eyes (Jonkman, 1967). All these factors are an advantage when working with unsophisticated and poorly cooperative patients. This study considers that the most important aims when considering the methods of visual stimulation are;

1) That the recording procedures must produce an 'optimal' VEP, that is we are certain of recording the maximum and most consistent response from a patient
2) That the recording procedures require a minimum of cooperation, cause minimum discomfort, and take the shortest time possible
3) That the recording techniques are easy to use by all staff concerned with assessment.

If flash evoked potentials are to be useful in the diagnosis of visual disorders, then they must vary consistently and uniquely with that disorder, and differ significantly from control groups with no visual disorders. It is therefore necessary to determine the degree of variation found in normal groups of individuals, or in control groups of patients when the recordings are made in the same conditions as the diagnostic clinic.

The normal VEP to flash stimulation was studied in 120 volunteers, whose ages varied between 6 and 78 years. The topography of

the flash VEP was studied to identify the site of the largest responses and the spread of time locked potentials to other scalp positions. At the same time, electrodes were identified that were vulnerable to interference from non-cortical sources, and assessment was made of possible reference sites. Variations of latency, amplitude and wave form of the VEP were measured, with particular reference to the age of the individual, so that normal VEP criteria, and significant age related changes could be firmly established.

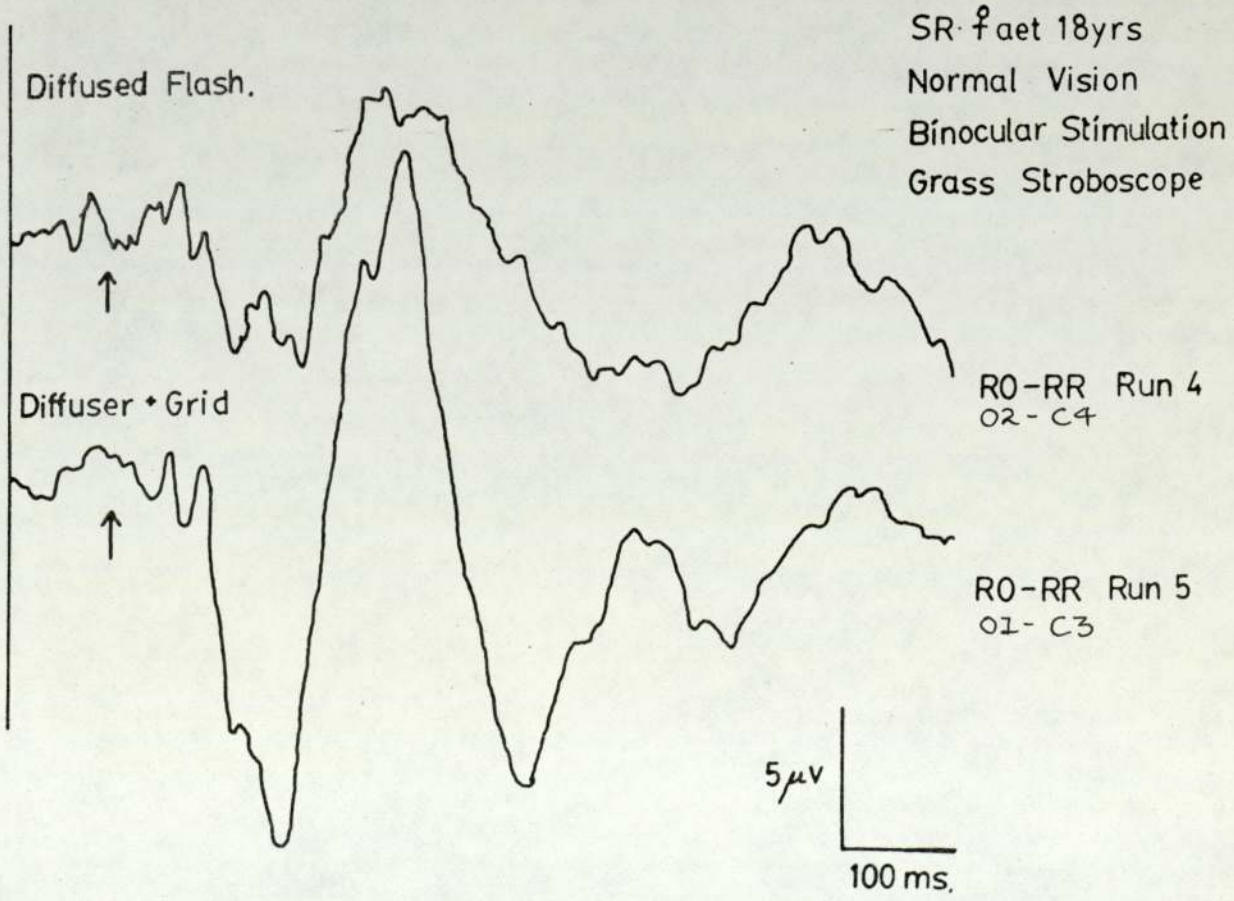
7.1. Equipment and Recording Procedures

Both subjects and patients either sat in a comfortable chair or lay on a bed in a quiet dimly lit, sound damped room, separated from the investigator and his equipment. Very few constraints were placed on the subjects except that they should relax and remain as still as possible, watching the stroboscope while the light was flashing. The eyes were not mydrilated, and the head was not fixed, although it was supported to reduce muscle activity. A careful check was made of eye movements, particularly if they were suspected of contaminating the recorded averages. There was no special instruction to manipulate attention, since this is a complex phenomenon depending on the task, and is difficult to manipulate even in a cooperative population. The best solution is to optimize the stimulus situation by using high intensity stimulation which minimizes the effects of attention which are small anyway (Rietveld, Tordoir and Hagenouw, 1966; Kopell, Wittner and Warwick, 1969). Schechter and Buchsbaum (1973) found that attentional effects only approached significance

when low intensity stimuli were used, and the pupil diameter had no effect on the results. They reported that the amplitudes of the VEPs with no instructional set were the most similar to vigilance tasks requiring attention, and suggested that it was best to maintain a relatively uniform, low attention state, since elaborate instructions may produce disparities between normal controls and the clinical population.

Occasionally, when appropriate in a clinical session a geometric pattern was superimposed on the diffused light flash to improve the amplitude and wave form of the VEP (Fig. 2).

FIG. 2.
CHANGES IN THE VEP WITH DIFFUSED AND PATTERNED FLASH STIMULATION.



Flashed patterns have been reported to produce larger evoked potentials (Harter and White, 1968; Armington, Corwin and Massetta, 1971; Ristanovic, 1971), and in a clinical setting this procedure can help to identify the various components of the VEP, which may be very variable with diffused flash stimulation.

7.1.1. Electrodes

Electrodes provide the essential interface between the subject and the recording apparatus, and sound techniques are vital if the results are to be reliable and unchanging through often a long recording session. The EEG was recorded using Beckman 7mm silver/silver chloride electrodes which were glued firmly in place to minimize artifacts arising from changes in the electrode contact area, and to ensure that the electrodes remained in place even with a restless child. The contact resistance of the electrodes was always between two and three kilohms , and care was taken that there were no significant differences in the resistances of the many electrodes applied to the scalp, as this can effect the form of the VEP recorded (Vaughan, 1972).

7.1.2. Electrode Placement

One important problem when reading and comparing the literature on VEPs is the large number of electrode sites used. One common method of selecting electrode positions is to measure a fixed distance from bony landmarks on the scalp (Michael and Halliday, 1971; Jeffreys and Axford, 1972). This method has the advantage that in closely matched individuals, with similar head sizes, the VEP findings are immediately comparable, since the electrodes

will be above the same cortical area and be the same distance apart. In adult populations Halliday et. al., (1977) were able to locate a maximum pattern response five centimetres above the inion. Nagata and Jacobson (1964) found the largest potential was from one to five centimetres anterior to the inion, and three centimetres lateral to the midline; Rietveld et al. (1967) specified one and a half centimetres above the inion, while Jeffreys (1971) found the largest response was somewhere between two and ten centimetres anterior to the inion depending on which area of the retina was stimulated. It is not advisable to use such a system of measurement when there are large variations in age, and in the head size of the individuals being studied. A constant distance measured in adults which places the electrodes over the occipital poles, would be far more lateral and anterior in a smaller head,over the visual association or parietal areas. For this reason the International 10-20 system of electrode placement was adopted in this study (Jasper, 1958). Since electrode positions are determined as percentage of the head size, which is measured from bony landmarks, a particular electrode will lie over the same area of the brain in all subjects. Also the standardization of the International 10-20 system makes research findings from different laboratories comparable (Vanzulli et. al., 1960; Kooi and Bagchi 1964 ; Celesia and Daly, 1977). Jasper verified the cortical areas under the electrodes in postmortem studies, and the position of the two principle fissures remain within one centimetre of that shown in Figure 3(page 136), while electrodes O1 and O2 lie over the occipital poles. It is not possible to ascertain whether the central electrodes Fz, Cz and Pz are always over

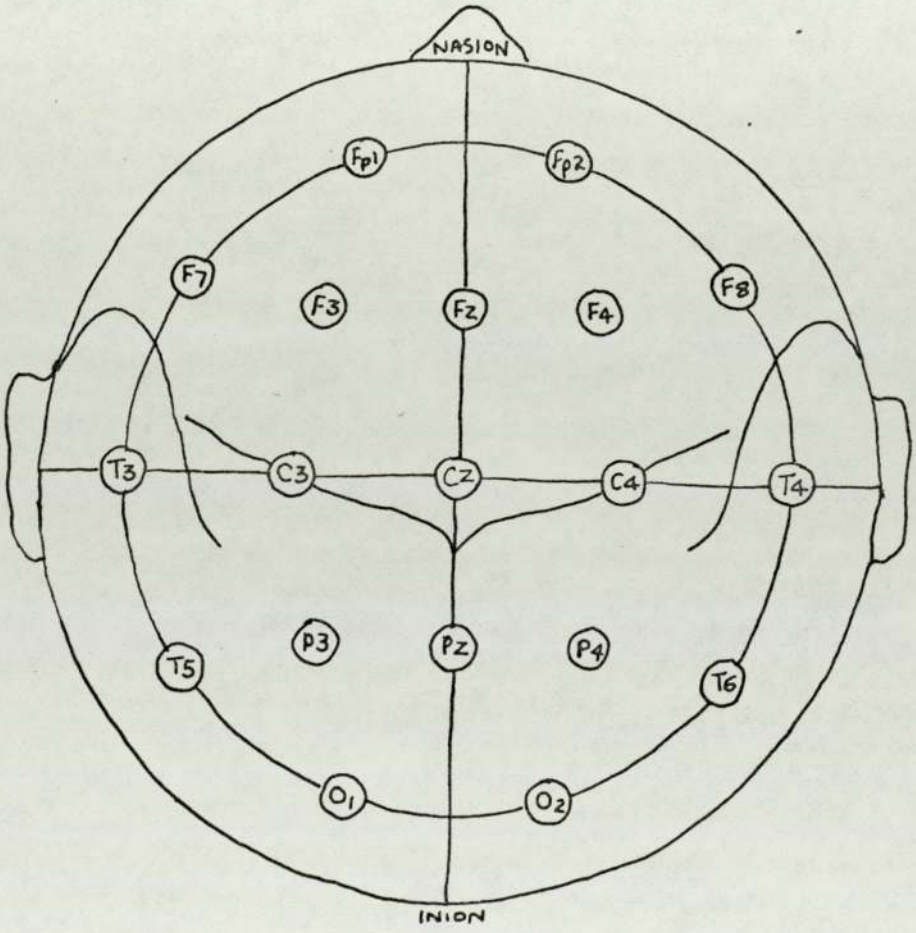


FIG. 3 The international system of electrode placement (after Jasper, 1958).

Alternative electrode notation
C4 - RR
C3 - LR
T4 - RMT
T3 - LMT
O2 - RO
O1 - LO
T6 - RPT
T5 - LPT

the midline because of individual differences in the size of the two hemispheres.

7.1.3. The Recording System

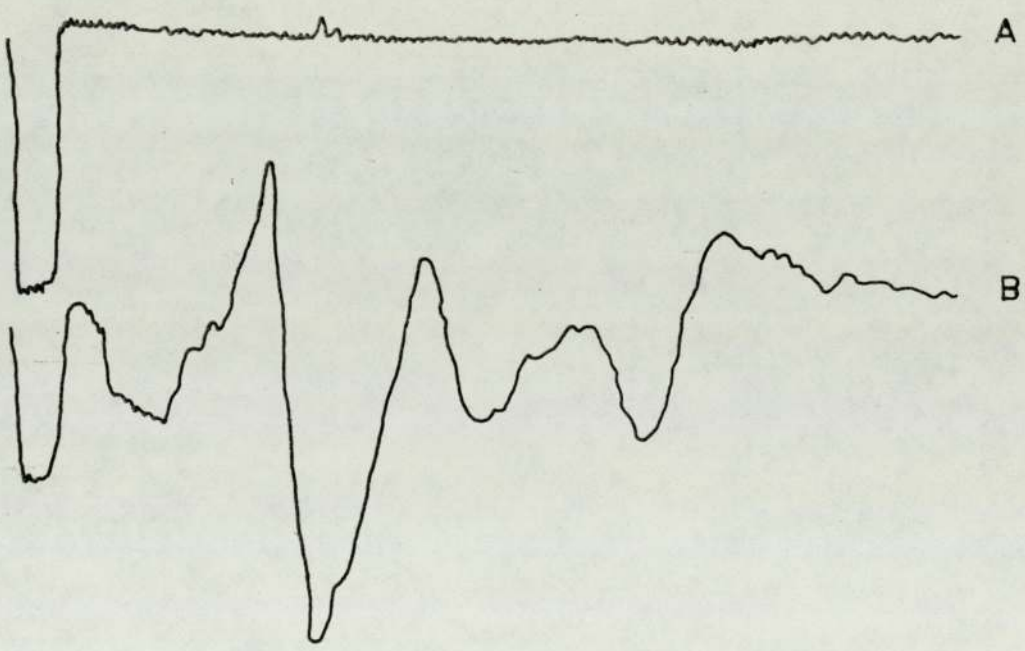
The electrodes were linked in pairs as either a monopolar or bipolar recording, and the potential differences between the two electrodes were amplified and recorded on an S.L.E. Galileo 8 channel EEG machine. The amplified gains were 100 μV/cm., with a time constant of 0.3 secs., and a high frequency filter setting of 70 Hz. The EEG was always recorded during the accumulation of an averaged evoked potential, so that any artifacts would be quickly recognized and corrected. Changes in EEG arousal were monitored, to prevent a subject from becoming drowsy, or producing an accessive amount of rhythmic alpha activity which can become time locked to the stimulus even at low flash rates, and obscure the averaged evoked potential (Schreinemachers and Henkes, 1968). In 1966 Rietveld, Tordoir and Hagenouw reported that any changes in habituation and attention during their experiments paralleled changes in the background EEG, with inattention significantly effecting the VEP and performance measures only when the alpha index was highest. Continuous monitoring of the EEG is important during all the VEP experiments, and particularly with patients when it is more likely that EEG abnormalities will be present, which can seriously effect the occurrence, waveform and distribution of cortical evoked potentials (Harding, 1974, 1977).

The EEG signals were fed into a computer of average transients Mnenotron model 400c (CAT). This special purpose computer can sample the analogue EEG signal from one, two or four channels

and retains the information in digital form in 400 stores. Only two channels were used for averaging, and the analysis time was 0.5 secs. This meant that the EEG was sampled every 2.5 msec, and EEG frequencies up to 200 Hz. were undistorted by the averaging process. This is an adequate sampling rate for the reported frequencies present in the VEP (Thompson and Patterson, 1974), and because of the limited frequency response of the EEG amplifiers of the S.L.E. machine. The CAT does not provide a true averaged evoked response, but adds successive samples without dividing the stored signal by the number of samples taken. Amplitude calibration of such a system is difficult, and usually not performed against the varying noise levels of the background EEG. A good, practical solution is an on line calibration system (Lindley and Harding, 1974). A 5μV calibration pulse, triggered simultaneously with the stimulus by the CAT, is induced into the recording system at the electrode and is processed simultaneously with the VEP to appear in the averaged write-out as a small positive deflection at the beginning of the trace (see fig. 4 page 139). This method provides a measurement of amplitude against varying background EEG "noise" levels, and also provides a constant on-line check of the efficiency of the recording system. If because of artifact or poor electrode contact no calibration pulse can be detected in the averaged trace, then it is unlikely that the VEP could be seen either.

Fifty light flashes were used to obtain each VEP, which was displayed on a storage oscilloscope and recorded on a Moseley XY plotter.

FIG. 4. CALIBRATION OF THE VEP.



A 5 μv Calibration pulse summated 50times on C.A.T.

B 5 μv Calibration pulse in circuit with the E.E.G. summated 50 times on C.A.T. to obtain a VEP.

A few experiments were run with a PDP-15 computer. A true average was performed on the data, and six EEG channels were sampled consecutively every 1.25 msec. The other parameters of the recording procedure were the same as when using the CAT. The VEPs were stored on magnetic tape, and graphs plotted offline on a Compicore plotter.

7.1.4. Method of stimulation

A Grass Model PS22 photostimulator was used in all the experiments; it is a cheap, frequently used stroboscope particularly in clinical departments and produces a wide range of flash intensities (Intensity 1 to intensity 16, 64 to 492 nit seconds, see Appendix I). The very brief 10 μsec. flash was viewed directly through an efficient diffusing screen at a distance of 30 cm, so that the field of view was 8^{o}. Only full field stimulation was attempted.

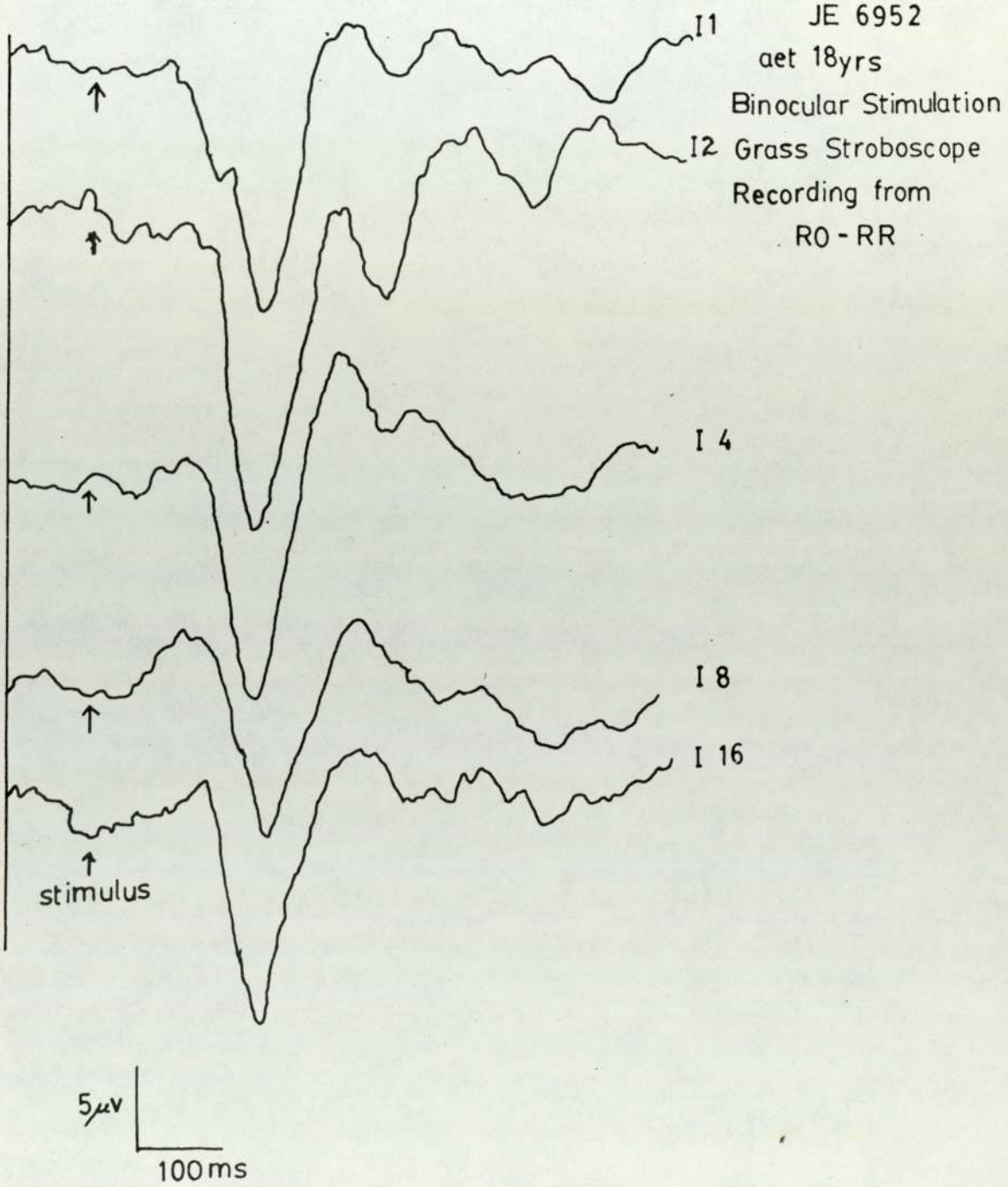
Low intensity stimulation provides interesting correlations between VEPs and psychophysical thresholds, and also raises the possibility of assessing rod and cone function separately. However, the VEPs produced under such conditions are variable and of very low amplitude, requiring a greater number of stimuli to produce a clear average (Vaughan, 1966). Such intensity levels are therefore not advisable for a clinical population where signal to noise levels are often very poor because the individual may be tense or restless, or has high voltage abnormalities in the background EEG. Superthreshold intensities produce VEPs with higher amplitudes, shorter latencies and often more complex wave forms (Kitajima, 1967; Dille, Vallecalle and Verzeano, 1968; Kopell, Wittner and Warrick, 1969;),

although a saturation phenomenon is seen at high intensities, with a levelling off or reduction in the amplitude of the VEP (Vaughan and Hull, 1965; Shipley, Wayne, Jones and Fry, 1966; Armington, Corwin and Marsetta, 1971). Unpublished work in the Neuropsychology Unit has found that in the majority of normal subjects there is some increase in the amplitude of the cortical response when the intensity is increased from Intensity 1 to Intensity 2 of the Grass stroboscope, with only either a small further increase or a levelling off at Intensity 4. Higher intensities produced similar or smaller evoked potentials (see fig. 5 page 142) Such findings agree with Vaughan's results in 1966, when he found maximum amplitudes at moderate flash intensities (Grass stroboscope Intensity 1), with the VEPs diminishing or remaining stable at higher intensities.

The VEPs of all normal and patient controls were obtained using Intensity 2 of the Grass stroboscope (94 nit seconds), and occasionally Intensities 2 and 4 were used in some patient groups especially if there were dense opacities of the media. Intensities 8 and 16 never improved the VEPs recorded and were only used in cases of cortical blindness where no VEP could be identified at lower flash intensities. No case has yet been recorded where clear visual responses were only recorded at a maximum flash intensity, that is intensity 16.

The number of stimuli presented and the interstimulus interval was predetermined by the CAT or PDP 15 averaging programmes, with a maximum flash rate of two per second, dropping to one per second or slower for young children, or when the VEP was

FIG.5. THE EFFECT OF STIMULUS INTENSITY ON THE VEP.

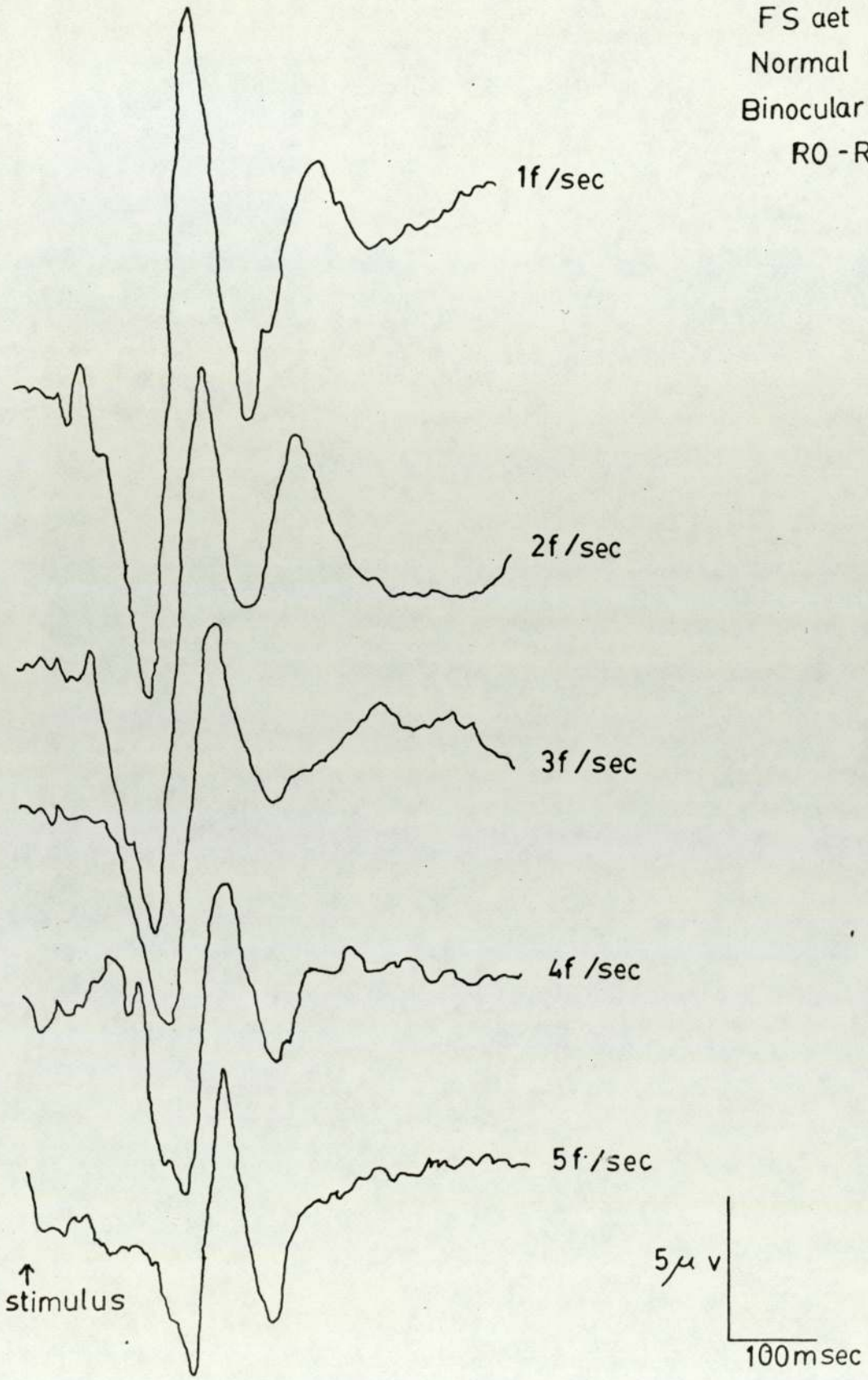


poorly formed. As the flash rate slows from two to one flash per second there is a slight increase in the amplitude of all the components (an increase of 0.5 to 2 μV) with little further change for interstimulus intervals of three or six seconds (Lehtonen, 1973). Our preliminary investigations confirmed these findings as is shown in Figure 6 (page 144). The largest VEPs were recorded at one and two flashes per second.

7.1.5. Part of the Aston Montage

It appears from our topographical studies (see section 7.3., page 189), and other research findings (Vanzulli et al., 1960; Ciganek, 1961, 1965; Kooi and Bagchi, 1964; Nagata and Jacobson, 1964; Vaughan, 1966; Remond, 1969; Kooi et al., 1972) that the maximum VEP occurs over the occipital regions. Of the electrodes placed within this area, OZ was considered unsuitable as there is always some doubt about its position relative to the right and left hemispheres (Jasper, 1958), and since we were interested in being able to detect visual field defects, an active recording electrode was placed over each hemisphere at O1 and O2. Electrode linkages can either be bipolar or monopolar. There can be difficulties in interpreting bipolar recordings, since the activity arising from the second electrode may confound the results recorded from the occiputs (Halliday, 1978) and so many researchers use monopolar recordings referring the active occipital electrodes to the mastoid, earlobes, chin, nose or midfrontal electrodes (Kooi and Bagchi, 1964; Werre and Smith, 1964; Vaughan, 1972; Michael and Halliday, 1971; Jeffreys and Axford, 1972). However, when averaging techniques are used to record minute potential differences, there is no true reference (Jeffreys, 1977), and for example Kooi and Bagchi

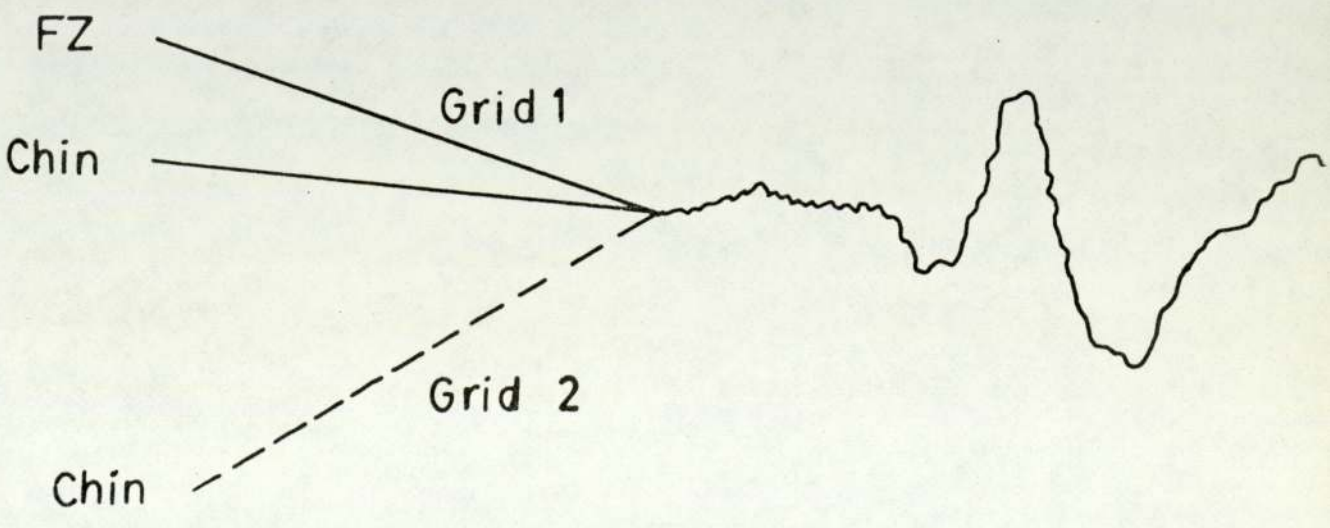
FIG.6. THE EFFECT OF STIMULATION FREQUENCY ON THE FORM OF THE FLASH VEP.



(1964) and Nagata and Jacobson (1964) found significant time locked activity in the frontal regions of the scalp, and Celesia and Daly (1977) had difficulties with a mastoid reference.

Five normal subjects were used in a preliminary investigation of various reference electrode sites. The subjects ages ranged between 20 and 33 years, and the standard procedure to evoke the visual potentials was used. In an attempt to ensure that any time locked activity was only arising from the electrode being investigated the activity from a second electrode was fed to both grid 1 and grid 2 of the EEG amplifier. For example in Figure 7., an average obtained during flash stimulation using

FIG. 7.
POTENTIALS EVOKED BY FLASH STIMULATION AT THE MIDFRONTAL ELECTRODE.



such an electrode combination, would only reflect activity from the frontal electrode, since any activity arising from the chin is fed to opposite sides of the amplifier, and does not appear in the trace. It was found that all central, frontal and temporal regions contained activity related to the flash stimulation (fig.8 . page 147) and although combined ear references and the chin position were relatively silent (fig. 9. page 148), these sites were frequently a source of EMG contamination if the subject could not relax sufficiently (fig.10. page 149). Artifacts arising from these electrode sites have often been reported in the literature (Bickford, Jacobson and Cody, 1964; Picton, Hilyard, Kransz and Galambos, 1974; Celesia and Daly, 1977) and the use of high frequency filters to eliminate the muscle contamination severely alters the waveform of the VEP (fig.11. page 150). In order to avoid these problems, and also because it is unwise to believe that any electrode linkage in evoked potential recordings is truely monopolar, it was decided to use bipolar recordings in all VEP investigations. Since the vertex is clearly active, and has been suggested as a secondary source of visual potentials (Ciganek, 1961; Nagata and Jacobson, 1964; Vaughan, 1966, 1972; Creutzfeldt and Kuhnt, 1967; Lehtonen, 1973), and since the temporal regions can be severely effected by muscle activity (Picton, Hilyard, Kransz and Galambos, 1974), positions C3 and C4, the right and left rolandic electrodes, which are quite distant from the occipital poles and generally pick up smaller time locked potentials than the vertex electrode, were selected as the Grid 2 electrodes (see fig.12. page 151).

FIG. 8

FLASH EVOKED ACTIVITY FROM VARIOUS DISTANT ELECTRODE POSITIONS ON THE SCALP.

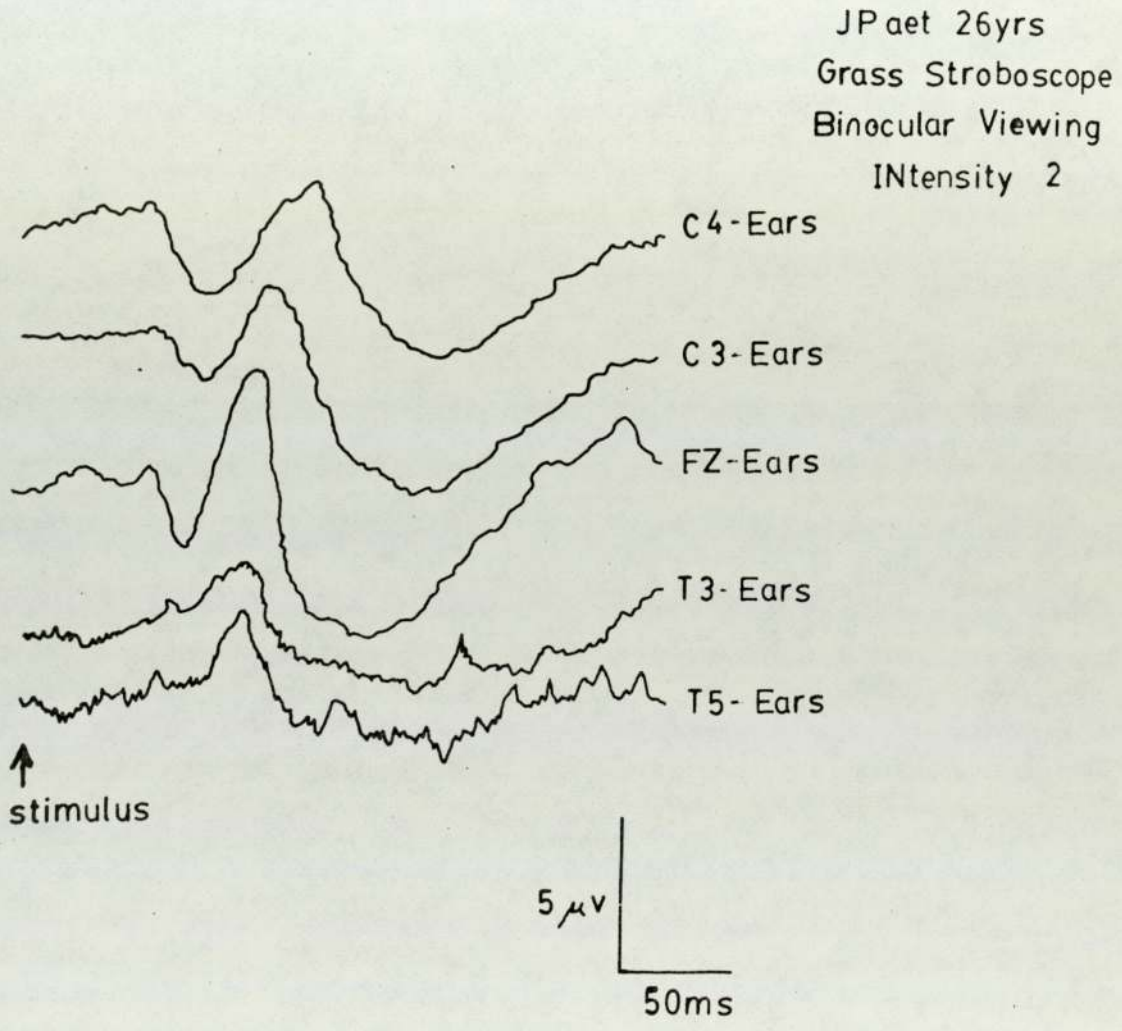


FIG 9. ELECTRODE REFERENCE SITES.

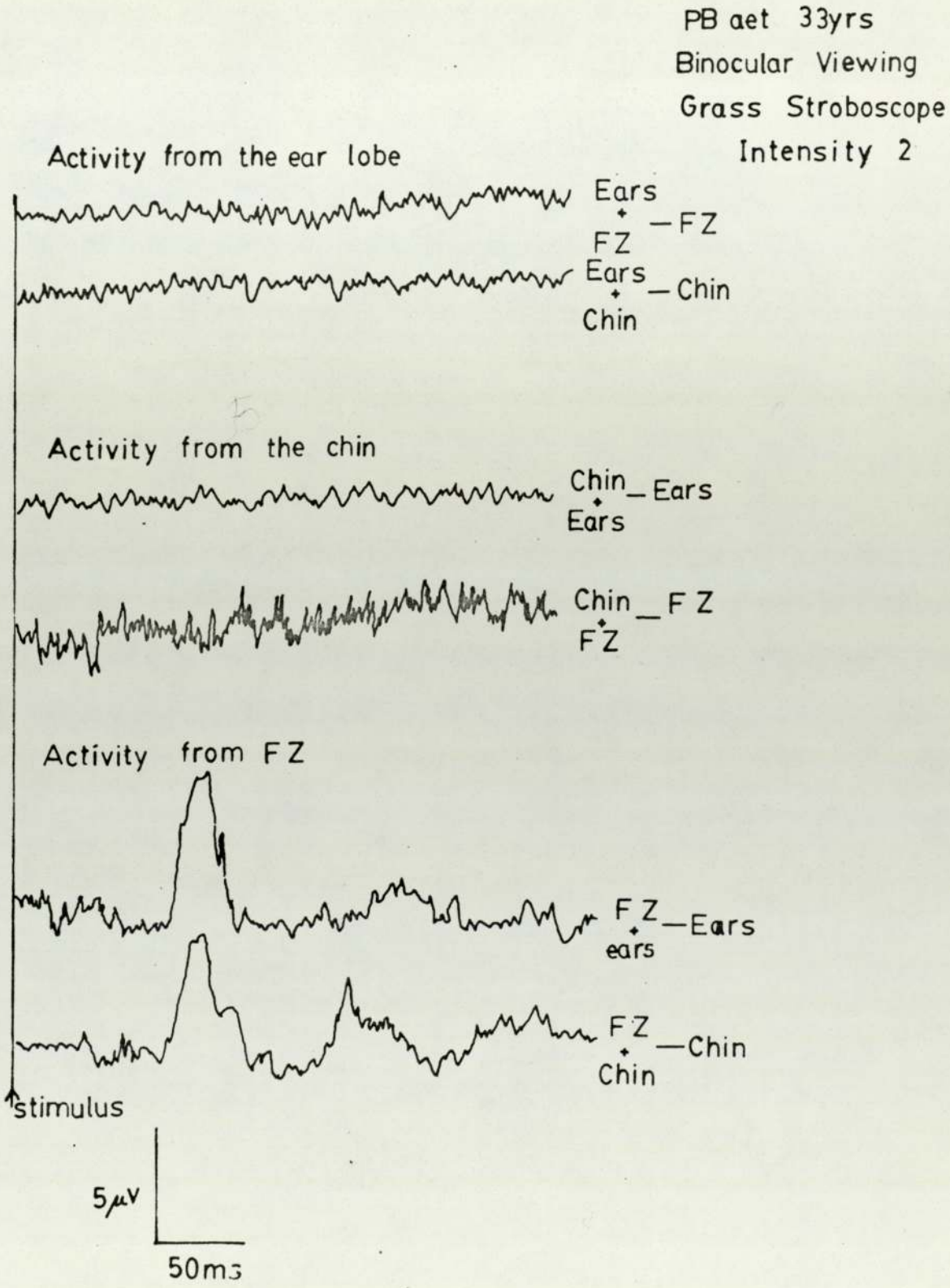


FIG. 10
MUSCLE CONTAMINATION OF THE EAR REFERENCE SITE.

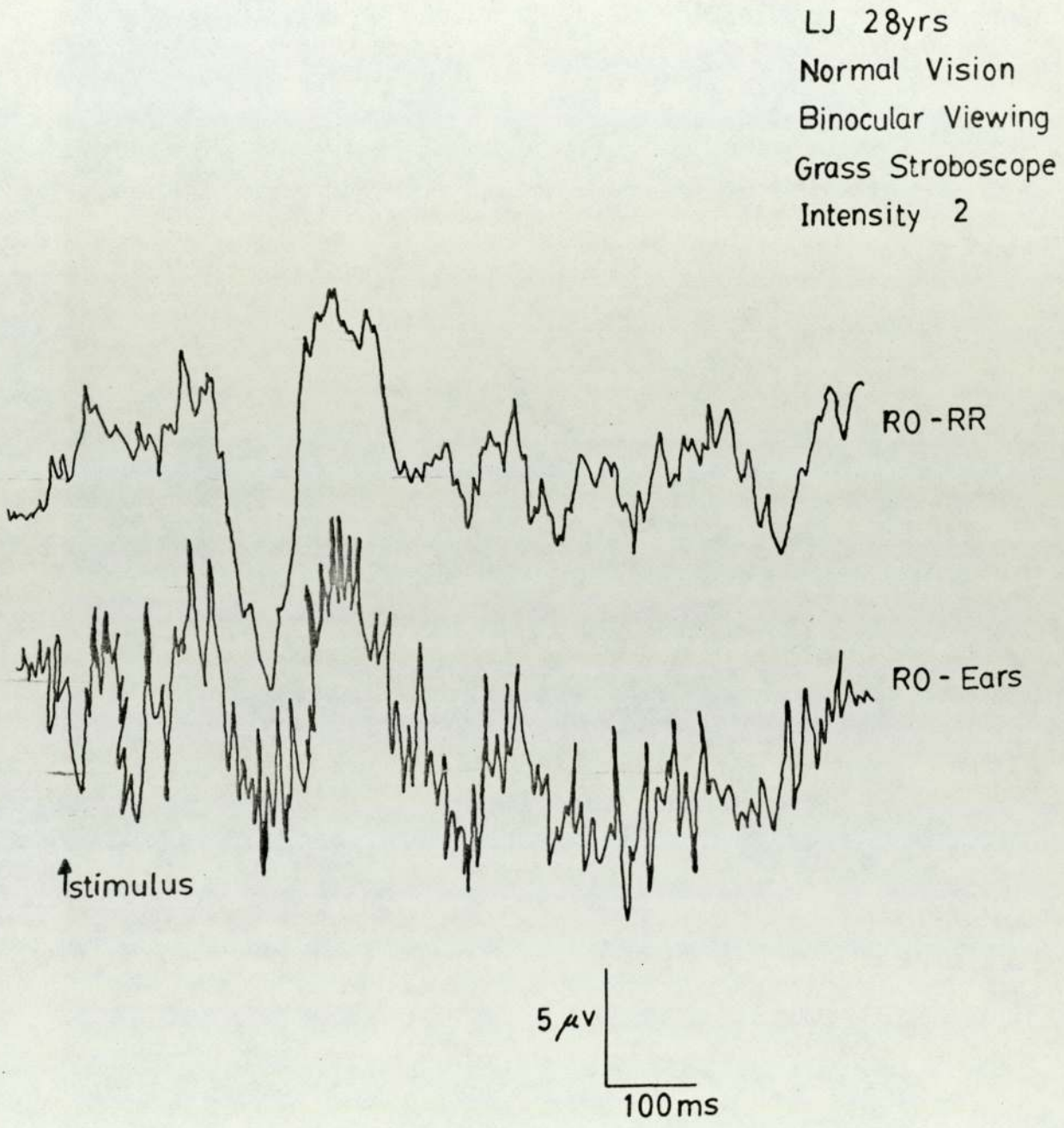


FIG.11.

THE EFFECT OF FILTERS ON THE FORM OF THE VEP.

Binocular Stimulation
OZ to Ear
Time Constant 0·3secs.

AJ aet 33yrs.
Normal Vision
Medelec Averager

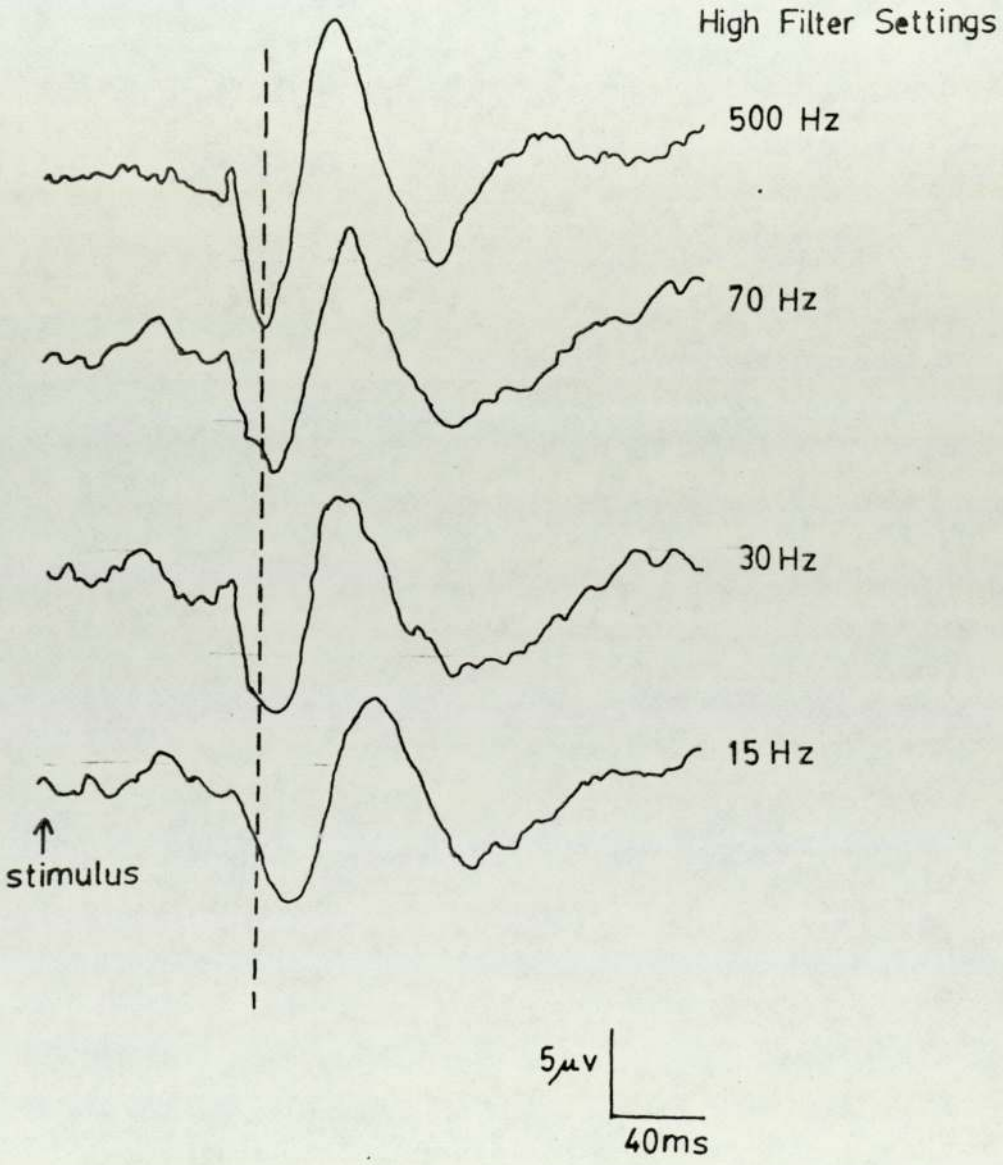
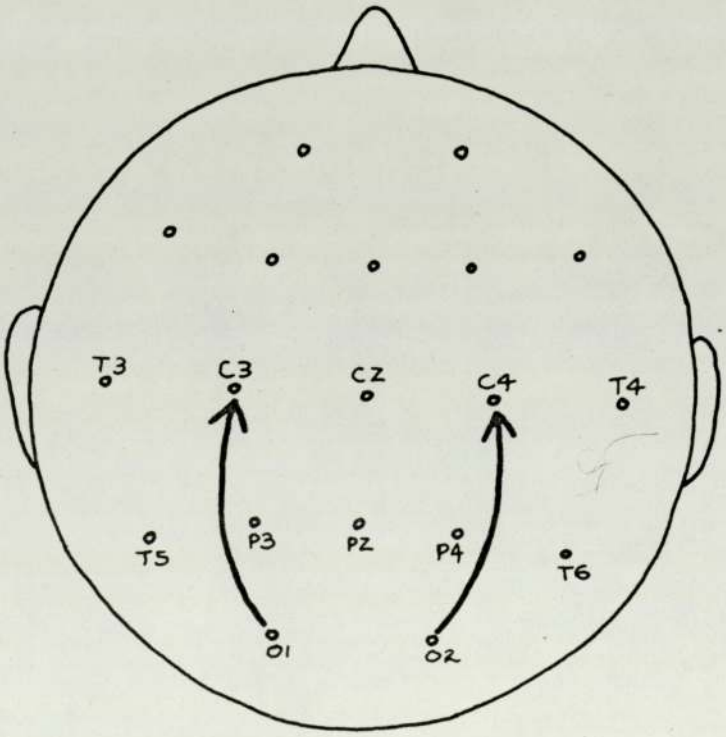


FIG. 12
ELECTRODE LINKAGE FOR RECORDING VEPS FROM THE RIGHT AND LEFT HEMISPHERE.



INTERNATIONAL 10-20 SYSTEM OF ELECTRODE PLACEMENTS (Jasper, 1958)

Data was collected from a further ten normal adult volunteer subjects, between the ages of 18 and 26 years, and the bipolar derivations were compared with 'monopolar' recordings of O1 and O2 refered to combined ear electrodes, to ascertain whether there could be any significant alteration in the occipital response by activity arising from the rolandic electrodes.

As can be seen in figure 13 (page 153) and Appendix II no significant differences were found in either the amplitude, latency or waveform of the flash VEP obtained by bipolar or monopolar recordings, which is consistent with the findings of other authors (McKay and Kinney, 1976; Celesia and Daly, 1977). In addition, changes in the VEP to flashed pattern were often larger from the bipolar derivations (see fig. 14. page 154), a result which may prove useful in a clinical setting, and a finding which is supported by Lifshitz, in 1966, when he found that the largest changes to flashed pattern occurred at the central derivations.

7.2. Normal parameters of the Flash VEP

Using the standard evoked potential procedures, described in earlier sections of this chapter, and with bipolar recordings from O2-C4 and O1-C3, the normal parameters of the VEP were investigated in a large population (85 individuals) with a wide variation of age (6 to 78 years). The EEG of each individual was within normal limits, visual function was normal for the age, and no one with a clinical history that might have effected the results was included. The older subjects had additional opthalmological examinations (see Section 7.2.3., page 174).

FIG. 13.
A COMPARISON OF MONOPOLAR AND BIPOLAR RECORDING OF THE VEP.

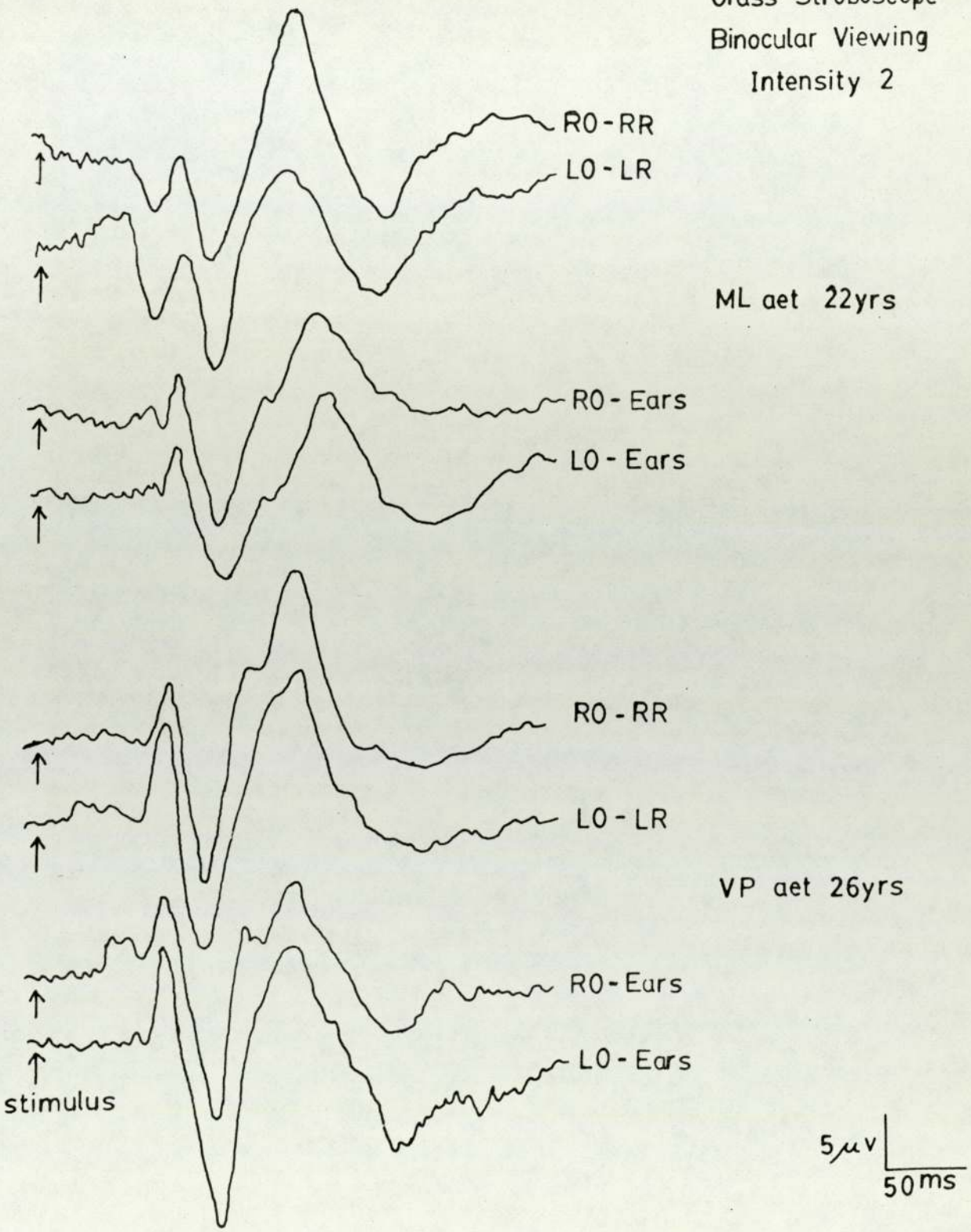


FIG.14. MONOPOLAR AND BIPOLAR RECORDINGS.

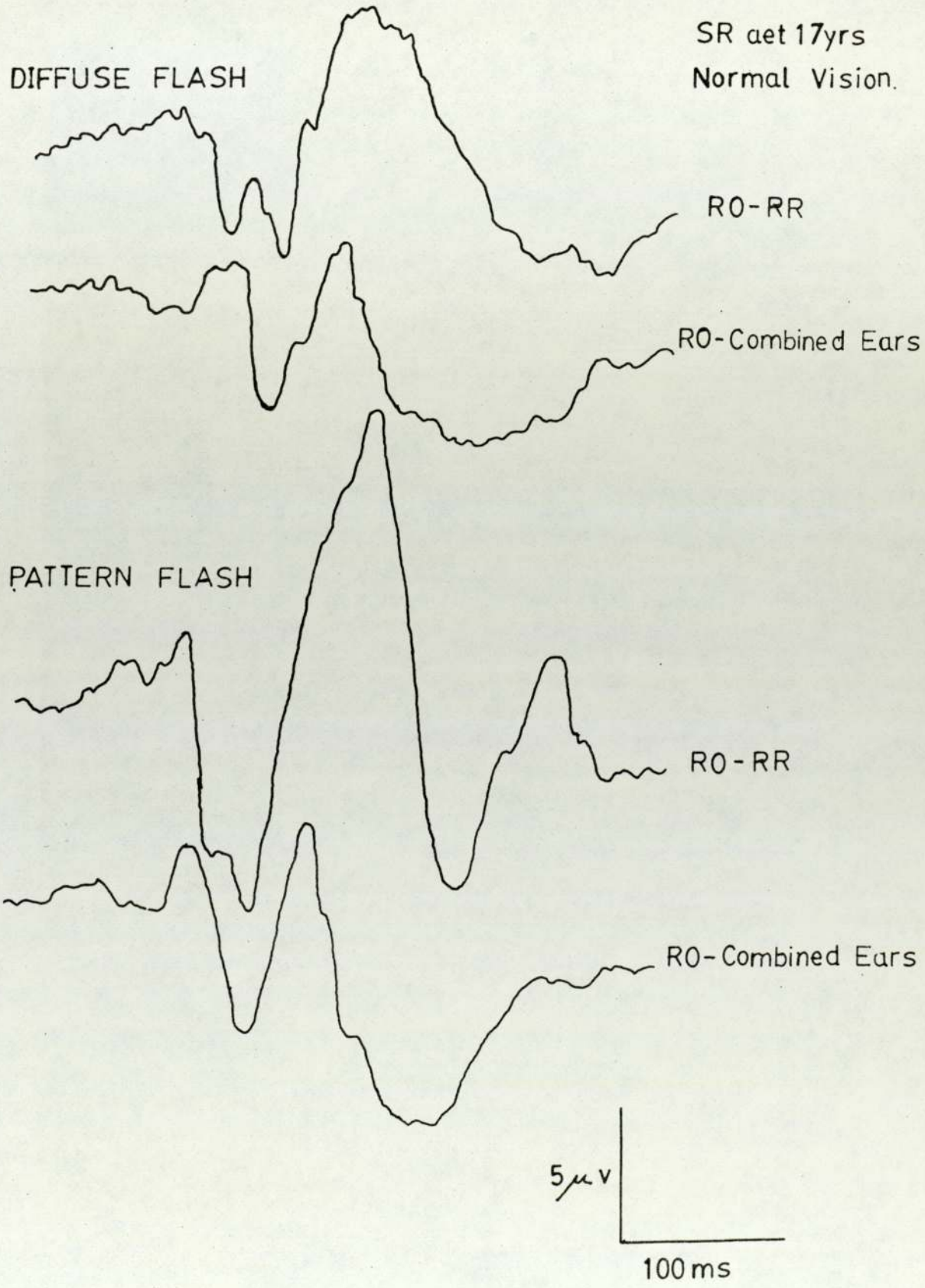


Figure 1. (page 43) shows an idealized flash VEP with all the main components that can be identified and measured. The earliest wave, when present was a small positive deflection, and from this component all subsequent components were numbered and named by the author as either negative (an upward deflection) or positive waves (a downward deflection) according to the EEG convention. In all subjects the following measures were taken:

1) Latency - the time delay from the stimulus to the peak amplitude of each component present.
2) Peak to peak amplitude - the amplitude difference in microvolts from the peak value of one component to the peak value of the succeeding component. In the old age group, base line to peak amplitude values were also measured.
3) The presence and absense of components in each hemisphere.

Statistical tests were used (Student T test for small samples) to assess any significant variations in the VEP.

7.2.1. The VEP in a young age group

Twenty children were investigated between the ages of 6 years and 9 years 11 months, mean age 7 years 8 months (see Appendix III, page 338 , for subject details). It was impossible to contact younger children, and the group sample was limited by the personal contacts of the investigator. However infants have been extensively investigated, see Chapter 3, section 3.3.2., and Dustman and Beck (1969) and Rhodes, Dustman and Beck (1969) report that the most dramatic changes in a child's VEP occur between the 5th and 6th years.

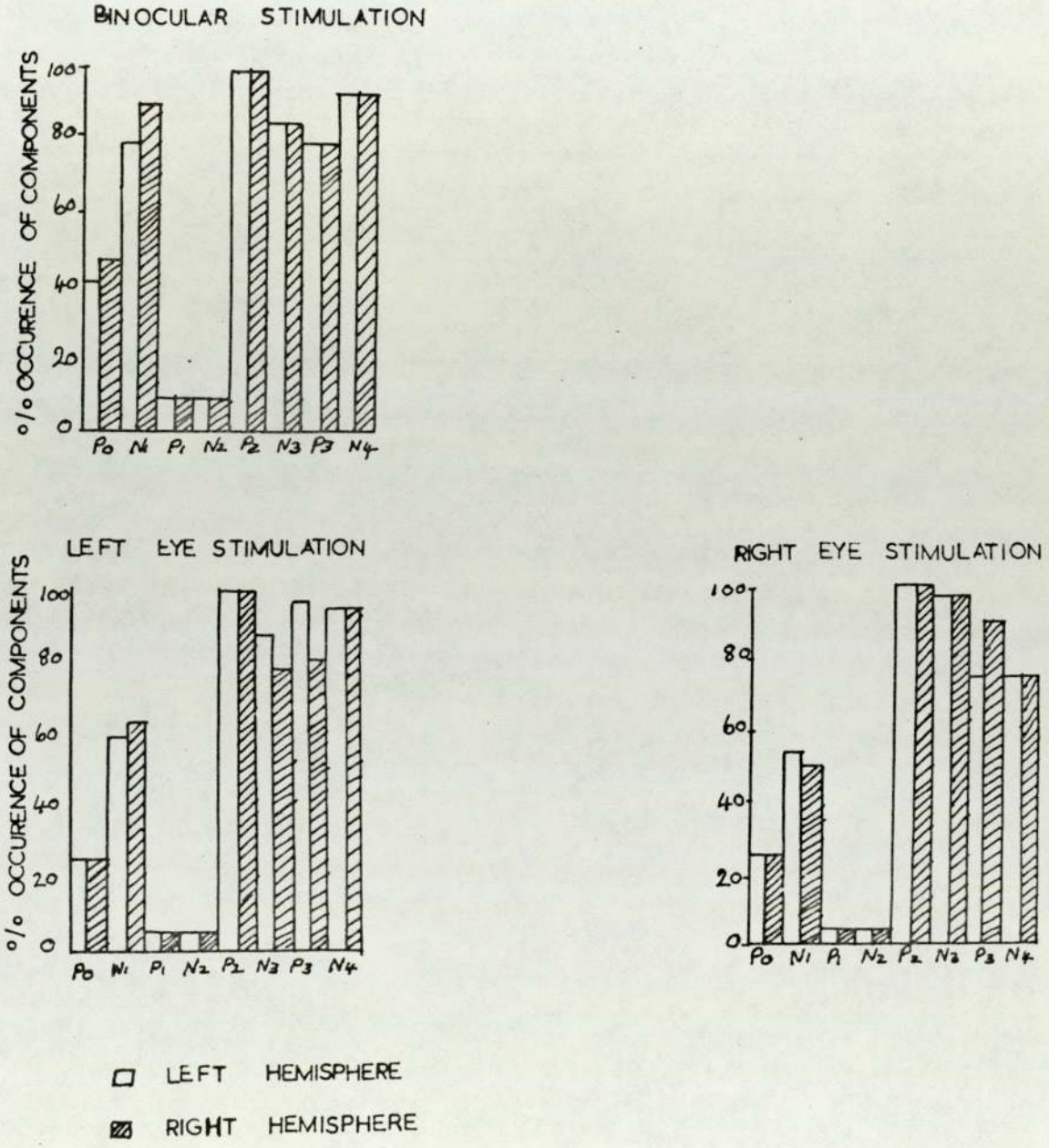
All children were stimulated binocularly. Only six viewed the light monocularly, as the main part of the experiment that they were participating in was pattern changes in the VEP. Thus, the results of monocular stimulation are unreliable, although the T test for small group data was applied. Figure 15 (page 157) shows the percentage occurrence of the major VEP components in this young population, and only the P2 wave was recorded in all individuals for all conditions. The later waves N3, P3 and N4, were present about 80 to 90% of the time, and the early components, before 100 msec, were often absent. Thus only the P2 component with a mean latency of 104.9 msec. was reliable and consistent between individuals, and could be expected to be present in a normal, young VEP.

Table 2 (page 158) is a summary of the amplitude and latencies of the VEP components and the group data is represented pictorially as the VEP of an average child (Fig. 16,page 159). The form of the VEP is dominated by high amplitude waves from 100 to about 300 msec., and there is often evidence of high amplitude rhythmic activity around the alpha and beta frequencies late in the averaged trace. Examples of the VEPs from this group are seen in Figure 17 (page 160); note that the gain of the recording system is lower than that used in adult subjects. It is also characteristic of young VEPs that few of the components before 100 msec. are present in an average, perhaps lost in the high 'noise' levels of the background EEG. It is therefore often difficult to identify the early components, and so few P1 and N2 waves were measured that population parameters could not be calculated. It can be seen that the mean amplitude of the major VEP components was greater than

FIG. 15

PRESENCE OF VEP COMPONENTS TO FLASH STIMULATION.

YOUNG AGE GROUP.



STIMULATING CONDITION		PRINCIPLE VEP COMPONENTS						
		N1	P1	N2	P2	N3	P3	N4
BINOCULAR	MEAN	57.0	(61)	(70)	104.9	160.7	198.8	243.0
	LATENCY S.D msec.	5.4	-	-	7.3	23.3	35.5	33.8
	RANGE	49-68	-	-	95-119	131-209	156-253	203-316
N=20	MEAN	4.1	(4.3)	(3.6)	21.5	25.1	13.2	18.3
	AMPLITUDE S.D	2.5	-	-	1.2	12.8	11.4	10.2
	$\mu V.$ RANGE	1.8-9.2	-	-	9.8-38.5	8.6-38.2	3.7-26.4	4.0-26.9
MONOCULAR RIGHT N=6	MEAN	60	-	-	111.5	157.3	181.3	245.0
	LATENCY S.D	2.8	-	-	6.19	22.6	21.9	20.8
	msec. RANGE	56-65	-	-	106-120	122-194	162-212	228-250
MONOCULAR RIGHT	MEAN	2.71	-	-	20.9	10.3	10.2	9.4
	AMPLITUDE S.D	1.72	-	-	11.8	7.5	6.1	5.4
	$\mu V.$ RANGE	1.0-4.1	-	-	10.2-32	4-22.3	4-13.8	4-14.0
MONOCULAR LEFT N=6	MEAN	59.2	-	-	112.8	169.8	201.5	251.8
	LATENCY S.D	4.8	-	-	6.3	21.6	26.2	31.6
	RANGE	54-65	-	-	109-125	145-200	175-231	230-275
MONOCULAR LEFT	MEAN	3.56	-	-	21.7	11.2	11.6	12.4
	AMPLITUDE S.D	2.1	-	-	11.5	9.0	7.1	8.9
	$\mu V.$ RANGE	12-5.7	-	-	10.7-36	4-24	3.5-17.5	3.5-23.1

TABLE 2

LATENCIES AND AMPLITUDE OF FLASH VEP IN YOUNG AGE GROUP (6-9 years 11 month)

( ) Denotes insufficient number present for statistical treatment.

FIG.16.

VEP of the AVERAGE CHILD

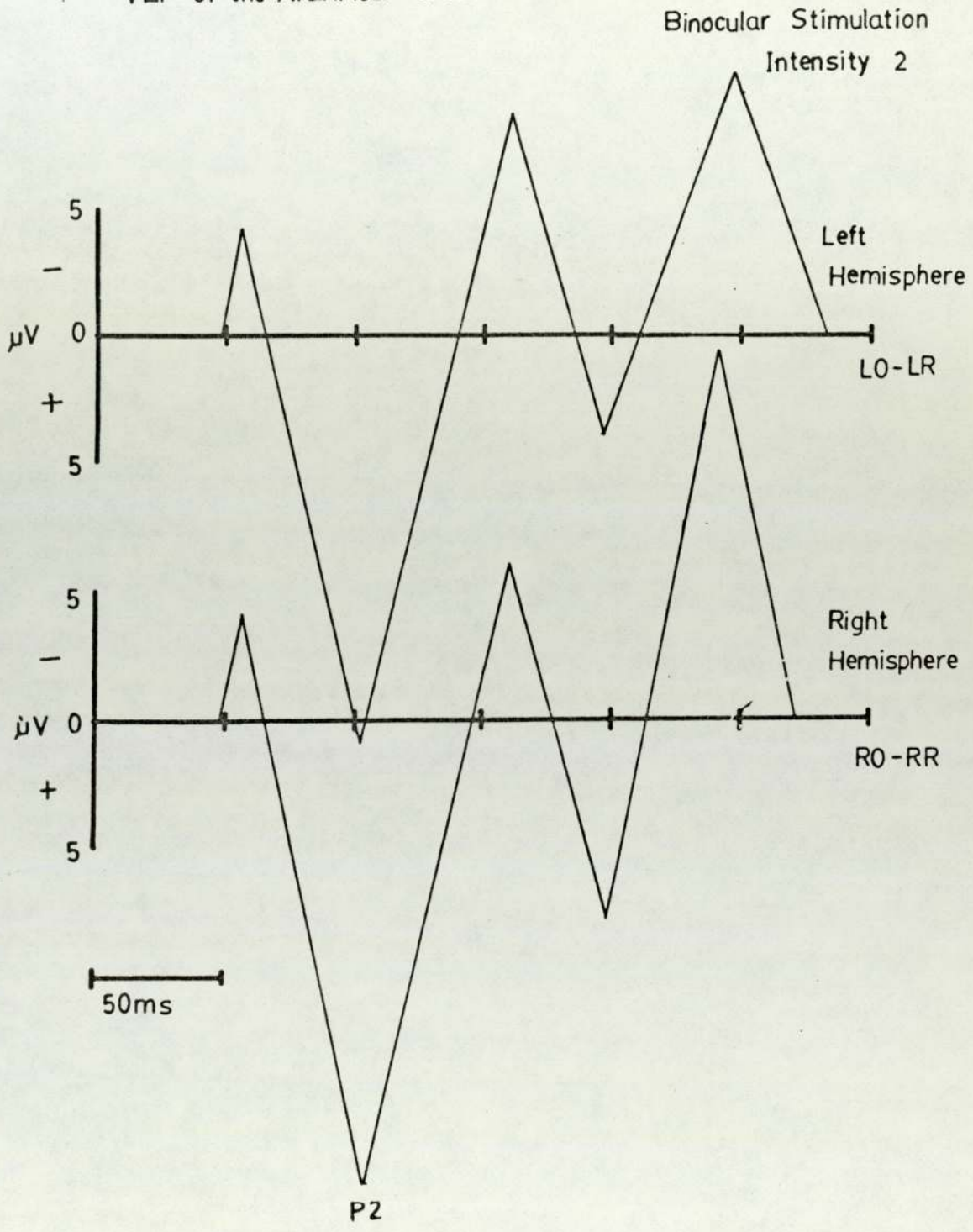
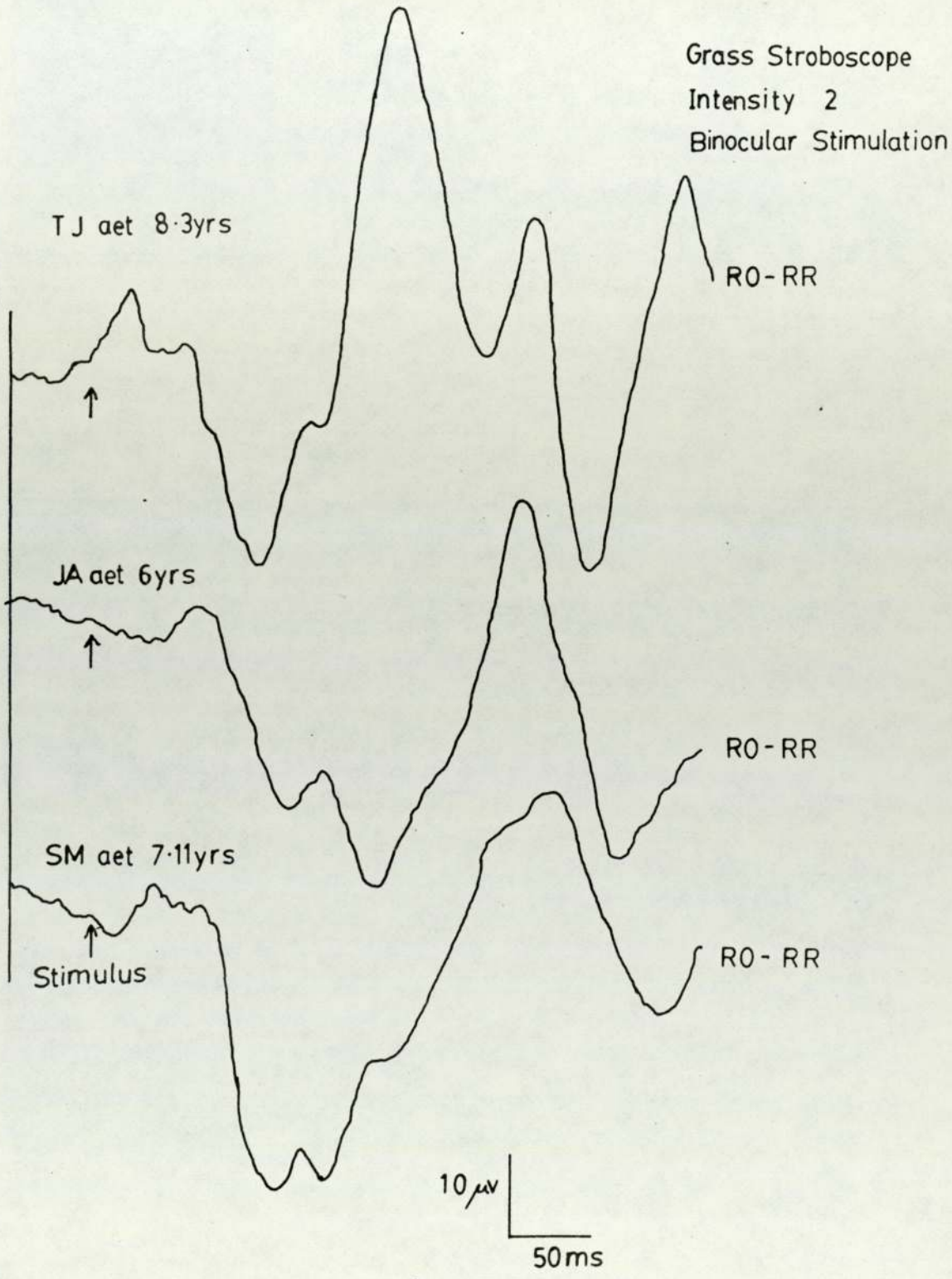


FIG. 17.

VEP TO DIFFUSE FLASH STIMULATION IN THE YOUNG AGE GROUP.



20 μV., and as has so often been reported, the variability of both amplitude and latency within the group was very high.

No significant differences were found between hemispheres, and between monocular and binocular stimulation for any of the components. The mean latency difference between the two hemispheres during binocular stimulation was 4.3 msec., range 0 to 12 msec. The difference was slightly larger with monocular stimulation (mean latency difference 6.1 msec., range 0 to 13 msec.). The mean amplitude hemispheric difference of P2, the most consistent component was 5.2 μV. for binoculation stimulation with a range of 0.5 to 17.0 μV. In 4% of the subjects there was more than a 50% amplitude assymmetry of this component, however such a large reduction in the P2 component in one hemisphere was never accompanied by a similar reduction of amplitude of the other evoked potential components as well. The mean hemispheric amplitude differences for monocular stimulation were very similar to the binocular findings (mean difference 4.2 μV, range 0.5 to 11.5 μV) with a clear trend (75% of VEPs) for higher amplitude over the contralateral hemisphere. No amplitude differences exceeded 50%. The mean amplitude difference between the two eyes was 4.6 μV, with only differences of up to 50% occurring. The mean difference in latency was 6.2 msec., with the largest difference between the two eyes being 16 milliseconds. The number in the group was very small.

It was very fortunate that one subject, a young boy T.J., was recorded on three occasions during a three year period, see Table 3 (page 162).

		N1	P1	N2	P2	N3
6 years 1 month	latency	-	50	75	113	190
	amplitude	-	5.7	7.0	24.3	45.0
8 years 5 months	latency	-	-	-	111	159
	amplitude	-	-	-	35.1	41.2
9 years 6 months	latency	-	-	-	112	147
	amplitude	-	-	-	25.7	13.5

Table 3. VEP changes with age - one subject

The latency and amplitude measures from both hemispheres have been combined, and only binocular stimulation was used. It is clear in this young subject, that inspite of the maturational changes during the three years, the VEP remained consistent, with no large changes in amplitude or latency of the main component.

Schenkenberg (1970) studied 160 normal individuals whose ages ranged from 4 to 86 years. He also used a Grass stroboscope at Intensity 2, and its light was reflected by a white sphere into both eyes of the subjects. His recordings were monopolar, with O1 and O2 of the 10-20 system (Jasper, 1958) refered to ear electrodes. As can be seen from Table 4 (page 163) his more detailed data agrees quite well with the results reported here, although the presence or absence of the various components was not reported.

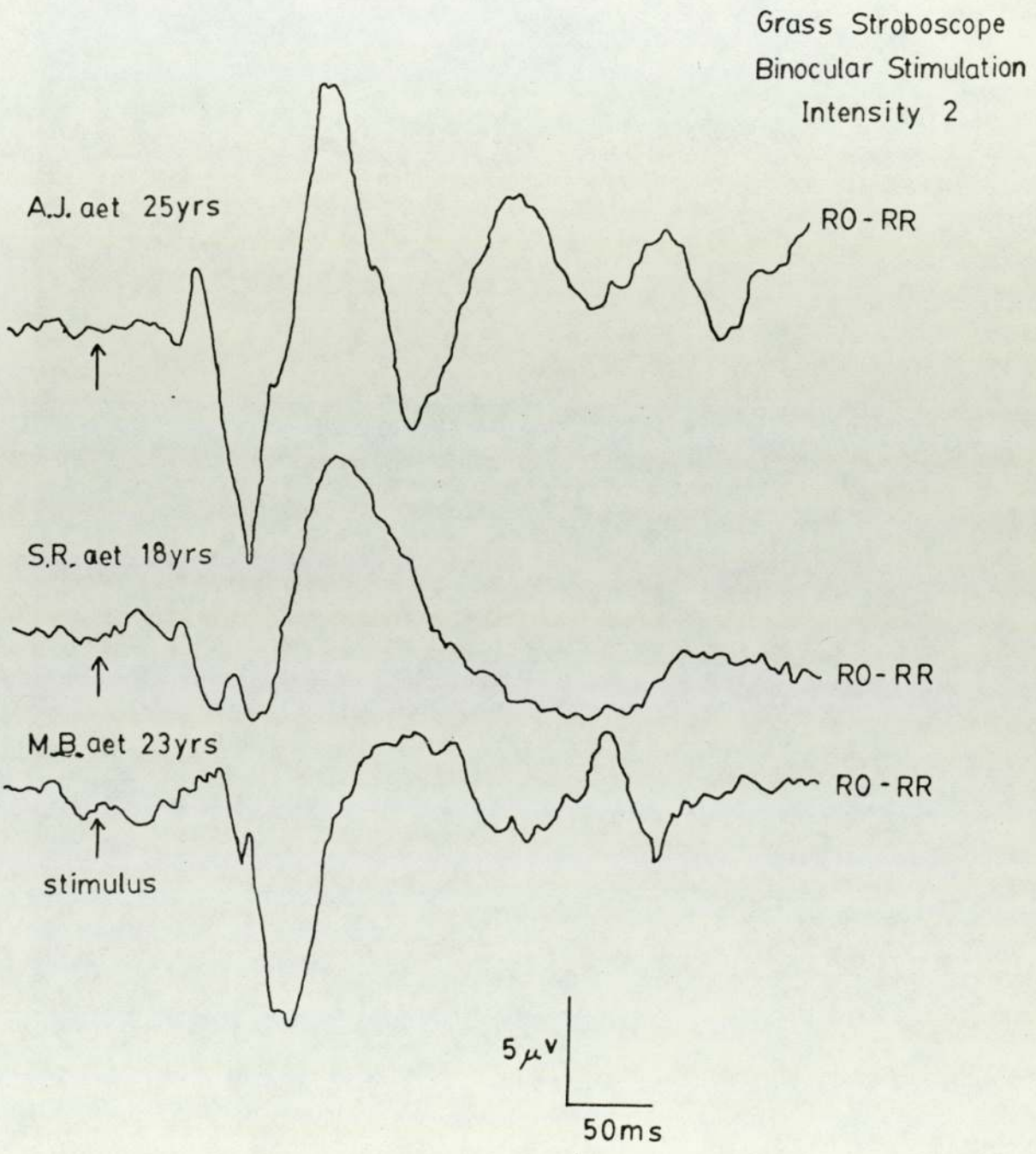
7.2.2. The VEP in an adult age group

Forty volunteers, whose ages ranged from 17 to 34 years were investigated, and in all cases both binocular and monocular stimulation were used. Three typical adult VEPs are shown in Figure 18 (page 164). The overall amplitudes of the VEPs are lower than in the younger

Schenkenberg notation	P3	N3	P4	N4
Thompson notation	P2	N3	P3	N4
LATENCY	mean SD	mean SD	mean SD	mean SD
N = 20 mean age 5 years	108.6 , 12.4	141.3 , 17.8	171.0 , 18.0	236.7 , 18.6
N = 20 mean age 7 years	108.1 , 8.0	143.1 , 14.5	172.0 , 13.2	232.7 , 14.4
N = 20 mean age 9 years	106.5 , 10.2	141.7 , 9.2	171.2 , 14.3	230.6 , 15.9
AMPLITUDE				
mean age 5 years	19.3 , 6.3	10.4 , 7.9	6.1 , 5.3	27.6 , 14.0
mean age 7 years	21.3 , 6.6	12.6 , 6.7	9.3 , 6.9	39.1 , 11.5
mean age 9 years	21.4 , 6.3	16.3 , 8.9	12.2 , 8.6	31.3 , 12.7

Table 4. Mean peak delays (m.sec.) and peak to peak amplitudes (μV) from the right occipital electrode (O2). Adapted from Schekenberg, 1970.

FIG 18. VEP TO DIFFUSE FLASH STIMULATION IN THE ADULT GROUP.



age group, especially for the portion of the VEP after about 140 msec. The primary components, before 100 msec., are more consistently recorded. In agreement with many authors (Gastaut and Regis, 1965; Donchin and Lindsley, 1969; Perry and Childers, 1969; Regan, 1972), the interindividual variability in waveform was very high, and it was rare to see a complete VEP with all the components clearly present (Fig. 19 , page 166). A complete VEP, with all the components recorded between N1 and N4, only occurred in 20% of the population. As with the young group the large positive component, P2 (mean latency 109.4 msec.) was the most reliable, and was always recorded both for binocular and monocular stimulation (see Fig. 20 ,page 167). The late components N3, P3 and N4 were usually seen, and their occurence varied between 75 and 95%. The reliability of the appearance of the early waves was much better than in the young age group, N2 being the most likely component to be present, although it was not seen in 30-40% of the population. The components P1 and N1 occurred in between 50 and 60% of the binocularly evoked potentials, and were seen in 25 and 55% of the VEPs when one eye was stimulated. With binocular stimulation only 30% of the adult group had present in the VEP all the primary components before 100 msec., and in 18% of the adult group there was a significant asymmetry in the first 100 msec. with a particular component being present in one hemisphere and absent in the other. With monocular stimulation 20% of the group VEPs contained all the components before 100 msec., and 24% had one or more of these components only occurring in one hemisphere. These findings

FIG. 19.
A COMPLETE FLASH VEP.

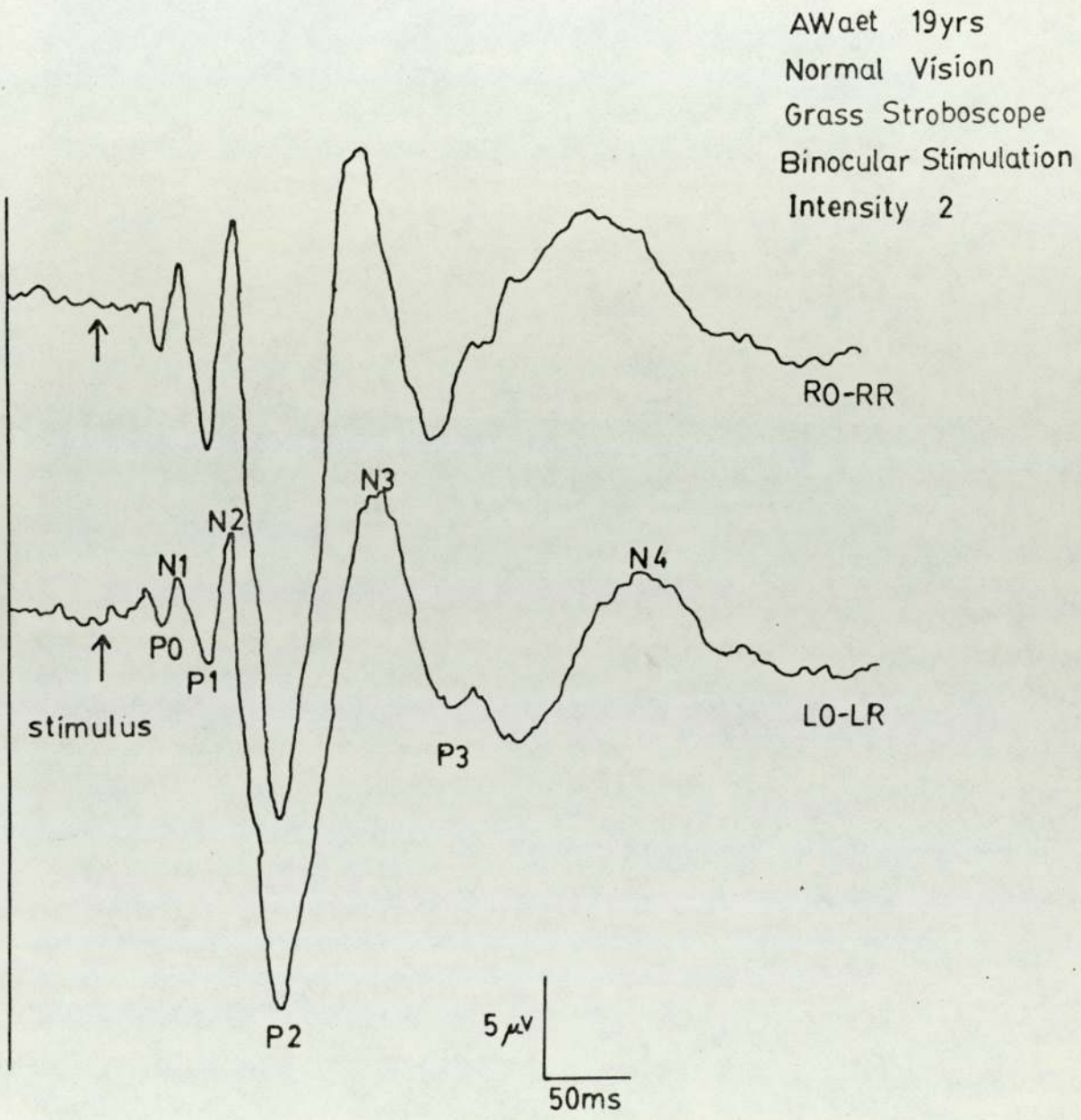
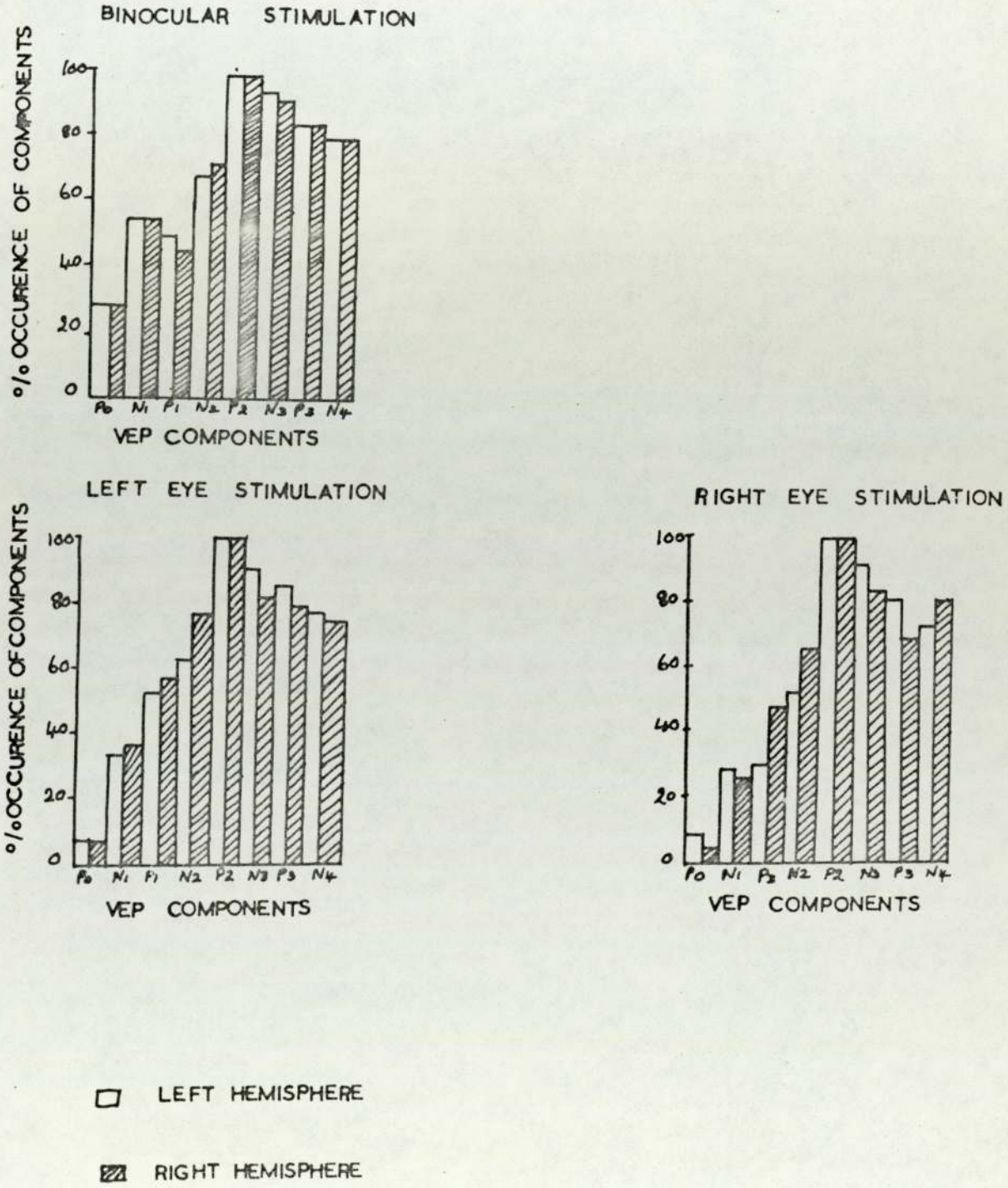


FIG. 20.

PRESENCE OF COMPONENTS OF THE FLASH VEP.

ADULT AGE GROUP



certainly suggest that the presence or absence of the early portion of the VEP can not be reliably used to predict visual field defects as suggested by Vaughan and Katzman (1964).

The mean and standard deviation of the latency and amplitude of all the VEP components is shown in Table 5 (page 169), and the results for binocular stimulation are displayed graphically as a "typical" VEP of the average adult in Figure 21 (page 170). The early components are small, with a prominent P2 component of mean amplitude 8.2μV, and late components of a similar amplitude.

There was a trend for longer latencies and lower amplitudes to be seen in the monocular evoked potentials, although this did not reach significance due to the large standard deviations of the data (see Fig. 22 page 171). Jeffreys and Axford (1972) also reported slightly longer latencies, of the order of 5 to 15 msec., when one eye was stimulated, and larger binocular responses have been reported by several authors (White and Bonneli, 1970; Harter, Seiple and Salmon, 1974).

Tables 6 and 7 (page 172) are a summary of some of the reported data on adult flash VEPs to binocular, full field stimulation. Despite the universal claims of the extremely large variability of the flash VEP, and despite different sources of flash stimulation, and different sites for the VEP recording (for example Ciganek, 1961, recorded the VEP from OZ to PZ, and Morrell and Morrell, 1966, from OZ to the mastoid) there is consistency in the form, latency and amplitude from laboratory to laboratory, which must offer some encouragement for the use of the flash VEP in a clinical setting. Indeed it is the author's opinion that the reported data from various laboratories on the pattern VEP can often be even more variable and conflicting particularly when different pattern sizes and stimulus fields are used (Rietveld et al., 1967; Michael and Halliday, 1971; Ristanovic, 1971; Holder, 1978).

STIMULATING CONDITIONS	STATISTICS		PRINCIPLE VEP COMPONENTS						
			N1	P1	N2	P2	N3	P3	N4
BINOCULAR N = 40	LATENCY msec.	MEAN	56.2	65.2	82.8	109.4	156.7	200.3	239.8
		SD	6.7	9.9	9.1	9.9	14.6	22.5	33.1
		RANGE	40-69	50-76	70-101	95-132	134-187	172-250	205-325
	AMPLITUDE	MEAN	1.74	2.1	2.8	8.2	11.1	6.3	6.4
		SD	1.4	1.7	1.9	3.1	5.6	5.6	5.6
		RANGE	0.5-4.7	0.4-7.3	0.4-7.5	24-21.2	2.4-27.3	2.4-28	3-16.4
MONOCULAR RIGHT	LATENCY msec.	MEAN	60.6	65.7	86.7	115.1	161.1	194.5	233.2
		SD	4.87	8.2	9.6	13.0	14.5	20.4	27.9
		RANGE	50-69	50-75	75-109	94-133	140-196	170-225	187-294
	AMPLITUDE	MEAN	1.9	1.9	2.2	6.3	6.9	4.7	3.5
		SD	0.9	0.9	1.7	4.2	4.9	3.9	2.5
		RANGE	0.5-0.5	1.0-3.9	0.5-8.0	2.0-20.8	2.5-23.9	1.0-14.4	1.0-9.7
MONOCULAR LEFT	LATENCY msec.	MEAN	57.0	65.5	86.4	115.5	161.7	208.5	243.2
		SD	6.6	10.5	7.2	14.0	13.8	29.5	32.1
		RANGE	45-68	50-80	69-102	100-134	135-190	162-275	200-294
	AMPLITUDE	MEAN	1.2	1.9	2.0	5.8	6.4	5.9	5.0
		SD	0.9	1.2	1.3	2.8	3.8	3.5	1.6
		RANGE	0.5-2.5	0.5-3.6	0.5-9.7	2.2-11.9	2.6-17.7	2.5-13.7	2.3-7.1

TABLE 5. LATENCIES AND AMPLITUDES OF THE FLASH VEP IN THE ADULT AGE GROUP (17-34 YEARS)

FIG. 21. THE VEP OF AN AVERAGE ADULT.

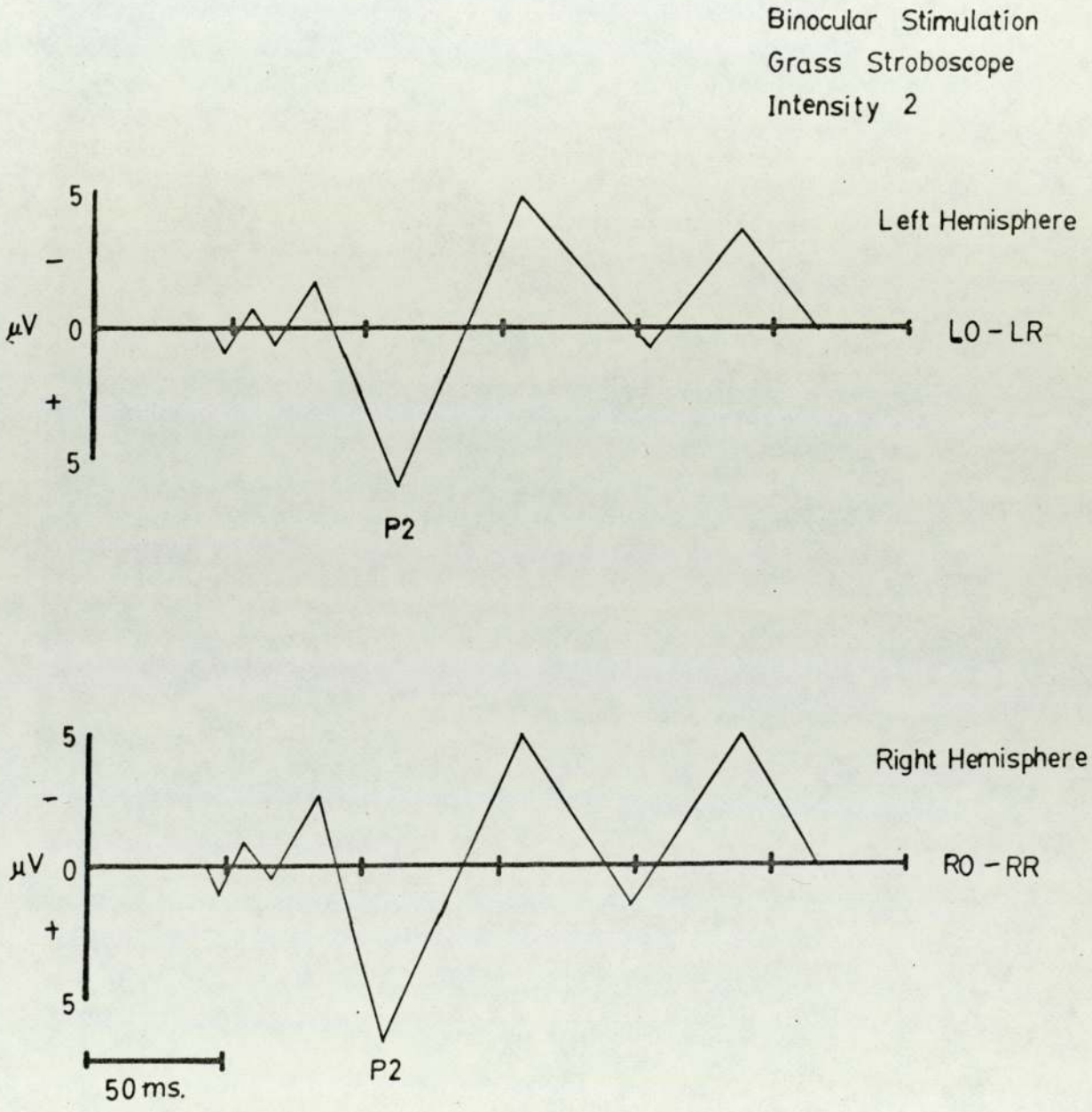
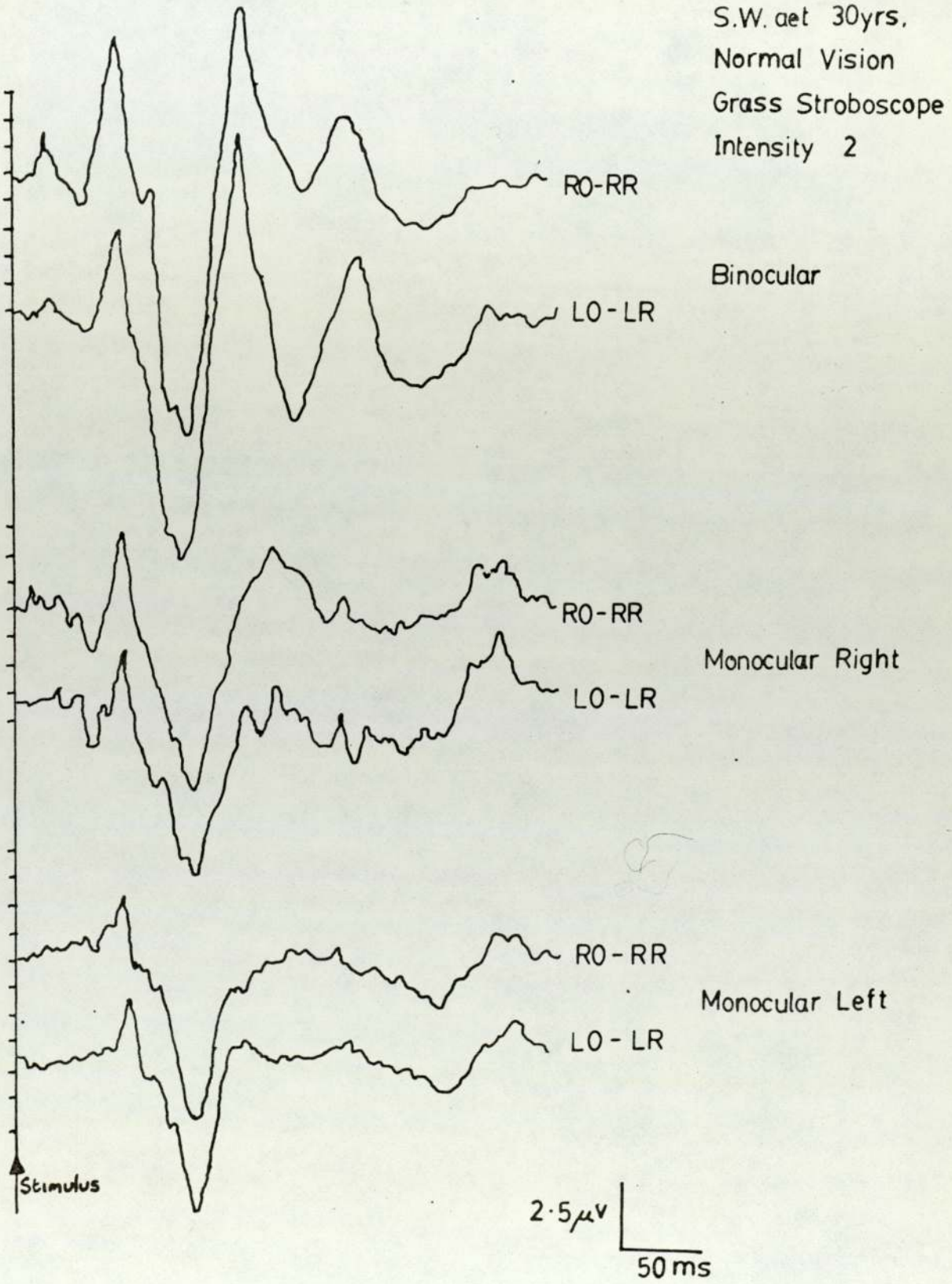


FIG 22.
DIFFERENCES IN THE VEP WITH BINOCULAR AND MONOCULAR STIMULATION



VEP NOMENCLATURE THOMPSON (1978), HARDING (1974)	PO	N1	P1	N2	P2	N3	P3	N4
Ciganek (1961)		39.1 (4.2)	53.4 (4.4)	73.3 (6.4)	94.2 134.5 114 (7.4) Triphasic	190		
Gastaut and Regis (1964)		40	60	80	130	140	160	220
Kooi and Bagchi (1964)		48	74	98	120	150-160		
Wicke, Donchin and Lindsley (1964)				80	120	175	210	
Morrell and Morrell (1966)			56 (lo)	77 (7)	107 (14)	135 (9)	179 (10)	
Jonkman (1967)		41 (4)	54 (4)	74 (5)	100 (7)	120	145	195
Rietveld, Toudoir, Hagenouw, Lubbers and Spoor (1967)				60	100	170-210	200-235	
Ciganek (1969)	40 (5.4)	55 (6.8)	75 (7.4)	95 5.9)	110 (10.9)	160 (20.2)		
Dustman and Beck (1969)		40.1 (8.2)	54 (9.9)	68.1 (13.5)	105.5 (10.9)	139.3 (14.6)	180.9 (18.7)	236.2 (28.3)
Schenkenberg (1970)	26.9 (2.9)	46.6 (6.2)	50.7 (7.5)	69.4 (10.2)	101.5 (10.2)	135.4 (7.7)	175.1 (11.7)	230.7 (23.1)
Kakigi, Miyazaki and Mori (1972)			48.50	65-75	100-120	155-175	225-250	
Korol (1972)			53.9 (3.5)	81.8 (4.3)	108.5 (7.0)			
Creel, Dustman and Beck (1973)	26.4 (1.4)	52 (6.6)	60.3 (10.9)	86.6 (7.8)	115.1 (6.6)	154.6 (11.2)	193.3 (11.9)	240 (13.2)
Lehtonen (1973)		30-50	50-70	70-90	90-100	120-175	176-260	
Babel et. al. (1977)			53.9 (4.3)	21.9 (4.2)	108 (7.14)			
Thompson Ph.D. thesis (1978)		56.2 (6.7)	65.2 (9.9)	82.8 (9.1)	109.4 (9.9)	156.7 (14.6)	200.3 (22.5)	239.8 (33.1)

TABLE 6

LATENCY AND POLARITY OF VEP COMPONENTS IDENTIFIED BY VARIOUS AUTHORS

( ) denotes the standard deviation. The data is shown as the mean or the range in m.secs of each component

AMPLITUDE AND POLARITY OF VEP COMPONENTS REPORTED BY VARIOUS AUTHORS							
VEP nomenclature Thompson 1978, Harding 1974	O-N1	N1-P1	P1-N2	N2-P2	P3-N3	N3-P3	P3-N4
Ciganek (1961)	2.9 (1.6)	3.5 (2.2)	5.2 (3.4)	7.2 (4.2)	6.9 (3.5)	5.5 (2.9)	
Ciganek (1964)	1.5 (5.3)	5.2 (5.2)	2.7 (4.2)	4.4 (3.8)	4.0 (2.7)		
Schenkenberg (1970)	3.7 (2.9)	3.3 (2.5)	4.4 (3.0)	17.0 (3.0)	15.8 (8.0)	12.4 (6.8)	18.0 (7.1)
Kakigi et. al (1972)			5-10	8-14	15-24	15-35	
Creel, Dustman and Beck (1973)	1.3 (0.4)	2.6 (0.9)	2.8 (1.4)	3.4 (1.1)	8.3 (1.1)	8.3 (2.6)	7.8 3.8)
Howe and Harcourt (1976)				12.5 8-23			
Thompson (1978)	1.7 (1.4)	2.1 (1.7)	2.8 (1.9)	8.2 (3.1)	11.1 (5.6)	6.3 (5.6)	6.4 (5.6)

TABLE 7.

PEAK TO PEAK AMPLITUDE MEASUREMENTS OF THE VEP COMPONENTS REPORTED BY VARIOUS AUTHORS

( ) denotes the standard deviation. The data is shown as the mean value or range

Statistical tests found no significant difference in the VEP from the two hemispheres, or between binocular and monocular stimulation. Only the P2 component, as it was always present, was analysed in detail. The mean value of the hemispheric difference of the P2 latency for binocular stimulation was 3.2 m.sec. (standard deviation 3.7, range 0-12 m.sec.). The mean amplitude difference was 2.3 μV (standard deviation 2.0, range 0-8 μV). In the majority of individuals there was very little difference in the size of the P2 component between the hemispheres. However in 12.5% of the group, there was an amplitude difference of 40-50%, and in a further 5% there was a greater than 50% reduction in the P2 component in one hemisphere. As with the younger group, this large reduction in amplitude was not accompanied by as large an asymmetry in the remaining components of the VEP.

In all but two of the adult subjects, P2 was the prominent early component, and the primary waves before 100 msec. were of much lower amplitude. In two subjects (5%) the P1 component was as large as P2. This was seen in both monocular and binocular conditions in one individual. The second only produced this unusual wave form when the right eye was stimulated, the other conditions producing the more usual form of the VEP, with the primary components being smaller than P2. In both subjects the P1 component did not exceed 5 μV in amplitude. That is the similarity in size of P1 and P2 components was not because of an unusually large early positive, but rather because of the low amplitude of the P2 component. In both subjects the addition of a pattern to the flash stimulus significantly improved the amplitude of the P2 wave.

When one eye was stimulated, the latency difference between the hemispheres of the P2 component was 4.2 msec. (standard deviation 2.7, range 0-12 msec.) and the mean amplitude difference was 1.9 μV (standard deviation 2.0, range 0.5-5.3 μV). Compared with the young age group, there was no evidence of a larger contralateral response, which agrees with the report of Groth, Weled and Barkin (1970) that a significant contralateral potential was only seen in young age groups. When the relative amplitude difference between the two hemispheres of the P2 component was measured there was a significant asymmetry (taken as more than 50% reduction on one side) in 6% of the subjects, when stimulated monocularly. In more than half of these people such a large symmetry was only seen for one eye, and it was not reflected in the rest of the VEP.

When the VEPs from the two eyes were compared, the mean latency difference between the responses was 5.8 msec. and the greatest difference was 15 msec. The mean amplitude difference between the two eyes was 2.8 μV.(range 0.75 to 11.5 μV.) with a reduction of more than 50% in the P2 wave from one eye compared with the other eye occurring in 9% of the adult population.

7.2.3. The VEP in an old age group

Twenty five individuals, whose ages ranged from 40 to 78 years were investigated, see Appendiv IV (page 339) for details. It is often difficult, particularly with the very old, to assess the normal ageing changes that occur in the visual system (see Chapter 3 , section 3.3.3) and so in addition to the checks made for all the age groups, that is normal visual acuity and

background EEG, and no relevant clinical history, volunteers over the age of 60 years visited the Birmingham Eye Hospital for a full visual examination with an ophthalmic opinion on the state of the retina, and a Friedmann Central Field analysis (for an example of the Eye Hospital report see Appendix V) All the subjects reported here were within normal limits for the age.

Only three subjects were aged between 40 and 49 years, and on inspection, their VEP results were very similar to those of the adult group. The VEPs of the four subjects aged 50 to 59 years showed features that are not seen in the younger and adult population (see Table 8 , page 176). One subject had a much longer latency evoked potential, and two others had high amplitude primary components (before 100 msec.), which has been reported as a characteristic sign in the elderly over the age of 58 years (Dustman and Beck, 1969; Schenkenberg, 1970; Schenkenberg and Beck, 1971). For these reasons only individuals over the age of 50 years were included in the old age group for analysis, and although there is not sufficient data in this sample, it seems likely that the adult VEP remains relatively unchanged into the fifth decade.

The presence of most of the components of the VEP was inconsistent, and as with the other age groups, only P2 was always recorded (see Fig.23 page 177). Fourty three percent of the group had a complete primary response (before 100 msec.) for binocular stimulation, and this fell to 39% of the group for monocular

SUBJECTS		COMPONENTS OF VEP					COMMENTS
			P1	N2	P2	N3	
DM	55 yrs.	A	65	92.5	121	161	Normal latency, early components high AMP
		B	10.2	8.9	12.4	7.6	
JW	50 yrs.	A	63	82	112	142	Normal latency, very high AMP. early components
		B	19.5	18.3	13.6	10.0	
FW	58 yrs.	A	70	86	125	165	Normal latency and form
		B	1.5	2.7	19.2	12.5	
ES	59 yrs.	A	76	102	140	190	Delayed latency normal form
		B	1.0	2.5	8.5	10.2	

TABLE 8.

AMPLITUDE AND LATENCIES OF THE FLASH VEP IN OLDER INDIVIDUALS AGED FROM 50 TO 59 YEARS

A MEAN PEAK TO PEAK AMPLITUDE IN μVOLTS, OF COMPONENTS FROM LEFT AND RIGHT HEMISPHERE

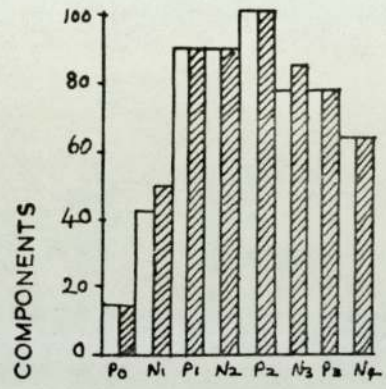
B MEAN LATENCY IN MILLISECONDS, OF COMPONENTS FROM LEFT AND RIGHT HEMISPHERE

FIG.23

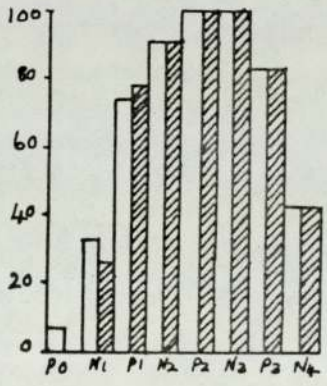
THE PRESENCE OF COMPONENTS OF THE VEP.

OLD AGE GROUP.

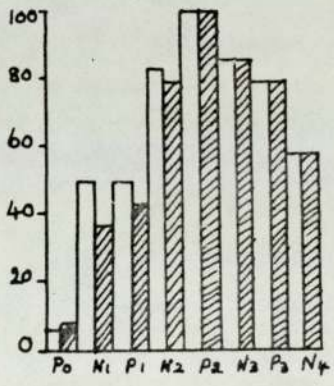
BINOCULAR STIMULATION



LEFT EYE STIMULATION



RIGHT EYE STIMULATION



LEFT HEMISPHERE

RIGHT HEMISPHERE

stimulation. One or more components within the first 100 msec. was unilaterally absent in 21% of the binocularly evoked potentials, and in 19% of the monocular VEPs. Since the late VEP components were also sometimes absent, only the P2 component was reliable enough to be analysed in detail. The group data on the amplitudes and latencies of the main components are seen in Table 9 (page 179), and the results of the 'average' individual for binocular stimulation are displayed in graphic form, which high lights the large amplitudes of the components N1, P1 and N2, which is typical of this age group (Fig. 24 , page 180). Such a VEP configuration is not always seen (see Figs. 25 , 26 , 27, pages 181 to 183) and the VEP may be very similar to younger age groups, or just show delayed latencies.

No significant differences were found in amplitude or latency between the hemispheres, between the right eye and left eye VEP, or between monocular and binocular stimulation. The latency difference between the left and right hemisphere of P2 for binocular stimulation was only 1.6 msec. (standard deviation 1.9, range 0-7 msec.) and the mean amplitude difference was 2.2 μV (standard deviation 1.8, range 0.5 to 8 μV). When the relative amplitudes of the right and left P2 component were examined, only one individual had greater than 50% asymmetry, and this was not seen in all the components of the evoked potential.

With monocular stimulation, the mean of the hemispheric latency differences of P2 was 1.5 msec. (standard deviation 1.4, range 0-6 msec.) and the amplitude difference was 1.8 μV (standard

TABLE 9

Latencies and Amplitudes of the Flash VEP in the Old Age Group (50 - 78 Years)

VEP nomenclature Thompson (1978) Harding (1974)			PRINCIPLE VEP COMPONENTS						
			N1	P1	N2	P2	N3	P3	N4
STIMULATING CONDITION	LATENCY m.sec.	MEAN	58.5	72.0	88.76	116.5	158.6	215.5	270.6
		SD	9.0	6.6	9.9	10.7	17.0	26.5	35.85
		RANGE	44-63	58-86	72-106	105-142	144-185	165-240	190-300
BINOCULAR	AMP μV	MEAN	2.36	7.45	10.35	11.97	9.24	10.36	8.46
		SD	2.14	7.18	9.86	4.19	6.1	5.87	4.27
		RANGE	.5-6.0	1.75-29.0	1.75-36.0	2.9-28.3	3.5-18.2	5-23.9	4-16.1
MONOCULAR RIGHT	LATENCY m.sec.	MEAN	50.7	68.6	87.7	117.8	165.4	218.3	257.7
		SD	4.7	6.7	8.7	11.013	17.18	21.2	19.4
		RANGE	47.62	56-75	70-104	102-144	135-187	181-256	210-292
	AMP μV	MEAN	2.24	5.09	5.2	10.7	10.6	7.1	7.4
		SD	0.8	4.0	5.4	3.7	5.17	2.4	2.89
		RANGE	1.3-3.9	0.5-12.9	0.5-27.4	2.4-20.7	3.5-21.4	3.5-11.5	4.3-11.5
MONOCULAR LEFT	LATENCY m.sec.	MEAN	50.6	69.3	88.7	117.9	161.9	207.7	268.6
		SD	6.6	5.5	6.7	9.6	8.2	15.2	22.5
		RANGE	42-59	62-77	78-100	100-143	147-175	187-231	220-300
	AMP μV	MEAN	1.9	5.1	7.8	10.8	9.9	8.0	5.6
		SD	0.8	4.2	8.4	5.7	4.1	3.8	3.51
		RANGE	1-2.9	0.5-14.0	0.5-30.3	2.3-24.3	3.0-20.0	2.9-16.6	3.0-11.00

FIG. 24.
VEP of the AVERAGE OLD INDIVIDUAL.

BINOCULAR STIMULATION
DIFFUSE FLASH

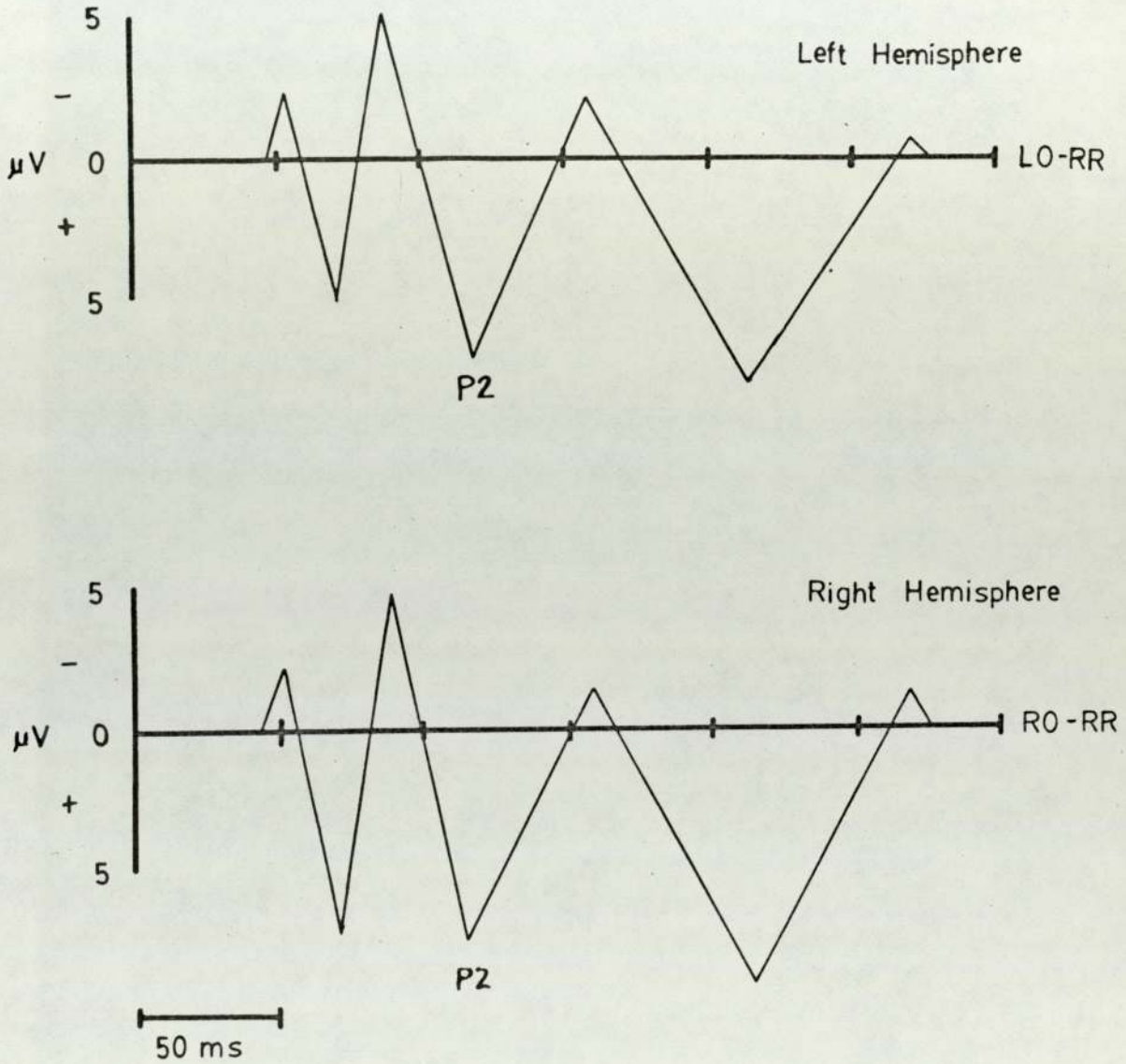


FIG 25. OLD CONTROL GROUP
Delayed Latencies

6/6 RE 6/6 LE
Binocular Stimulation

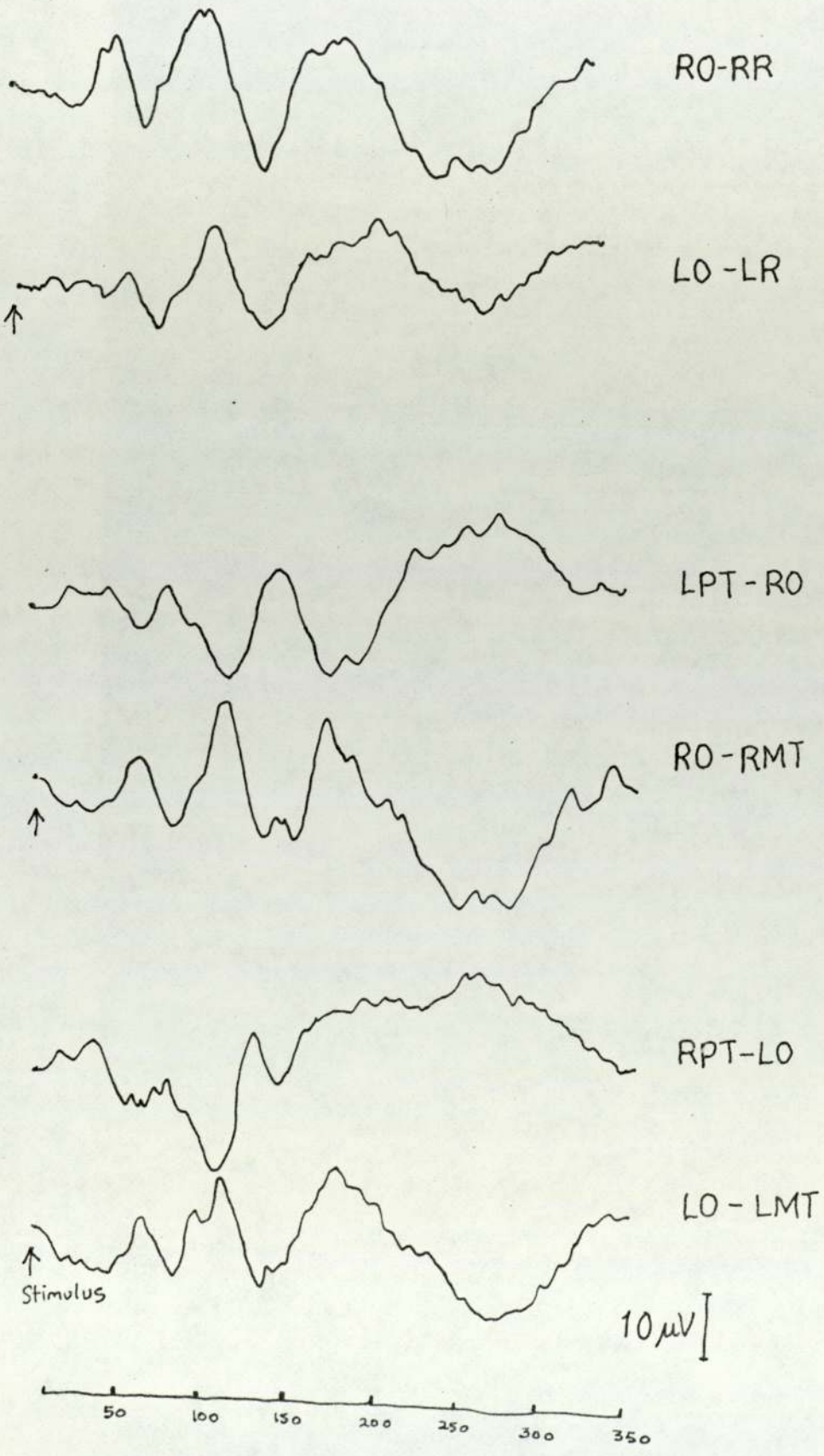


FIG 26.
OLD CONTROL GROUP.

Normal Wave Form and Latency

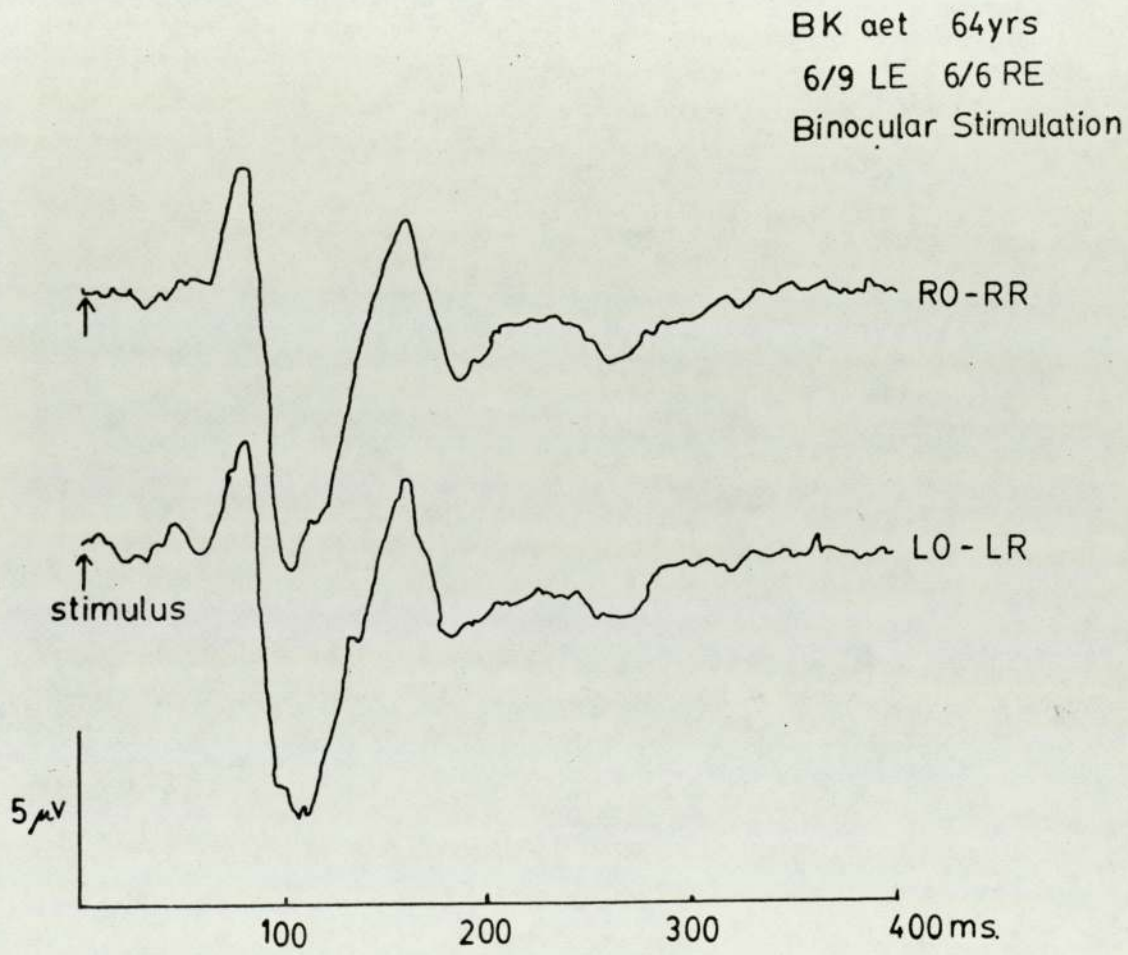
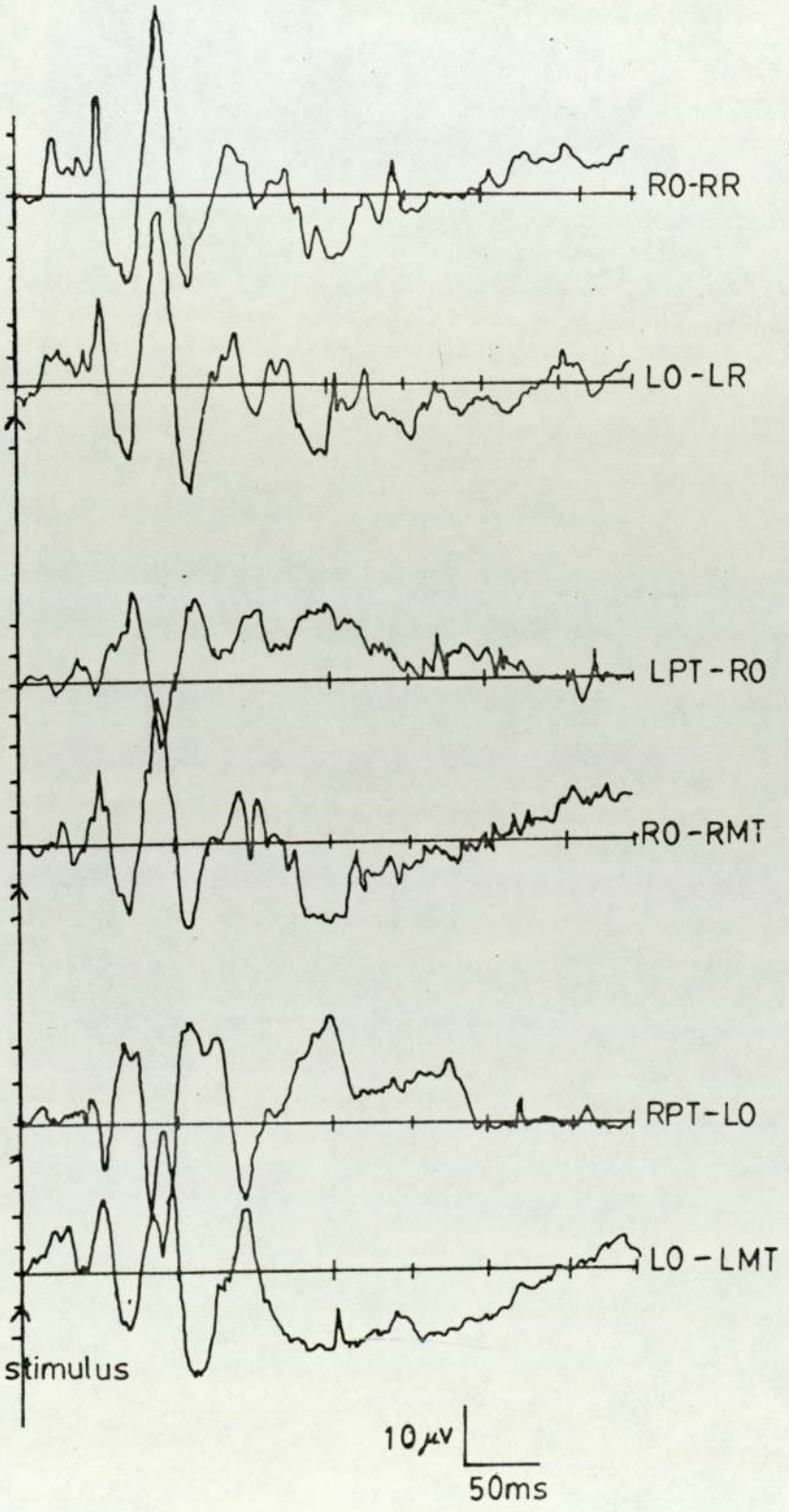


FIG 21. OLD CONTROL GROUP
High Amplitude Early Components
Normal Latences.



deviation 1.8 μV, range 0.5 to 6.5 μV). There was no consistent trend of larger contralateral responses, and in fact the ipsilateral response was more often slightly larger. Again asymmetries in amplitude of more than 50% was only seen in the same one individual (4%). When the VEP results from one eye were compared with the other eye, 90% of the results showed a latency difference of the P2 component of less than 10 msec., and an amplitude difference of less than 5 μV.

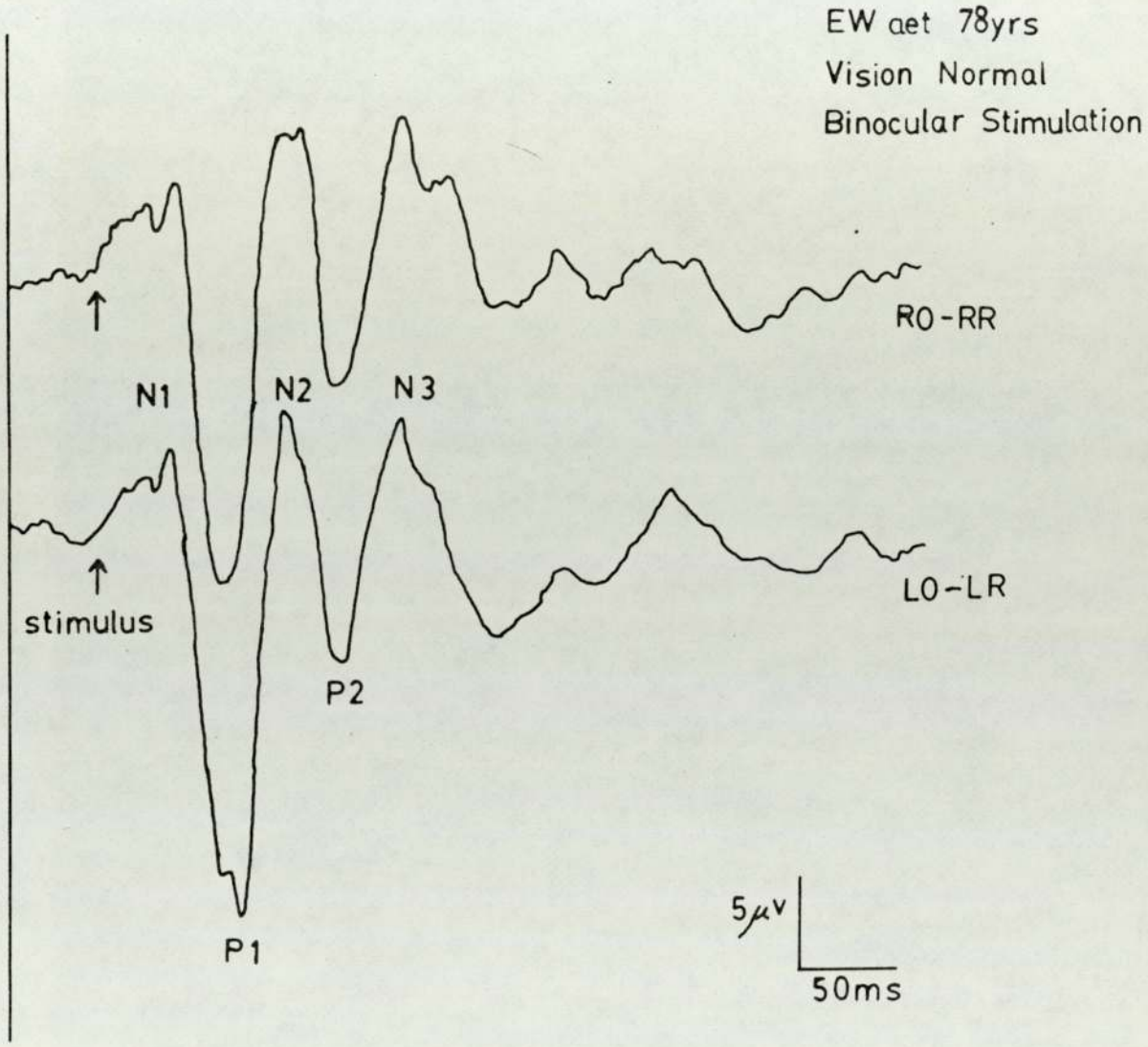
Although the early components were often of high amplitude, the P1 component was larger than the P2 component in only 14% of the group, and in all cases the P2 was well formed and never less than 5 μV in amplitude (base line to peak amplitude) or 10.6 μV, peak to peak amplitude. The most striking example was seen in the oldest subject tested (Fig.28 page 185). The VEP is dominated by a large P1 component, and the following P2 is smaller, but well formed.

Schenkenberg's study (1970) of the normal flash VEP included two groups of 20 volunteers each, whose mean ages were 66 and 77 years. It can be seen in Table 10, (page 186) that his data on these age groups are similar to the author's group (mean age 66 years) although the latter was very much smaller in size (22 individuals).

7.2.4. A comparison of the VEP in different age groups

There is a difference in the wave form of the cortical potential of the three groups studied with a characteristic VEP for the different ages. The childrens' responses generally have few early components, and the P2 component and later waves are all of high amplitude. The P2 component dominates the adult VEP, while in the elderly the early components before P2 tend to become larger, while those after P2 become smaller.

FIG28. LARGE AMPLITUDE EARLY COMPONENTS IN THE VEP OF THE OLD AGE GROUP.



Schenkenberg notation	N1	P2	N2	P3	N3	P4	N4
Thompson notation	Ni	P1	N2	P2	N3	P3	N4
LATENCY	mean SD	mean SD	mean SD	mean SD	mean SD	mean SD	mean SD
N=20 mean age 66 yrs	50.9 , 4.6	70 , 7.2	93.7 , 9.0	123.9, 11.2	152.7, 8.2	187.9, 14.5	243.9, 16.4
N=20 mean age 77 yrs	53.2 , 5.9	71.2 , 8.2	91.1 , 5.3	118.6, 9.5	152.1, 13.2	188.9, 14.0	262.7, 16.7
AMPLITUDE							
mean age 66 yrs	2.7 , 2.1	6.1 , 4.1	8.8 , 4.0	10.0 , 4.0	7,1 , 4.9	6.1 , 2.4	7.3 , 4.6
mean age 77 yrs	3.2 , 0.4	6.0 , 4.0	9.3 , 6.0	11.2 , 7.5	7.9 , 4.4	6.3 , 7.6	7.9 , 4.6

TABLE 10.

Mean peak delays (m.sec) and peak to peak amplitude ( ) from the right occipital scalp electrode (O2).

Adapted from Shenkenberg, 1970.

The combined data for all of the normal experimental group is presented in Appendix VI (page 342). It is however, advisable when commenting on clinical data, to compare the results with age matched controls, rather than total group data.

The N1 component of the children (the only primary wave that occurred frequently) was significantly larger than the adult group ($p < 0.05$) as was the N1 component of the elderly compared with young adults ($p < 0.001$). There was no significant difference between the young and the old groups.

The subsequent waves P1 and N2 were also significantly increased with age compared with the two younger groups ($p < 0.01$ in both cases). There were no significant differences between the two adult groups in the later portions of the VEP. When the children were compared with the rest of the population, the P2 component was significantly larger than that found in young adults ($p < 0.001$), however, there was no significant difference when comparison was made with the old group. The next two components N3 and P3 were both significantly larger in the young VEP than in the adult and older individuals ($p < 0.01$ and 0.001 respectively), while the N4 component did not approach significance. These findings agree very closely with those reported by Schenkenberg, Dustman and Beck (Dustman and Beck, 1969; Schenkenberg, 1970; Schenkenberg, Dustman and Beck, 1971), and do not support the reports of no change, or a significant reduction in the amplitude of the VEP in an ageing visual system (Perry and Childers, 1969; Celesia and Daly, 1977).

Fewer significant differences were found in the timing of the evoked potential. There was no significant difference between the latencies of a child or young adult's VEP, and in the elderly only the P1 component

was significantly delayed compared with the other two groups at the 0.05 level. The N2 and P2 latencies approached a significant delay (p between 0.1 and 0.05), while there was no significant difference in the latencies of any of the remaining components. Schenkenberg (1970) reported significant delays in most of the VEP components in the elderly, as have Celesia and Daly (1977). In this case the elderly population was rather small, and the high variability in the flash VEP generally may have been the reason for the failure to find significant differences.

Maturation and ageing changes in the VEP are firmly established, although somewhat surprisingly similar processes do not occur in the auditory and somatosensory evoked potentials (Schenkenberg, 1970). The underlying physiological processes that cause such surface electrical changes are yet to be understood.

7.2.5. Some suggestions on the criteria of a normal VEP

Vaughan and Katzman (1964) and Vaughan (1966) suggested that the first 100 msec. was the most consistent portion of the VEP, and wave III (equivalent to N2) was found in all normals; thus if this wave was reduced by more than 50% or absent in one hemisphere it was suggestive of a homonymous hemianopia. Oosterhuis et al. (1969) also adopted this criteria, and Howe and Harcourt (1976) used amplitude asymmetries in the primary response to diagnose their patients with visual defects.

Together with many other researchers, the author finds the early portion of the VEP too inconsistent to be used for any criteria of abnormality (Van Balen and Henkes, 1960; Creel, Dustman and Beck, 1973; Babel et al., 1977). Gastaut and Regis (1964, 1965) found a complete primary response in only 20% of their normal population. The findings in

this study were equally dissapointing. No child had a complete primary evoked response, and all the early components were present in only 30% of the adult group, and in 43% of the elderly. The early response was less likely to be seen with monocular stimulation.

From the data presented, the P2 component (around 100 msec.) is the most reliable component to use for the development of normal criteria of the VEP. It is always recorded, is always of significant amplitude, and shows less variability in latency compared with later waves. Other investigations also find that the P2 component is the most consistent wave when comparing different individuals (Van Balen and Henkes, 1960; Creel, Dustman and Beck, 1973; Jeffreys, 1977). There is the added advantage in the selection of the P2 component in that there is some suggestion that it is primarily a foveal response (Harding, 1974; Jeffreys, 1977; Sprekreijse, Estevez and Reits, 1977), and may thus provide valuable information on central visual function which is of prime importance when assessing visual acuity.

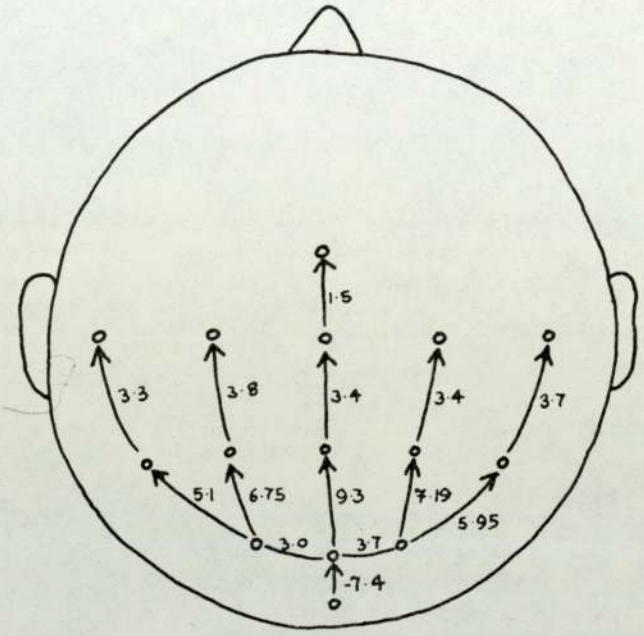
7.3. Topographical studies of the VEP

Because of the very large variations in the flash VEP, a simple criterion for an abnormal response of, for example, a large reduction (greater than 50%) of the P2 component, fails to exclude a significant number of normal individuals (see previous sections 7.1.2, 7.2.2., and 7.2.3.). More information needs to be obtained about the VEP in order to improve the reliability of any judgement about a normal or abnormal response, and more information can be obtained about the visual potential by using multiple channels

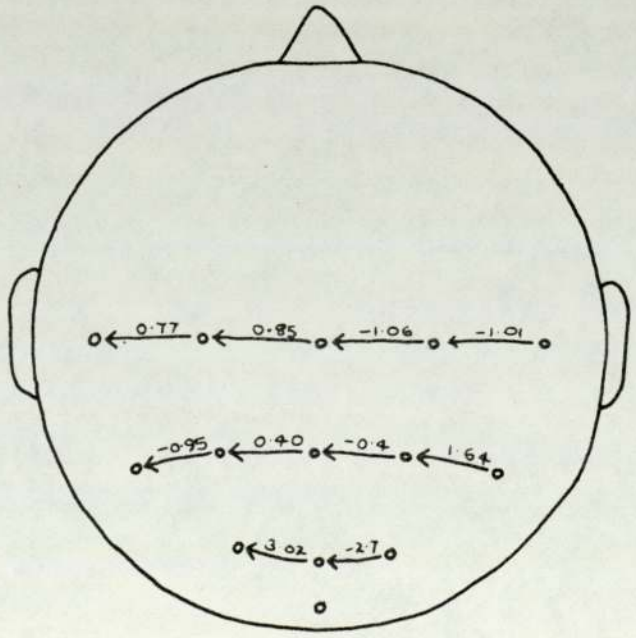
to record the distribution of the scalp potentials (Kooi and Bagchi, 1964; Kooi, Guvener and Bagchi, 1965; Kooi, Yamanda and Marshall, 1973; Harding, 1977).

In order to obtain additional criteria with which to describe the normal VEP, and also in order to assess the optimal placement of electrodes for recording the VEP from the left and right hemispheres (see section 7.1.4., page 140), the distribution of the flash VEP was investigated in 14 normal subjects. Most of the volunteers were aged between 18 and 26 years, only two were elderly and aged 62 and 64 years. All the subjects were screened in a manner similar to the other normal control groups. The international system of electrode placement was used (Jasper, 1958), and bipolar and monopolar recordings were obtained from fifteen posterior electrodes. The bipolar derivations consisted of anterior-posterior and transverse chains of electrodes. An example of the electrode combinations is shown in Figure 29 (page 191). A monopolar record was also obtained from each electrode used in the bipolar recordings, and the combined ear lobes were used as a reference. To collect such a large number of VEPs was time consuming, and the process was speeded up by using a PDP 15 computer. Six EEG channels could be recorded simultaneously and a permanent record and analysis performed later, offline. Thus forty VEPs could be recorded in a forty five minute session. Only binocular stimulation was investigated, although two subjects were stimulated monocularly, and the VEP distribution appeared to be very similar. The VEPs could not all be recorded simultaneously, and so the order of recording from different areas of the head was randomized to reduce the effects of fatigue, inattention, etc.

FIG 29.
THE AVERAGE POTENTIAL DIFFERENCES EVOKED BY FLASH STIMULATION IN THE POSTERIOR REGIONS OF THE SCALP.



ANTERIOR-POSTERIOR BIPOLAR RECORDINGS.



TRANSVERSE BIPOLAR RECORDINGS.

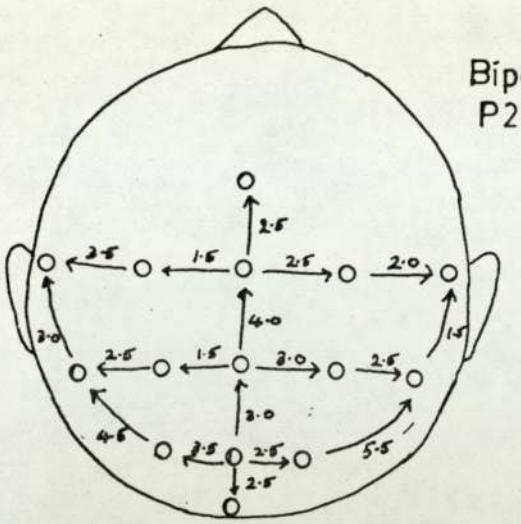
There was inevitably some variation in the results obtained, however there was generally good agreement between the potential difference information from the bipolar recordings and the monopolar data, particularly for the sites of the largest amplitudes of the VEP. In this group of volunteers there were again inconsistencies in the appearance of VEP components except the P2 wave, and so only the distribution of P2 was calculated and plotted. An inspection of the data confirmed that the spatial properties of P2 were closely related to the distribution of the rest of the VEP components, with a tendency for a greater attenuation of early components within the first 100 m sec. in anterior locations.

There was no consistent trend of increasing peak latency of P2 with increasing distance away from the occipital poles. Frequently the slowest response occurred at electrode positions O1, O2, and Oz, as is shown in Figure 30(page 193), with much shorter latencies further forward on the scalp. From this common finding it seems likely that the latency, at least of the P2 component varies with the amplitude of the wave. This has also been suggested by Schechter and Buchsbaum (1973), and would mean that latency variations of perhaps up to 10 msec. between individuals, between hemispheres, and between anterior and posterior recording sites, may primarily reflect amplitude differences rather than differences in timing. Perhaps a better measure of the latency of a component would be the 'onset' latency, that is the beginning of the positive or negative going wave. However, in practice, with such a complex waveform of overlapping components, a measurement of onset latency would be extremely difficult to calculate.

FIG.30.

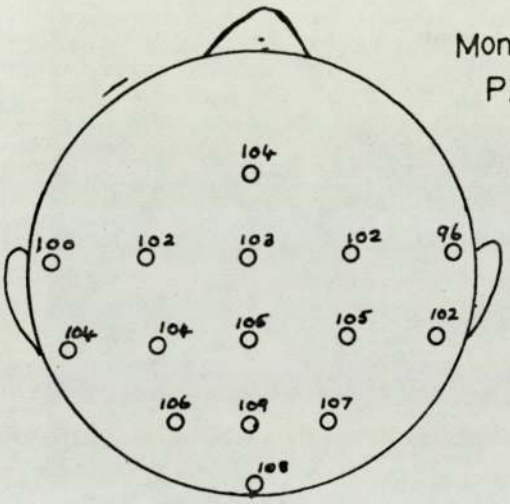
TOPOGRAPHY OF THE P2 COMPONENT OF THE VEP.

A Comparison of Monopolar and Bipolar Recordings.

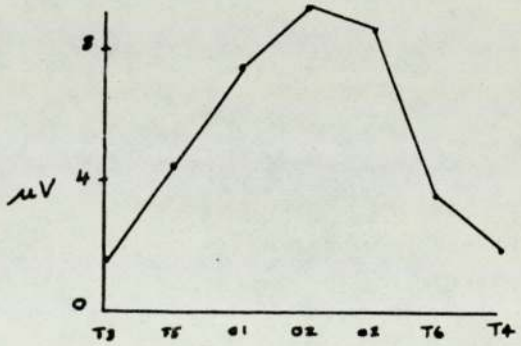


Bipolar Recordings
P2 Amplitude Differences (μV)

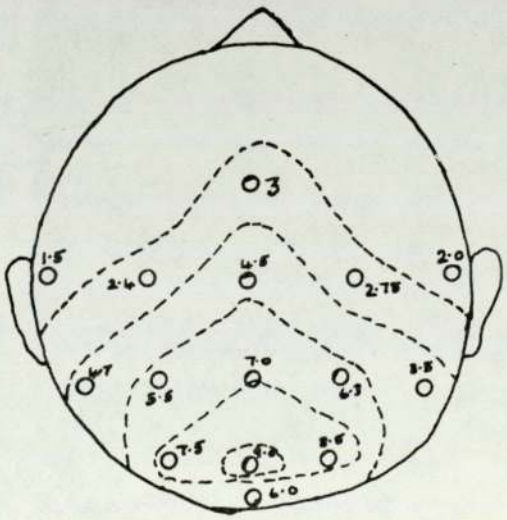
C 12 aet 33yrs
Normal Vision
Binocular Stimulation



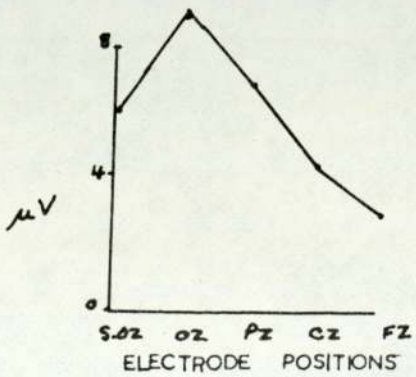
Monopolar Recordings.
P2 Latency (ms)



Monopolar Recordings ELECTRODE POSITIONS.



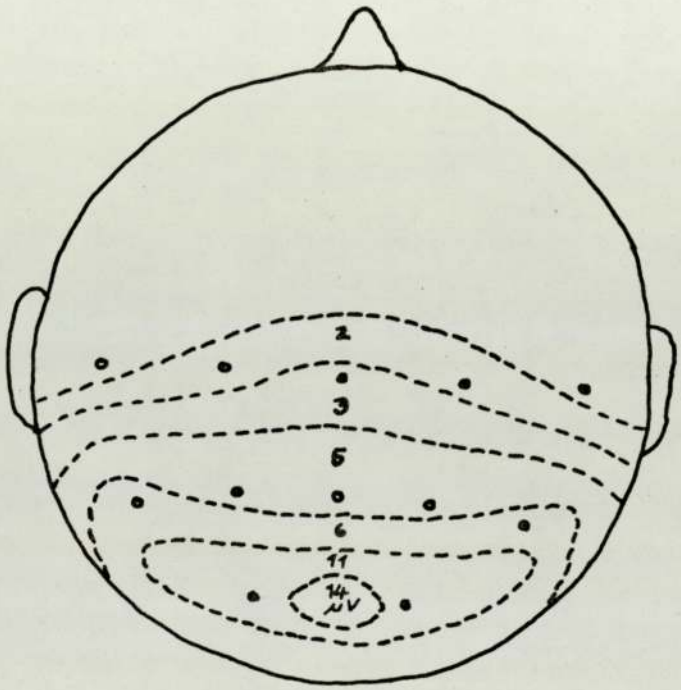
P2 Amplitude (μV)



ELECTRODE POSITIONS

From the topographical information obtained from 12 of the volunteers, the mean value of the potential difference between adjacent electrodes was calculated, together with the mean amplitude data from the monopolar recordings. From this information a spatial map of the P2 component of the VEP was constructed (Figs. 29 & 31 pages 191, 195). The dotted lines are not true contours, but are designed to enclose areas from which similar amplitudes of the P2 component are recorded. In all 12 subjects, the largest P2 wave was recorded at OZ, with high amplitude waves also arising from the right and left occipital poles. The amplitude declined in anterior and antero-lateral directions, and the lowest potentials were recorded at T3 and T4, the mid temporal derivations. Larger responses were often seen at all the midline electrodes compared with adjacent positions, and although this is apparent in the map of the 'average individual', the phenomenon is more clearly seen in subject C12 (Fig. 30 , page 193). Larger midline responses have been reported in the literature (Ciganek, 1961, 1965; Gastaut and Regis, 1965; Vaughan, 1966; Jeffreys, 1977), but no explanation has been presented to explain the finding. Large midline responses may occur in some individuals as a result of the synchronous arrival and additive effects of the potentials arising within the left and right hemispheres, while in other individuals, the timing and waveform of the potentials from the two hemispheres may vary and not contribute to a large midline response. In all the subjects recorded there was no evidence of a secondary source of the P2 component at the vertex as has been reported by Vaughan (1969). The P2 wave was always smaller at this site than at more posterior positions, and although of higher amplitude than adjacent

FIG 31. THE SPATIAL DISTRIBUTION OE THE P2 COMPONENT, AVERAGE DATA FOR A NORMAL ADULT GROUP



-------- denotes the approximate area of the scalp from which similar P2 amplitudes are recorded.

central sites (C3 and C4), the vertex response is best described as part of the overall pattern of gradually diminishing size of the VEP as it spreads out from the occipital poles.

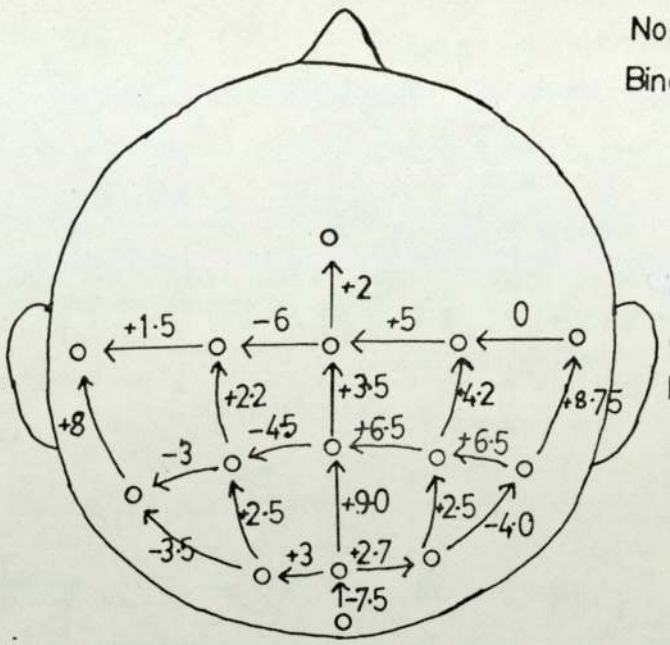
Two subjects were excluded from the group data, as their VEP distributions were different. (See Figs. 32 & 33 pages 197, 198). Both subjects did not have larger responses in the midline positions, and significant amplitudes were recorded laterally in posterior-temporal and midtemporal positions. Subject CO2 appears to represent the extreme form of this 'unusual' distribution of the P2 component, with in fact larger potentials arising close to T5 and T6 than were recorded at the two occipital poles. How such distributions relate to the wide variation in individual visual anatomy, and the occurrence in a minority of the population of a significant exposure of the striate cortex across the lateral surfaces of the hemisphere (see Chapter 2, section 2.3 page 24) can only be a matter of speculation. The author has not read of any other reports of such findings, however data on the distribution of scalp VEPs is scant.

From the topographical findings, and from investigations of suitable reference sites, it was concluded that reliable records of right and left hemisphere responses could be obtained from the bipolar derivations O2 to C4, and O1 to C3 (see Section 7.1.4, page 140).

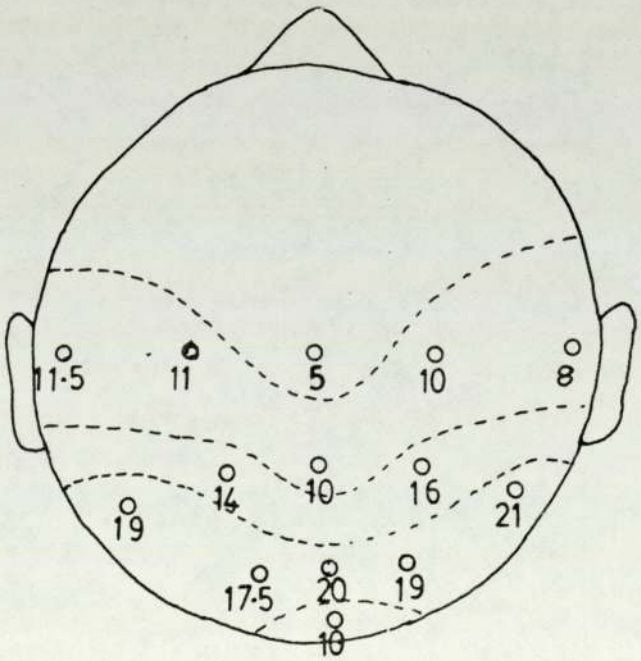
To obtain topographical information about the VEP, particularly when no large computer is available in a clinical department, is time consuming, and an unsuitable technique for investigating unwell patients, young children and the uncooperative. A system

FIG. 32.
AN UNUSUAL DISTRIBUTION OF THE P2 COMPONENT.

Subject CO 2. aet 18yrs.
Normal Vision.
Binocular Stimulation



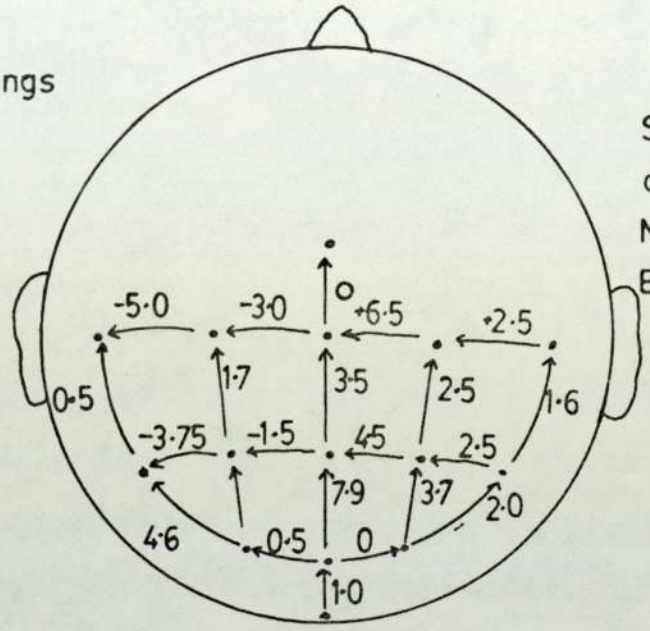
Bipolar Recordings of P2 Amplitude Differences (μv)



Monopolar Recordings of P2 Amplitudes (μv)

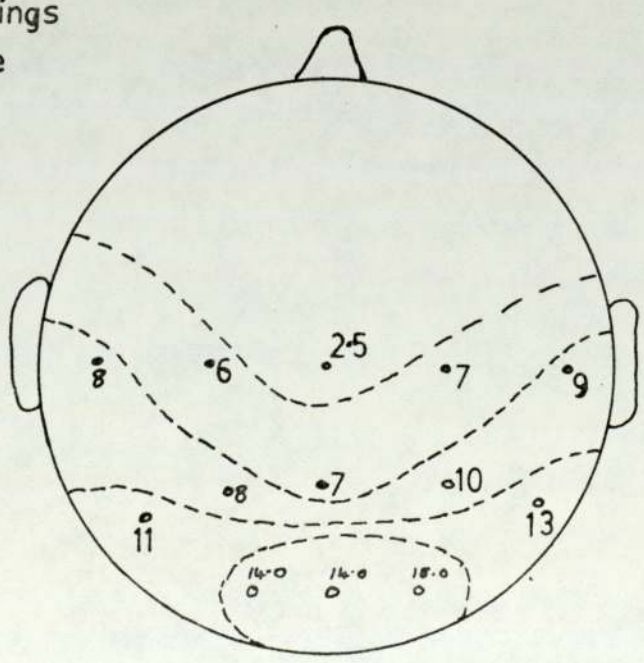
FIG. 33.
AN UNUSUAL DISTRIBUTION OF THE P2 COMPONENT.

Bipolar Recordings of P2 Amplitude Differences (μV)



Subject C.09
aet 19yrs.
Normal Vision
Binocular Stimulation

Monopolar Recordings of P2 Amplitude (μV)



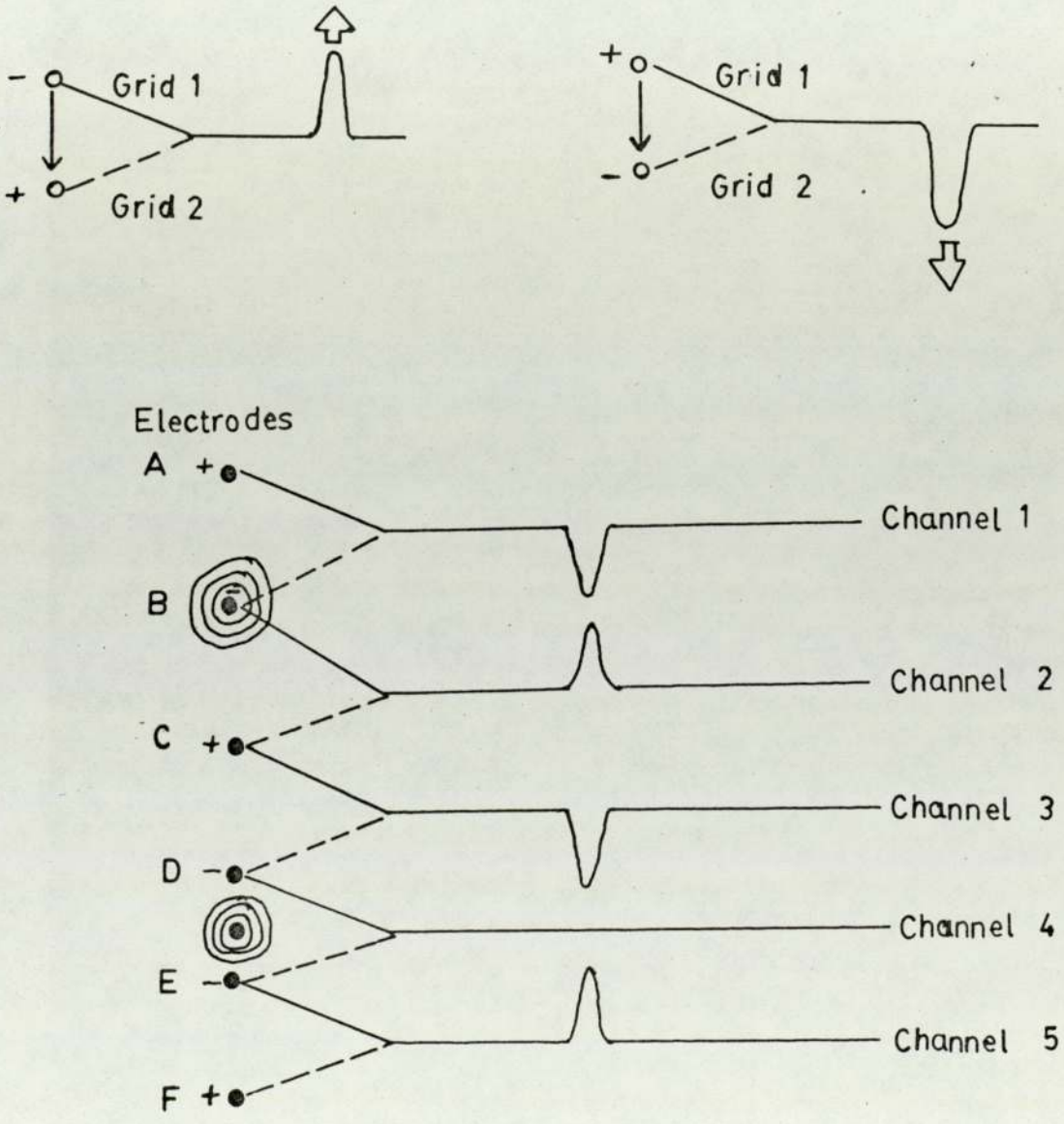
of recording was therefore devised by Professor G. F. A. Harding and the author to provide sufficient information of the VEP distribution using only a minimal number of channels (Harding, Thompson and Pananayiotopoulos (1969; see Appendix VII).

7.4. The Aston VEP montage

The most difficult problem when recording VEPs, particularly if one visual cortex is damaged and not responding to visual inputs, is the close proximity of the two occipital poles and the great distance of the scalp electrodes. The activity recorded for example on the right, from the O2 electrode will reflect not only the potentials arising from the right occiput, but also, since the brain is an efficient conducting medium, activity from the adjacent left occiput. Many authors report that VEPs are recorded over the hemisphere contralateral to homonymous hemianopic field defects (Kooi, Guvener and Bagchi, 1965; Bergamini and Bergamasco, 1967; Jacobson, Hirose & Suzuki 1968; Lehmann, Kavanagh and Fender, 1969; Cohn, 1973; Kooi, Yamanda and Marshall, 1973; Howe and Harcourt, 1976), and it is sometimes difficult to reliably distinguish between the normal and pathological response from the two hemispheres (Vaughan, Katzman and Taylor, 1963; Gastaut and Regis, 1965; Oosterhuis, Jonkman and Magnus, 1969).

In order to overcome the volume conduction effects of the two medially placed visual cortices, whose contributions can not be reliably differentiated by assymmetries in the response from either hemisphere, we adopted the simple EEG technique of phase reversal to localise the sources of the VEP (Harding, Thompson and Panayiotopoulos; 1969; Harding, 1974, 1977). Figure 34 (page 200) illustrates this

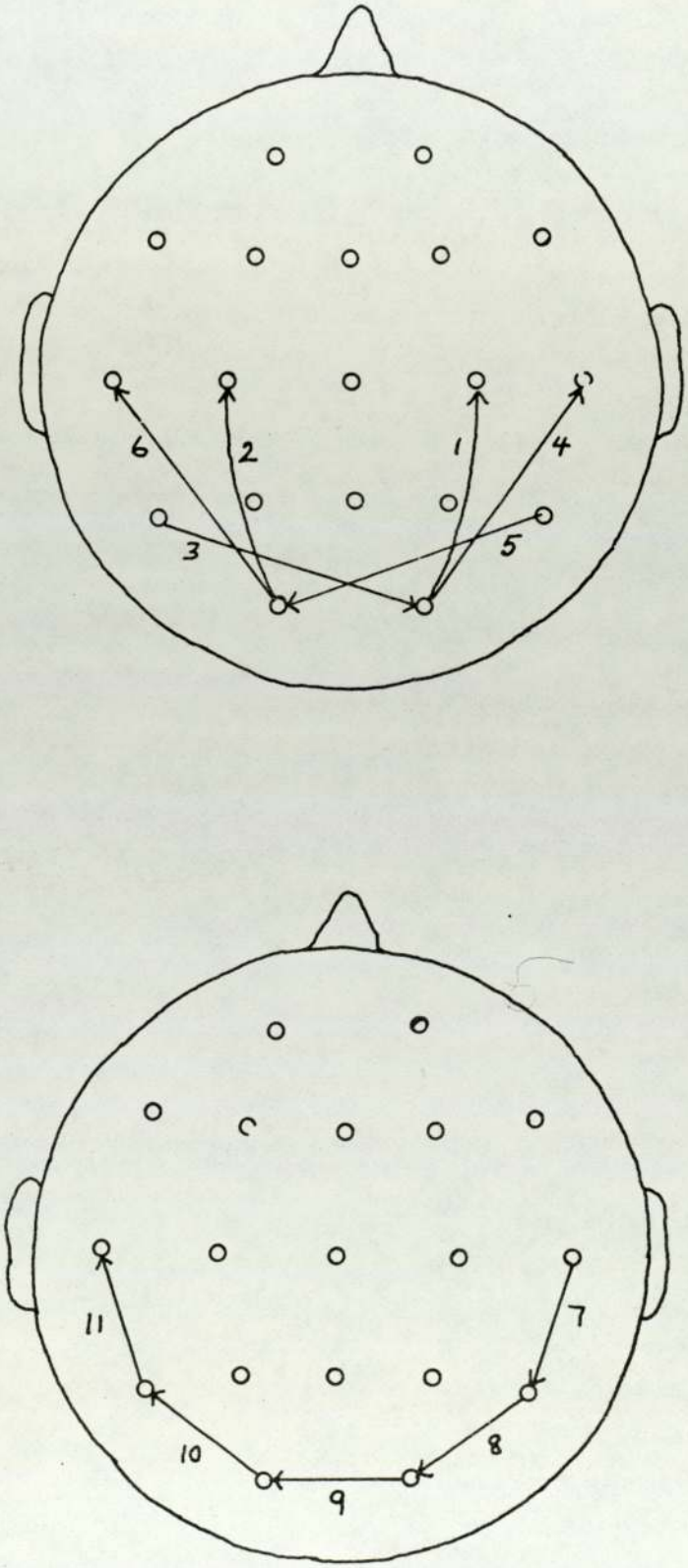
FIG34. BIPOLAR RECORDING TECHNIQUES.



technique. A source of activity beneath the electrode B, that is the common link between two adjacent bipolar channels (channels 1 and 2), produces an out of phase, or phase reversed signal, and it is this sign which is used to locate the source of the electrical activity. If an electrical source lies equidistant between two electrodes as for example between electrodes D and E, then the two electrodes are similarly effected, that is equipotential, and the same signal is fed to opposite grids of the amplifier, and does not appear on channel 4.

The electrode positions used are according to the 10-20 system (Jasper, 1958), and from the topographical data obtained in normal subjects (see Section 7.3. page 189) we have assumed a simple, symmetrical model of the brain and therefore of scalp visual potentials. Figure 35 (page 202) shows the full Aston montage for recording VEPs. Channels 1 and 2, recording activity from the right and left hemispheres have already been described in detail (see Section 7.1.5., page 143). Channels 3 and 4 are used to locate activity arising from the right occiput. In channel 3, grid 1 is connected to the left posterior temporal electrode (T5), and grid 2 to the right occipital electrode (O2). Since the left occipital electrode (O1) is an equal distance from T5 and O2 in the 10-20 system of electrode placement, then it may be assumed that any activity originating at O1 will effect equally T5 and O2, and thus be equipotential in channel 3. That is activity arising from the left occiput will not contribute to the potentials recorded in channel 3. Grid 1 of channel 4 is connected to the right occipital electrode, and grid 2 to the

FIG 35. THE ASTON MONTAGE FOR RECORDING VEP



right midtemporal electrode, T4. Since O2 is the common electrode in channels 3 and 4, any signal arising from the right occiput will appear as an out of phase signal in these two channels, while more distant activity will either appear in phase or unrelated. The same technique is used to locate activity arising from the left occiput by recording from channels 5 and 6.

Typical results for the flash VEP using the six channel montage can be seen in Figure 36(page 204). The young adult volunteer has symmetrical and synchronous potentials over the left and right hemispheres (channels 1 and 2), and equal phase reversal over the right occiput (channels 3 and 4), and the left occiput (channels 5 and 6).

Similar results can be seen in a normal child (Fig.37, page 205), and in one of the elderly subjects (Figure 27 , page 183), with clear phase reversals occurring of the VEPs to both the right and left occiputs.

It was the standard procedure to record the six channels of the Aston Montage during each investigation, and phase reversal data was obtained for all of the 85 normal volunteers previously described in section 7.2. (page 152). Both binocular and monocular stimulation were investigated, and there were no significant differences between the results obtained when stimulating only one eye or both eyes (Chi squared test of significance). The phase reversal results for binocular stimulation are seen in Figure 38(page 206), and are shown as the number of occasions phase reversal occurs of each component, expressed as a percentage of the total number of VEPs recorded. Only the major positive component (P2) always

FIG. 36.

FULL VEP RECORDING MONTAGE WITH PHASE REVERSAL TO THE TWO OCCIPUTS.

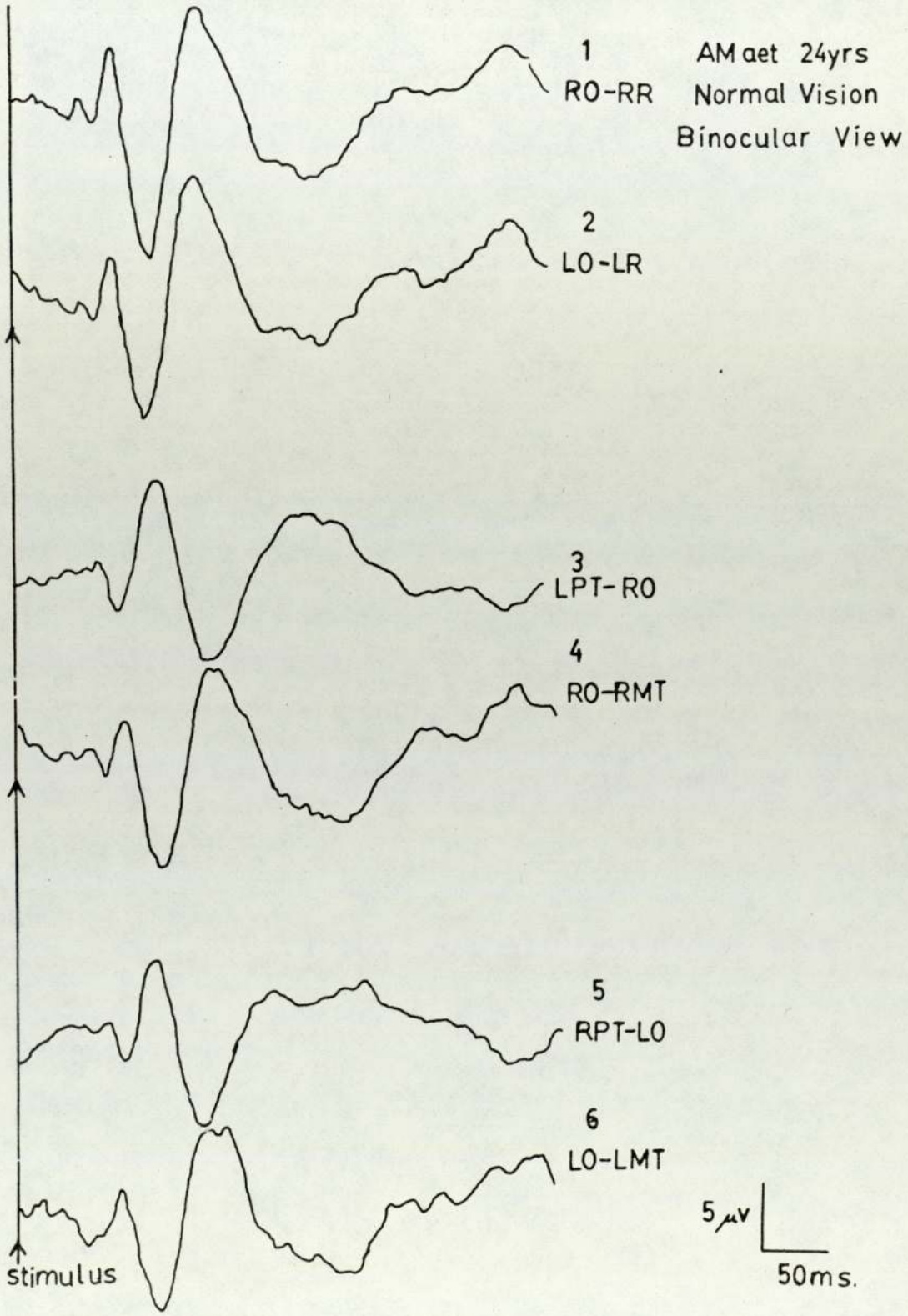


FIG. 37.

Normal

J.A. age 6

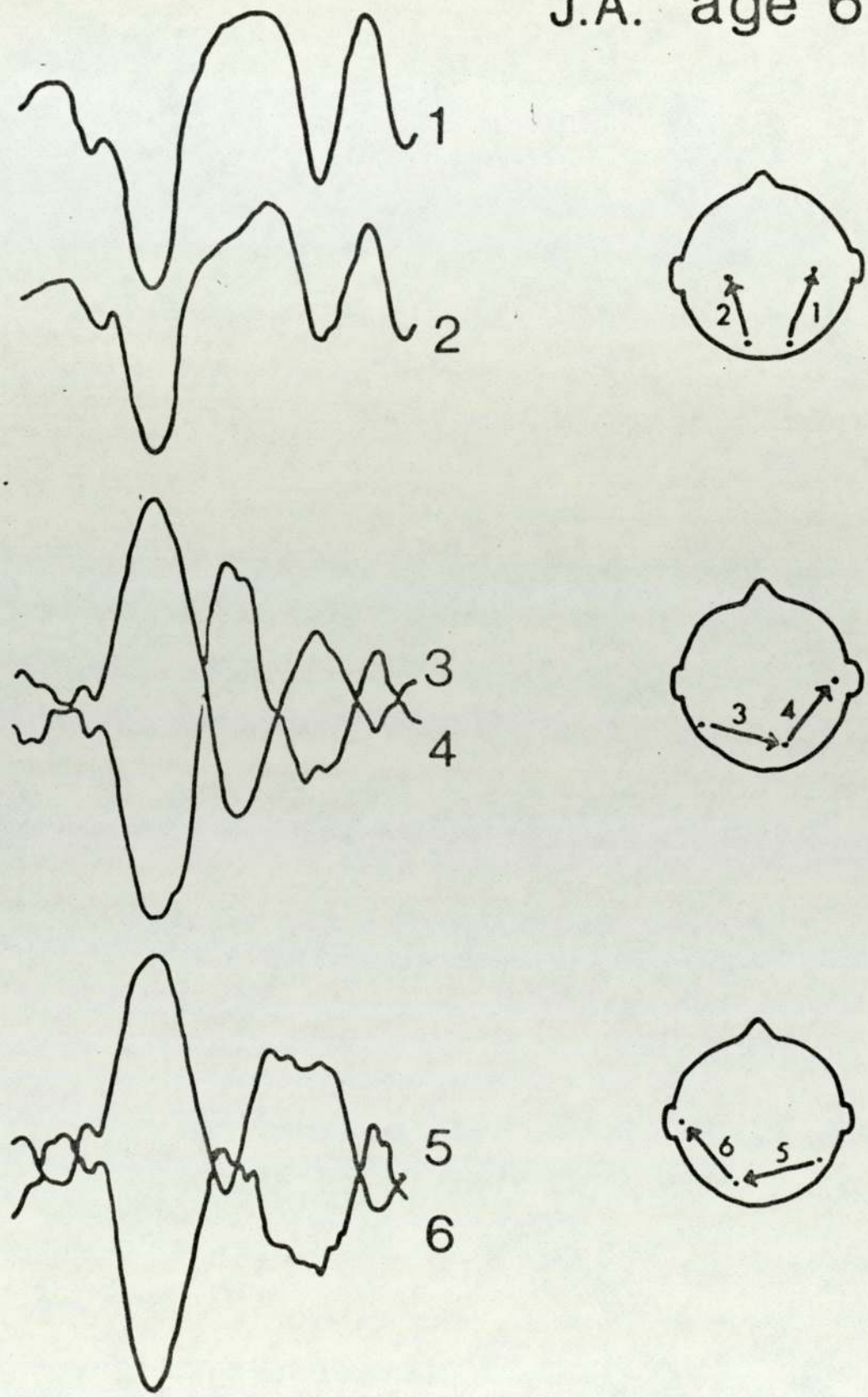
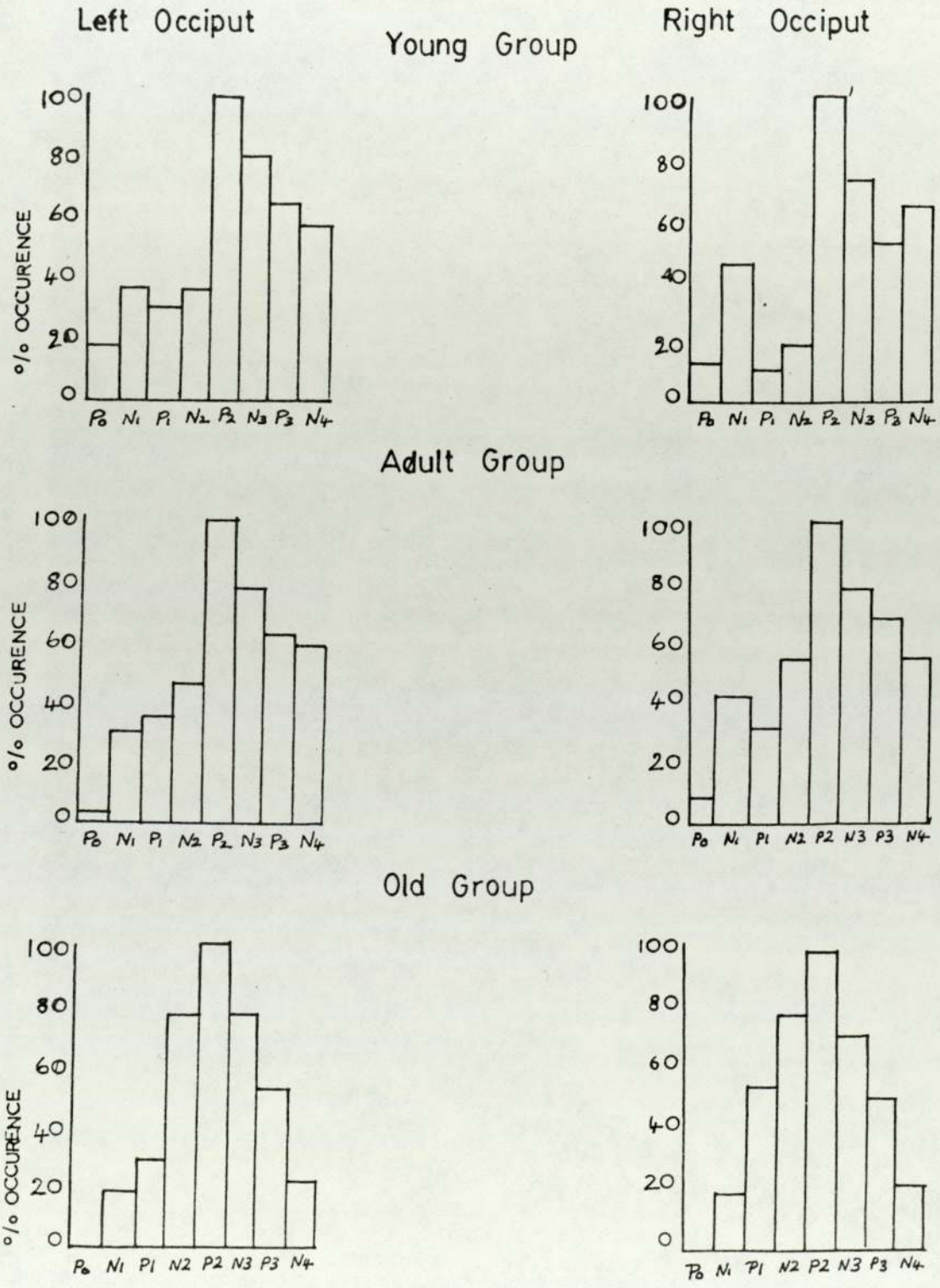


FIG. 38.

PHASE REVERSAL OF THE VEP COMPONENTS TO THE TWO OCCIPUTS: % OCCURRENCE IN THE NORMAL POPULATION.

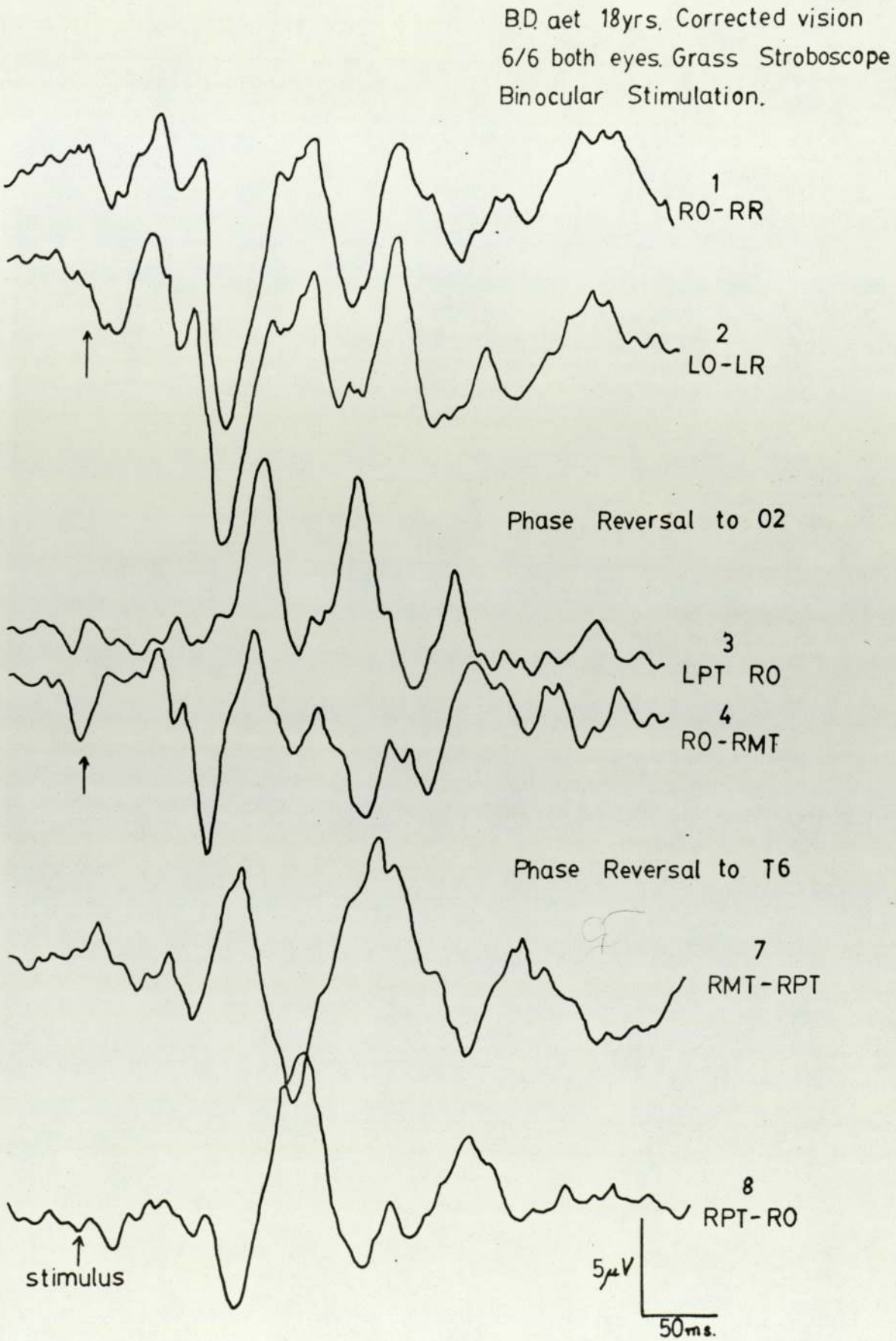
Binocular Stimulation.



phase reversed in all the normal subjects, which is consistent with the previously reported finding (section 7.2.5.) that only P2 occurred in all normal VEPs. In the majority of subjects phase reversal was obtained to the right and left occipital, and the maximum difference in latency between the two phase reversing channels was 9 milliseconds. Phase reversal was not always obtained of the other VEP components, and the later components succeeding the P2 component were more consistent than the early waves (see Appendix VII, page 343). Asymmetry in the number of components which phase reversed to the right and left occiput was a common finding. The P2 component was consistently located in both occiputs in all individuals, but in 58% of the normal controls either fewer components phase reversed to one occipital electrode than the other, or different components did so. There was a tendency, although it was not significant, for there to be more assymmetry and fewer components phase reversing for monocular stimulation than binocular. The asymmetries did not vary consistently between the eye being stimulated and the ipsilateral or contralateral hemisphere.

In two children (10% of the group), and in one adult (2% of the group), phase reversals of the P2 component were obtained at sites more lateral than the occipital pole. In both children P2 was of very low amplitude and clearly phase shifted in channels 3 and 4 by 30 msec. or more. However, clear phase reversals were obtained to the right posterior-temporal electrode. In the one adult subject phase reversal of P2 and the early components could not be obtained to either occiput. Figure 39 (page 208), shows the responses recorded from the right hemisphere. Again

FIG. 39
UNUSUAL LOCALIZATION OF THE VEP IN A NORMAL SUBJECT.



consistent phase reversal results were obtained to the more lateral right and left post-temporal positions. With such a scarcity of data on VEP topography the reason for these few anomalous results has to be speculative. Perhaps the midline position in the two children was eccentric, so that the occipital poles are shifted to the right. Yet this cannot explain the usual localization of the VEP in the left occiput of both children. It would be difficult to explain the adult's results in such a way. A similar unusual distribution of the VEPs was recorded in two other adult volunteers in a separate experiment, which is reported in Section 7.3. (page 189). Unfortunately, the phase reversal technique was not used on either of these subjects, however a similar, more lateral location of the site of maximal left and right hemisphere VEPs might be anticipated in both cases.

To accommodate the possibility of the sources of maximum amplitude of the flash VEP arising under more lateral electrodes than either O1 or O2, an additional electrode chain was devised, using the existing electrodes of the standard Aston montage, to locate activity in the right and left posterior temporal regions. Figure 35 (page 202) shows an additional five channels forming a "horse shoe" bipolar linkage running transversely across the back of the head from the right to the left mid-temporal electrodes. In the vast majority of the normal individuals tested, no phase reversal was obtained between either channels 7 and 8 to T6, or between channels 10 and 11 to T5.

One further normal volunteer showed poor phase reversal results, but they were of a slightly different nature to those mentioned previously. One of the oldest volunteers, a female aged 71 years, showed poor phase reversal to both occiputs only when the left eye was stimulated. The P2 component when recorded from the two hemispheres (O1 to C3 and O2 to C4) was clear, of good amplitude, was larger than the preceding P1 component, and was not significantly delayed. In the phase reversal channels the P2 was ill defined and of low amplitude, often lost of the descending slope of the N2 component which always phase reversed as did the earlier N1 and P1 components. The subject's fields and visual acuity were normal for the age, and whether this phase reversal result had revealed a subclinical sign of some visual impairment, or whether the positioning of the electrodes attempting to localize the occipital sources was particularly unsuitable for the potential spread of the VEP in this case could not be determined.

The overall failure rate of the phase reversal technique for the old age group was very small, and where it did fail, the VEP recorded from other channels was well preserved and of normal wave form for the age.

7.5. A Summary of the criteria for a normal flash VEP

From the research carried out in a large normal population, it was found that VEPs could be satisfactorily recorded from the right and left hemispheres using the bipolar derivations O1 to C3 and O2 to C4. Further useful information concerning the topography of the VEP could be obtained with a minimum number of four additional

channels phase reversing to the right and left occipital electrodes. With just six EEG channels the form, timing, amplitude and distribution of the visual potentials can be quickly recorded even if only a two channel averager is available, and an instant, initial assessment during a research programme or an investigative clinic is easy to perform without any detailed measurements of the VEP.

Further conclusions about the normal VEP are as follows:

1. There are clear age differences particularly in the form and amplitude of the visual potentials, which suggest that the results of any clinical population must always be compared with the appropriate age matched controls.
2. All the early components of the VEP, that is waves occurring before 100 msec., do not appear consistently in the normal population (this part of the VEP is unilaterally absent in 24% of the adult population and in 19% of the old group), and are therefore not reliable enough to be used alone in the identification of a normal or pathological response. Similarly the late components of the VEP, waves occurring approximately 135 msec. after the stimulus, do not appear consistently in the normal response, and are also the most variable components. Only the P2 component with a mean latency of 116 msec., and a standard deviation of 11.5 m.sec. (statistics for the total population) is seen in every normal VEP, and because this component is the most reliable measure of interindividual differences, detailed criteria of the normal VEP can only be applied to the P2 component.
3. Assuming a normal distribution for the two older age groups, confidence interval estimates were calculated for the latency

of each VEP component from the mean and standard deviation data (Speigel, 1961). The latency values for each confidence level are shown in Tables 11, 12 and 13 (pages 213, 214, 215).

4. Amplitude criteria of the normal evoked response were estimated by calculating the percentage occurrence of P2 components of low amplitude, and again only the two older groups were considered. Thus in the adult population binocular stimulation produced a P2 of less than 3μv in 5% of the group, and a P2 potential of less than 2.5 μv was seen in only 1% of the group. Therefore a P2 amplitude as low as 3 μv will occur in one individual in every twenty, and an amplitude of 2.5 μv or less is seen in only one normal individual in every one hundred recorded. These values at the extreme end of the normal distribution correspond to amplitude data beyond two and three standard deviations of the mean (Speigel, 1961), and using these facts the probability of occurrence of low amplitude values of the P2 component have been calculated for the normal population as is seen in Table 14.

5. In the normal population there was no significant difference in the VEP recorded from the two hemispheres. Similar calculations were made of the probability of occurrence of large asymmetries in the VEPs from the right and left hemispheres; again only the P2 component was examined in detail. The results are summarized in Table 15 (page 217), and the data from binocular and monocular stimulation has been combined as the values were the same.

6. When the hemispheric differences in the early components were analysed, a large asymetry or unilateral absence of one or more of the waves before 100 msec. was a common occurrence in

CONFIDENCE LEVELS		0.1	0.05	0.01	0.005	0.002
CONDITIONS	VEP COMPONENT	LATENCY (m.secs)				
BINOCULAR VEP	P2	115.29	117.61	122.16	123.85	125.84
	N3	198.96	206.29	220.72	226.08	232.36
	P3	257.22	268.42	290.45	298.63	308.22
	N4	298.45	309.12	330.10	337.89	347.03
MONOCULAR VEP	P2	116.04	118.17	122.37	123.92	125.75
	N2	222.46	210.61	226.67	232.62	239.61
	P3	264.35	276.91	301.61	310.78	321.54
	N4	295.02	304.89	324.31	331.51	339.97
	P4	335.77	346.60	367.90	375.00	385.08

TABLE 11

The confidence level estimates of the major components for binocular and monocular stimulation derived from the latency data in the young age group.

CONFIDENCE LEVELS		0.1	0.05	0.01	0.005	0.002
CONDITIONS	VEP COMPONENTS	LATENCY (m.sec.)				
BINOCULAR VEP	N1	67.19	69.29	73.43	74.97	76.77
	P1	81.60	84.75	90.94	93.24	95.94
	N2	96.70	99.56	105.19	107.27	109.73
	P2	124.00	127.15	133.34	135.64	138.34
	N3	179.89	184.49	193.53	196.89	200.83
	P3	236.14	242.99	256.47	261.48	267.35
	N4	294.35	304.78	325.33	332.95	341.90
MONOCULAR VEP	N1	67.20	69.33	73.51	75.07	76.89
	P1	82.64	85.92	92.38	94.77	97.58
	N2	99.93	101.81	107.49	109.59	112.06
	P2	125.48	133.22	140.57	143.30	146.51
	N3	180.53	185.12	194.14	197.49	201.42
	P3	239.23	246.69	261.38	266.83	273.23
	N4	292.30	302.59	322.95	330.36	339.18

TABLE 12

The confidence level estimates of the major components of the flash VEP for binocular and monocular stimulation derived from the latency data in the adult age group

CONFIDENCE LIMITS		0.1	0.05	0.01	0.005	0.002
CONDITIONS	VEP COMPONENTS	LATENCY (m.sec)				
BINOCULAR VEP	N1	70.26	73.47	79.79	82.13	84.89
	P1	82.82	84.90	88.88	90.49	92.27
	N2	103.76	106.64	112.29	114.39	116.85
	P2	134.76	138.12	144.74	147.19	150.07
	N3	181.08	185.69	194.77	198.14	202.03
	P2	257.02	265.27	281.52	297.55	294.63
	N4	329.57	340.97	363.09	371.34	381.02
MONOCULAR VEP	N1	67.33	70.15	75.71	77.78	80.20
	P1	85.30	88.01	93.34	95.32	97.64
	N2	105.22	108.36	114.54	116.83	119.52
	P3	135.72	139.58	147.17	149.99	153.30
	N3	186.60	192.02	202.57	206.49	211.08
	P3	259.10	267.44	283.86	289.95	297.10
	N4	326.16	337.13	358.72	366.72	376.13

TABLE 13

The confidence level estimates of the major components of the flash VEP for binocular and monocular stimulation derived from the latency data in the old age group.

	Adult Group				Old Group			
	Binocular		Monocular		Binocular		Monocular	
P2 amplitude (μv)	≤3	≤2.5	≤2.5	≤2 ≤1.5	≤3.5	≤3	≤3	≤2.5 ≤2
% occurrence	5%	1%	5%	2% 0	2%	1%	5%	2% 0
Probability rating	.05	.01	.05	.02 .01	.02	.01	.05	.02 .01

TABLE 14.

Estimated probability of occurrence of low amplitude values of the P2 component in the normal adult population.

	Adult Group		Old Age Group	
P2 Amplitude difference (% difference of other eye)	50%	>60%	>50%	>60%
% occurrence	5%	0	4%	0
probability rating	.05	.01	.05	.02
P2 latency differences (m.sec)	>5ms	>7ms	>5ms	>7ms
% occurrence	9%	5%	10%	5%
probability rating	-	.05	-	.05

TABLE 15.

Estimated probability of occurrence of large differences in the P2 components from the right and left hemispheres in the normal adult population.

both monocularly and binocularly evoked potentials of the adult population. Significant asymmetries were seen in one adult in every six recorded. Similar hemispheric asymmetries were seen in one of the older volunteers in every ten. However, a consistent reduction or absence of early components in one particular hemisphere no matter which eye was stimulated occurred in only 2% of the total adult population.

7. Detailed analysis of the phase reversal material again revealed that only the P2 component was reliably located in the right and left hemispheres. A failure to obtain phase reversal of earlier components of the VEP occurred too frequently in the normal population (N2 failed to phase reverse in 44% of the elderly and in 48% of the younger adults during monocular stimulation)to be used reliably in the diagnosis of a clinical population, although in every normal individual at least one other component was always seen to phase reverse with the P2 component to both hemispheres.
8. No significant differences were recorded between monocular and binocular stimulation, although there was a tendency for the VEP to have longer latencies and lower amplitudes when only one eye was stimulated. Variation in the response between the two eyes was greater than the variation between the two hemispheres and Table 16 (page 219) shows the probability of large differences occurring in the VEP from the two eyes.

From the information presented in this section it is clear that a VEP can be identified as probably a normal or abnormal response by several criteria, the absolute amplitude and latency of the P2 component, the relative differences in the responses from the

	adult group		old age group	
P2 amplitude difference (% difference of the other eye)	50%	60%	50%	60%
% occurrence	5%	2%	5%	-
probability rating	.05	.02	.05	.02
P2 latency difference (m.sec.)	12ms	14ms	11ms	14ms
% occurrence	5%	2%	5%	-
probability rating	.05	.02	.05	.02

TABLE 16.

Estimated probability of occurrence of large differences in the P2 component of the VEP from the left and right eyes in the normal adult population.

two eyes or hemispheres, and the phase reversal of the P2 component to the left and right occiputs. Clearly the more criteria that are used to make the decision as to whether the visual potential is pathological or not, the more certainty there is that such a decision is correct.

CHAPTER 8

The flash visual evoked potential in patients with known visual field defects.

8.1. Patients with homonymous and bitemporal hemianopia.

One of the most extensive conditions of visual impairment is hemianopia. This occurs when the damage to the visual system is central rather than peripheral, and usually damage to the right or left visual cortex results in a complete loss of vision in either the right or left visual field (right or left homonymous hemianopia). Macula sparing frequently occurs, and very often EEG abnormalities are localized in the abnormal posterior cortical region. This abnormal EEG activity can be present with or without visual losses, and there are reports that EEG asymmetry alone may produce significant asymmetry in the VEP (Creutzfeldt and Kuhnt, 1967; Harding, 1977), thus providing a false VEP sign of the presence of a visual field defect. Conversely patients with dense hemianopias have not produced significantly asymmetric VEPs that were recognisably abnormal (Vaughan and Katzman, 1964).

The problem of unilateral EEG abnormalities confounding the diagnostic value of the VEP is not usually seen in a second group of patients who exhibit bitemporal hemianopia after subcortical damage, usually in the area of the pituitary, has destroyed the optic chiasma. The background EEG remains normal or will typically show diffuse, nonspecific abnormalities.

If the criteria developed from the normal data in chapter 7 are to be at all useful clinically, then they must be able to identify with certainty a significant number of patients possessing such gross visual defects. To test the normal criteria, patients were sought who exhibited total half field visual defects, and with the assistance of Dr. C. Panayiotopolous, a Senior Registrar at Dudley

Road Hospital in Birmingham, and at the Neurological Institute at Smethwick, some patients who were willing to be investigated were found. Unfortunately all the patients were acute cases waiting for imminent surgery, and the long distance that they had to travel to the laboratory proved impractical. No mobile facilities were available at the time, and the study was curtailed before a sufficient number of patients could be studied. The greatest lack was in brain damaged control patients with similar CNS lesions but with no accompanying visual defects. However some tentative conclusions can be drawn from the study with the proviso that a great deal more work needs to be done on improving the descriminative capabilities of the flash and pattern VEP.

Details concerning the patients clinical histories are to be found in Appendices VIII and X . Six patients aged between 41 years and 63 years had complete homonymous hemianopia, and in two of them only binocular stimulation was performed. A further three patients had optic pathway damage which resulted in complete bitemporal hemianopia in one young female aged 22 years, and partial hemianopia in the other two older patients. Only monocular stimulation was used in these three patients. Visual fields were checked in all the patients using a Goldmann field analyser, and although central fixation was difficult, only one patient showed any significant central sparing. This was a patient (S.G.) aged 44 years, with a suprasellor meningioma compressing the optic nerve and producing a right visual field defect in the right eye. There was no perception of light in the left eye.

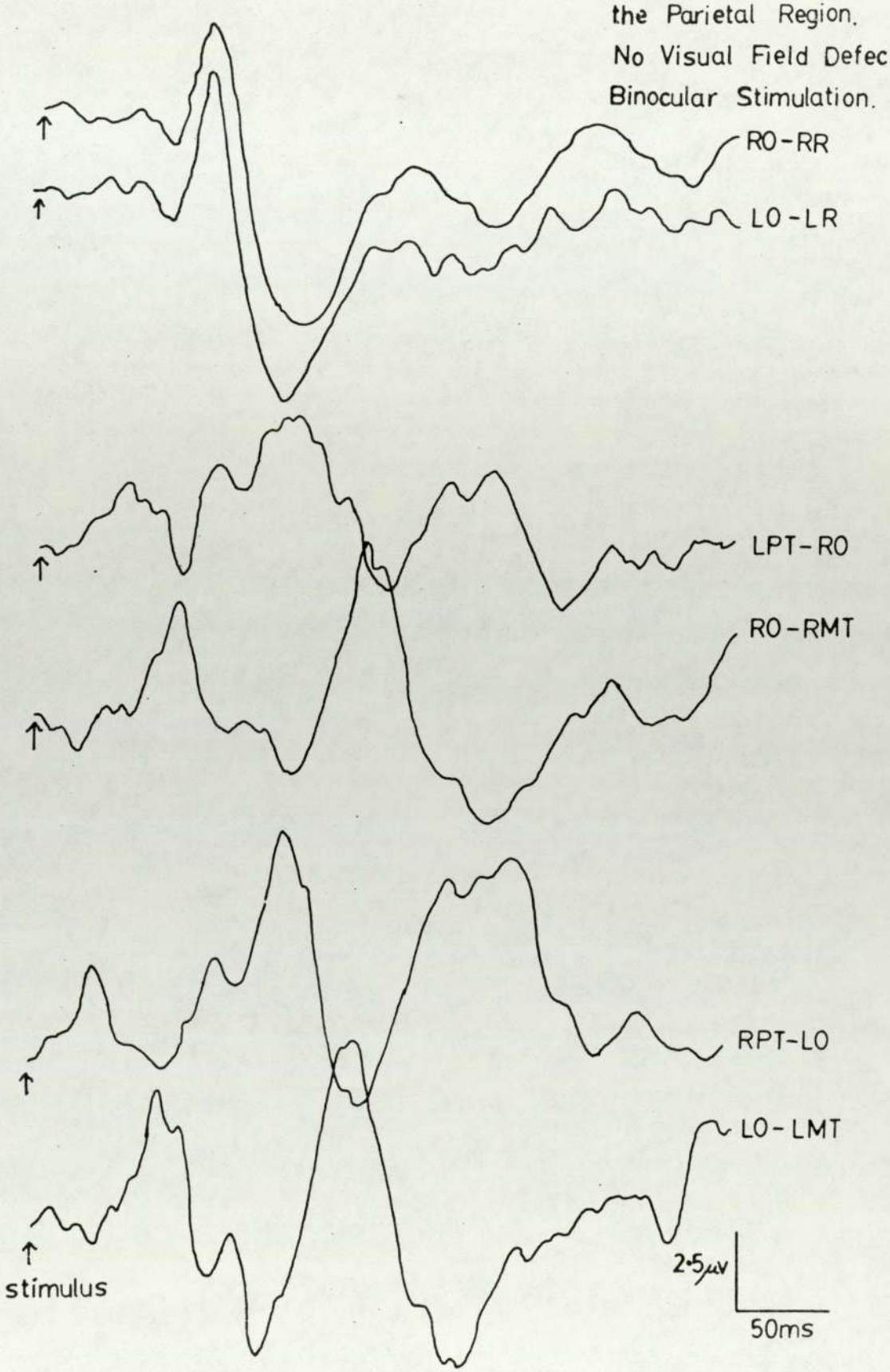
Unfortunately only four patients were recorded as brain damaged controls. Three patients had central lesions with no visual disturbance, the fourth patient had a pituitary tumour with only very early signs of visual involvement, that is enlarged blind spots in both eyes, and a small peripheral defect in the right eye.

8.2. The VEP in the brain damage control patients.

The VEP to binocular stimulation was recorded in the three patients with central lesions (the results are presented in Appendix XI). Two of the patients had asymmetric EEGs, with more slow activity over the involved hemisphere. Only monocular stimulation was used in the patient with the pituitary tumour. No statistics have been performed on such a small, heterogeneous group, but their results can be compared with the criteria indicative of a normal response. Despite the EEG abnormalities, and evidence of early visual pathway involvement, the VEPs were within normal limits. There were no significant delays in latency or reductions in amplitude of the P2 component. The responses from the two hemispheres were fairly synchronous and symmetrical, and phase reversal was obtained of the P2 wave and several other of the VEP components to both hemispheres. The results typically obtained in the brain damaged group can be seen in Figure 40 (page 224). Thus the tentative conclusion from a very small sample is that it is possible that brain damage which produces no visual field defect, does not significantly alter the VEPs to flash stimulation, as judged by the normal criteria developed in chapter 7.

FIG. 40.

THE VEP IN A BRAIN DAMAGE CONTROL PATIENT.



8.1.3. The VEP in hemianopic defects.

Two of the first patients to be investigated, who both presented with homonymous hemianopia, only received binocular stimulation. Also all the patients with bitemporal hemianopia were only stimulated monocularly, and so the data of this patient group have been divided into those individuals receiving binocular stimulation, and those who received monocular stimulation, with four of the homonymous hemianopics appearing in both groups. The detailed individual data is to be found in Appendix XI , and the mean values of the latencies and amplitudes of the major VEP components for the two groups are presented in Table 17 , page 226 . No other group statistics have been calculated because of the small numbers in each group and the great variations in the age of the patients, aetiology of the field defect etc. within each group. For the same reason non parametric statistics were used to establish any differences in the VEP from the involved compared with the non-involved hemisphere (Wilcoxon matched-pairs signed-ranks test, which takes account of both the direction and the magnitude of the differences in the results within each individual). Differences were also sort in the VEP of the patients with visual field defects compared with the brain damaged control patients (the Mann-Whitney U test). Finally the patients' VEPs were compared with the confidence limits of the normal age matched controls.

The mean values for the binocular and monocularly evoked responses (table 17) reflect the clear trend in the data of lower amplitude VEPs, and less frequently for longer latencies over the damaged hemisphere. It should be noted that patient S.G. did not have

		Undamaged hemisphere						Damaged hemisphere					
		N1	P1	N2	P2	N3	P3	P1	N2	P2	N3	P3	N4
6 patients	Binocular latency (ms)		57.8	87.3	119.7	169.2			88.3	122	166		
6 patients	Monocular latency (ms)		56.8	92.4	124.7	158.8		61	96.4	127.4	159.4		
6 patients	Binocular amplitude (μv)		1.65	3.5	5.6	5.9			1.8	4.1	5.0		
6 patients	Monocular amplitude (μv)		4.1	5.5	7.4	4.2		2.3	4.2	5.8	3.7		

TABLE 17.

The mean amplitude (μv) and latency (m.sec.) of the major VEP components from the two hemispheres in patients with hemianopic defects.

any significant asymmetry in his VEP (see figure 41 , page 228), and clear phase reversal was obtained of all the VEP components to the right and left occiput. Since many researchers believe that the VEP to high intensity stimulation primarily reflects central visual function (Eason, Oden and White, 1967; de Voe, Ripps and Vaughan, 1968; Wooten, 1972; Armington, 1977; Jeffreys, 1977), then it is likely that the normal findings in this patient are a result of the central sparing of his visual field. This suggests that the diffuse, whole field stimulation used in these experiments may fail to detect paramacular and peripheral field defects, and perhaps more discrete stimuli would need to be used. The patient's data was not included in the analysis.

In four of the six patients with homonymous hemianopia who were stimulated binocularly, the early P1 component was only recorded over the normal hemisphere, and although this finding cannot be diagnostic since unilateral absenses of P1 occur too often in the normal population, in all the patients the absence occurred over the predicted hemisphere. The asymmetry of the P1 component was not always followed by asymmetry in the rest of the primary response and significant hemispheric differences occurred in only one third of the patients. Thus Vaughan and Katzman's (1964) criteria of a large reduction in the amplitude of the early VEP waves contralateral to the field defect was not a reliable indicator in this group of patients. Large asymmetries in the early components were recorded in a few of the patients (see figure 42 , page 229), but a significant reduction (that is greater than 50%) of all the VEP components arising over the damaged hemisphere was never recorded.

FIG. 41.

RIGHT VISUAL FIELD DEFECT WITH CENTRAL SPARING

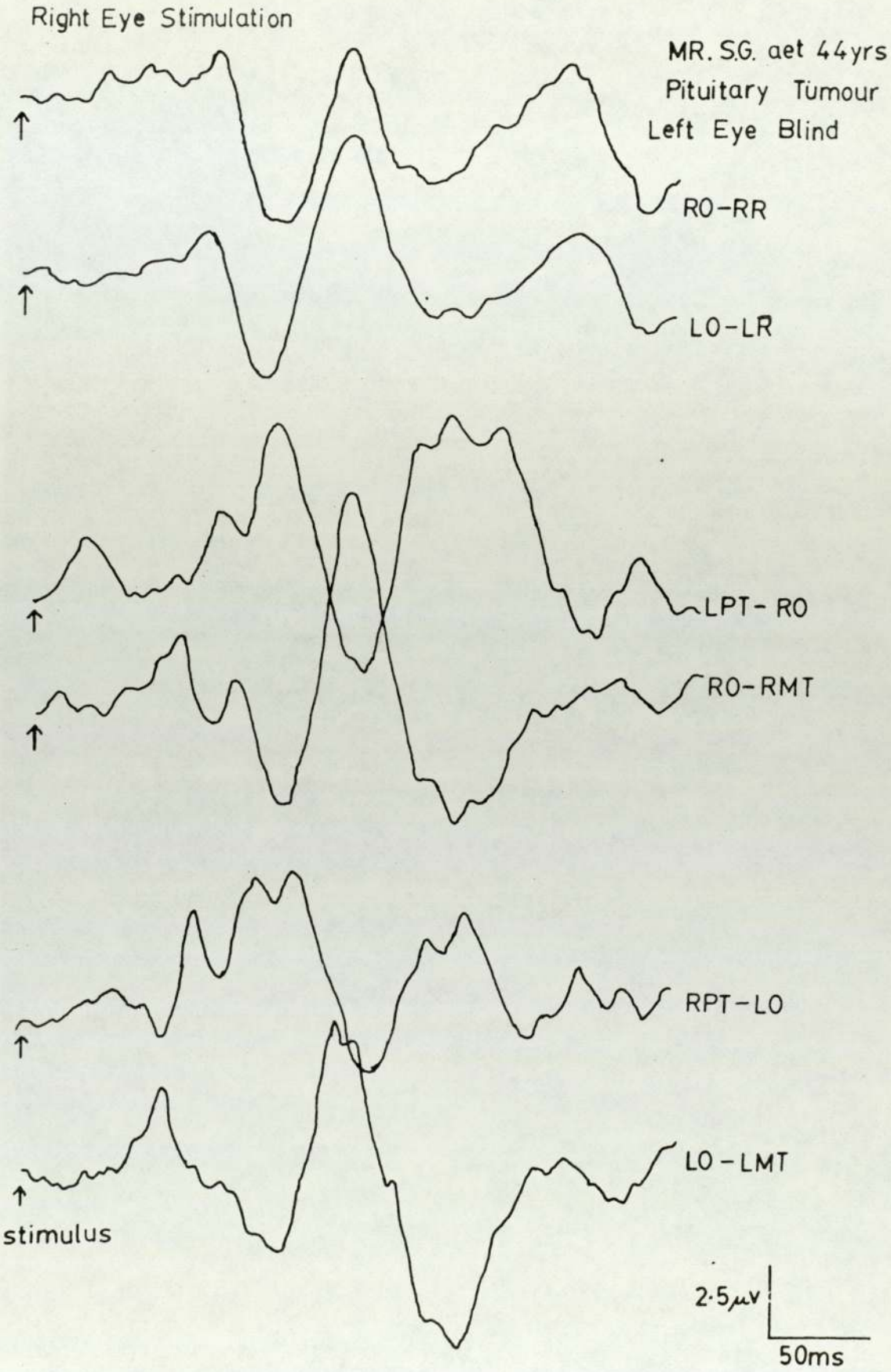
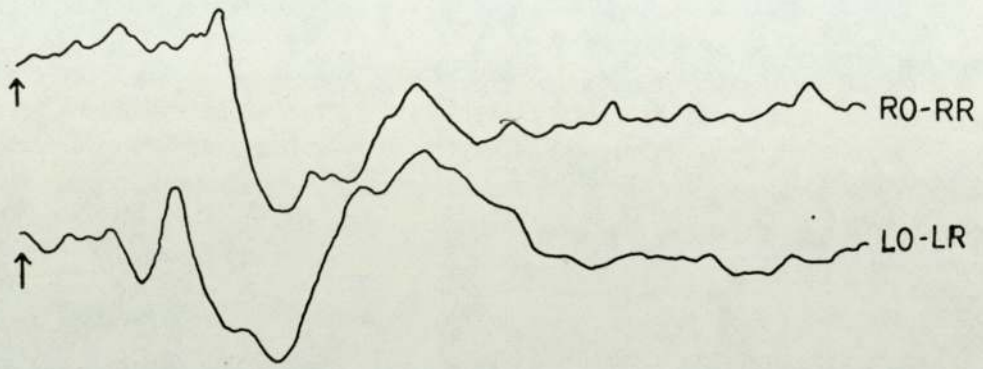


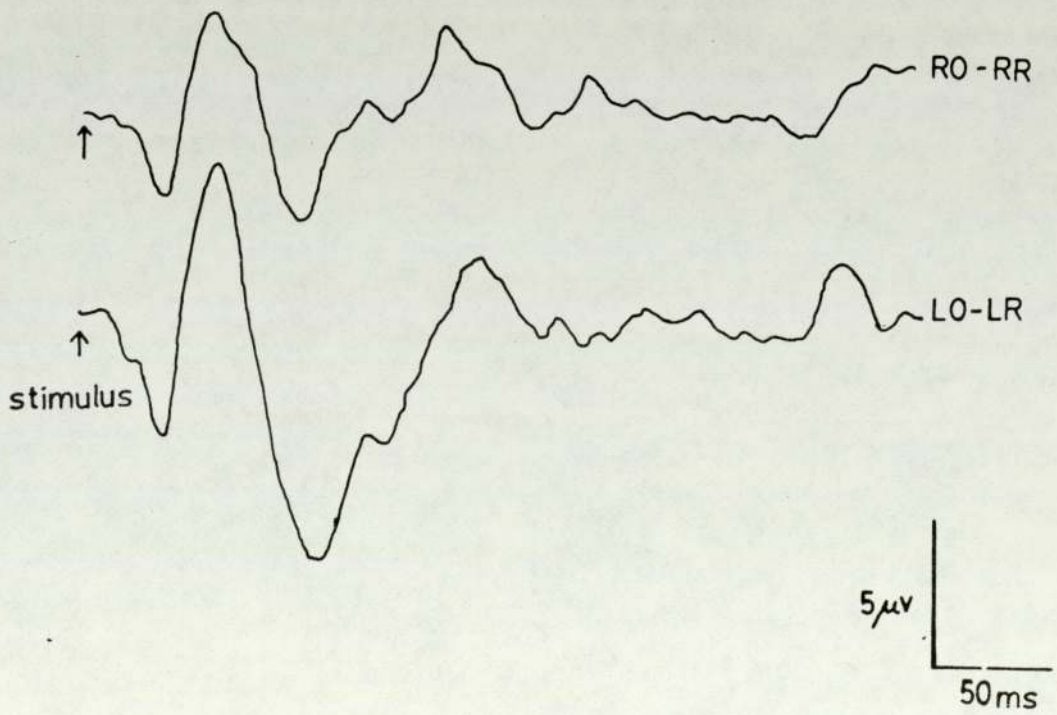
FIG. 42.
ASSYMMETRY IN THE EARLY PORTION OF THE VEP
IN HOMONYMOUS HEMIANOPIA: THE EFFECTS OF PATTERN.

Mr. M.C. aet 54yrs
Complete left homonymous hemianopia. Occassional headaches and loss of memory. Binocular view.

FLASH STIMULATION



FLASHED PATTERN STIMULATION



In the monocularly evoked potentials there were fewer cases of the P1 or N2 components occurring unilaterally, but in all the patients the P1, N2 and P2 waves were always of lower amplitude over the involved visual cortex, although this frequently did not reach significance. The VEPs of three patients were recorded using a long time sweep of two seconds so that the hemispheric differences in the after discharge and background rhythmic activity could be recorded. As can be seen in Figure 43 (page 231) no significant asymmetries were found in the very late VEP events, as has been suggested by Oosterhuis et. al (1969).

A typical finding in some of the patients, which is not seen in the normal population, was the extreme variability of the VEP which varied in shape, amplitude and latency from one time to the next. This variability was inevitably associated with ill-defined, very low amplitude components, and was more often seen in patients with visual pathway involvement (see figure 44, page 232), which raises the possibility that damage to the optic pathways may differentially effect the conduction velocity of the many visual inputs, and disrupt the synchrony of the arriving impulses, resulting in a small averaged response of long duration. Such large variability did not appear to be so characteristic of the patients with cortical damage with the exception of the patient JB (figures 45 and 46 , pages 233, 234). This patient was unusual in that as well as having right homonymous hemianopia he also had very impaired vision in his left visual field and his sight was too poor for him to read. The cause of the deteriorating left visual field was not known.

FIG. 43.

LEFT HOMONYMOUS HEMIANOPIA
SYMMETRY IN THE VEP AND AFTERDISCHARGE

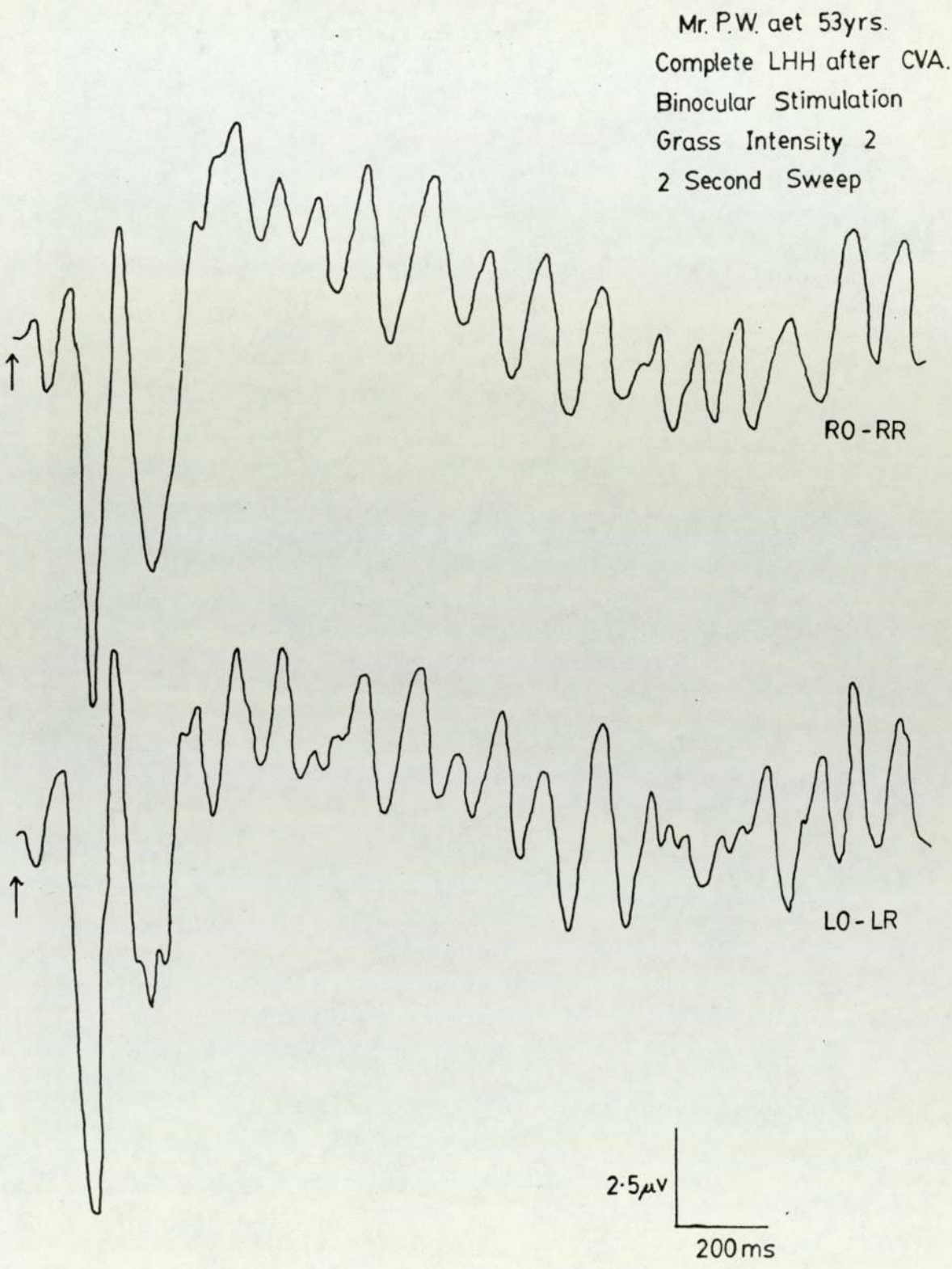


FIG. 44.

A POORLY FORMED VEP IN A PATIENT WITH A PITUITARY TUMOUR.

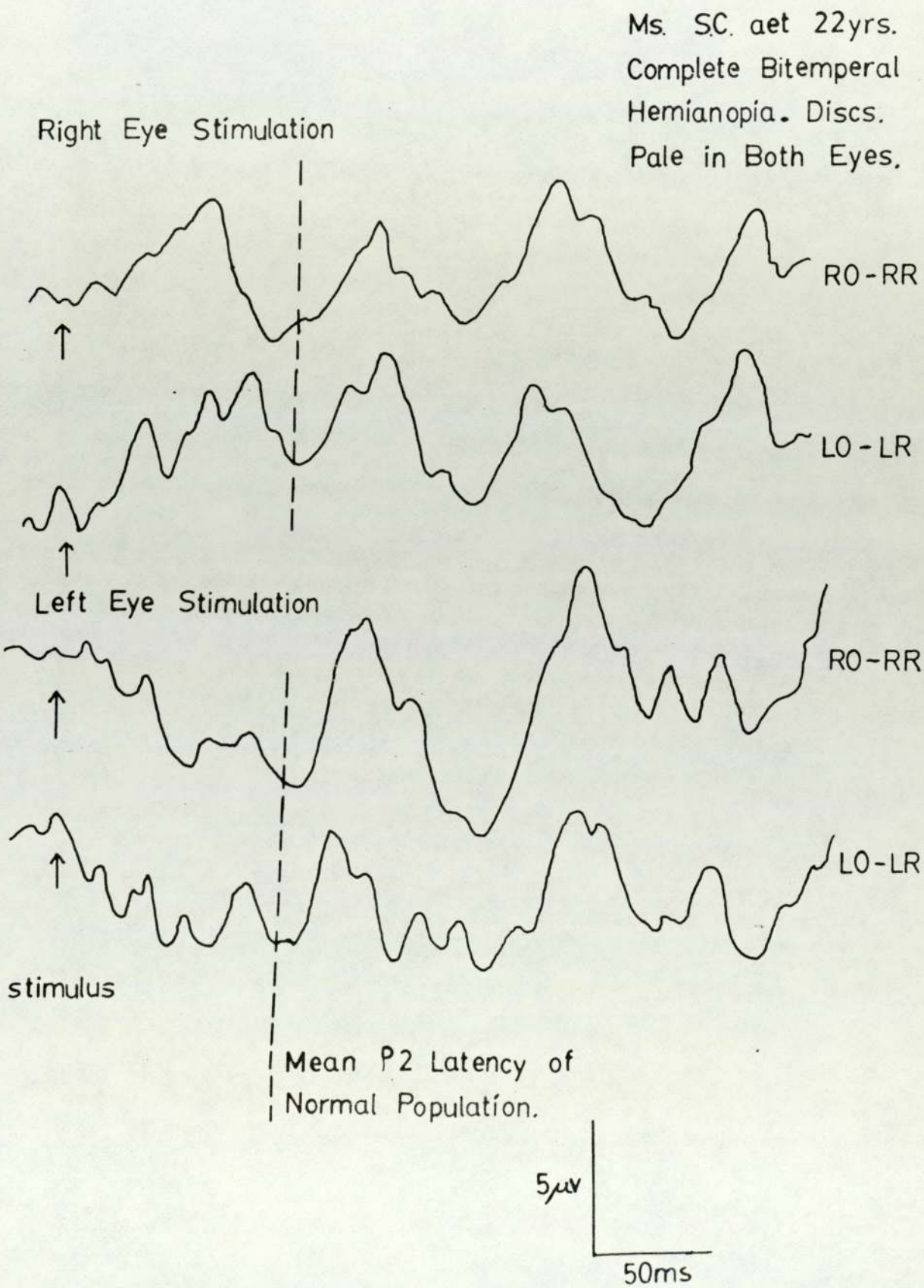


FIG. 45.
VARIABILITY IN THE FLASH VEP.

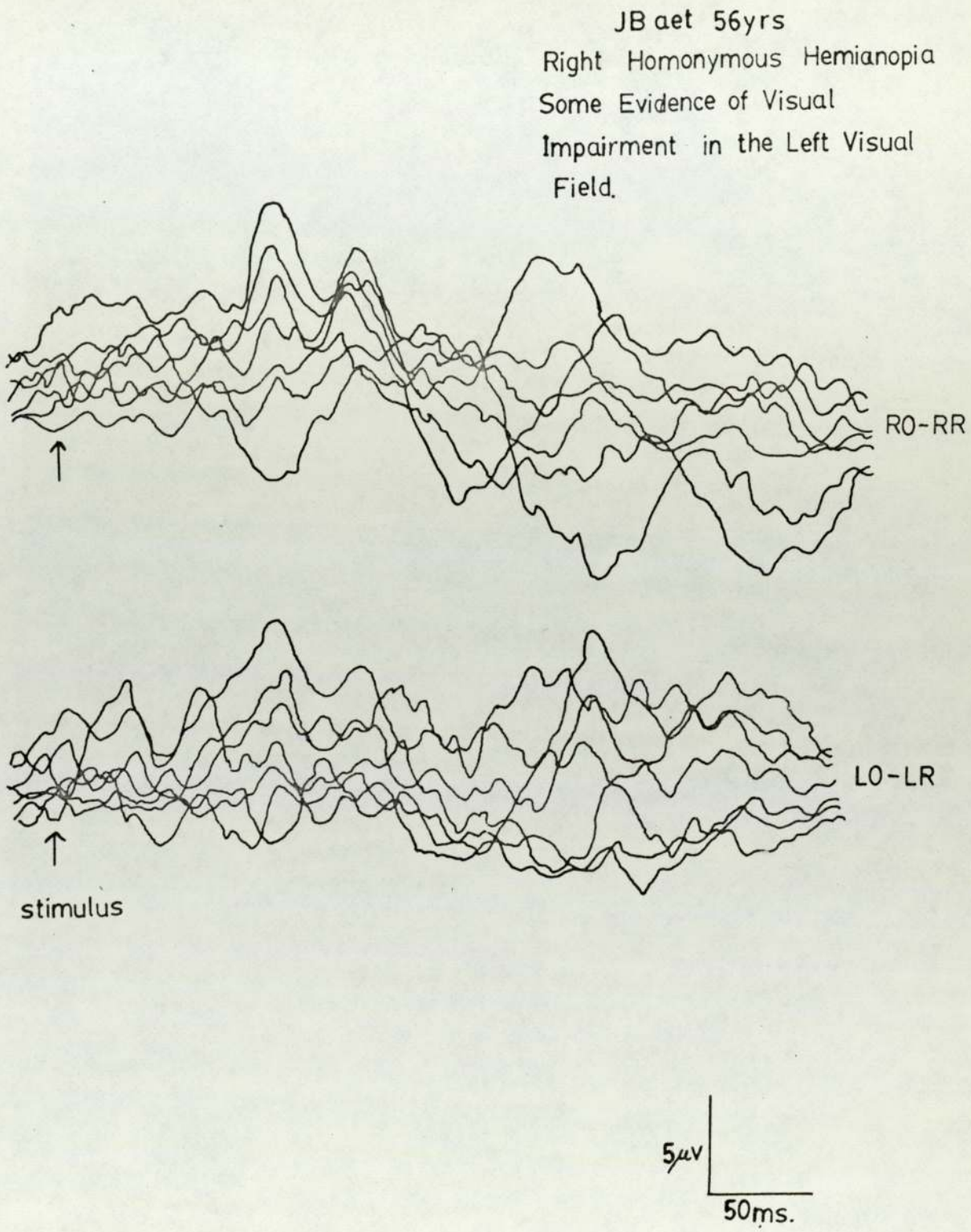
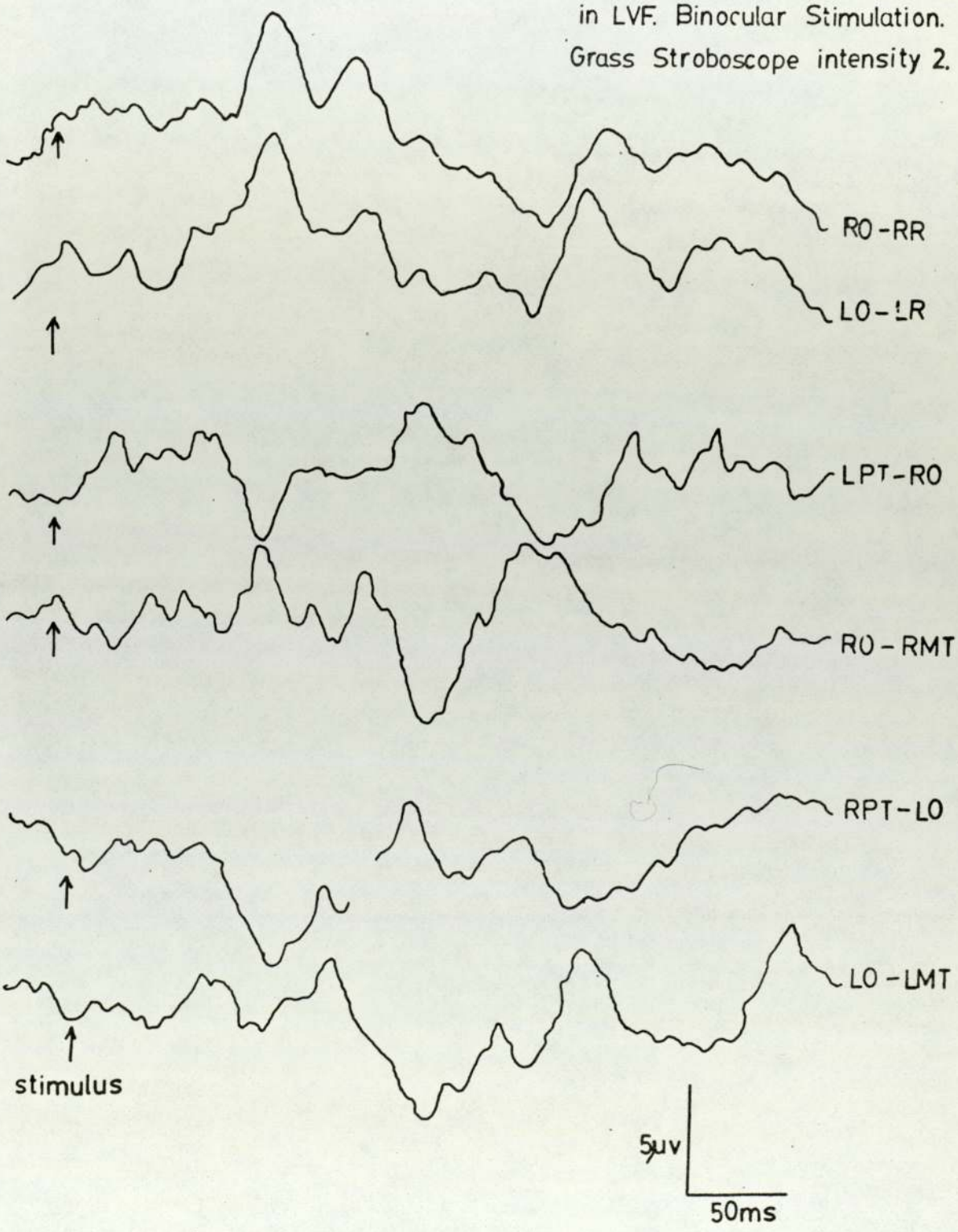


FIG. 46.
RIGHT HOMONYMOUS HEMIANOPIA

Mr JB aet 56yrs. 2yr history of visual impairment, clear right hemianopia with some evidence of lowered acuity in LVF. Binocular Stimulation. Grass Stroboscope intensity 2.



When the binocular VEPs of the patients with homonymous hemianopia were compared with the patients with central lesions but no visual impairment, no significant difference was found in the VEP from the noninvolved hemispheres of the two patient groups. When the VEPs over the involved hemispheres were compared the only significant finding was a reduction in the P2 amplitude in the patients with hemianopic defects (Mann Whitney U test, $p < .01$). When the same hemianopic patients were compared with the confidence limits of the normal VEP, none,with the exception of JB had a significant delay in the latency of any of the VEP components recorded from either hemisphere, and in only one patient (H.E.) was there a significant reduction in the P2 component over the involved hemisphere ($p < 0.05$). The patient J.B. possibly because of the existence of extensive visual impairment in both fields had significantly delayed P1 ($p=0.05$) N2 ($p=0.01$) and P2 components ($p=0.05$) in the hemisphere ipsilateral to the visual field defect. The P2 component was also significantly reduced ($p=0.05$) in this hemisphere. Over the involved hemisphere P1 was absent, N2 and P2 were significantly delayed ($p=0.05$), and P2 was significantly reduced in amplitude ($p=0.02$).

When all the binocular VEPs from the involved hemisphere were compared with the responses from the other visual cortex in the hemianopic patients, there was no significant difference in the latency of the components between the two sides (Wilcoxon matched pairs test). This is contrary to other findings and may be mainly due to the very small sample as there was a clear tendency for VEPs to be delayed over the damaged hemisphere. Therefore

the group as a whole did not show significantly delayed responses over the damaged hemisphere compared with the uninvolved hemisphere, and only one individual (H.E.) had a large delay in the P2 component (17 m.sec. later) contralateral to the field defect. The latencies of the other VEP components were no more reliable in reflecting unilateral visual damage, with again only one patient (M.C.) having a significantly delayed N2 component over the damaged hemisphere.

When the amplitude differences between the responses from the two hemispheres were compared for this group (Wilcoxon matched-pairs test) although there was a clear trend for all components to be smaller contralateral to the field defect, only the P2 component reached significance ($p<0.02$). When considered individually just one patient (E.J.) exceeded the normal criteria of hemispheric asymmetry, with P2 reduced by more than 50% over the damaged hemisphere.

Unfortunately the monocular VEP recorded from both homonymous and bitemporal hemianopics could not be compared with the brain damaged controls as only one of the control patients was stimulated monocularly. When the monocular VEP of the patients with visual field defects were compared with the confidence levels of the monocular VEP of the normal population, 50% of the patients had a significantly delayed P2 component over the undamaged hemisphere (p 0.05 or less, see Appendix XII , page 349). This is a much higher percentage of abnormal responses than was obtained with binocular stimulation, and the results do not appear to depend

on the inclusion of the two patients with bitemporal hemianopia since one patient had an abnormally delayed VEP, the other did not. The results of course, included patient J.B. whose VEP was bilaterally abnormal both in terms of the latency and amplitude of the major components, reflecting the same results as were obtained with binocular stimulation. None of the other patients with significant delays in the VEP over the normal hemisphere also had a significant reduction in the amplitude of the response, although two other patients (S.C. and P.W.) only displayed a significant reduction in the P2 component over the uninvolved hemisphere.

In all the patients there was a consistent trend for later and smaller VEPs to be recorded over the involved hemisphere, so that in all patients with significant abnormalities over the uninvolved hemisphere, the VEP was also abnormal in the other hemisphere. Two patients had no significant delays in the latency of any component the rest of the patients had significant delays contralateral to the visual defect. The three patients who had very low amplitude P2 components over the uninvolved hemisphere, also had significant reductions in this component over the damaged side. No other patient had significantly reduced components contralateral to the visual defect.

The relative differences in the amplitude and latency of the monocularly evoked responses from the undamaged and damaged hemispheres of the group were compared (the Wilcoxon matched-pairs, signed-ranks test) and P1 and N2 were found to be significantly delayed on the damaged side ($p=0.01$) while P1, N2 and P2 were significantly reduced in amplitude on the damaged side ($p=0.01$). Although

this result reflects a consistent trend occurring in all the individuals, it is more important in clinical research to be able to identify each patients' response as abnormal compared with the normal response. One patient (S.C.) exceeded the normal criteria for amplitude differences, that is a greater than 50% asymmetry when the left eye was stimulated. A second patient (E.J.) exceeded the normal criteria of difference in latency between the two hemispheres, with a significantly delayed response on the damaged side.

To summarize the detailed analysis of the monocular VEP recorded from the two hemispheres in patients with hemianopic defects, patient J.B. had abnormal responses over both hemispheres both in terms of latency and amplitude; there were therefore no clear localizing signs in his VEPs. A further five patients had abnormal responses, but two of them showed no clearly localized abnormality which related to the field defect. The other three patients did have more abnormal responses over the damaged cortex. Therefore only 50% of the patients with hemianopic defects when stimulated monocularly had significant abnormalities in the VEP recorded from the right and left hemispheres which corresponded specifically with their visual field defect.

In the patients with visual field defects who were stimulated binocularly only 33% had abnormal VEPs which corresponded to the visual field defect.

It was noted that in this patient group with central damage to the visual system, none of the individuals had very large amplitude

early components. That is, although the P2 component was often of much lower amplitude than is seen in a normal population, this component was always of higher amplitude than the preceeding positive waves.

8.1.4. Phase reversal results in patients with hemianopic defects.

The results of the phase reversing channels in the brain damaged controls were very similar to those of the normal population, with the P2 clearly phase reversing to both occiputs together with several other components, as is seen in patient E.R. shown in figure 40 (page 224). Similar results were obtained in the patient S.G. who had significant macular sparing (see figure 41 page 228), with clear phase reversal of all the major VEP components to both occiputs.

The phase reversal results in the patients with visual field defects and no central sparing were very encouraging, and provided additional useful criteria to differentiate unilateral damage in the visual system. The group data for the incidence of phase reversal of the VEP components to the undamaged and damaged hemispheres are summarized in Figure 47 (page 240).

With binocular stimulation the P2 wave was always located in the undamaged hemisphere, ipsilateral to the visual field defect, and this was probably seen even in the patient J.B. with poor vision in the other, left visual field (see figure 46 , page 234), although the phase reversal of the P2 wave to the right occiput was at times very uncertain.

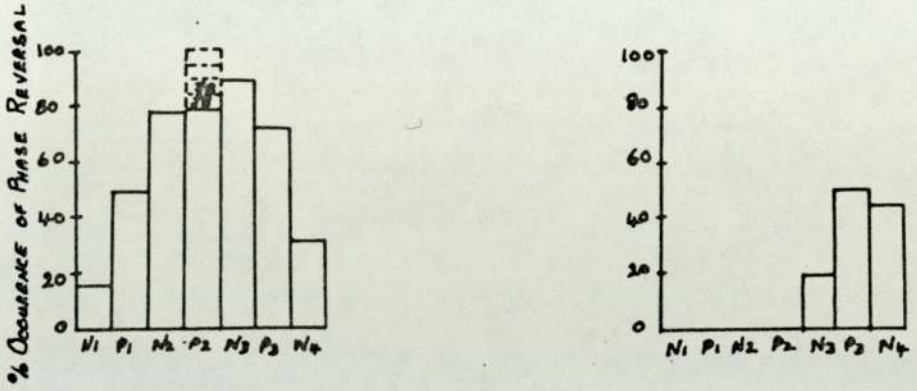
FIG. 47.

THE PERCENTAGE OCCURENCE OF PHASE REVERSAL OF THE VEP COMPONENTS IN PATIENTS WITH HEMIANOPIC FIELD DEFECTS.

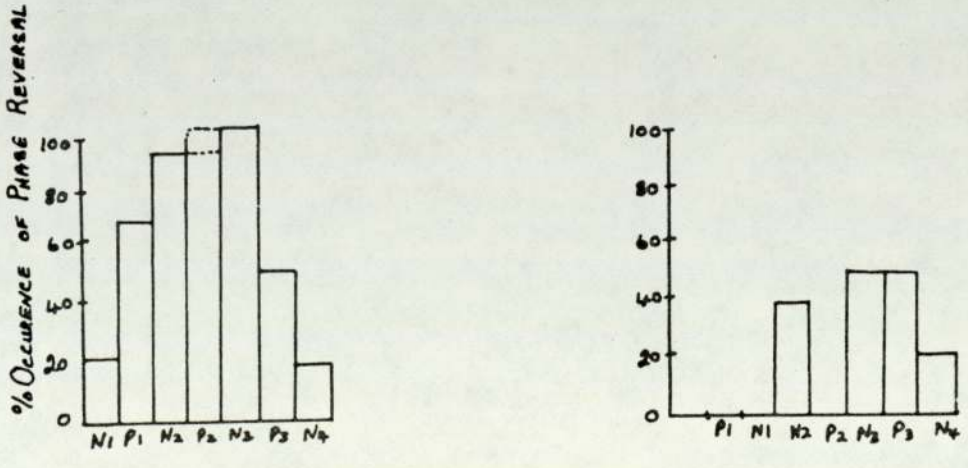
Undamaged Hemisphere

Damaged Hemisphere

Monocular Stimulation



Binocular Stimulation



The P2 component was never located in the damaged hemisphere and frequently none of the components before the N3 wave around 160 to 170 m.sec. phase reversed to the damaged occiput.

With monocular stimulation the results were very similar. Again it was uncertain whether the P2 phase reversed in patient J.B. to the uninvolved occiput. Two other patients M.M. and S.C., the second of whom had extremely variable responses, had doubtful phase reversal results to the uninvolved hemisphere when one eye was stimulated, although the results of the other eye were within normal limits. In these two patients the difficulty was in the very low amplitude P2 component, and in the occurrence of phase differences between the channels that were greater than the differences normally seen which is approximately ten milliseconds. In both these patients the other criteria of the VEP from this hemisphere that is component asymmetries, latencies and amplitudes were within normal limits. In all the patients stimulated monocularly no phase reversal was obtained of any components before the N3 wave to the occiput contralateral to the visual field defect.

The VEP results typically obtained in a patient with complete homonymous hemianopia can be seen in Figures 48 , 49 , and 50 (pages 242 , 243 , and 244) which show the VEP recorded from the right and left hemisphere, and the results of phase reversal to the right and left occiput during monocular and binocular stimulation in a patient with left homonymous hemianopia. The VEP is clearly reduced and cannot be localized over the visual cortex contralateral to the visual field defect. Similar results are seen in patient W.W. with a pituitary tumour (figures 51 and 52

FIG. 48.

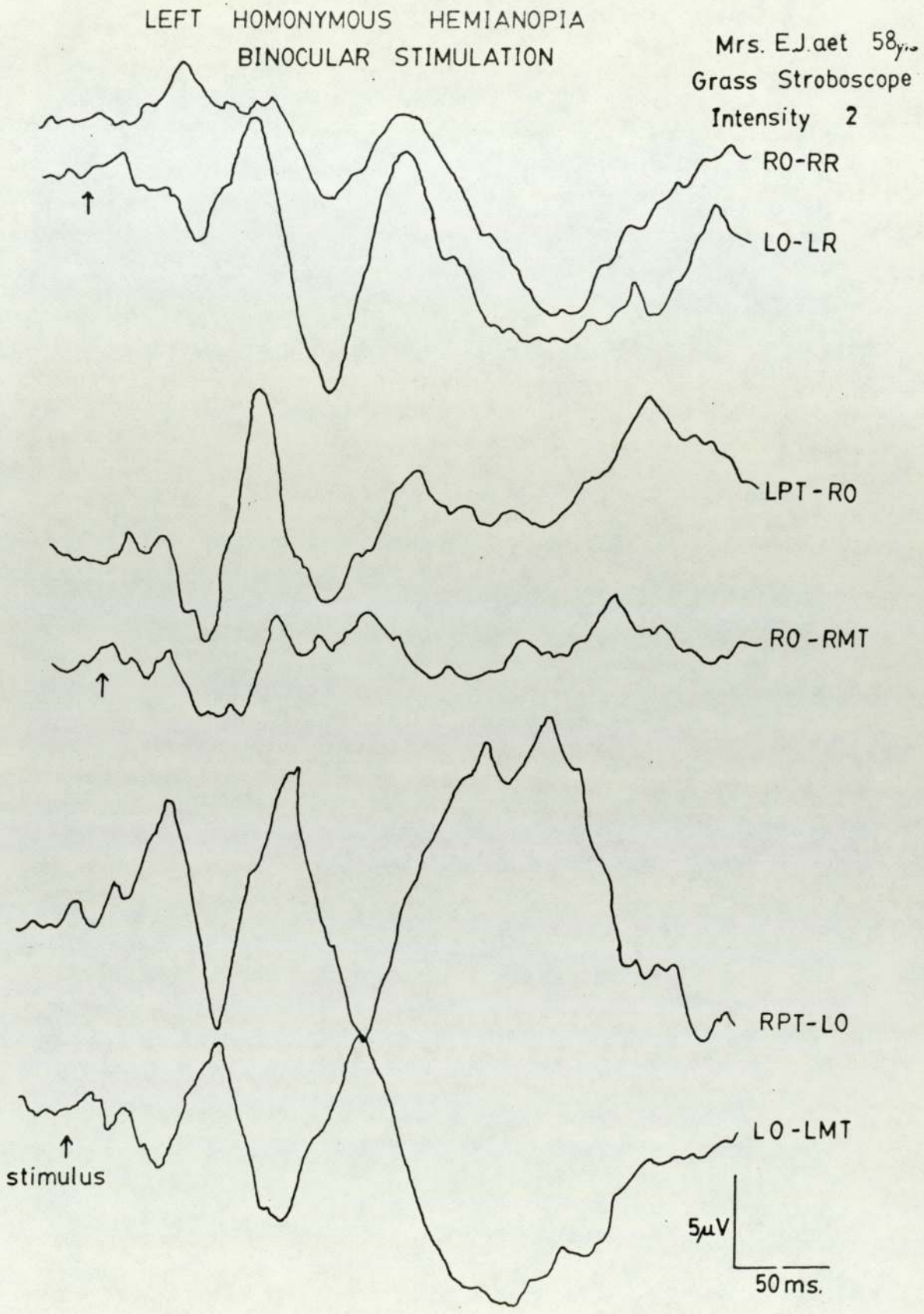

LEFT HOMONYMOUS HEMIANOPIA
BINOCULAR STIMULATION
Mrs. E.J. aet 58y.
Grass Stroboscope
Intensity 2
RO-RR
LO-LR
LPT-RO
RO-RMT
RPT-LO
LO-LMT
stimulus
5μV
50 ms.

FIG. 49.

LEFT HOMONYMOUS HEMIANOPIA

RIGHT EYE STIMULATION.

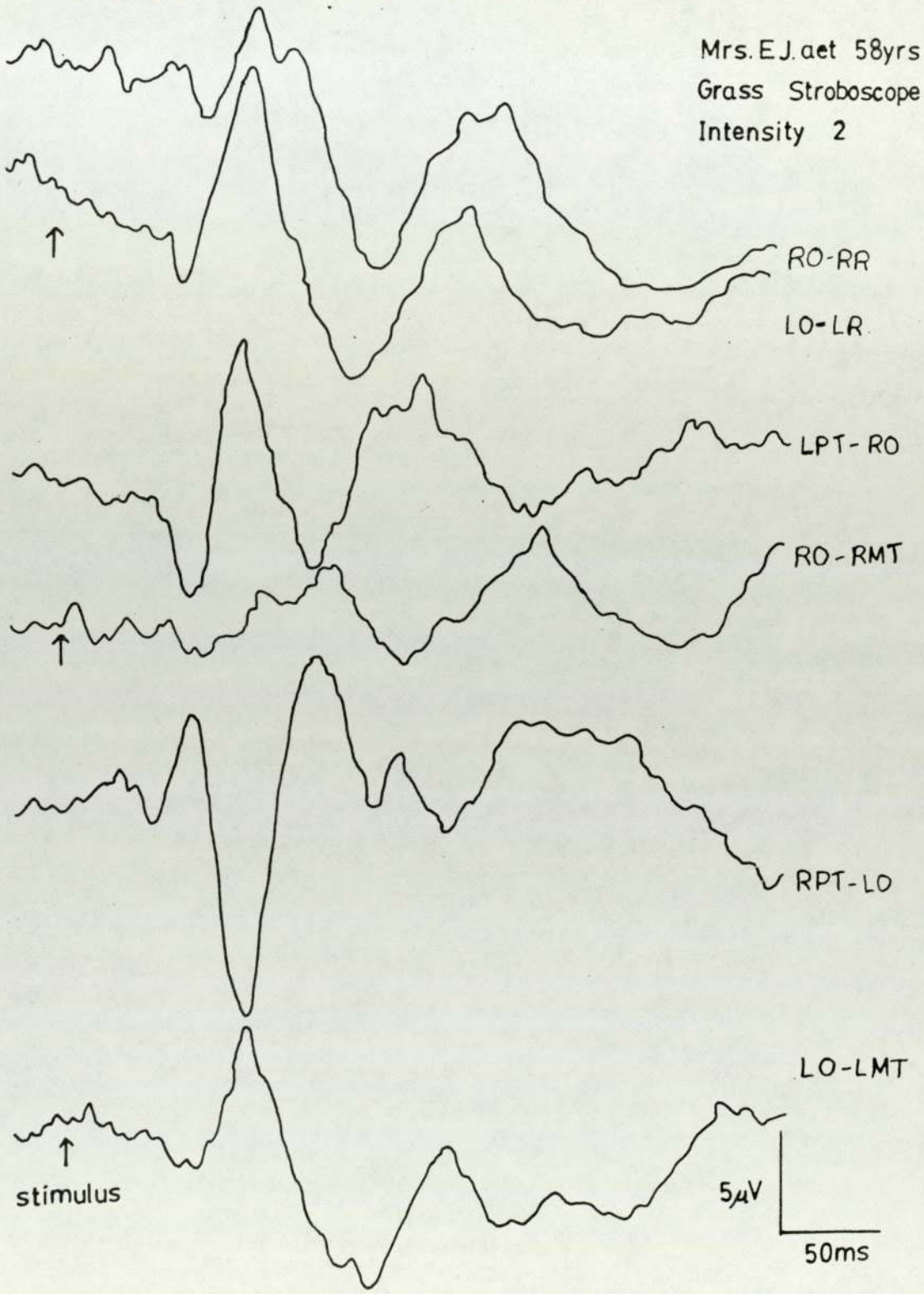
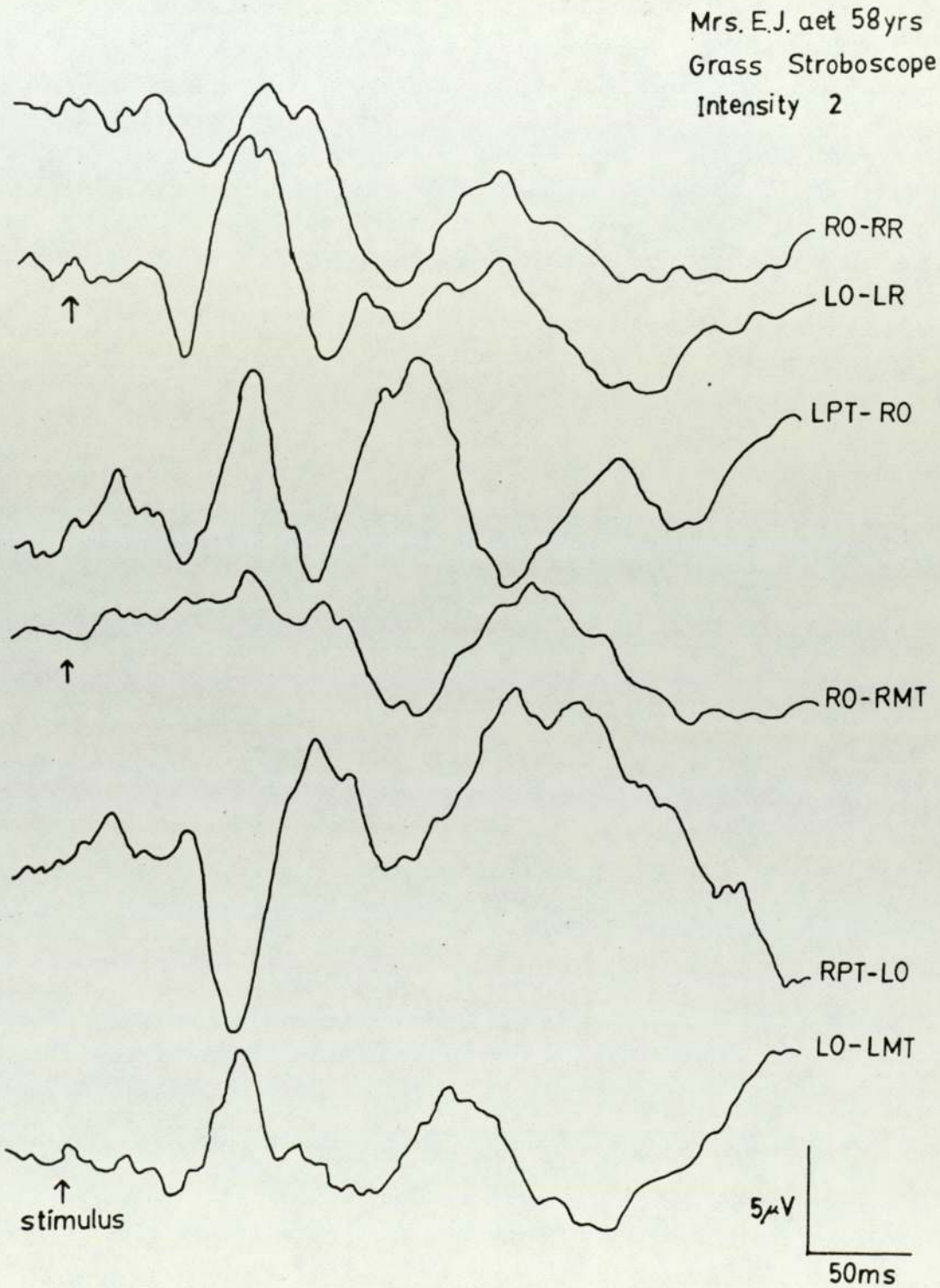


FIG. 50.

LEFT HOMONYMOUS HEMIANOPIA

LEFT EYE STIMULATION



, pages 246 , 247). The left eye has normal fields and all the VEP results are within normal limits. The right eye has a right visual field defect, and although this is not reflected in the symmetry and synchrony of the visual potentials recorded from the two hemispheres, the abnormality is clearly picked up in the phase reversing channels, with no VEP components being located in the left occipital region.

Thus the phase reversal technique precisely located an abnormal VEP over the involved visual cortex, and contralateral to the visual field defect. Since one of the patients was not a good example of complete homonymous hemianopia, having significant visual impairment in the other visual field of unknown aetiology, it is justified in removing his results from those of the whole group which improves the predictive value of the phase reversal technique to a correct localization of the VEP abnormality in 85% of the patients with hemianopia. In two patients the phase reversal results suggested bilateral damage when only one of their eyes was stimulated. It cannot be certain in these patients that there was no bilateral involvement, although from the nature of the C.N.S. damage it would seem unlikely. In both patients the VEP waveform was within normal limits over the uninvolved hemisphere, which could be weighed against the suggestion of bilateral involvement.

The percentage of abnormal responses detected in these patients with known visual defects is higher than has been reported in the literature (Vaughan and Katzman, 1964), and suggests that the Aston Montage can provide additional valuable information on unilateral abnormalities in the visual system. Such a suggestion

FIG. 51.
RIGHT EYE STIMULATION

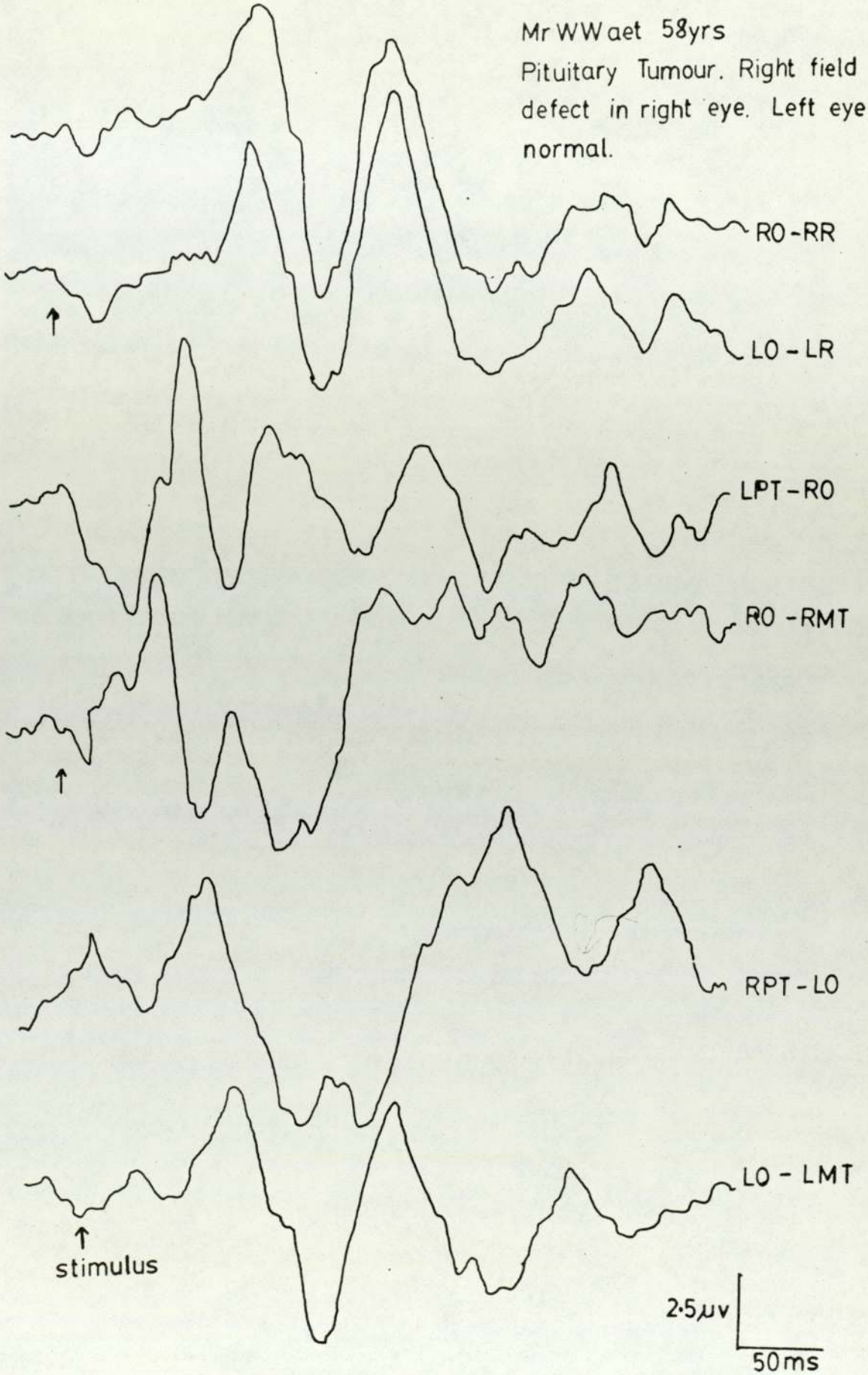
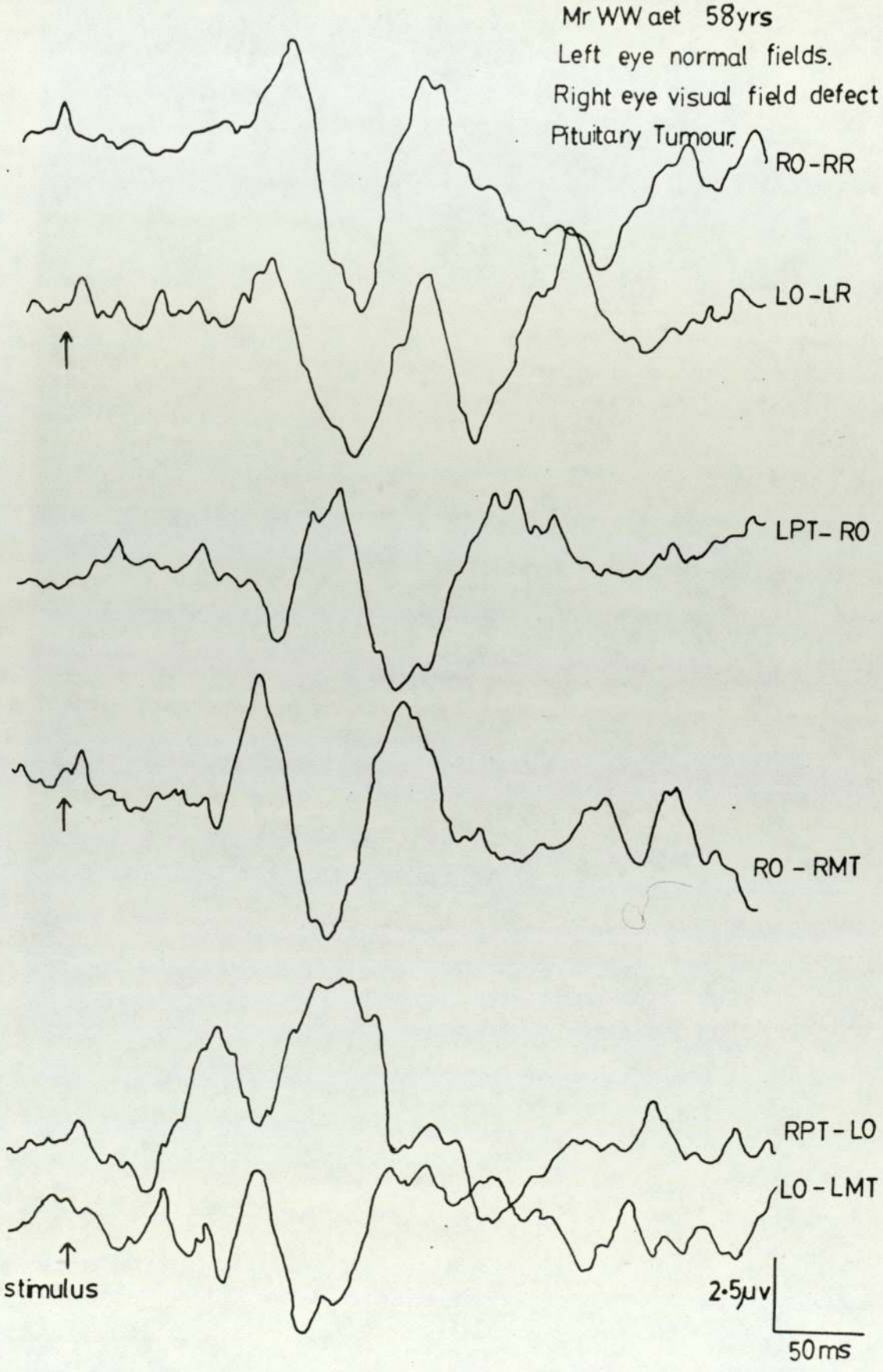


FIG 52

LEFT EYE STIMULATION



needs to be tested empirically and so far data has not been analysed on patients with central damage whose visual fields cannot be tested at the time of the investigation The greatest problem of course, is collaborating the predictions of the VEP results by using other methods of assessment in difficult patients whose vision was and usually remains, in doubt. Figure 53 and 54 (pages 249 , 250) show two brain damaged children with VEPs which would be consistent with complete homonymous hemianopia, and whose behaviour, clinical history and responses to attempts at visual field testing when they were older would also be consistent with a significant visual field loss.

The author is sure that the techniques of stimulating the eyes and recording the VEP can further be improved perhaps by using lower flash intensities or more discrete flash stimuli, or in uncooperative patients ensuring that a pattern is focused on the retina after voluntary accommodatory changes have been prevented by mydrilating the eyes.

8.2. Patients with central macula degeneration.

Although not a sufficient number of patients were tested, it seemed likely that patients with visual field defects but significant central sparing produced normal VEPs to diffuse whole field stimulation over both hemispheres, and even the phase reversal technique failed to locate any unilateral field defect. This seems a likely result since many authors (Regan, 1972; Harding, 1974; Jeffreys, 1977) believe that the VEP, particularly to bright light flashes is the result of stimulation of the central two

FIG. 53.

Right Hemianopia

P.M. age 6

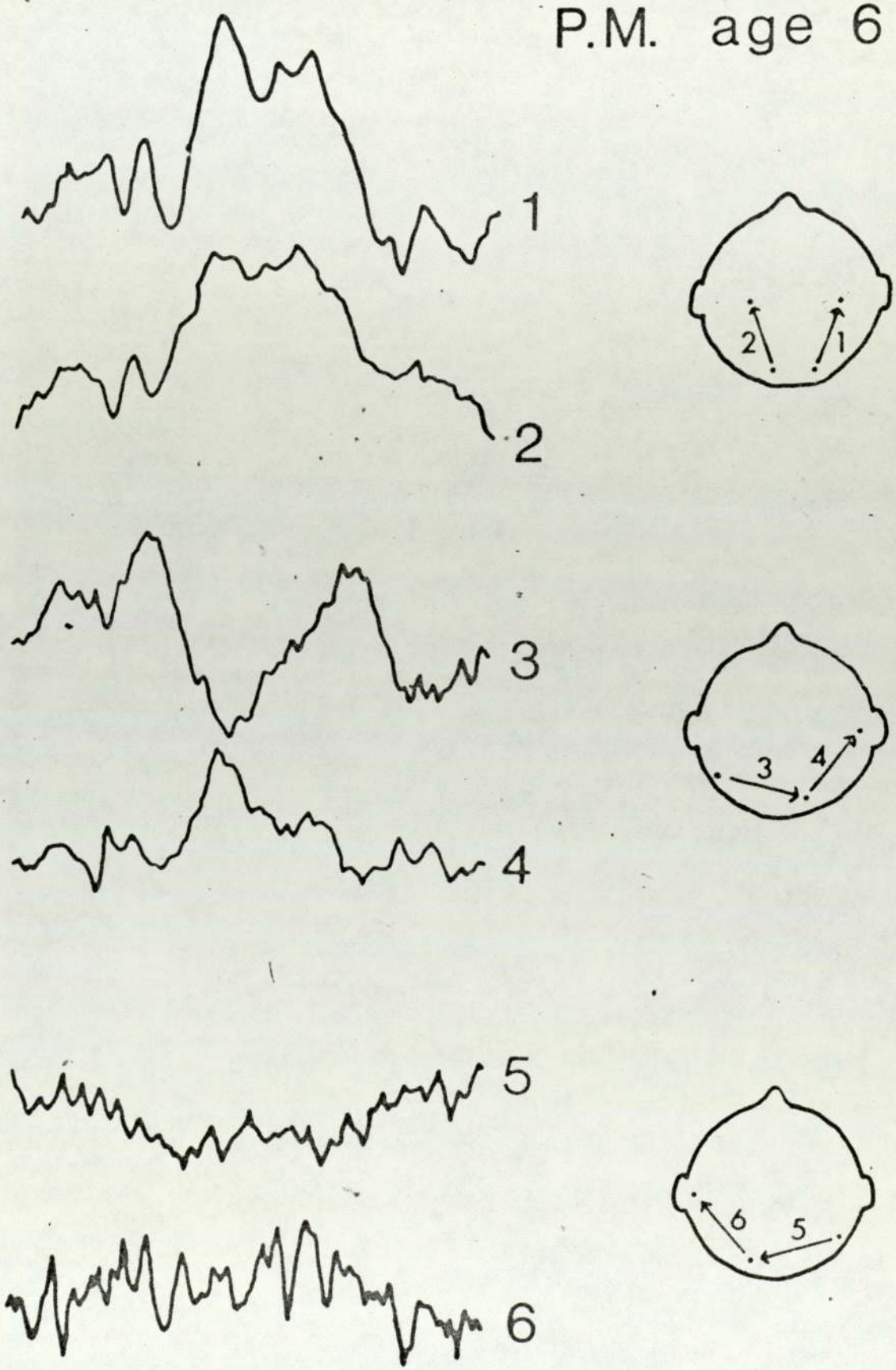
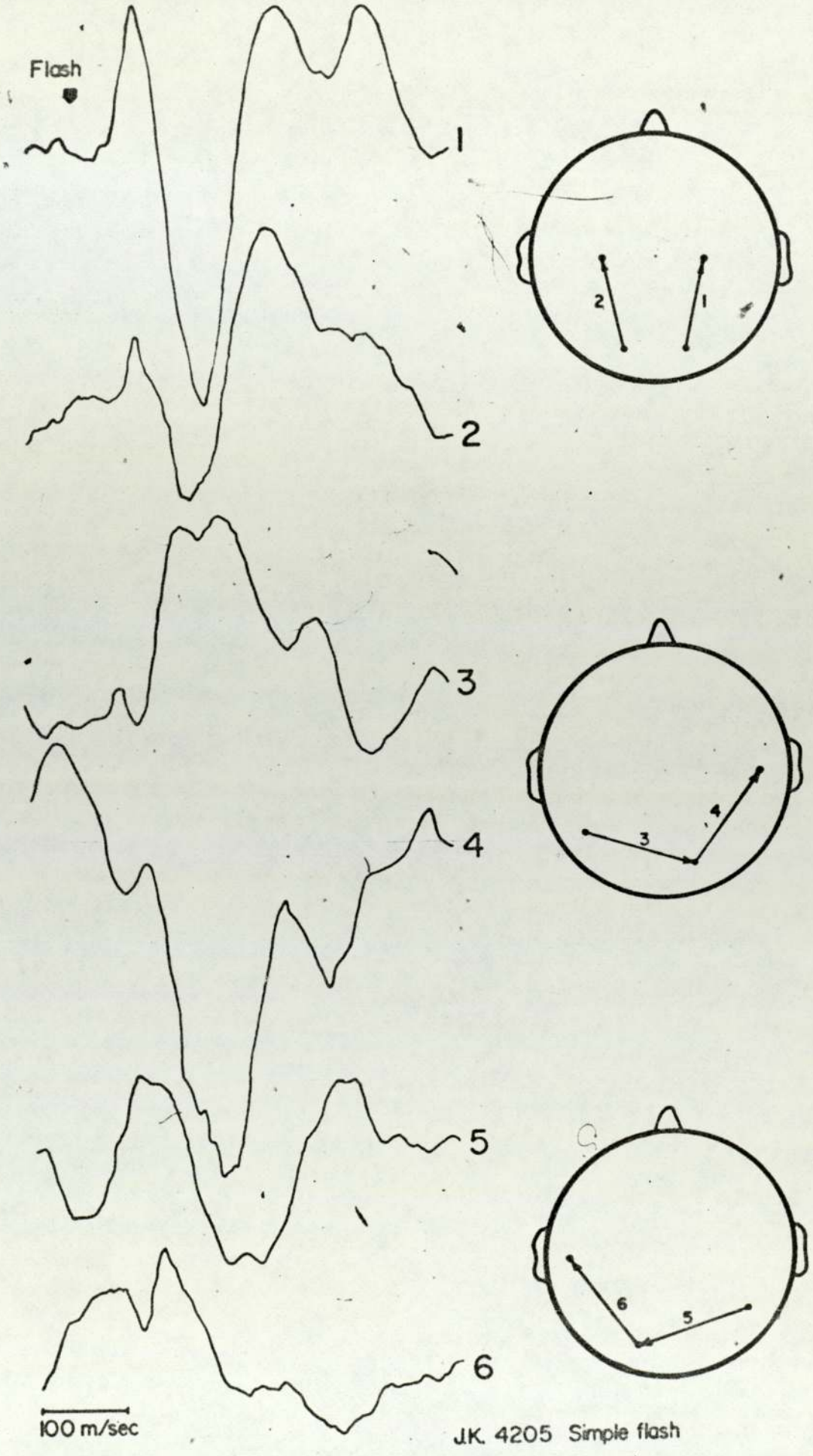


FIG. 54.



J.K. 4205 Simple flash
Binocular

to five degrees of vision. That is the VEP is a useful sign of central visual function. In order to test further the established criteria of normal VEPs, and to assess whether all or only some of the VEP is altered when there is a significant central field loss, patients with known central field losses were investigated. Complete central loss in a circumscribed central visual area is seen most consistently in senile macula degeneration of the retina, since other macula degenerative disorders are more fragmentary often leaving small portions within the central area with some vision remaining (Davson, 1975). Central nervous system lesions involving the visual system, do not produce just a central field defect (Polyak, 1957).

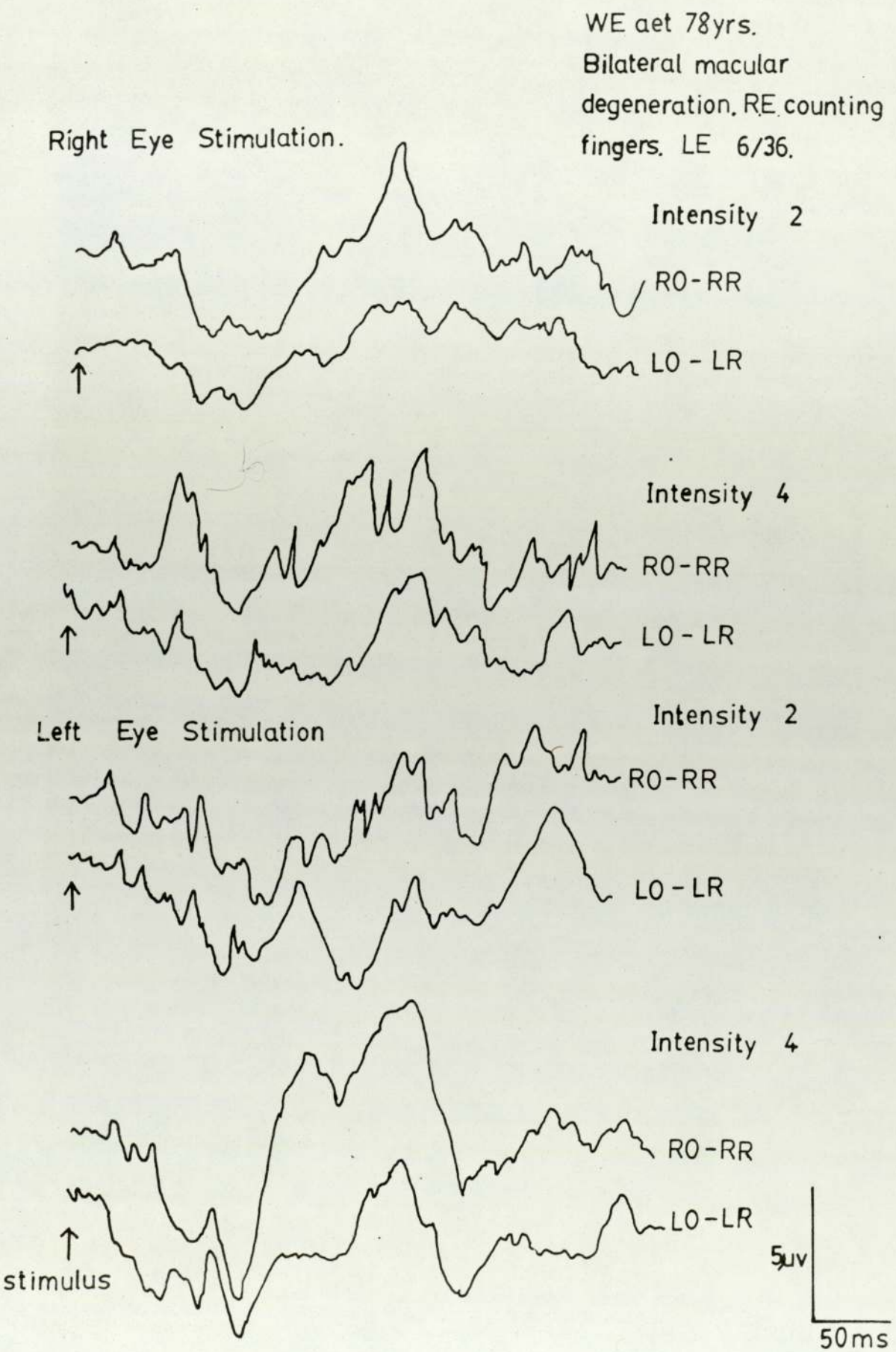
It was hoped to select patients with unilateral macular degeneration so that stimulation of the other, normal eye could provide the best control condition with which to compare the abnormal eye's VEP, particularly as this clinical condition is only seen in the elderly and it was likely that age matched controls would be difficult to find for the very old. As is so often the case in clinical research, unilateral defects were searched for but not found, since a complete loss in the central field of one eye which occurs after some time of gradually dimming acuity, is so often accompanied by similar, earlier changes in the other eye.

Details of the patients are presented in appendix XIII. They were selected and assessed by Mr. Michael Roper-Hall a consultant surgeon at the Birmingham Eye Hospital. All the patients had their visual defects plotted with a Goldmann Field Analyser, and their retinas were examined by Mr. Roper-Hall. Only three patients aged between 53 and 70 years had macula degeneration in only

one eye which resulted in a significant reduction in the visual acuity. The other eye was normal. Six patients aged between 64 and 88 years had bilateral central deterioration but one eye was significantly worse with vision ranging between 6/60 and the perception of hand movements. The other eyes had signs of early macula degeneration often precipitated or accompanied by a retinal haemorrhage with visual acuities varying between 6/12 and 6/36. Finally three patients aged between 76 and 88 years had bilateral and equal involvement of the two eyes with visual acuities of 6/60 or less. One thirteen year old girl was included in the bilateral involvement group although her results were kept separate. She had Stargharts disease with bilateral degeneration of the macula region, and 6/36 visual acuity in both eyes. It was interesting and pertinent to compare her results with those of the older group who although presenting with a central loss of vision, were also a very old group, whose results may primarily have reflected their great age rather than the loss of central vision. It should be noted that no normal elderly individual with good visual acuity could be found over the age of 78 years, ten years younger than the oldest patient with macula degeneration.

All the patients were investigated using the standard procedure, and only monocular stimulation was used with flash intensities of either Intensity 2, 4 or 8 of the Grass stroboscope. In some patients a slight increase in the flash intensity (to intensity 4) occassionally improved the form of a low amplitude poorly defined VEP (see figure 55 , page 253), and all the descriptions of the VEP are of the best response obtained at either of the two lower intensities. The brightest flash intensity used in this

FIG. 55
BILATERAL MACULAR DEGENERATION



experiment (intensity 8) did not improve the VEP any further, and none of the data using this flash intensity are included in the results.

The VEP results were divided into three groups, those produced from the eyes with normal vision, those from eyes with some impairment of vision, and finally from eyes with significantly impaired vision. The differences between the monocular VEPs produced by each subject were compared firstly where there was unilateral macula degeneration and one eye was normal, and secondly where there was asymmetric involvement, and one eye was more effected than the other one.

8.2.1. The VEP in patients with macula degeneration.

The first group of patients to be considered are the three individuals who had unilateral macula degeneration. No significant differences were found in the amplitudes and latencies of the VEP arising from the right and left occiput and the results are combined and presented in Tables 18 and 19 (pages 255 and 256). No component in the VEP from either the effected or uneffected eye was significantly reduced or delayed compared with the criteria of the normal population. When the results of the two eyes were compared for each individual (Wilcoxon matched pairs test) there was no significant difference in latency. All three had lower P2 components in the effected eye's response but the group data did not quite reach significance. In one patient (B.E.) this reduction was significant with a greater than 60% assymmetry ($p<0.02$) and a second patient (D.K.) had a 55% reduction in the P2 component from the effected eye ($p<0.05$). All three patients had a typical old VEP as did the majority of the individuals recorded, with high amplitude P1 and N2 components,

		LATENCY OF THE VEP COMPONENTS (m.secs)													
		GOOD EYE							BAD EYE						
Subject	Age	N1	P1	N2	P2	N3	P3	N4	N1	P1	N2	P2	N3	P3	N4
Mrs D.S	58		67	90	111.5	147	179	212		69	84.5	109	147.5	179	
Mrs D.K	70		70	97	122	153	209	262	55	69	94	128	156		
Miss B.E	53		49	6.5	99	125	288	255		59	86	111	149	170	200

TABLE 18.

Unilateral macular degeneration. Latency of the VEP components from the affected and unaffected eye.

		AMPLITUDE OF THE VEP COMPONENTS (μv)													
		GOOD EYE							BAD EYE						
Subject	Age	N1	P1	N2	P2	N3	P3	N4	N1	P1	N2	P2	N3	P3	N4
Mrs D.S.	58		7.5	16	22.2	8.9	5.8	4.0		8.1	12.0	14.3	12.5	6.8	
Mrs D.K.	70		8.0	14.5	9.9	6.9	10.6	8.7	3.8	3.4	5.7	4.5	4.5		
Miss B.E	53		6.8	10.2	13.6	13.2	9.7	5.2		7.5	8.0	4.0	12.4	10.2	3.5

TABLE 19.

Unilateral macular degeneration. Amplitude of the VEP components from the affected and unaffected eye.

although only in one of them (B.E.) did the P1 amplitude exceed the P2 amplitude by 57% in the damaged eye response which is rarely seen in ght normal VEP of the elderly.

A VEP recorded in a patient with unilateral macula degeneration is seen in Figure 57 (page 258) together with the visual fields and acuity for each eye. Clear differences can be seen in the configuration of the flash VEP from the two eyes with the most marked differences being the reduction in amplitude of the P2 wave when the central vision is impaired. Phase reversal is also abnormal in the eye with poor vision, with only the early P1 and possibly N2 phase reversing to the two occiputs.

The data from the second larger group of subjects with bilateral, unequal involvement of the two eyes is presented in Appendix XIII (page 354) and the mean changes are summarized in Table 20 . The results reflect the general trend of delayed latencies and lower amplitudes recorded from the more effected eye.

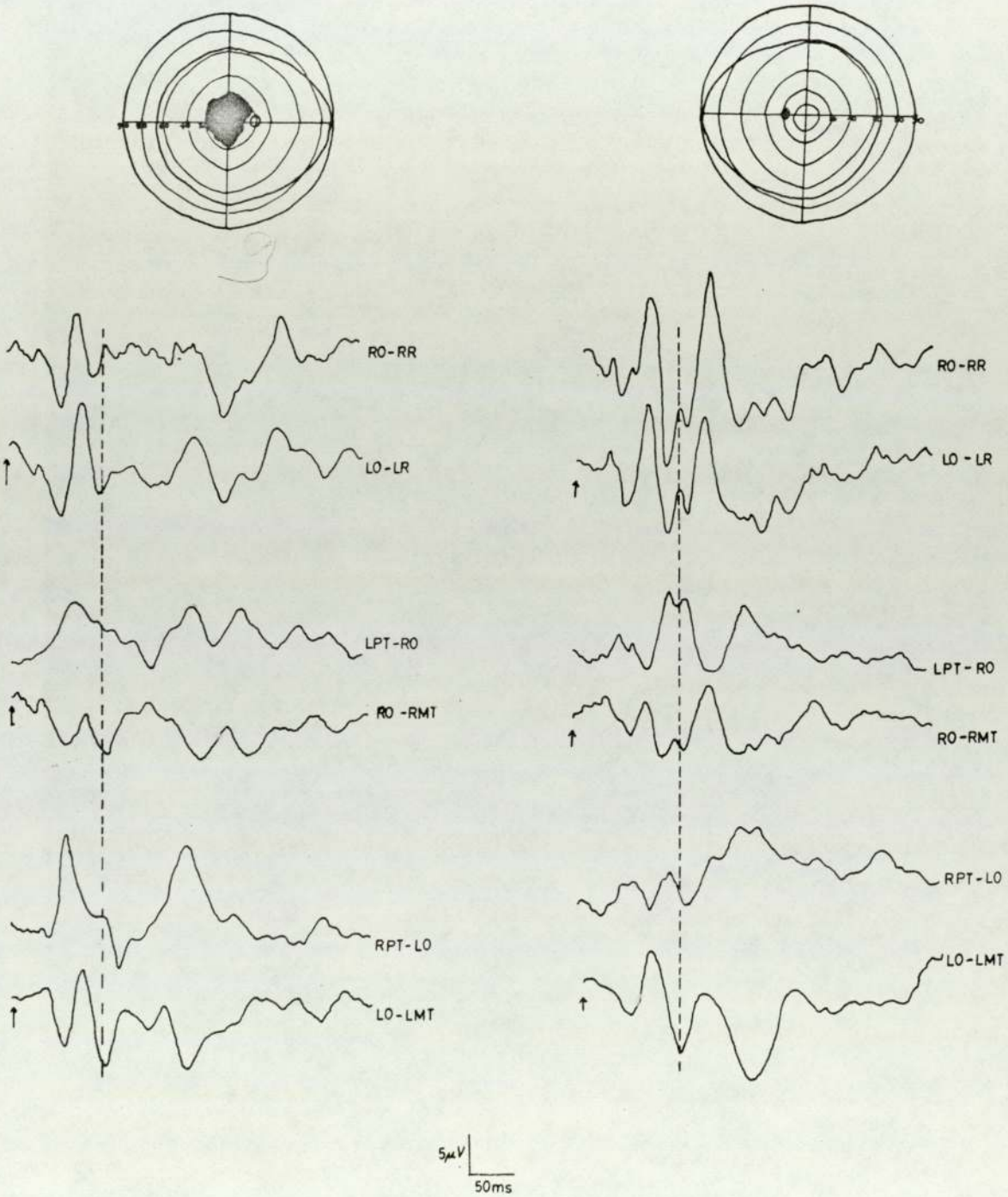
There were no significant differences in the latency of the VEP from the two hemispheres when each eye was stimulated, but in three of the six patients there was a significant reduction in the amplitude of the P2 component arising in one occiput, and this asymmetry between the hemispheres appeared to correspond closely with an eccentric field defect. For example patient G.G. (Figure 58 page 260) had a significant reduction in the P2 wave and no phase reversal to the right occiput. That is the abnormal P2 results were contralateral to the larger left central field defect in the left eye.

FIG 57. UNILATERAL MACULAR DEGENERATION

RIGHT EYE.
Disciform Degeneration VA 6/60

LEFT EYE.
Retina Normal. VA 6/6

Mrs. B.E. aet 53
Grass Stroboscope.
Intensity 2.



	Less effected eye							More effected eye						
	VA range 6/12 to 6/36							VA range 6/60 to hand movements						
	N1	P1	N2	P2	N3	P3	N4	N1	P1	N2	P2	N3	P3	N4
Mean latency (ms)		68.2	98.8	129.3	165.4	207	241.3		5.3	72.8	104.5	133.6	187.5	230.6
Mean Amplitude (μv)		5.2	6.9	5.4	4.1	3.6	2.7		1.2	3.2	6.0	3.9	2.9	4.4

TABLE 20.

The mean amplitude (μv) and latency (m.sec) values of the major VEP components in 6 patients with bilateral disciform degeneration and unequal involvement of the eyes.

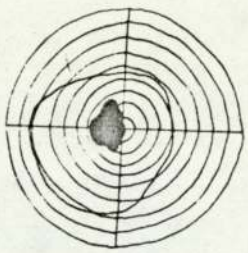
FIG. 58.

SENILE MACULA DEGENERATION

Right Eye Visual Activity 6/24

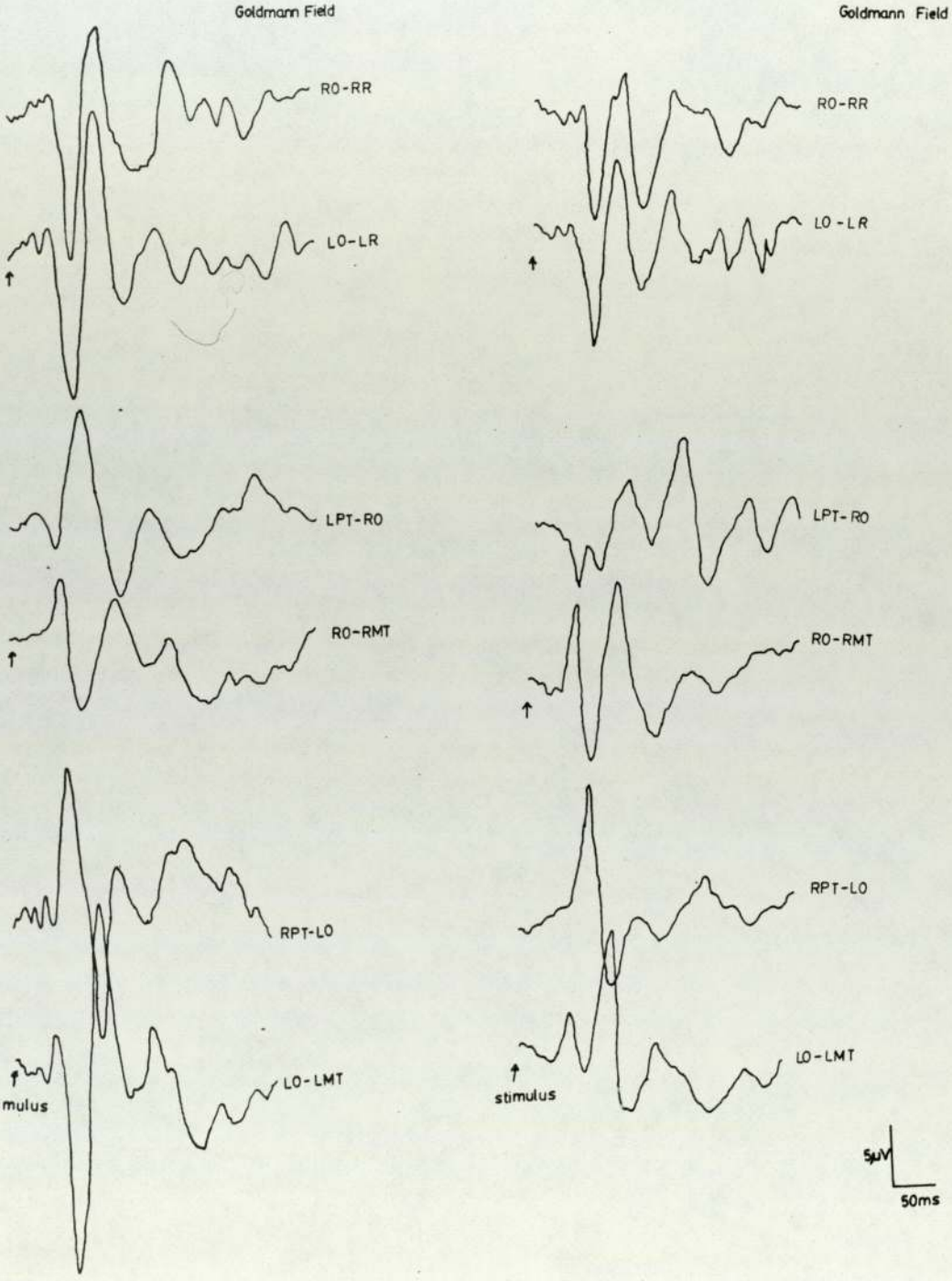
Left Eye Visual Activity < 1/60

GG
Grass Stroboscope
Intensity 2



Goldmann Field

Goldmann Field



When the VEPs from the two eyes were compared in this group of patients with unequal impairment (Wilcoxon matched-pairs test), there was no significant difference in either the latency or amplitude of the N1, P1, N2, P2 and N3 components and some individuals had shorter latency and higher amplitude components in the more effected eye's response. When each individuals VEP was compared with the criteria of normal differences between the potentials from each age, only two of the six patients showed a significant increase in the P2 latency in the expected direction, that is a greater delay with poorer vision. A further patient showed a significant reduction of more than 60% in the P2 amplitude from the more effected eye.

The final group of patients, had extensive bilateral macula degeneration and their results are presented in Tables 21 and 22 . It can be seen that some of the VEP components are reduced or delayed, but as could be expected there were no significant hemispheric differences for each eye, and also no significant difference between the responses from the two eyes.

As well as comparing every patients VEPs obtained from stimulating each eye separately, all the VEPs were placed into one of three groups, those arising from eyes with good vision (3 eyes), those arising from eyes with reduced acuity ranging from 6/12 to 6/36 (7 eyes) and finally responses arising from eyes with significant central retinal damage and very poor vision (14 eyes). The results of these three groups were compared with the criteria for normal VEPs.

As can be seen in Table 23 , the mean values of the amplitudes and latencies of the most frequently recorded components reflected

	LATENCY (m.sec.) OF VEP COMPONENTS													
	Left eye							Right eye						
Patients	N1	P1	N2	P2	N3	P3	N4	N1	P1	N2	P2	N3	P3	N4
R.P.		53	106	150			250		74	103	162	230	300	
R.B.		64	98	150			244	42	63	98	148			250
A.W.		73	103	117					76	103	117			
M.F.				112	170	195	280				112	170	190	262

TABLE 21.

The latency (m.sec.) of major VEP components after monocular stimulation in patients with extensive bilateral macula degeneration.

	AMPLITUDE (μv) OF VEP COMPONENTS.													
Patients	Left eye							Right eye						
	N1	P1	N2	P2	N3	P3	N4	N1	P1	N2	P2	N3	P3	N4
R.P.		7.0	5.3	10.6			16.8		7.4	9.5	9.06	11.0	10.75	
R.B.		1.4	3.8	5.6			4.6	2.9	1.9	2.1	5.3			7.1
A.W.		9.6	5.4	0.9					12.2	3.4	1.5			
M.F.				0.7	19.5	16.5	5.9				1.7	10.0	8.6	6.2

TABLE 22.

The amplitude (μv) of major VEP components after monocular stimulation in patients with extensive bilateral macula degeneration.

Category of vision	Good vision				Reduced vision				Poor vision			
Visual acuity	6/6				6/12 - 6/36				6/60			
Main Components	P1	N2	P2	N3	P1	N2	P2	N3	P1	N2	P2	N3
Mean Latency (ms)	62	88	111	142	60.5	95.3	126.4	161	58.3	103.2	137.2	193.6
Mean Amplitude (μv)	7.4	13.6	15.2	9.6	9.9	8.4	6.6	6.8	4.9	5.6	4.5	4.1

TABLE 23

Mean latency (m.sec.) and amplitude (μv) values of the major VEP components in each of three categories of visual acuity in patients with macula degeneration.

a trend which is apparent in the individual data of eyes with poorer vision producing VEPs of longer latency and lower amplitudes. Using the Mann Whitney U test of significance, no significant differences were found in the VEP from the eyes with either good or reduced vision when compared with a normal control group, however, in the group with poor visual acuity there was a significant delay in the N2 and P2 components ($p=0.001$) and the later N3 wave ($p=0.01$), and a significant reduction in the P2 component ($p=0.001$) and N3 component ($p=0.02$). When each monocularly evoked visual potential was compared with the criteria for a normal response, no VEP from a normally seeing eye was abnormal. In the VEPs from eyes with reduced vision two eyes had abnormally small P2 components ($p=0.02$) and a third patient had an abnormal delayed P2 wave ($p=0.05$). Two patients also had significantly delayed N2 components ($p=0.01$ or less) one of them also having a reduced P2 component. Thus four patients (57%) had an abnormal VEP from an eye with reduced vision as judged by normal criteria.

Far more strickingly abnormal VEPs were evoked from eyes with very poor vision when compared with normal criteria. Fifty per cent of the P2 components were significantly reduced in amplitude and a further 50% of the P2 components were significantly delayed ($p=0.005$ or less). Only two eyes with vision of 6/60 or less produced VEPs with no significant delays in any of the components and with no significant reduction in the amplitude of the P2 wave. Several patients had significantly delayed early components, but these delays always occurred in conjunction with a significant delay in the P2 component.

To summarize, when the normal criteria for the amplitude and latency of the P2 wave were compared with the results of this patient group, no eye with good vision produced an abnormal VEP, 57% of eyes with reduced vision had abnormal VEPs, while 86% of the VEPs from eyes with poor vision were abnormal. When the normal criteria for the expected differences between the VEP from the two eyes were compared with the responses of the patients with unequal or unilateral macular degeneration, only 44% of the patients had a significantly abnormal response from the more effected eye, which is a poor detection rate, although the results were better in the cases of unilateral involvement.

8.2.2. Phase reversal results in patients with macula degeneration.

There appeared to be a distinct and significant difference in the VEP elicited from eyes with very poor sight, there were however very few significant distinguishing features to identify the VEP from an eye with reduced vision, compared with the VEP from the normal eyes of older patients.

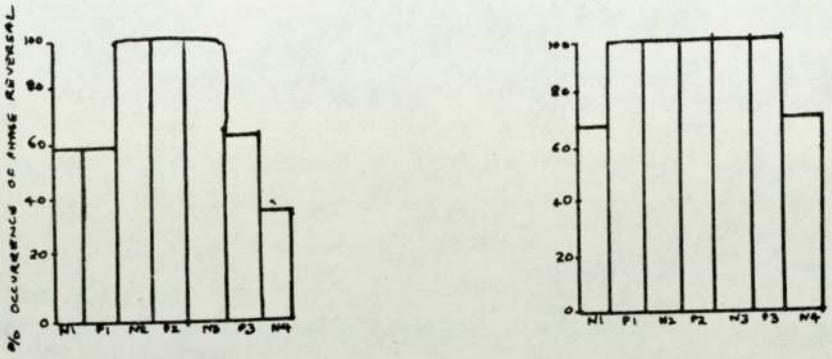
Extra information concerning the topography of the VEP was collected as part of the standard recording procedure by phase reversing the evoked response's components to the right and left occiputs. Checks were always made to ensure that more lateral phase reversal to the left and right posterior-temporal electrodes could not be obtained. The phase reversal results are summarized in Figure 59 (page 267). It should be remembered that only three eyes had good visual acuity, and in all of them normal phase reversal results were obtained, with all the major components, particularly

FIG. 59.
THE PERCENTAGE OCCURENCE OF PHASE REVERSAL OF EACH OF THE MAJOR VEP COMPONENTS IN SENILE MACULA DEGENERATION.

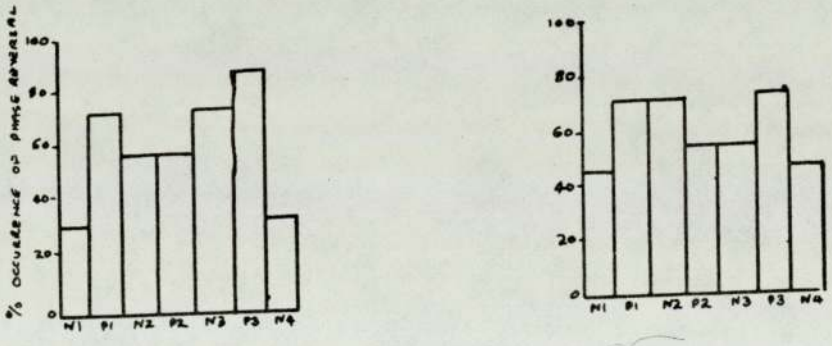
Left Occiput

Right Occiput

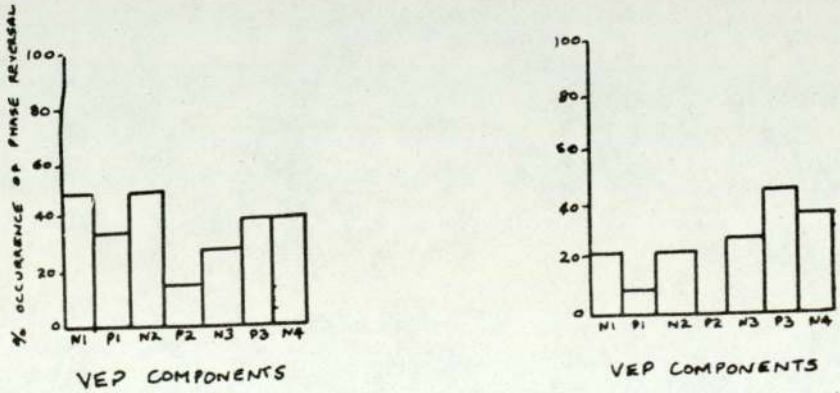
GOOD VISION 6/6



REDUCED VISION 6/12 - 6/36



POOR VISION ≤ 6/60



P2 being clearly located in both occiputs. The results of the second group with reduced visual acuity were particularly interesting. It was frequently found that the early components (P1 and N2) and the N3 wave phase reversed to the left and right occiput, while the P2 component failed to do so on 43% of the occassions to either one or the other occiput. That is components preceeding and succeeding the P2 wave phase reversed more frequently than the P2 wave itself, a result never seen in the normal population. This also contrasts with the phase reversal results in homonymous hemianopia, when a failure to locate the P2 component in the hemisphere contralateral to the field defect, was invariably accompanied by a failure to locate most of the other VEP components, particularly the early portions of the response, over the same hemisphere. So it appears that with central retinal degeneration, the P2 component may well be preferentially effected. In hemianopic defects the whole of the initial portion of the VEP up to approximately 140 m.sec. after the stimulus is disturbed by central visual system damage.

A second interesting factor concerning the patients with reduced vision was that, with the exception of one individual (G.G.) for whom the P2 wave was located in both occiputs even though the vision of the eye was reduced to 6/24 (see figure 58 , page 260), in the other six patients the P2 component phase reversed to only one occiput, and was not present or was in phase over the second occiput. In the great majority of patients this asymmetry, only clearly apparent in the phase reversal results, corresponded to eccentric central degeneration with one field being more

effected than the other. For example patient D.S. had a central loss involving twenty degrees in the left visual field, and a loss of approximately five degrees for the central right visual field. The P2 component was only located over the left occiput. A far more careful field analysis needs to be done with patients who have central field losses as the Goldmann field analysis is often quickly and roughly done, and the VEPs of a great many more patients need to be recorded, but these results raise the possibility that in patients with macula degeneration, providing some central retina remains functional, possibly within the central 5 to 10^{o}, which can support a visual acuity of 6/36 or better (which still represents useful sight for the patient), then phase reversal of the P2 component is likely to occur in at least one occiput depending on the site of the central retinal damage.

The phase reversal results for the eyes with poor vision were again significantly different from the results for the eyes with good or reduced visual acuity. In the majority of eyes (85%) no phase reversal was obtained of the P2 component to either the left or right occiput. Although earlier and later components were more frequently located in the two occiputs, this was only seen in 50% or less of the eyes. In two eyes (patients G.G. and R.P.) phase reversal was obtained of the P2 component to the left occiput. G.G. had a visual acuity of 1/60, and R.P. had 6/60 vision, and in both individuals the location of the P2 in the left occiput corresponded with better right visual fields. The VEP of patient G.G. can be seen in Figure 58 (page 260).

Although the P2 component was located at the left occipital electrode in patient R.P., the P2 component, and the preceeding N2 wave were significantly delayed at the 0.05 probability level. Therefore the phase reversal results have improved the identification of abnormal VEPs reflecting extensive retinal damage, and there was only one eye (7% of the experimental population) which failed to be identified as having very poor vision. It would have been interesting, but not possible practically to recheck the visual fields and acuity of this one patient since even the standard and well practiced methods of assessment have been known to produce variable results depending on the difficulties the patient is having during the test and the skill of the technician involved in the assessment.

Examples of the phase reversal results can be seen in Figure 57 (page 258). The left eye has normal vision, and the VEP consists of a large P2 wave, while the major components phase reversed to both occiputs. The right eye with 6/60 vision produces a VEP with only an early P1 component that can be located at both occipital electrodes. The typical results of reduced visual acuity can be seen in Figure 60 (page 271). The left eye has 6/24 acuity and the P2 component is of lower amplitude than the P1 component but still clearly seen. Phase reversal is obtained of all components to the right occiput, but only of P1 to the left occiput. The right eye with very poor acuity, has a significantly reduced P2 component, which cannot be located at either occiput.

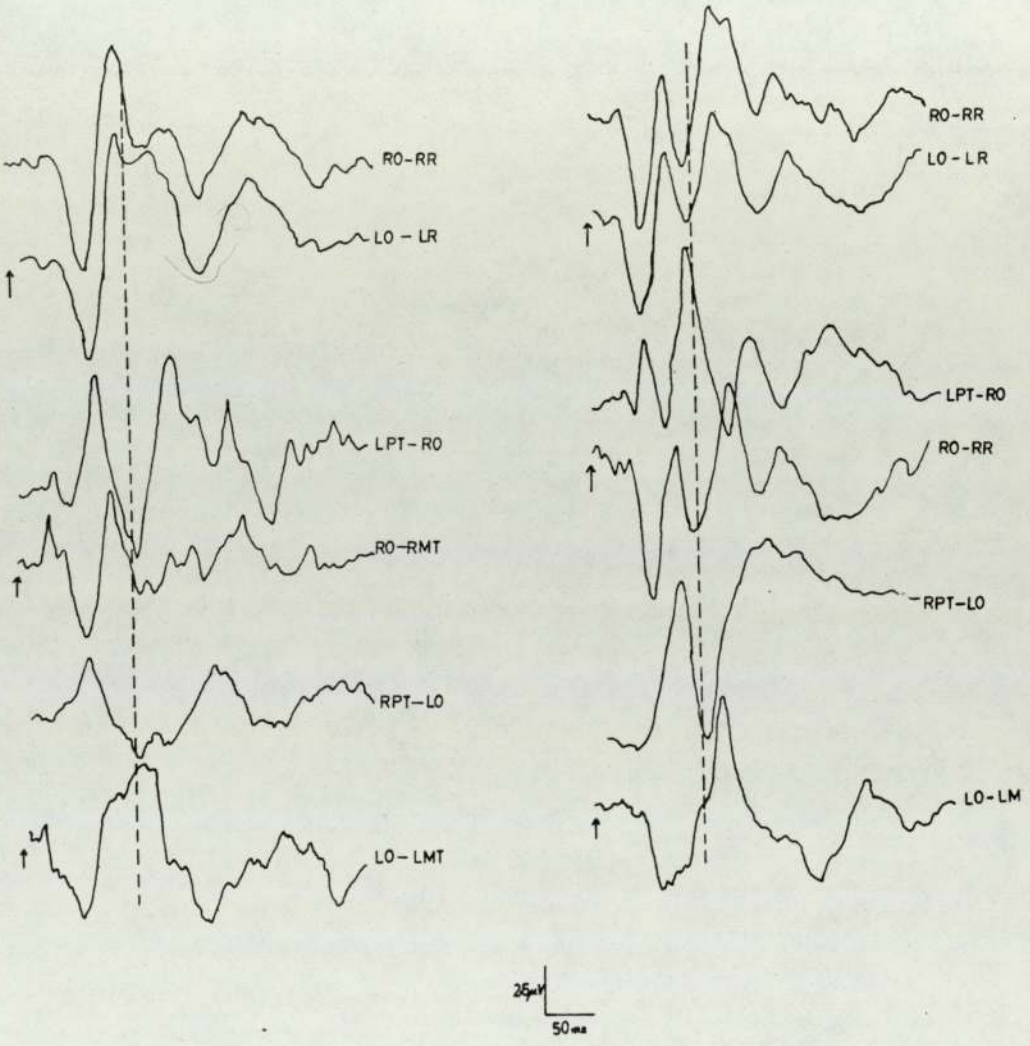
The conclusions from these patients with known central retinal defects are that when vision is very poor, that is less than

FIG 60. BILATERAL SENILE DISCIFORM DEGENERATION

Mrs E.J aet 72yrs
Diffuse flash stimulation
Grass Stroboscope Intensity

RIGHT EYE.
Long standing disciform degeneration.
Visual acuity hand movements.

LEFT EYE
Early disciform degeneration
Visual acuity 6/24

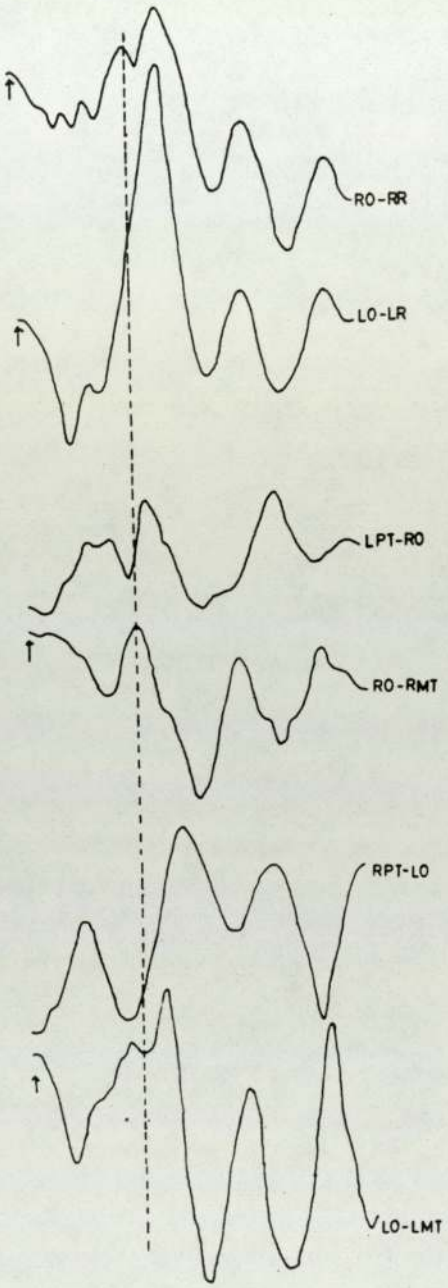


6/60, the typical VEP has a P2 component that is significantly reduced in amplitude and may also be significantly delayed.

Since in this elderly group of patients with known visual defects so many of their VEPs possessed early P1 components that were of larger amplitude than the succeeding P2 waves irrespective of the acuity of the eye, it was concluded that the relative amplitude of these two positive components may well be a feature of the age of the individual, and it is the absolute amplitude of the P2 component that is more prognostic of the vision in that eye. Secondly, when acuity is very poor, the P2 component cannot be located in either occiput, although earlier and later waves may arise at both occiputs. With some reduction in vision, but still with some useful sight remaining, the P2 component may fail to be located in one hemisphere.

The patients in this group possessing central retinal defects were extremely old and displayed one specific type of retinal degeneration, and it is therefore not possible to say with certainty whether the findings in this group can be applied to all patients with a central loss of vision, or whether many if not all of the results may be specific to the age of the group. In this context it is interesting to look at one young patient (M.F.) aged 13 years, who was investigated at the same time (see figure 61 , page 273). She had Stargardt's Disease, which involves bilateral macula degeneration, and the VEP was typified by an absence of positive components particularly the usually prominent P2 wave.

FIG 61. MACULAR DEGENERATION : STARGARTS DESEASE



MF aet 13yrs
Deteriorating vision over last 3yrs.
Bilateral pigmentary changes in the macular area, more marked in the left eye. Visual activity 6/36 both eyes.
Grass Stroboscope Intensity 2
Binocular Stimulation.

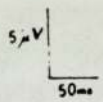
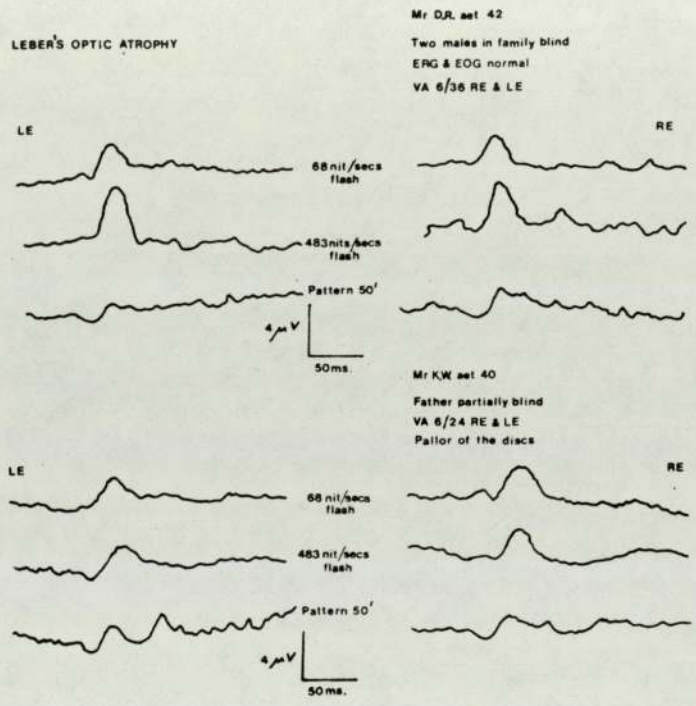


FIG. 62. VEP IN OPTIC ATROPHY.



Also no clear phase reversal could be obtained of the P2 wave to either occiput, although the earlier P1 and N2 components did phase reverse. Of course, a great deal more research needs to be done with a greater variety of patients and clinical conditions, but it is possible that the tentative conclusions drawn from an old patient control group may be applicable to other patient populations with central macula degeneration. Much later work at the Birmingham Eye Hospital has revealed that the typical VEP in many patients with Leber's Optic Atrophy, an inherited disease involving primarily central macula degeneration, is a response with a noticeable absence of positive waves in the flash VEP, and in particular a reduction in the P2 component (see figure 62 , page 274).

CHAPTER 9

The use of the flash VEP in the prediction of visual function in patients with dense opacities of the optic media

Despite the crudity and biological inappropriateness of the flash VEP, and the very variable responses recorded in a normal population, the VEP findings in patients with known visual field defects, suggest that the VEP is significantly abnormal and can be reliably identified as such, when there is a severe reduction in vision or blindness. With the techniques used subtle disturbances in vision can not be detected. However, even a reliable electrophysiological sign differentiating between poor vision or some visual function remaining can provide useful information to the clinician to help in his decision to save an eye, or to restore the visual capabilities of the eye, since a patient can be successfully trained to use their sight even when only a little remains.

As long as the patient can cooperate and understand the testing procedures most visual disorders can be diagnosed with more sensitive standard opthalmological proceedures, however this is not the case in any patient with dense opacities of the optic media that obscure the retina and prevent assessment of retinal and visual capabilities. Modern technology has meant that the surgeon can replace or remove opaque accessory structures for example the cornea, lens and vitreous humour, and can rebuild the anterior segment of the eye after serious damage, whereas perhaps ten years ago the eye was either enucleated or left unseeing. However, such operations are obviously ineffective if the retina is extensively damaged, and it is far better for both the patient and the hospital service if some form of visual assessment can be performed prior to surgery. Pattern stimulation through the eye opacities is impossible, and even

the use of laser beam pattern stimulation produces unreliable results with subjective assessments of contrast thresholds (Green and Cohen, 1971; Goldman, 1972). Cortical potentials evoked by laser stimulation is still very experimental, and both quantitative assessment and the prognostic value of this method remains to be confirmed (Arden and Sheoney, 1977). It is possible that high intensity flash VEPs could be usefully applied in this field in an attempt to predict whether opthalmic surgery would result in improved vision.

9.1. The prognosis of visual function in patients with dense unilateral cataracts.

Surprisingly little has been published on the VEP from eyes with dense opacities. Fricker (1971) recorded SSEPs to high frequency stimulation in unilateral cataracts, and reported encouraging findings on the predicitive value of the cortical potential. However, of his 52 patients, 25% whom he predicted would have poor vision, had good post operative acuity, while 28% of the group who were predicted to have good acuity, had in fact poor vision.

A prospective study to assess postoperative acuity was carried out by the author on 21 patients with dense unilateral cataracts which obscured any sight of the retina prior to surgery. All the patients had undergone a general opthalmological examination, and were kindly referred to the Neuropsychology Unit by Mr. John Pearce, an eye surgeon at the Bromsgrove Hospital in Worcestershire. Mr. Pearce subsequently operated on all but one of the patients, who refused surgery, and provided post operative assessments of

each patients vision. Details of the patients clinical history and postoperative results are presented in Appendix XIV (page 357). The group was very mixed with a wide range of ages from one young girl of ten years who had a congenital cataract, to an old lady of 94 years who had sustained damage to the left eye three years previously. Because of the heterogeneity of the group an interocular comparison between the cataract eye and the eye whose visual acuity was known was considered the most appropriate means of predicting visual function. The mean age of the group was 55 years with 66% over the age of 50 years. The most common clinical history was ocular trauma (52% of the eyes), while in 24% of cases the history was not specified or not known, and in a further 24% there was some evidence of ocular pathology, for example two eyes had raised intraocular pressure, and a third eye was believed to have had a detached retina 36 years previously.

Each patient attended the diagnostic clinic for an investigative recording. The standard recording procedures that have already been described in Chapter 7, Section 7.1. were used, the only difference was that the eyes were stimulated with higher flash intensities (68 to 483 nit seconds intensity range of the Grass Stroboscope).

In all patients only the vision in one eye, behind the cataract was in doubt, and in the majority of cases the vision of the good eye was 6/9 or 6/6. In three patients the non-cataract eye had reduced vision of 6/24 due to either early opacities, early senile changes or amblyopia. Interocular differences in

the flash responses were analysed and compared with an age matched normal control group. The three eldest patients aged 80, 86 and 94 years could not be age matched with the normal volunteers, and were compared with individuals aged between 74 and 78 years. The mean difference between the amplitude of the P2 component from the two eyes of the control group was 18% and a difference of more than 33% (2 standard deviations of the normal variation) was the criterion of an abnormal response from one eye. Similarly a latency difference of not more than 12 m.sec. and localization in both occiputs were also indicative of the expected VEP variation between normal eyes.

The results of the cataract eyes were also compared with the VEP criteria for the normal monocular variations of the young adult and elderly individuals which were discussed in Chapter 7. These criteria differed slightly from the age matched group in that the normal amplitude variations between the two eyes was greater (up to 50%). The group of patients with central macula degeneration could provide no reliable information on interocular differences as in all but three cases both eyes were involved. However, the results had suggested that absolute (compared with relative differences between the eyes) criteria of the latency and amplitude of the P2 component were a helpful sign of severely reduced vision, while phase reversal provided valuable information, since a failure to localise the P2 component to either occiput was a clear indication of poor visual function, and localisation in only one hemisphere was suggestive of some reduction in visual function.

With these criteria in mind the VEPs were rated as either grade 1 predicting good visual function, Grade 2 as indicating that there was some doubt as to the visual function, and grade 3 suggesting severely reduced visual acuity. The VEPs were rated independently by the author and a second rater who was experienced in clinical VEPs, and who had no knowledge of the age, clinical history, preoperative acuity or the final outcome.

An example of a grade 1 VEP can be seen in figure 63 (page 281) where the response from the cataract eye was similar to the normal eye, and all the main components phase reversed to both occiputs. In this patient the postoperative acuity was 6/6. A grade 3 VEP (figure 64 , page 282) had a noticeable reduction in the amplitude of the P2 component, and frequently the rest of the VEP was of low amplitude as well. There was no clear localization of the components in the left and right occiputs. A Grade 2 rating was used to represent a category of VEP where judgement was difficult and questionable. Generally there was a significant reduction in the VEP amplitude and phase reversal was inconsistently obtained. In some of the cases stimulation of the good eye produced visual potentials of unusual configuration.

One of the difficulties in assessing the VEP elicited from the cataract eye was the far greater variability from time to time of both the latency and amplitude of the VEP components compared with any of the normal control groups and the patients with known senile macula degeneration. This variability may have been due in part to the diffusing properties of the very dense cataracts, which scattered, refracted and reflected the strong

FIG. 63.

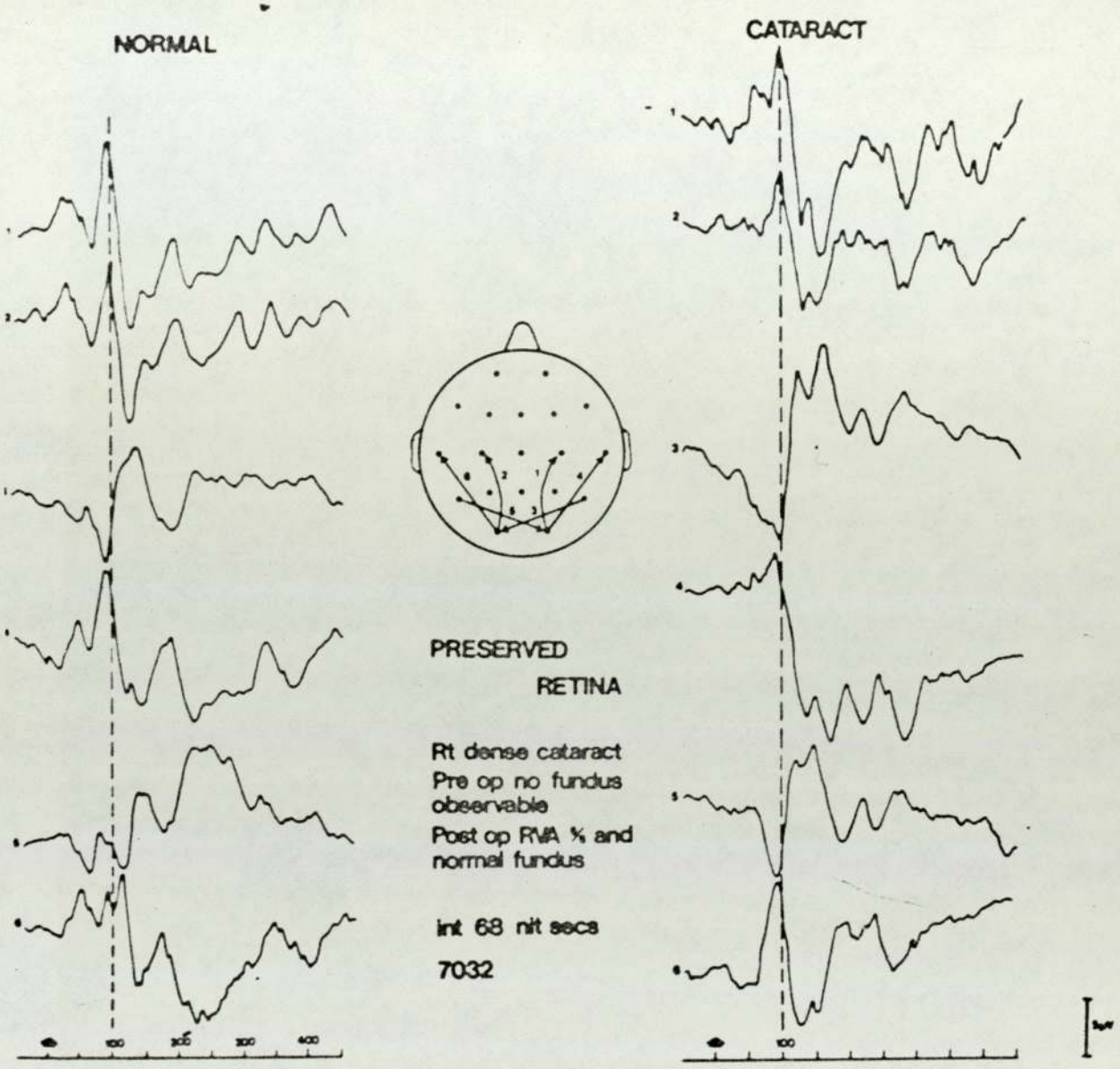
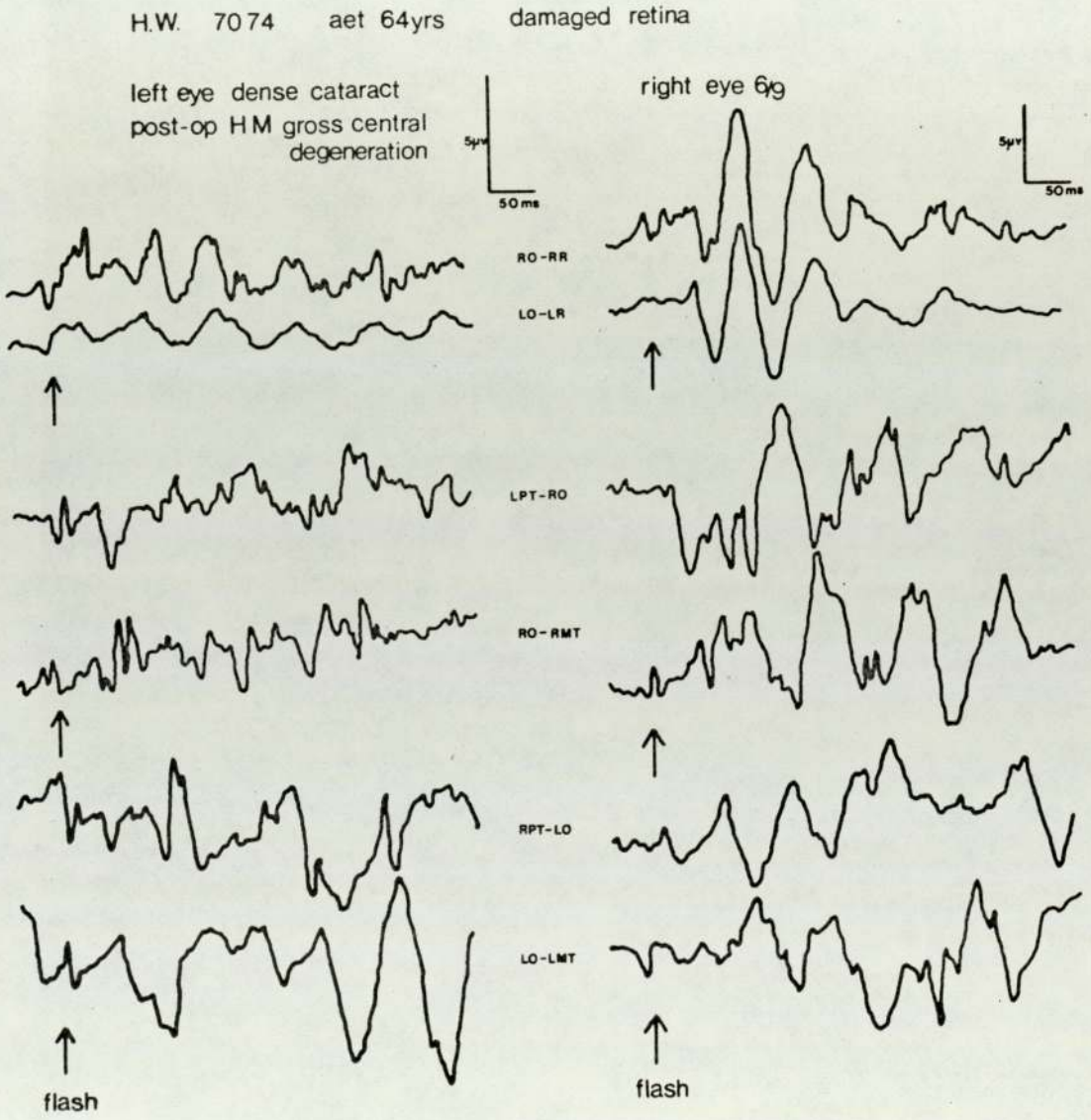

NORMAL
CATARACT
PRESERVED
RETINA
Rt dense cataract
Pre op no fundus
obeervable
Post op RVA ⅓ and
normal fundus
int 68 nit secs
7032

FIG. 64. GRADE 3 VEP.



light flashes, thus significantly changing the properties of the stimulus. Secondly, the background EEG was invariably altered when the cataract eye was stimulated with a significant increase in the alpha rhythm that could both enhance or reduce the amplitude of the VEP. On many occassions when alpha activity dominated the background EEG and entrained onto the frequency of stimulation, the VEP could either be totally obscured by the rhythmic waves or the alpha activity could be mistakenly identified as the evoked response (see figure 65 , page 284). This difficulty was never completely overcome, although random stimulation did slightly reduce the amplitude of the averaged alpha. Attempts to arouse the patients were not successful. Simulation of the cataract effects by closing the good eye during a VEP record was attempted, but this did not produce the same subjective effects, and the VEP recorded was not similar to a VEP elicited from a normal retina behind a dense cataract. A better simulation of a cataract effect on a normally seeing eye would undoubtedly improve our diagnostic criteria of normal and abnormal function in cataract eyes.

Despite these difficulties the agreement on the VEP ratings of the two observers was good with complete agreement on all the VEPs graded 1. There was dispute over the two VEPs placed in the other two categories, and the gradings were adjusted after some discussion.

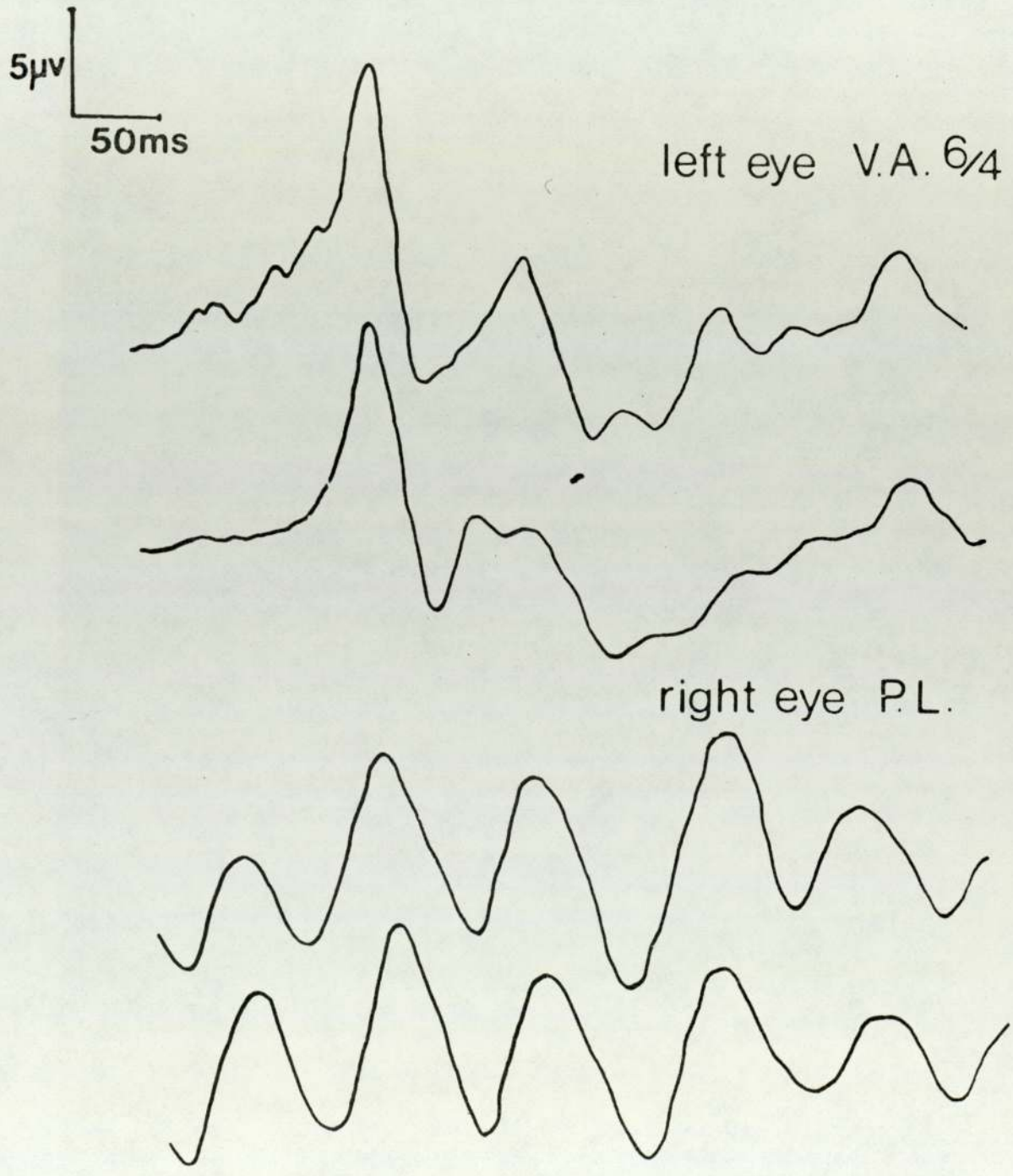
9.3. The flash VEP results in unilateral cataracts.

In the majority of patients the normal eye produced the expected VEP and this was true of two of the patients with reduced vision

FIG. 65.

D.E. 4894 aet 43

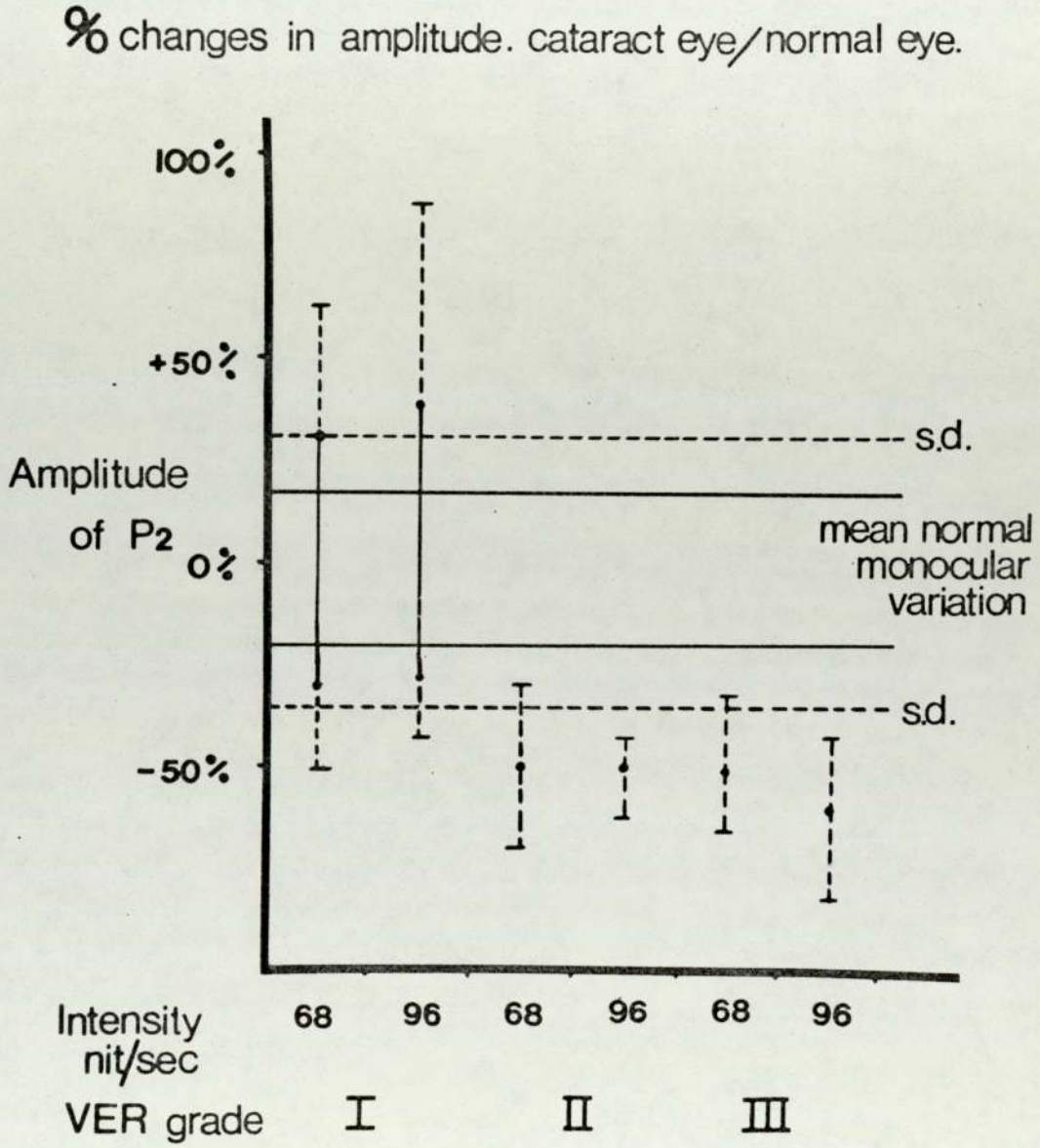
OLD TRAUMATIC CATARACT



(N.T. and O.T.). The third patient with early senile changes in the noncataract eye (M.G.) was very old (78 years) and produced unusually large amplitude VEPs. The eldest patient (I.T. aged 94 years), had very delayed VEP latencies in both eyes, which were significantly delayed at the .002 level compared with the latency criteria of the normal old population. However the author has no experience of what the configuration and timing of the flash response would be like at this age, and judgement of this patient's sight would have been difficult if the vision had been in doubt in both eyes. A third patient (R.M. aged 65 years) had poorly formed VEPs when both the good and cataract eye was stimulated,with a P2 wave of only 2 to 3 μv. Such an amplitude reduction is significant at the .05 level. One final patient had a delayed VEP from the good eye although the amplitude was normal. Despite the fact that there were some unusual results in the response evoked from the good eye in this patient group, the P2 component always phase reversed to both occiputs. The mean percentage reduction or percentage increase in the amplitude of the P2 component from the cataract eye compared with the normal eye was calculated for two of the flash intensities (intensities 2 and 4, 68 and 96 nit seconds). It was found that a slight increase in intensity often improved the amplitude and form of the VEP, and the best response obtained was always used to predict the visual acuity. Further increases in the intensity of the stimulus did not significantly improve the results,which suggests that the retina was adequately stimulated at intensity 2 or intensity 4 of the Grass stroboscope despite the presence of dense opacities.

Figure 66 (page 286) shows the results of the amplitude

FIG. 66.


% changes in amplitude. cataract eye/normal eye.
100%
+50%
Amplitude of P2
0%
-50%
s.d.
mean normal monocular variation
s.d.
Intensity nit/sec
68
96
68
96
68
96
VER grade
I
II
III

differences between the two eyes of each patient for the three VEP grades. Twelve patients had grade 1 VEPs (for more detailed results see Appendix XIV , page 359). Five of these patients had a larger P2 component from the cataract eye. This was possibly due to the diffusing effect of the cataract, and a greater degree of contamination from the background EEG activity. At intensity 2, nine patients had a reduced VEP from the cataract eye and in four, this reduction was around 50%. However, increasing the flash intensity to intensity 4 improved all the results of the grade 1 patients, and there was less difference between the two eyes. The greatest reduction was 42% and three other patients still displayed quite large differences (between 38 and 34%).

Three patients had a grade 2 VEP. One of these patients (M.G.) had a very large reduction in the P2 component from the cataract eye, although as mentioned previously the VEP from her good eye was of unusually large amplitude, so therefore the cataract eye's response was not of very low voltage (the P2 amplitude was 5 μv). In the other two patients with grade 2 VEPs the responses were also of much lower amplitude in the cataract eye, and increasing the flash intensity did not improve the VEP recorded. The range of VEP reductions compared with the good eye was between 30 and 70% at intensity 2, and between 44 and 60% at intensity 4.

In five patients who had grade 3 VEPs, the response from the cataract eye was noticeably smaller than that obtained from the good eye, and in three eyes the reduction was larger than 50%. In one other eye the reduction was slightly less at 45%.

In the fifth eye there was only a 33% reduction at intensity 2 and 42% reduction at intensity 4. However, the amplitude of the cortical responses from the good eye were only 3 to 4 μv, and this contributed to the apparently small relative reduction. Increasing the intensity of the flash stimulus from intensity 2 to intensity 4 or higher did not improve any of the grade 3 VEP amplitudes and indeed in two thirds of the patients even greater amplitude differences were recorded with increasing intensity, as the response from the good eye became larger.

The latencies of all grades of VEP from the cataract eye were extremely variable but only 3 VEPs were significantly delayed at all flash intensities, while another 3 responses were borderline. Only two of the delayed responses were rated as grade 3 VEPs.

It is apparent from the range of amplitude and latency variation in each of the three VEP categories, that the two independent assessors could not and did not use latency criteria unless there was a consistent and excessive difference between the two eyes. This was seen in only one patient whose grade 3 VEP was delayed by more than 30 m.sec., which lies beyond the range of normal variation and beyond that seen in cataract eyes with grade 1 VEPs which were found later to be functioning normally. The largest latency difference for the grade 1 VEPs was 14 m.sec. Similarly relative amplitude criteria were not used indescriminately by the two raters and it was apparent that the absolute amplitude of the VEP was as important as the relative amplitude differences, particularly when the visual potential from the cataract eye was of normal amplitude and was well formed.

Thus 4 of the 12 eyes graded 1 exceeded the matched control criteria of 33% of amplitude difference between the eyes.

In fact it was apparent that the most prominent criteria that were used to grade the VEPs were the phase reversal results. In all the VEPs graded 1,P2 was located in both the right and left occiput, while in all the Grade 3 VEPs there had been a failure to locate the major VEP component P2 in either hemisphere. In the grade 2 VEPs the phase reversal results were inconsistent, with P2 sometimes being located in just one occiput. Thus it was apparent that with such high variability within these patients only gross differences in wave form could be consistently assessed by the raters and the phase reversal technique provided the most useful and easily recognisable criteria with which to judge whether a VEP was normal or abnormal.

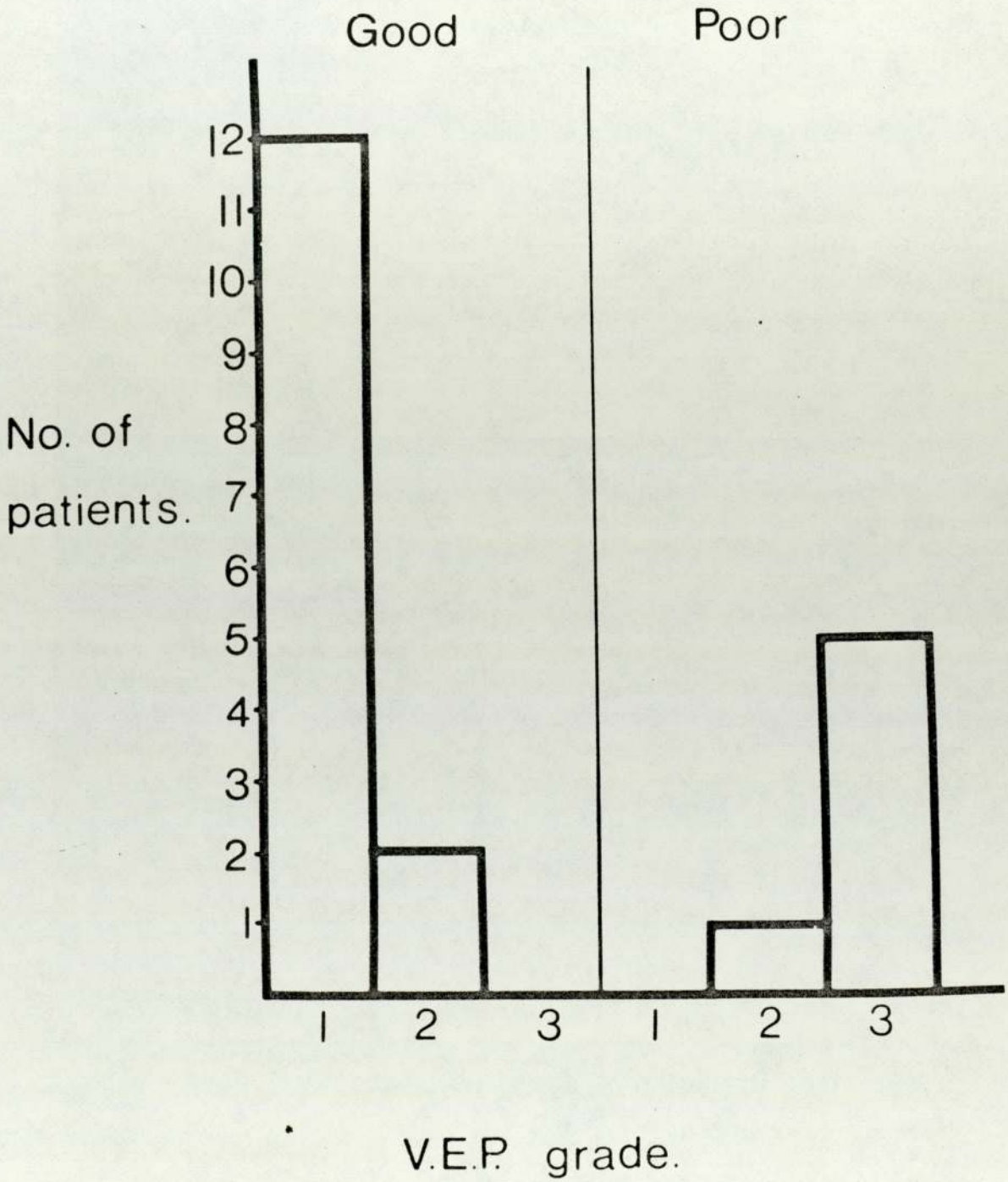
In the post-operative findings of 21 patients (see Appendix XIV for further details) 14 patients recovered good vision, that is a visual acuity of 6/12 or better. Seven patients had poor postoperative acuity which ranged from 6/36 for an amblyopic eye to perception of light after a retinal detachment. In none of these cases did the surgeon believe that the sight would improve any further. Of ten cases with a history of eye trauma, seven eyes still had good vision, while all five eyes with no history of any pathology, had normal functioning retinas. In the five eyes where there was some evidence of opthalmological abnormalities three had very poor final vision as might have been anticipated. One eye was amblyopic due to a congenital cataract, and the other two eyes with high intraocular pressure

had a detached retina and gross central choreoretinal degeneration. Perhaps surprisingly in the three very elderly patients all over the age of 78 years, the operation was a success, with good final acuity. Two eyes, which had developed opacities when the patients were young, were amblyopic with no structural abnormality. A third patient who had damaged his eye at the age of 7 years had 6/9 vision, a far better result than had been anticipated from the clinical history.

The VEP prognostic grades were compared with the final vision after surgery (see figure 67 page 291). Twelve of the fourteen patients with normal retinas had had grade 1 VEPs. The remaining two patients had grade 2 VEPs. Both were elderly, aged 78 and 87 years, and we have no knowledge of the normal findings at this age. Also as has been mentioned previously one of the patients (M.G.) had early lens opacities and macula degeneration in the other eye which produced VEPs of unusually high amplitude.

Six patients had poor postoperative vision and in five individuals this had been predicted by grade 3 VEPs produced by retinas with significant deterioration or with detachment. One of the grade 3 VEPs was recorded from the youngest patient aged ten years, who had a congenital cataract, which had resulted in an amblyopic eye with vision no better than 6/36. It was unexpected to record such an abnormal flash evoked potential with this clinical history. The one patient with poor acuity which had not been predicted by the VEP, had an early traumatic cataract at the age of 4 years, and the eye was also slightly divergent. Postoperatively the fundus was normal, and there was no technical

FIG 67. Post-operative vision.



reason why the vision was only counting fingers. It was concluded that the eye was amblyopic.

The correlation between the VEP grade and the final vision was 0.57, which was significant at the 0.01 level (Spearman rank correlation coefficient), but 14% of the prognostic results were false negative, that is the vision was better than the VEP indicated, and 16% were false positive, although all the wrong predictions were in the doubtful grade 2 category.

When the final visual outcome was known the VEP elicited through the cataract was reanalysed and compared with the various criteria for a normal or abnormal response to assess the special difficulties of stimulating a retina behind a cataract. The results are presented in Appendix XIV (page 359) and the group statistics of the amplitudes and latencies of the cataract VEP are presented in Table 24 (page 293) together with the results from the patients with senile macula degeneration.

The shorter mean latency of the cataract group probably reflected the younger mean age, whereas the larger amplitudes particularly elicited from the eyes with good vision may have been due to contamination by the alpha rhythm and the diffusing effects of the cataract.

In the patients who ultimately had good vision, 43% had more than a 33% amplitude reduction in the cataract eye, while only one patient (M.G.) had more than a 50% reduction. In all these patients the absolute amplitude of the P2 component was not significantly reduced in the eye being investigated. When the latency criteria were considered, 21% of the eyes with good

Patients	Good vision						Poor vision					
	P2 latency			P2 amp.			P2 latency			P2 amp.		
	Mean	SD	R	Mean	SD	R	Mean	SD	R	Mean	SD	R
Senile Macula Degeneration	126.4	11.1	109 - 143	6.6	4.4	1.8 - 14.3	137	13.6	111 - 162	4.5	2.8	0.9 - 10.6
Cataract Patients	123.3	10.4	110 - 150	11.2	7.7	2.4 - 29	131.5	11.6	115 - 157	4.8	2.6	2 - 10.2

TABLE 24.

The latency (m.sec.) and amplitude (μv) of the P2 component of the flash VEP in the cataract patients and patients with senile macula degeneration.

vision produced a P2 which was delayed by more than 12 m.sec. compared with the other eye, and in two from this group the P2 component was significantly delayed compared with the normal population. In no patient with a good visual outcome was the P2 component both significantly delayed and reduced in amplitude. Phase reversal to the two occiputs was the most consistent sign associated with good vision with P2 located in both occiputs in 86% of the patients while in two patients P2 was clearly located in one hemisphere.

In the patients with poor postoperative acuity, all of the VEPs were reduced by 33% or more compared with the normal eye, while in 50% of the group the VEP could be recognised as abnormal by at least one or more of the following criteria; there was a greater than 12 m.sec. relative delay, more than 50% the amplitude reduction, or a significantly small or delayed P2 component (see Appendix XIV, page 360).

Although the 33% difference between the two eyes identified all the damaged retinas, this criteria did not exclude normally functioning eyes and therefore it was decided post hoc that this was not a useful criterion, and had in fact not been relied upon to make the original VEP gradings. In the VEPs from the poor vision eyes, two out of three of the patients with greater than 50% asymmetry also had significantly low amplitude P2 components. One further patient had both a 50% difference between the eyes, and also a significantly delayed VEP from the cataract eye. Finally, one patient had an excessively delayed VEP from the cataract eye, which was greater than 30 m.sec. far beyond any

differences recorded from normally functioning retina (see figure 68 , page 296). None of these combined findings were seen in any normally functioning eye. These criteria, therefore identified two thirds of the poor vision cases and excluded all eyes with useful sight. Two patients with poor vision did not meet these criteria, one (D.E.) produced normal responses in the cataract eye, which was found to be amblyopic.

If the phase reversal results were combined with the other VEP criteria, five of the patients with poor vision (83%) failed to show clear phase reversal to either occiput. In the patient with an amblyopic eye the evoked potential was located in one occiput, thus the flash VEP failed to distinguish this eye from a normally functioning retina.

9.4. Conclusions.

It was possible that the surgeon referring the patients was pre-selecting for cataract surgery on the basis of the patients history and the accurate perception of light behind the cataract, since of the 20 patients investigated 70% had good postoperative vision. It would be interesting to see whether the flash VEP was as sensitive to abnormal retinal function in a larger group of damaged eyes.

The inherent variability of the flash VEP is significantly increased when eyes are stimulated through a dense cataract, and this in part may be due to the high voltage rhythmic alpha activity. The main difficulty is identifying the normal or degenerated eye at the extreme of the overlapping ranges of good or poor vision, either in terms of latency or amplitude.

RC 8142

Grass strobe intensity 4

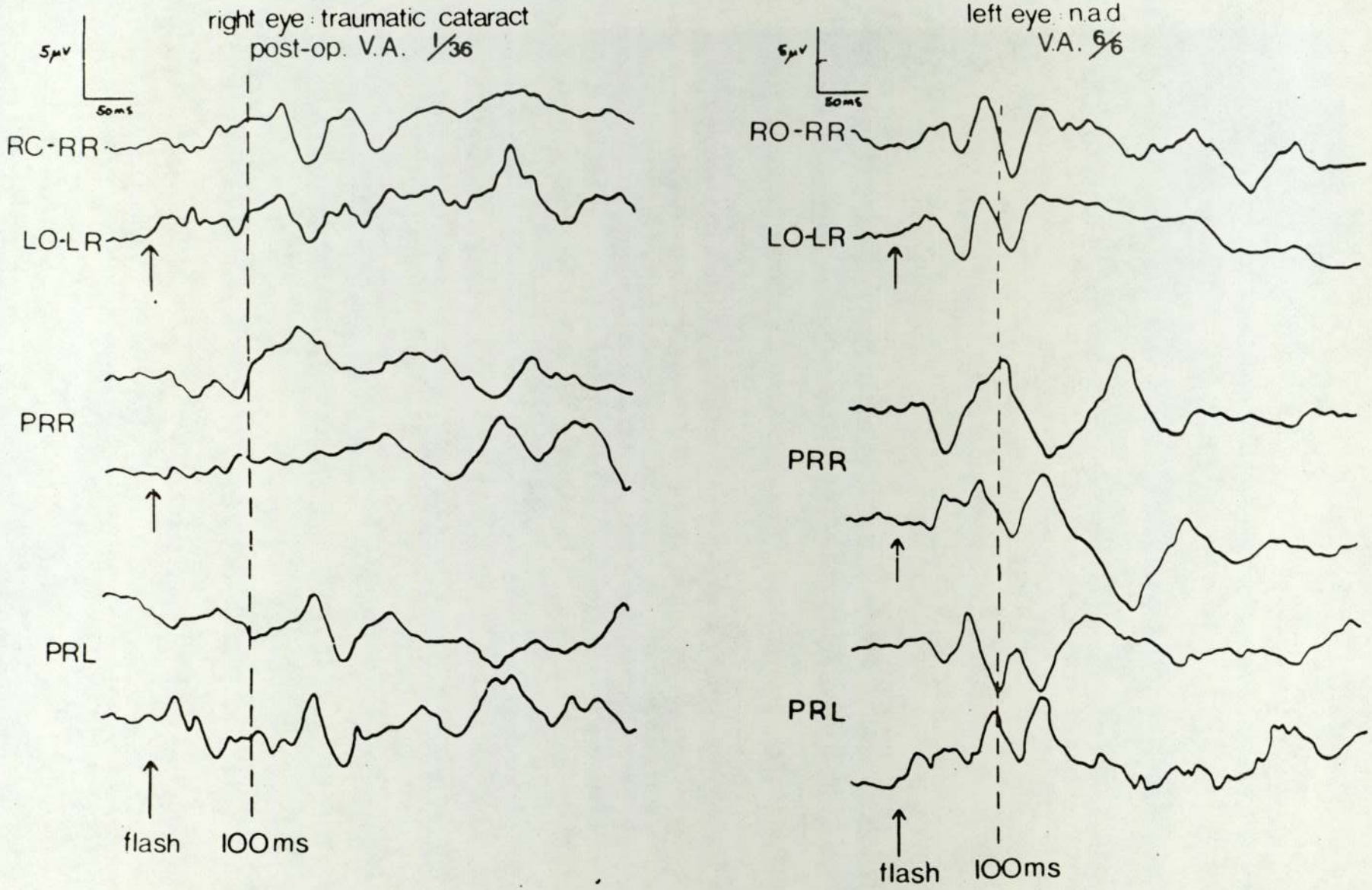


FIG. 68.

Initial concern about dense cataracts significantly reducing the effectiveness of the flash stimulus was rapidly dispelled. The effect of the cataract alone on the amplitude and latency of the VEP appeared to be minimal and could be corrected by an increase in intensity of 50%, that is from intensity 2 (68 nit secs.) to intensity 4 (96 nit secs.). An improvement in the form of the VEP relative to the noncataract eye with this increase in intensity was generally a good sign and was seen in the majority of eyes with final acuities of 6/12 or better. Figure 69 (page 298) shows the pre and postoperative visual potentials in one patient with a very dense calcified cataract, and there is very little difference in the pre and post operative evoked potentials.

Post hoc it seems that the greater the number of criteria used in assessing the VEP grade the more reliable the prognosis. The following criteria distinguished between a VEP from a normal or a degenerated retina behind a dense cataract, thus

1. A significantly reduced P2 amplitude ($< 2.5\ \mu v$) which is also reduced by more than 50% compared with the normal eye
2. A P2 wave which is reduced by more than 50% and is delayed by more than 12 m.sec. compared with the normal eye
3. A P2 component which is excessively delayed (by more than 30 m.sec.)
4. A failure to phase reverse the P2 component to either occiput

are indicative of poor post operative vision.

It seems inevitable that there will always be some VEPs which fall on the borderline of the criteria listed above. In this doubtful category, graded 2 in this experiment, it appears that

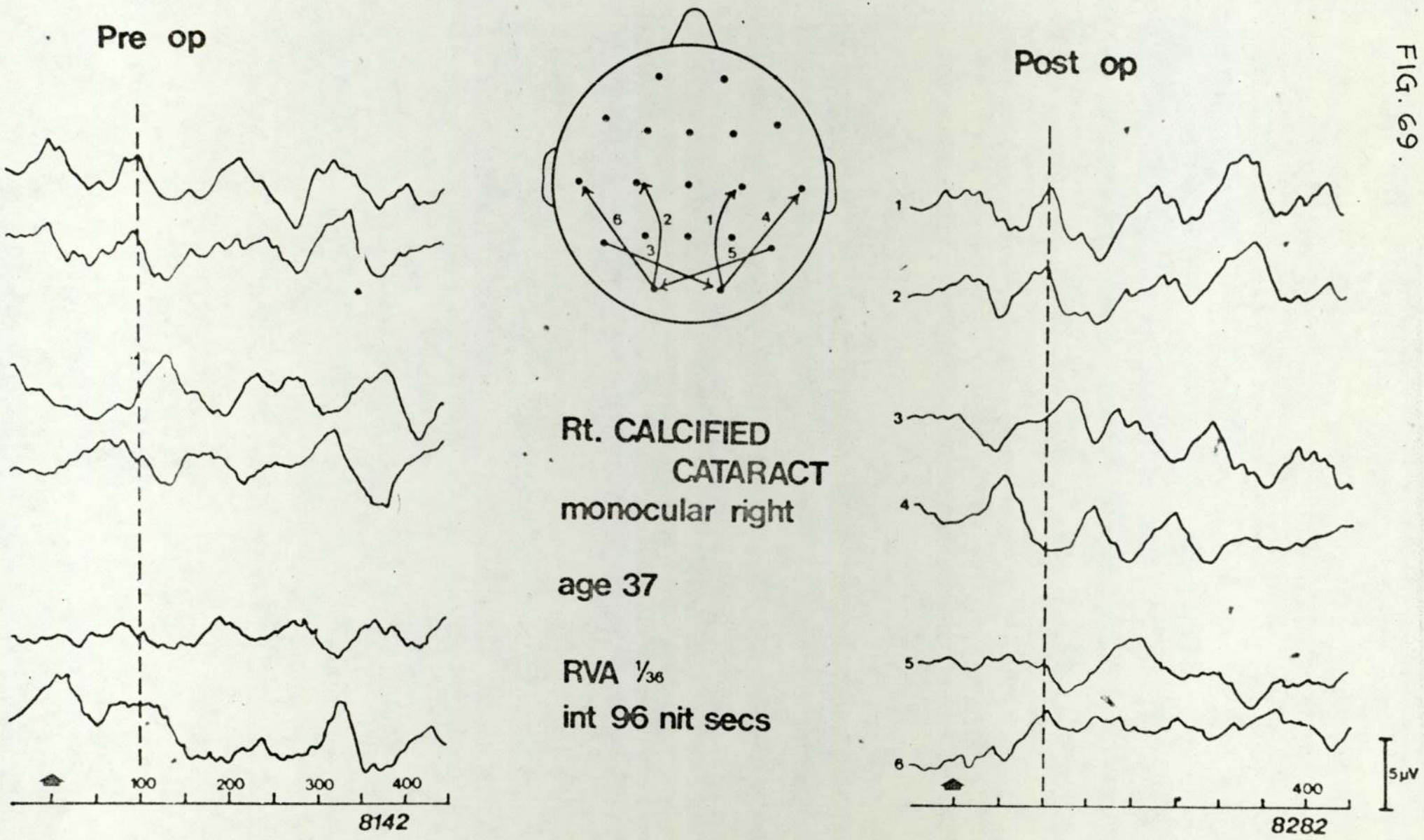

Pre op
Post op
Rt. CALCIFIED CATARACT
monocular right
age 37
RVA 1/36
int 96 nit secs
100
200
300
400
8142
400
8282
5μV
1
2
3
4
5
6

FIG. 69.

vision may either be normal or reduced and varying between 6/24 and 6/60. No patient with very poor vision produced a VEP that fell within this category.

Finally not unexpectedly, the flash evoked potential was not useful in predicting postoperative visual acuity if the patient's history suggested the possibility of amblyopia, especially in the presence of strabismus. With this reservation it appears that the flash evoked potential can provide a useful prognosis for the vision of quiet eyes behind opaque media.

9.4. The predictive value of the flash VEP in patients with severe eye injuries.

From the prospective study of the flash VEP in patients with dense cataracts it was clear that this test provided a useful prognosis of postoperative vision (Thompson and Harding, 1978). The ERG is also useful in evaluating postoperative visual function in eyes with opacities of the media (Karpe and Vainio-Mattila, 1951; Burian and Burns, 1966; Tassey, Jayle and Graveline, 1968; Jayle and Tassey, 1970; Kennerdell, 1973) although Jayle and Tassey found that simulation of the diffusing effects of hyphaema reduced a normal ERG by 20 to 80% and suggested therefore that only gross abnormalities in the ERG should be regarded as significant. A previous study of several electro-diagnostic measures (Crews, Hillman and Thompson, 1975) had confirmed that such tests would have prognostic value in major trauma.

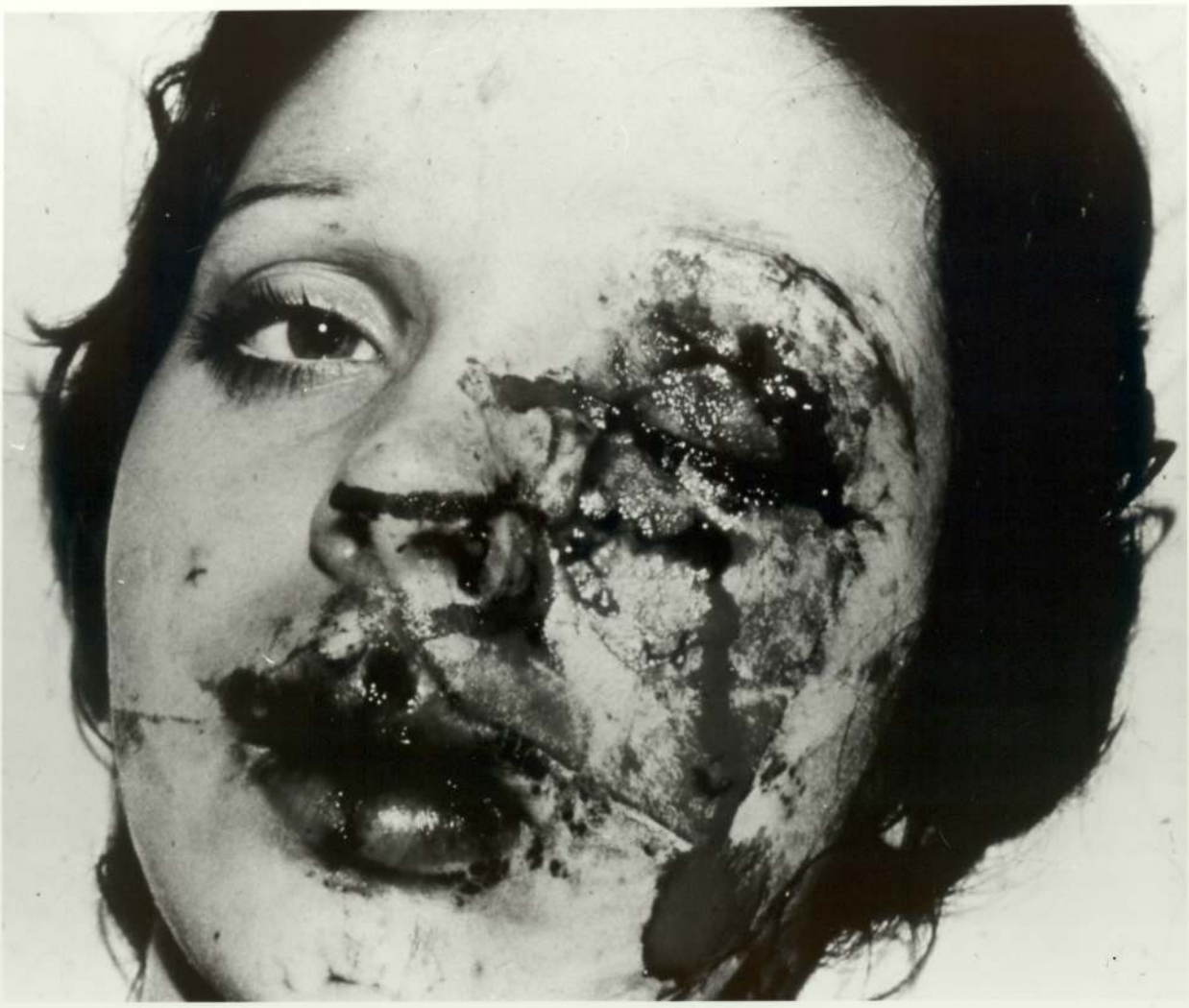
In severe eye injuries a decision has to be made within one or two weeks as to whether the eye can be retained. The visual

potential of the eye has to be weighed against the risks of sympathetic opthalmia and the chances of a painful blind eye. The decision is one of the most difficult in opthalmology, and opinions are often divided about any one patient. With the tremendous advances in ophthalmic surgery in the past decade, there is an increasing trend towards the retention of seriously injured eyes with the possibility of a long period of reconstructive surgery after the initial eye repair.

The author collaborated with Mr. James Crews, an eye surgeon, and his technical staff at the Birmingham and Midland Eye Hospital in conducting a prospective study of severe perforating and contusive injuries in 64 eyes of 60 patients. Electro-physiological measurements were performed within a fortnight of hospital admission, and all eyes had significant opacities of the media, so that no accurate measurement of visual acuity could be made using direct or indirect opthalmic microscopy (see Figure 70, page 301). Hyphaema was the commonest problem with cataracts another important cause of unsatisfactory opthalmoscopy. All these were acute cases where the disturbance of the retina from the concusive effects of the trauma, and the retino-toxic effects of vitreous haemorrhages was severe and resolving rapidly. Therefore, in clinical terms these eyes presented a very different picture from the quiet eyes behind longstanding or slowly evolving cataracts.

Skin ERGs were performed to avoid any possibility of further damage to the eye. The active electrodes were placed midway along each lower lid and referred to electrodes on the outer canthii.

FIG. 70



The flash evoked potential was recorded from the standard scalp positions O1 to C3 and O2 to C4. As in all the previously mentioned experiments a Grass stroboscope was used and the full intensity range was employed (intensity 2 to 16, 68 to 483 nit secs.). A few patients were stimulated with a Devices stroboscope which had a more limited range of intensities which corresponded to approximately intensity 2 and 4 of the Grass stroboscope. This clinical investigation differed from the previous ones in that it was performed at the Birmingham and Midland Eye Hospital by the technicians of the Retinal Department, Mr. P. Good and Mr. R. Carter. The VEP and ERG were amplified using two AA6 Mark II Medelec amplifiers with a bandpass of 0.8 to 100Hz and gains of 50 μv/cm., and averaged using a Medelec special purpose computer. The method of stimulation was the standard one and the sample length and number of visual potentials summated to obtain each averaged VEP was also standard. Because the other electro-diagnostic tests were performed on each patient, and also as each investigation could not take long in unwell patients, there was not sufficient time to record the full Aston Montage and phase reversal to the left and right occipital electrodes was not recorded. However, it was anticipated that the information that was lost by this would be compensated by the information of the ERG.

The patients had a wide age range, from 4 to 81 years, although the majority were in their 20's and 30's and the mean age for the group was 30.4 years. Males predominated and the highest number of accidents were surprisingly domestic, although there

were also many industrial and road traffic accident cases.

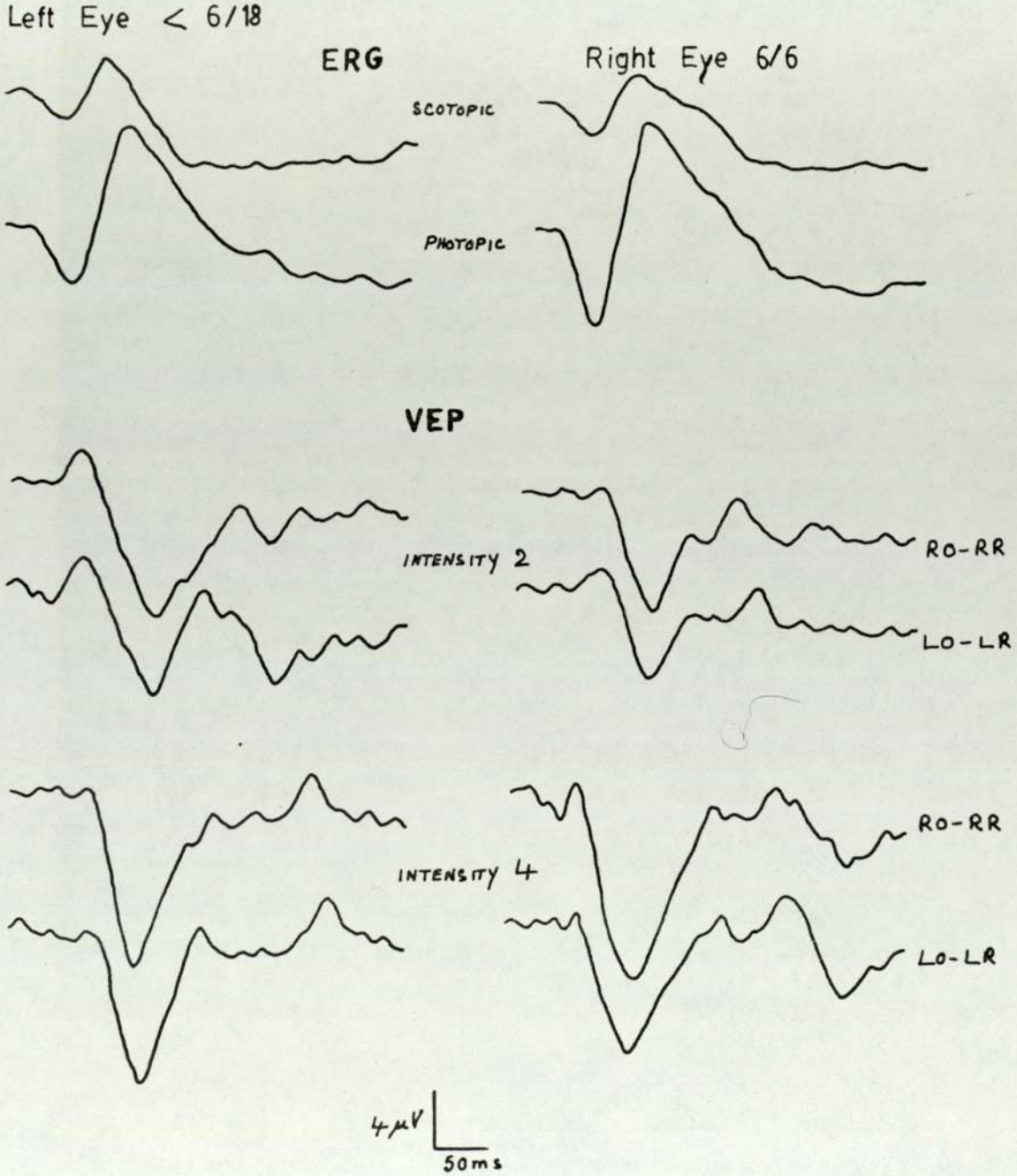
9.5. The Hyphaema control group.

Because of the severity of the eye injuries and the unknown effects of hyphaema upon the VEP, cortical responses were recorded in 39 patients with unilateral blunt eye injuries using exactly the same procedures as for the major trauma patients. In blunt injuries the major problem was hyphaema although a few patients had commotio retina with oedema and intraretinal or vitreal haemorrhages (Eagling, 1974). In all cases visual assessment was possible shortly after the injury and all but one eye recovered, 92% retaining an acuity of 6/4 to 6/18. The VEP was only analysed in those patients who recovered good visual acuity (6/18 to 6/4). It was satisfactory to note that the VEP was clearly seen in all cases, and even in a patient with damage extending into the posterior segment and involving the retina, a flash VEP was still consistently and reliably evoked (see figure 71 , page 304). There was no significant difference in either the latencies or the amplitudes of the N2, P2, N3 complex of the injured eye compared with the uneffected eye (see table 25, page 305), although there was tendency for longer latencies and lower amplitudes to be recorded in an eye with hyphaema. It was not entirely appropriate to compare these patients results with those of the young normal population since although the mean age of the patients was 21.3 years, there was an age range from 6 years to over 70 years with about half the group under 20 years of age. The results were therefore compared with the total normal population investigated in the university laboratories.

FIG. 71.

THE FLASH VEP & ERG IN BLUNT EYE INJURIES.

DB aet 10yrs. Blunt eye injury 24hrs previously to the Left eye. Moderate hyphaema and commotio retina. Grass' flash stimulation.



		Normal population			Hyphaema Patients					
		Monocular VEP			Good eye			Damaged eye		
Components		N2	P2	N3	N2	P2	N3	N2	P2	N3
Latency (m.sec.)	Mean	88.4	116	163	69.6	117.6	185.6	70.4	118.2	188.1
	S.D.	9.1	10.4	16.4	12.2	11.8	23.5	13.1	14.5	26.1
	Range	75-109	95-144	135-220	45-90	95-190	136-270	40-90	90-150	145-250
Amplitude (μv)	Mean	3.4	9.3	9.1	2.9	7.1	11.2	2.5	7.2	9.5
	S.D.	3.9	4.4	5.4	2.4	4.4	8.3	2.8	4.9	4.9
	Range	.4-9.7	2.4-36	2.5-23.9	.4-1.0	3.0-15.0	2.5-36	0.2-8.0	2.5-18.0	2.4-21.0

TABLE 25.

The amplitude and latencies of the major components of the flash VEP in patients with blunt eye injuries compared with a normal population.

The most significant differences that were found were in the variability (F ratio) of the cortical responses, with larger variations occurring in the amplitude of the N2 and P2 components in the damaged eye, and the N2 amplitude in the other eye of the patient group (p:0.002). Similarly the N3 component had a more variable latency for both eyes in the patient group. The N2 component was suprisingly earlier in the hyphaema eyes, this may have been due to problems of identification, and N3 was significantly delayed (p:0.002) compared with the normal population. Therefore again it appeared that the latency and amplitude of the P2 component was the most useful sign of visual acuity and less effected by other clinical changes.

From the hyphaema control group, and from the criteria developed for the normal population and for the patients with known visual defects, the flash VEPs recorded in the major trauma series were graded according to the following criteria.

Grade 1 Prognostic of good function	Within the normal criteria of the VEP and with less than 12 m.sec. difference in the response from the two eyes.
Grade 2 Prognostic of useful function	Up to a 50% reduction in amplitude compared with the other eye, or within two standard deviations of the hyphaema patients. Two standard deviations represented a delay of 30 m.sec. (which is equivalent to three standard deviations of the total normal population) that is absolute latency of the P2 component of 148 m.sec.

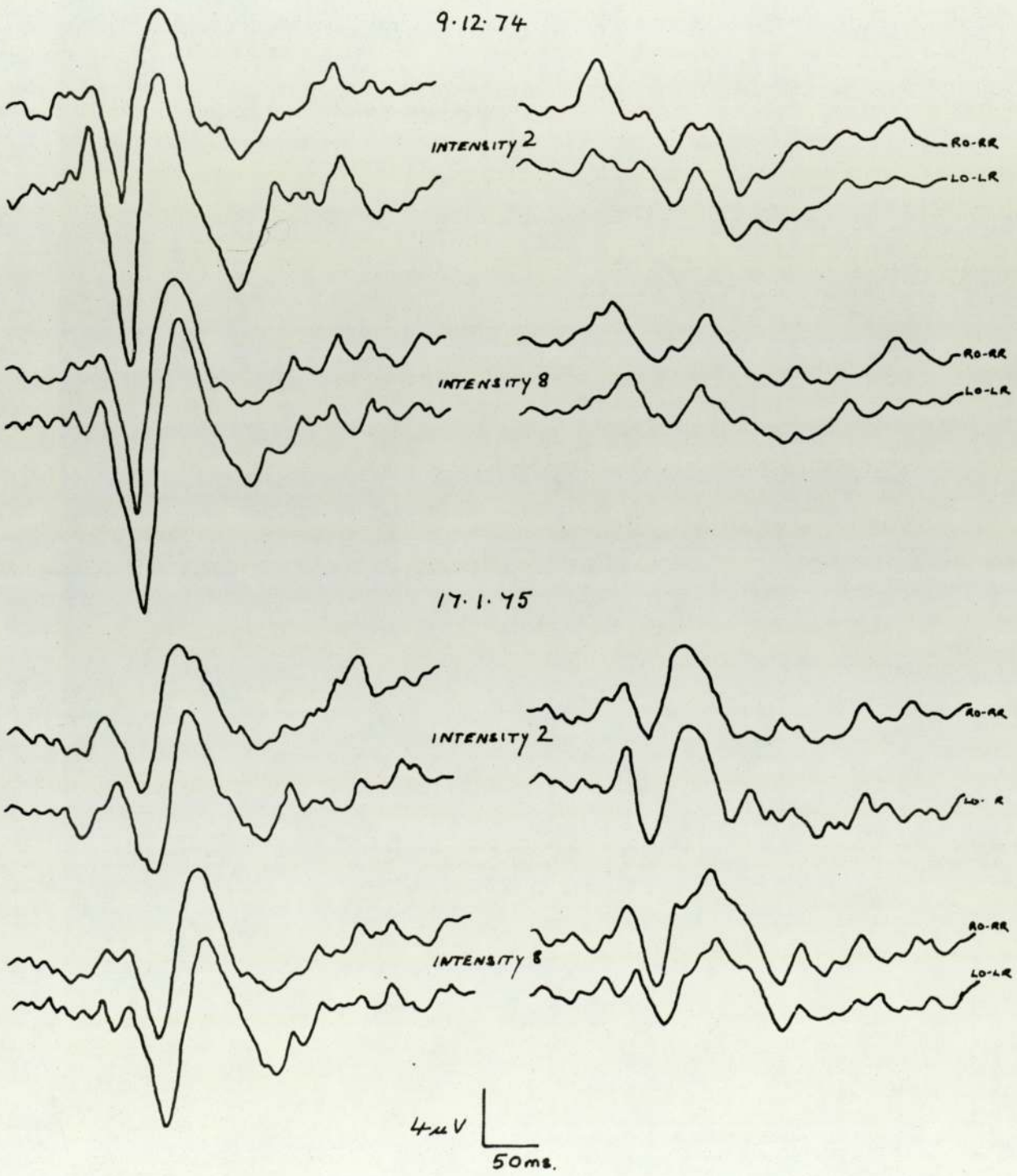
Grade 3 prognostic of poor function	More than 30 m.sec delay compared with the hyphaema group, and more than 50% reduction in amplitude or an absolute amplitude of less than 2.5 μv (the 0.05 probability level of the normal group, which excluded all the hyphaema patients).
Grade 4 prognostic of no visual function	No or a minimal response (< 1.5 μv).

9.6. The results of the major trauma series.

The flash VEP was assessed by the author prior to the operation, and was later rated independently by a second observer who had no information concerning the clinical history, other electrodiagnostic findings or the postoperative outcome. There were no significant differences between the two gradings for each VEP (Wilcoxon matched pairs test). Although 20% of the patients had two different ratings, in the majority this was only a disagreement within the prognosis of good vision (that is a Grade 1 or 2) or prediction of poor function (that is a grade 3 or 4). In four patients the difference was greater than this. One case concerned an optic nerve avulsion which the author had graded with an early VEP recording which appears in this condition to provide misleading information as will be discussed later. A second case involved a young girl with bilateral eye damage and 'supernormal' responses from one eye (see figure 72 page 308), a case which seems bound to remain equivocal.

FIG72. THE FLASH VEP IN MAJOR OCULAR TRAUMA

AS. 26yrs. Bilateral penetrating injuries. Grass flash stimulation



The ERG was also graded from 1 to 4 by the staff of the Retinal Department at the Birmingham and Midland Eye Hospital according to the b wave amplitude of the response compared with the other eye, or compared to the mean normal eye when both eyes were damaged. Best predictions were obtained from the scotopic ERG. The criteria were similar to those proposed by Kennerdel (1973) which had been validated by an earlier assessment of a smaller group of patients (Crews,Hillman and Thompson, 1975). Grade 1 and 2 had amplitudes between 100 and 50% of the fellow eye, prognostic of some useful function remaining. Grade 3 was a reduction of more than 50% indicative of significant retinal damage, while Grade 4 was an absent or minimal response.

The electrodiagnostic findings were compared with the best visual outcome. The followup of the patients varied between six months and four years, the majority being longer than eighteen months. In most patients the final visual outcome was equivalent to their best vision, but in a few cases the final vision had not yet been resolved or in four eyes there was a subsequent deterioration of vision, three of these being due to the complications of later surgery. The best visual outcome was also graded between 1 and 4:

Grade 1a	6/6 - 6/12
Grade 1b	6/18 - 6/60
Grade 2	less than 6/60 with accurate projection (eyes with opacities still present).
Grade 3	inaccurate projection.
Grade 4	no perception of light.

The last category included enucleated eyes both with the retina detached (R.D.) and retina in situ (R.S.).

When the ERG prognostic gradings were compared with the final visual outcome (figure 73 , page 311), the correlation was 0.75 (significant at the .001 level - Spearman Rank correlation), the skin ERG thus provided a reliable indication of the visual potential of the damaged eyes. Seventy-three percent of the ERG grades 1 and 2 achieved useful vision. Of those eyes with good ERG's but poor visual outcome, two were centrally blind, the remaining eyes were in situ with possible visual potential. In the ERG grades 3 and 4 a few achieved useful vision, the majority were blind.

As was apparent with the VEP results from the hyphaema patients, the VEPs in this group were more variable than in a normal population even when the undamaged eye was stimulated. Since we were investigating acute clinical cases shortly after a serious accident which inevitably involved psychological trauma, head injuries and other physical injuries it was likely that the background EEG was far from normal, although unfortunately it could not be monitored at the time. A repeat investigation if possible is useful (see figure 74 page 312) and can improve the reliability of electrodiagnosis in a rapidly changing clinical situation. This was particularly so in optic nerve avulsion where in both of the cases is this series early recordings showed a consistent delayed VEP of rather low amplitude and with a P2 component of particularly long duration. (see figures 75 and 76 , pages 313 and 314). In subsequent recordings the cortical response

FIG. 73.

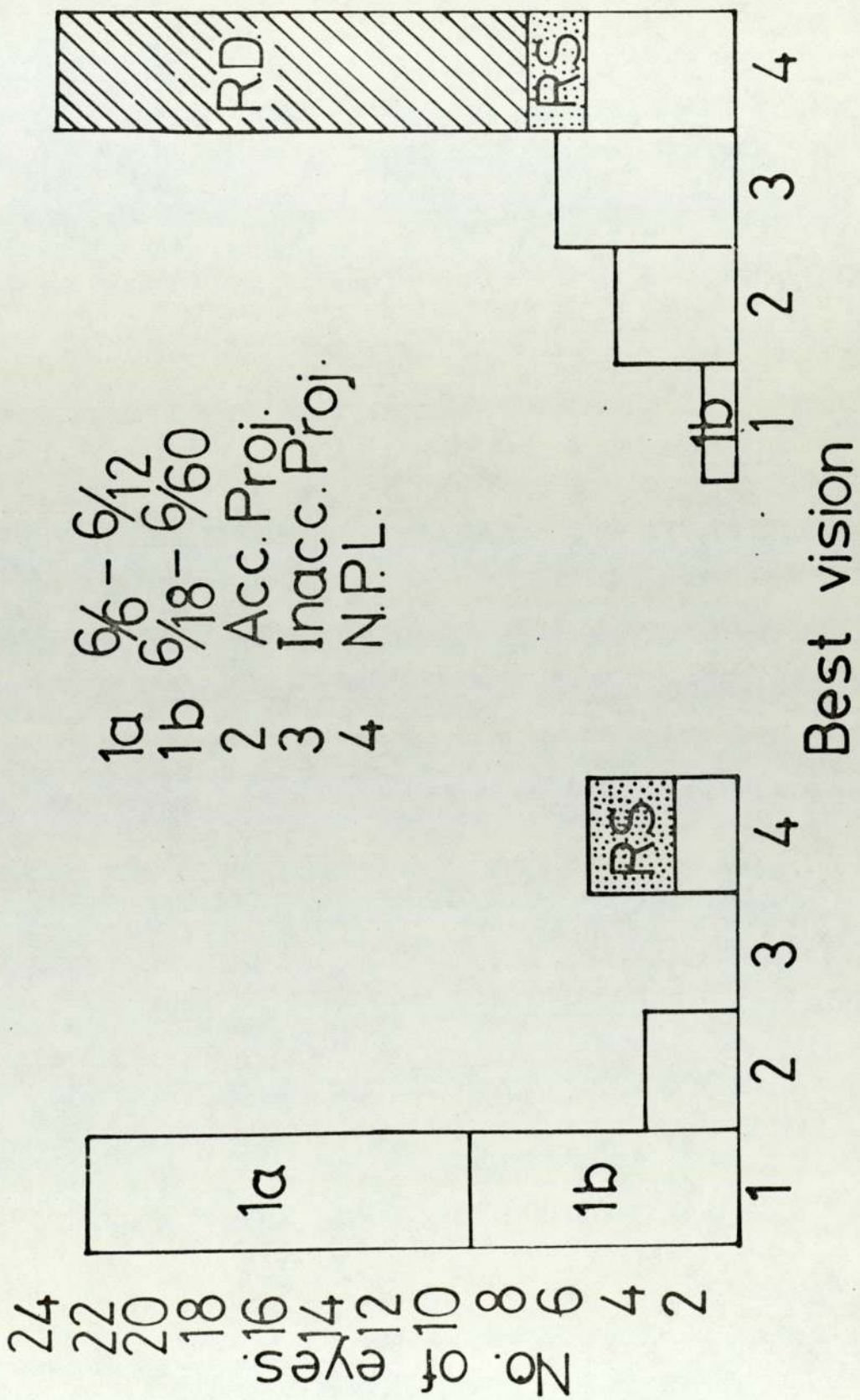

E, R. G..
Grades 1 + 2
Grades 3 + 4
1a 6/6 – 6/12
1b 6/18 – 6/60
2 Acc. Proj.
3 Inacc. Proj.
4 N.P.L.
No. of eyes.
24
22
20
18
16
14
12
10
8
6
4
2
1a
1b
R.D.
R.S.
1
2
3
4
Best vision

FIG. 74.

MAJOR TRAUMA

G.S. aet 25 years
Right perforation ?PL→6/18
Date of injury 9.1.74

V.E.P.

Devices stimulation

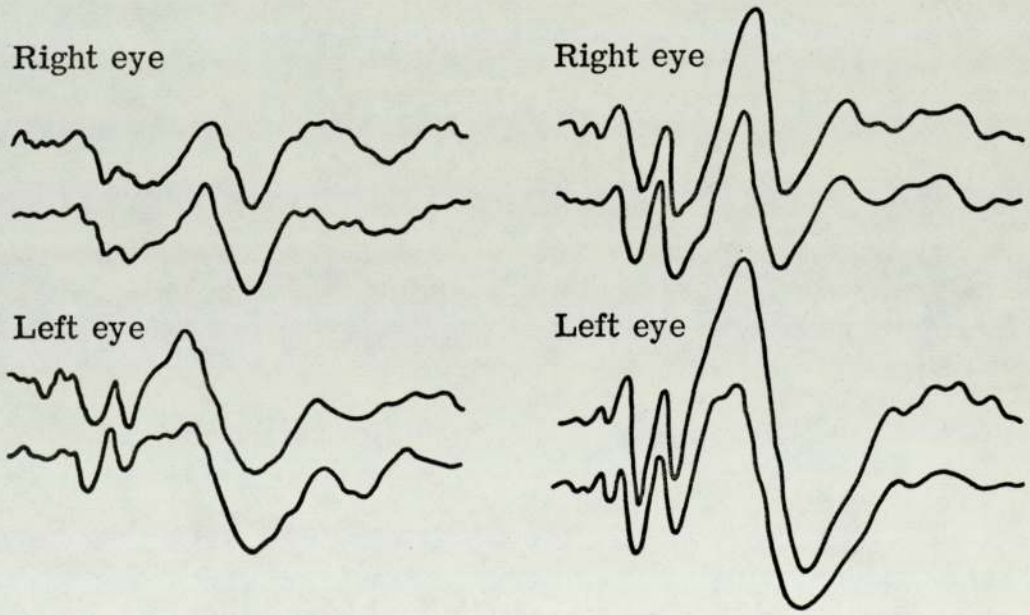
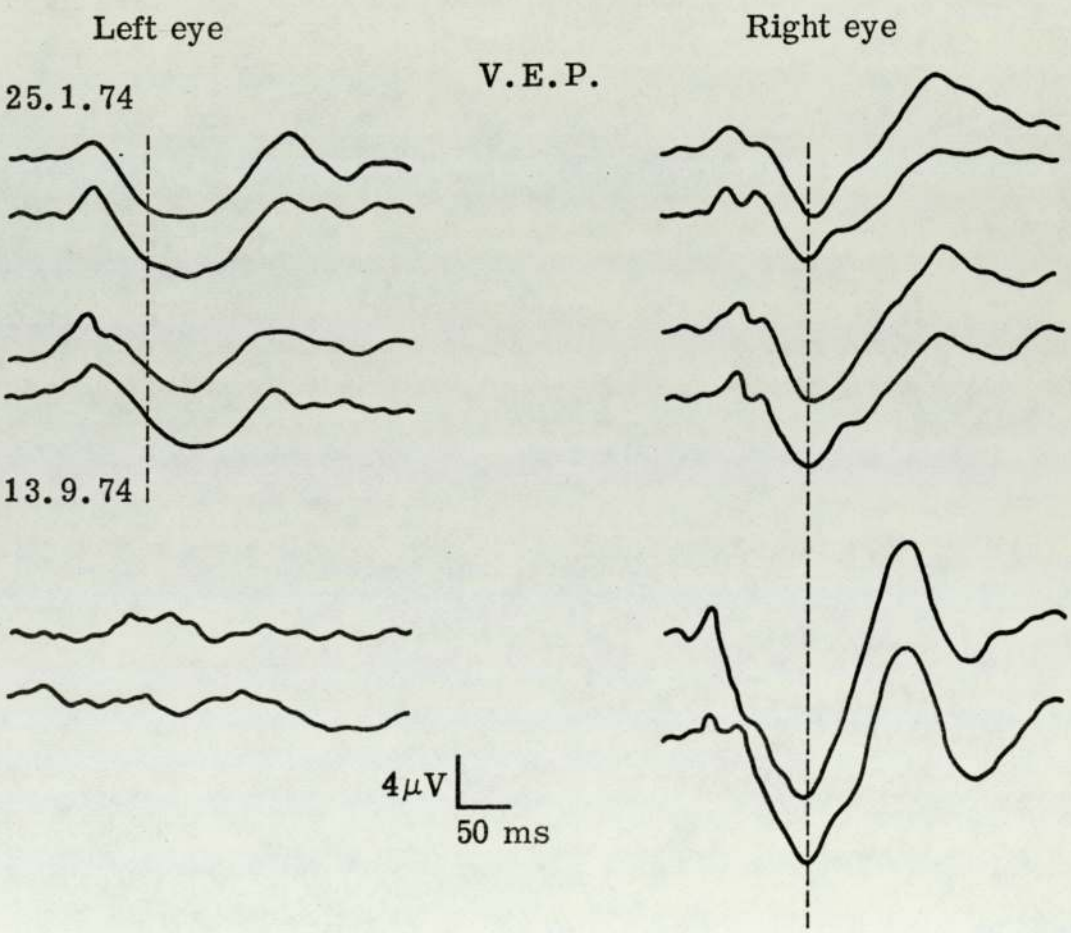


FIG. 75.

MAJOR TRAUMA

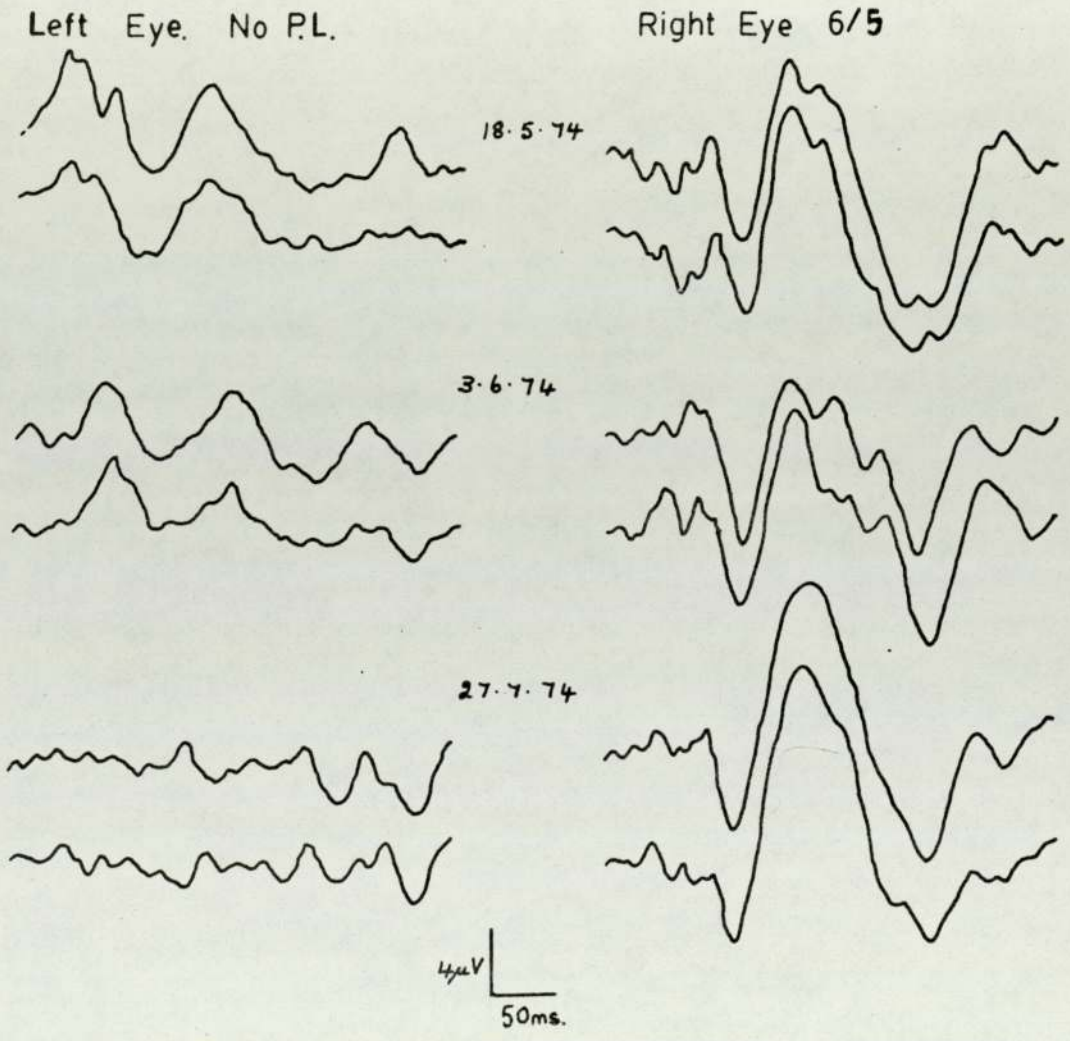
D.W. aet 7 years
Air pellet in left eye 20.1.74
E.R.G. GRADE 4.
Devices flash stimulation



OPTIC NERVE AVULSION

FIG 76. MAJOR TRAUMA

MJ aet 26yrs
RTA Left optic nerve
avulsion, Grass Stimulation.
Intensity 4.



OPTIC NERVE AVULSION

was entirely extinguished and did not return. It was interesting to monitor this slow change which occurred over several weeks, although the underlying pathophysiological events are not understood.

Figure 77 shows the relation between the VEP grades and the best vision of each patient. When the VEP prognosis was compared with the final acuity the correlation was high (.72) which was significant at the 0.001 level. Sixty seven per cent of VEP grades 1 and 2 achieved useful vision, all the remaining eyes were enucleated and the retina were in situ. Such a case is seen in figure 78 (page 317) where a clear VEP and ERG was elicited from the injured eye, although the eye was removed later and the retina was in situ. The majority of eyes with grade 3 and 4 visual potentials went blind or were enucleated. One eye graded 3, with a good final visual outcome, had severe commotio retina, which may have temporarily reduced the VEP.

The flash VEPs were also analysed in relation to the final visual outcome of each eye, which in most cases corresponded closely with the original VEP grading. The results are presented in table 26 (page 318), together with the hyphaema control group. It can be seen that in this series no VEP from eyes with good vision was less than 3.5 μv and the greatest delay recorded was a P2 latency of 140 m.sec., results which remain within two standard deviations of the hyphaema patients. As expected the flash VEP could not reliably differentiate between the visual grades 1a and 1b, that is the flash VEP could not predict whether an eye still had 6/6 to 6/12 vision, or whether

V. E. P.

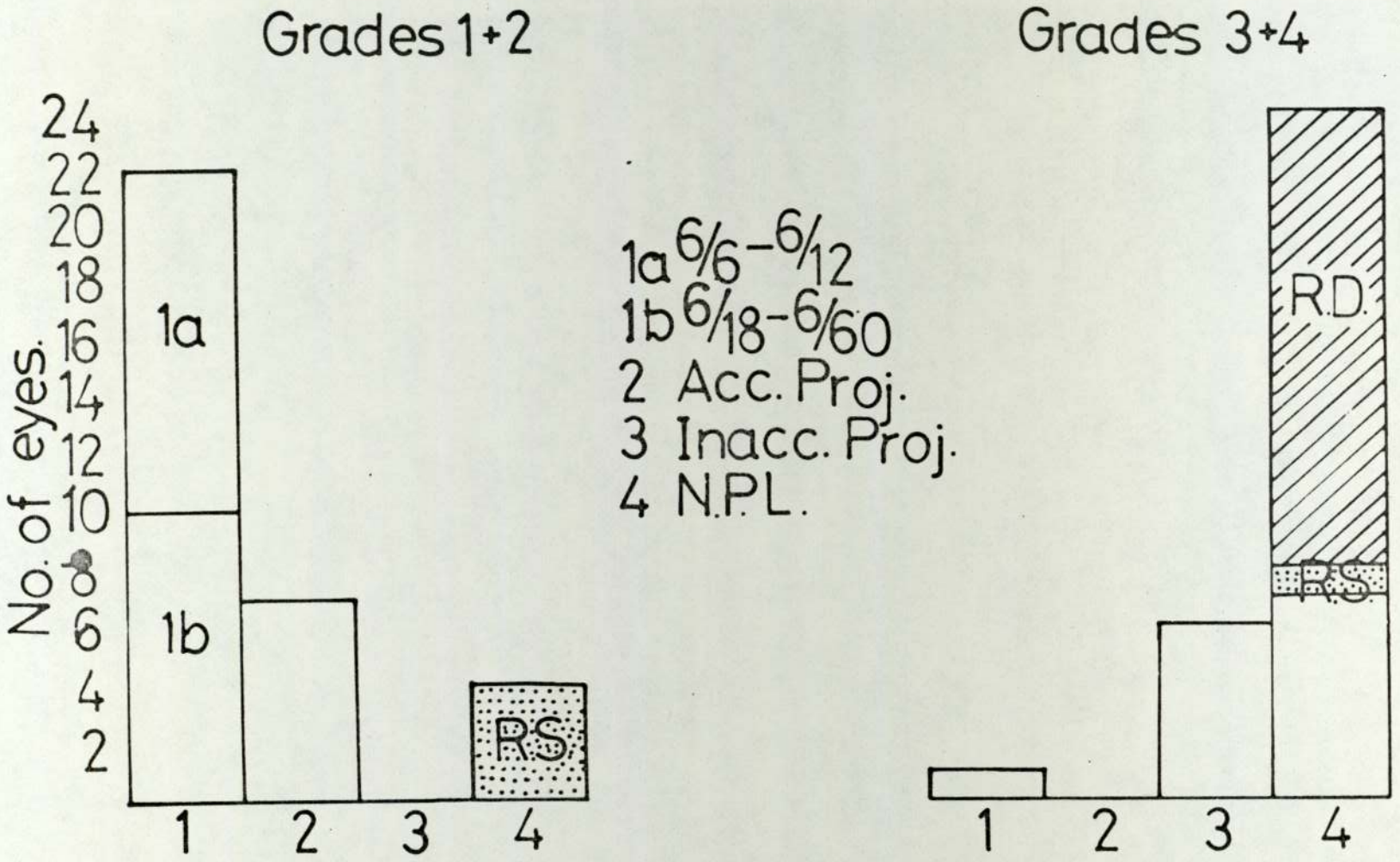
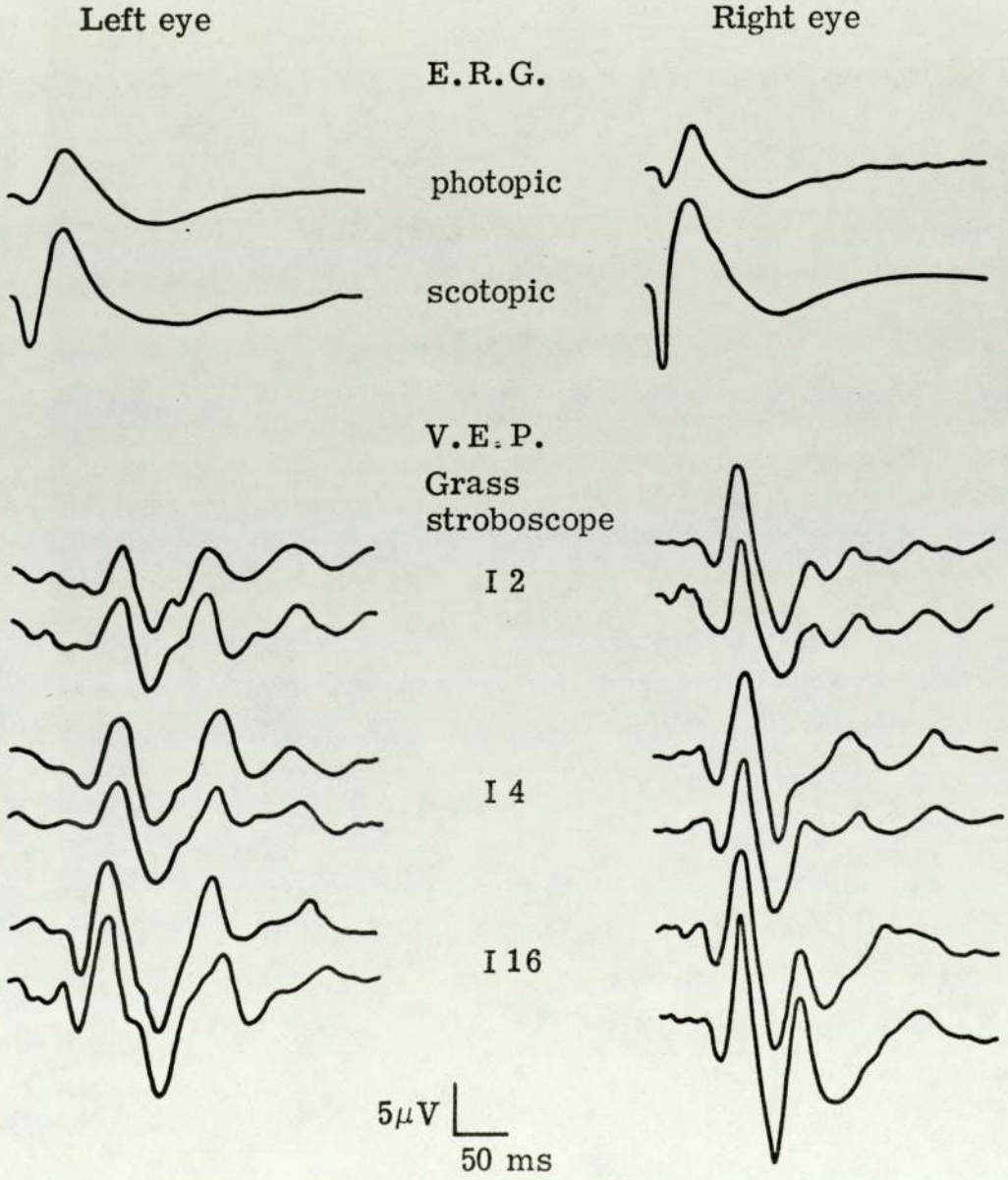

Grades 1+2
Grades 3+4
No. of eyes.
24
22
20
18
16
14
12
10
8
6
4
2
1a
1b
RS
R.D.
1a 6/6 - 6/12
1b 6/18 - 6/60
2 Acc. Proj.
3 Inacc. Proj.
4 N.P.L.
1
2
3
4
Best vision

FIG. 78.

MAJOR TRAUMA

G.P. aet 41 years
Left perforation & exit wound.
Eye enucleated, retina in situ.



	Latency (msec)			Amplitude (μv)		
Patients	Mean	SD	Range	Mean	SD	Range
Hyphaema	118	14.5	90-150	7.2	4.9	2.5-18
la	112		100-140	8.2		4-12
lb	120		100-136	6.8		3.5-11
MTS Grade 2	124		115-130	6.5		3.5-9
3	145		120-185	2.8		1-8
4	151		120-170	2.0		.75-6

TABLE 26.

The latencies (m.sec.) and amplitudes (μv) of the P2 component in the hyphaema control group and in each of the visual gradings of the major trauma patients.

	FINAL VISUAL OUTCOME GRADING					
		1a 6/6 - 6/12	1b 6/18 - 6/60	2 6/60	3 inaccurate projection	4 no perception of light
FLASH VEP GRADING	1	8	7	3	0	1
	2	5	4	4	0	4
	3	0	0	0	3	6
	4	0	0	0	3	16

TABLE 27.

The relation between the VEP gradings and the final visual outcome, showing the number of major trauma patients within each of the four VEP and final vision gradings.

there was some reduction in acuity to between 6/18 to 6/60 (see table 27 page 319). The grade 2 visual category of less than 6/60 vision could also not be reliably predicted since again a similar number of patients had either grade 1 or grade 2 preoperative flash VEPs. There was a great deal of overlap between the latency and amplitude variations within each category, and a decision concerning each VEP grading was always made on both the amplitude and the latency and also the consistency of the cortical response throughout the recording.

When the ERG and VEP gradings were compared (see Table 28 , page 320), there were no significant differences in their predictions within any of the four final visual outcomes. That is in the majority of cases the ERG and VEP results agreed that the visual outcome would be good or poor. In a few cases there was a discrepancy between the two electrodiagnostic predictions which could be explained by individual case histories.

		VEP Grading			
		1	2	3	4
ERG Grading	1	15	11	0	0
	2	2	1	0	1
	3	2	3	1	1
	4	0	2	8	17

TABLE 28.

The relation between the ERG and VEP gradings showing the number of major trauma patients within each of the four VEP and ERG gradings.

One patient had been in a road traffic accident five days previously, with a perforation of the left eye. The ERG was graded 4, although this improved later to grade 2, the VEP was well formed and graded 2. The eye had to be enucleated and the retina was in situ, but the structure was disturbed with apparent separation of the receptors from the outer membrane, a factor which may have selectively effected only the ERG. In a second case the right eye was enucleated after a firework blunt injury. The ERG had been graded 1, but the VEP was grade 3, a poor prognosis. The retina was in situ, but there was traumatic damage localized in the macula area with a normal peripheral retina. A third case is illustrated in figure 79 (page 322). A 26 year old patient had a right penetrating wound. On examination both the photopic and scotopic ERGs were normal, but the VEP gave a poor prognosis. Later examination revealed a small scar close to the macula region and an intraocular foriegn body embedded in the right optic nerve. There was no perception of light. A final case was a young boy of 4 years who had fallen from a window and suffered multiple injuries (see figure 80 page 323). He had been admitted into an intensive care unit and his vision was clinically in doubt. While the ERG recorded from each eye was graded 2, no cortical response could be detected at any flash intensity which would be consistent with cortical blindness or optic nerve damage subsequent to extensive skull fractures. His discs and fundii showed some generalised atrophy.

FIG. 79.

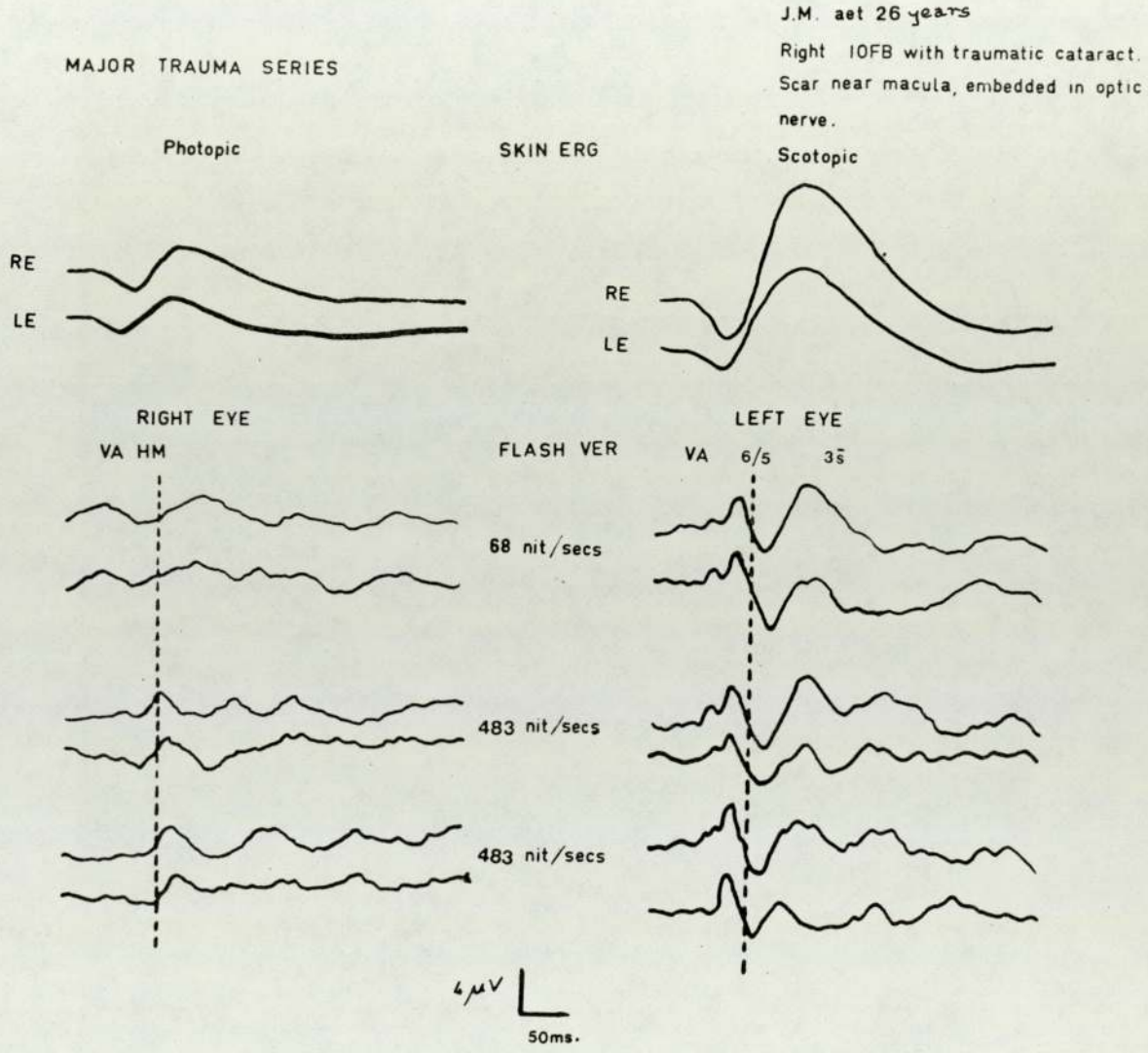

J.M. aet 26 years
Right IOFB with traumatic cataract.
Scar near macula, embedded in optic nerve.
MAJOR TRAUMA SERIES
Photopic
SKIN ERG
Scotopic
RE
LE
RE
LE
RIGHT EYE
VA HM
FLASH VER
LEFT EYE
VA 6/5 3s
68 nit/secs
483 nit/secs
483 nit/secs
4μV
50ms.

FIG. 80

MAJOR TRAUMA

S.D. aet 2 years
Fell from window & fractured skull

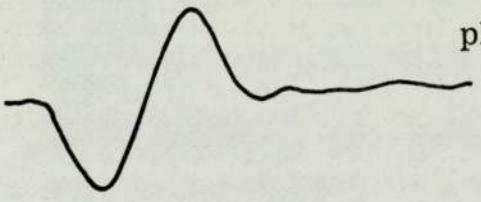
V.E.P. GRADE 4

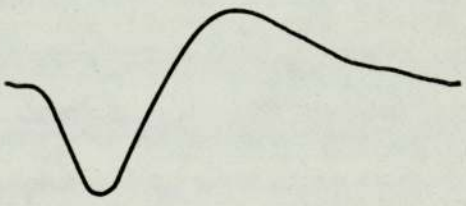
E.R.G.

Left eye

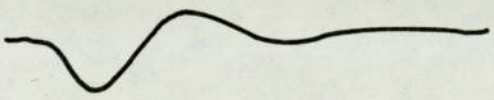
Right eye

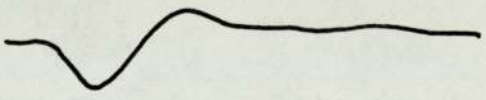
photopic





scotopic





CENTRAL DAMAGE

9.7. Conclusions.

It is clear that the ERG and VEP can produce accurate assessments of the extent of eye damage, although each method may fail to detect certain types of pathology. The ERG assesses the integrity of the whole of retinal function with the amplitude of the b wave being directly proportional to the area of detachment or damage (Black and Behrman, 1967). The ERG fails to detect local central retinal pathology or optic nerve and brain damage. The VEP does not detect peripheral retinal damage and because of EEG contamination is subject to far greater variability than the ERG, but is useful in assessing central visual function.

When added together as a simple additive combined score however, the failings of either method are largely compensated for by the other measure with the result that the combined gradings give a better indication of the extent of damage, and provide a more reliable visual prognosis. In figure 81 (page 325) it can be seen that a combined electrodiagnostic score of from 2 to 4, that is both measures having a good prognosis, 90% of the eyes with this grading did recover or have potentially useful sight. The remaining eyes within this group were enucleated, but the retinas were in situ with the possibility of visual potential. Of those eyes with a combined score from 5 to 8, that is one or both measures clearly predicting a poor visual outcome, 91% had no perception of light or inaccurate light projection. In the remaining eyes the visual outcome is still uncertain.

There had been some concern at the beginning of the research

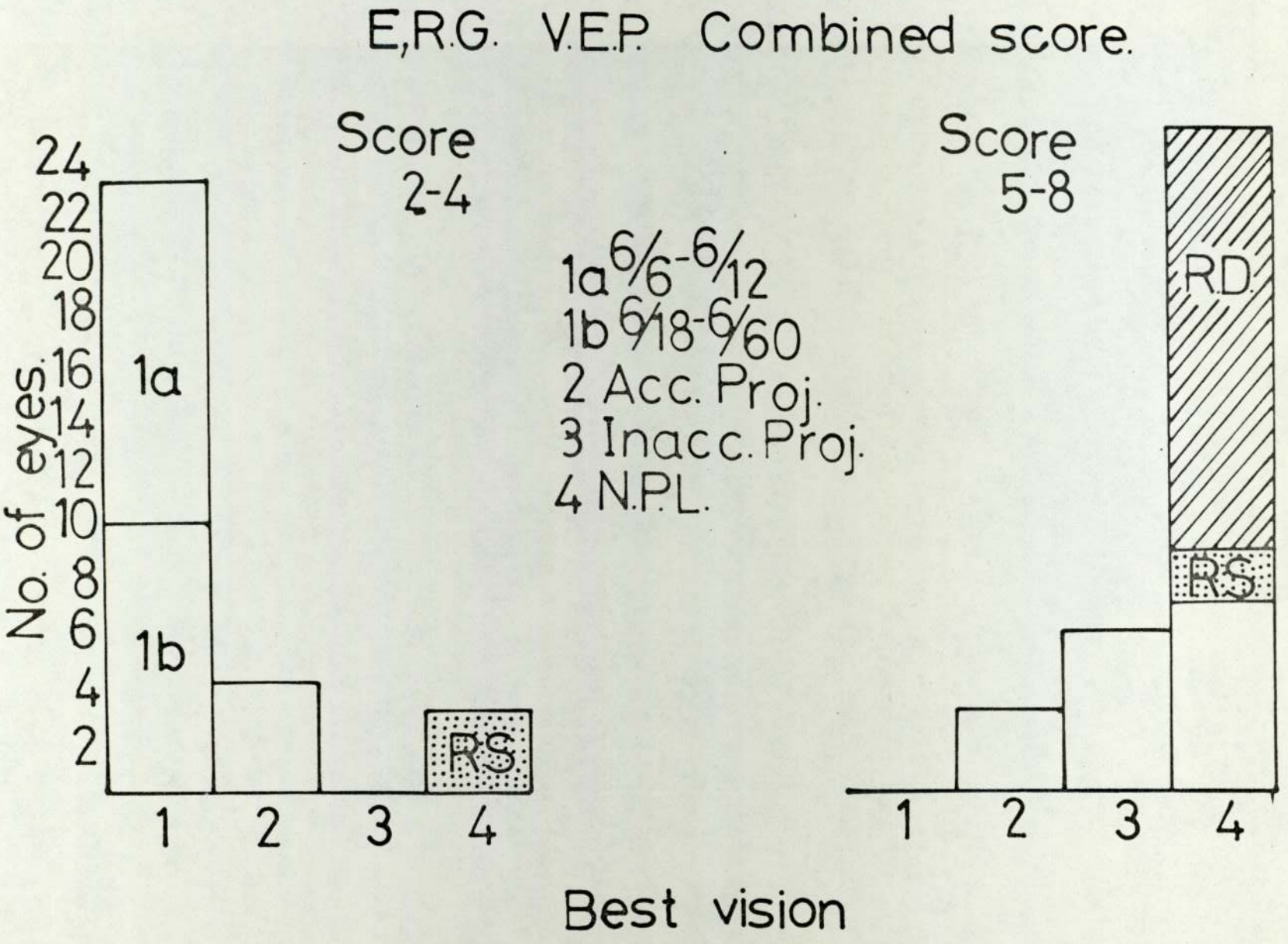

E,R.G. V.E.P. Combined score.
Score 2-4
Score 5-8
No. of eyes.
24
22
20
18
16
14
12
10
8
6
4
2
1a
1b
RS
R.D.
1a 6/6-6/12
1b 6/18-6/60
2 Acc. Proj.
3 Inacc. Proj.
4 N.P.L.
1
2
3
4
Best vision

FIG. 81.

programme as to whether the range of flash intensities used could adequately stimulate the retina behind the dense opacities of blood filled eyes, particularly as Jayle and Tassey (1970) had reported that the diffusing effects of hyphaema could reduce the ERG by between 10 and 80%. However, the very high correlation between the electrophysiological findings and the final visual outcome must be indicative of adequate retinal stimulation. No eyes with a VEP grade 3 or 4 at low flash intensities (Grass stroboscope intensity 2 and 4) produced a better evoked response to intensity 16, and the majority of VEPs from eyes with good visual function could be graded at intensity 4 although occassionally the brightest light flashes helped the final decision.

These are very encouraging findings and as with the cataract patients where multiple EEG channels were used, it was clearly essential to use as many electrophysiological criteria as is practically possible, to improve the reliability of the prognosis. The ERG is particularly useful in cases of major trauma when the first VEP can be severely effected by the sequelae of a serious accident. Both objective tests were very easy to obtain, despite some particularly severe eye injuries and required very little cooperation from the patients. The tests were also reported by the medical personnel to increase the patients' confidence in the management decision which was ultimately made. Thus electrodiagnosis provides an enhancement of the traditional methods of clinical opthalmological assessment in severe eye injuries.

GENERAL CONCLUSIONS

The main conclusions have been drawn at the end of Chapters 7, 8 and 9, and the following description is a brief summary of the dissertation.

1. The cortical evoked potentials to diffuse flash stimuli from a Grass PS 22 photostimulator were similar in configuration to many of the studies reported in the literature. The nomenclature adopted to describe the VEP was similar to Dustman and Beck (1969) with the first consistent potential, which was negative in relation to the occipital electrode, being termed N1. The subsequent alternating positive and negative components were labelled P1, N2, P2, etc., up to the final component, N4, which occurred from between 200 and 350 m.sec.

2. The flash VEP was extremely variable in the normal population both in terms of the variation in the latency and amplitude of the VEP components, and also in terms of the number of components present.

3. Characteristic wave forms were recorded for each of the three age groups studied. Very few of the early components (0 to 100 m.sec.) were consistently recorded in the young age group (6 to 9 years), while the remaining components were of high amplitude. The adult VEP (17 to 34 years) was dominated by the central P2 component (mean latency

109 m.sec.), and the early components were always of low amplitude and less consistent. The late portion of the VEP from N3 to N4 was variable in both the amplitude and latency of the components. The VEP of the old age group (50 to 78 years) characteristically possessed high amplitude early components (P1 and N2), which at times approached or exceeded the amplitude of the P2 wave. The later portion of the response was reduced or absent.

4. Significant differences were found in the latencies and amplitudes of the VEP components in the three age groups which indicated that it is important to use matched age controls groups in any research programme.

5. Only the P2 component was recorded in every normal VEP, and this wave was primarily used to identify a normal VEP. Thus both absolute criteria of latency and amplitude of the P2 component and relative criteria of amplitude and latency differences between the two eyes and between the right and left cerebral hemispheres were identified which described a significant majority of flash VEPs recorded in a normal population (see Chapter 7 for details).

6. In the vast majority of the normal population the largest amplitude VEPs were located at OZ, or between O1 and O2 (Jasper, 1958) although in a small number of individuals an unusual, more lateral maximum response was recorded which could not be explained by the author on the basis of any

known vision physiology. Undoubtedly multichannel recordings of the VEP distribution provided valuable additional information on the nature of the cortical response to flash stimulation, but the data collection was very time consuming. A quicker method was devised using a phase reversal technique to locate the flash VEP at O1 or O2. This method provided promising information about the topography of the VEP, and the central P2 component phase reversed to both occiputs in all the normal population.

7. Some patients were studied with known visual field defects to establish how successfully the normal criteria of the flash VEP distinguished between an abnormal and normal response. Unfortunately only a very small group of patients with hemianopia were studied and there were not a sufficient number of control patients with central damage which did not involve the visual system. However a few tentative conclusions could be drawn from the study. Firstly the flash VEP was often far more variable than in the normal population, a feature of the VEP which was found in a wide selection of patient groups. The finding is not unexpected since complicating physical and psychological factors of the patients' illnesses are likely to be reflected in the cortical potentials which are reported to be sensitive to distraction, arousal, attention, etc. (see chapter 4), however, such findings are rarely recorded or recognised in the literature except with psychiatric patients (Callaway. 1974). The flash VEP appeared to be particularly variable in patients with visual pathway lesions, although more

research would be needed to confirm this result.

8. The criteria of asymmetry in the latency and amplitude of the early portion of the VEP proposed by Vaughan and Katzman (1964) did not exclusively describe the patients with hemianopic field defects, since the VEP was not always reduced and delayed contralateral to the visual defect; the VEP could be abnormal over the hemisphere ipsilateral to the defect; and finally the early portion of the VEP showed similar asymmetries in a significant portion of the normal population. No criteria of the flash VEP waveform could be found that exclusively identified hemianopic defects, however the phase reversal channels provided an extremely important sign, with no localization of the VEP in the occiput contralateral to a dense, complete hemianopia. Brain damaged control patients and a patient with central sparing showed the normal phase reversal results to both occiputs. These results are promising and suggest that only multichannel VEP mapping in gross visual field defects can provide reliable information on the nature of the visual disorder. More research needs to be done to confirm these findings, improve the results, and develop more rapid techniques of accumulating the data.

9. The flash VEP was investigated in patients with central retinal scotomatas. In senile macula degeneration the P2 component was selectively reduced which would be consistent with this component reflecting primarily macula function. The early components (P1 and N2) were well preserved and

often of high amplitude, which the author suggested was a reflection of the old age of this clinical group, although the physiological significance of these large early components is not understood. Significant correlations were found between the latency and amplitude of the P2 component and good or poor vision, with poor vision (less than 6/60) being associated with significantly low amplitude and delayed P2 components which could not be localized in either occiput. Patients with reduced vision (6/12 to 6/60) could not be reliably identified from the group with good vision, except in the phase reversal channels when frequently there was inconsistent and poor phase reversal of the P2 component to one of the occiputs. The suggestion that the P2 component primarily reflects central retinal function needs to be confirmed by investigating a far wider range of clinical conditions and patients of different ages. It appeared that the phase reversal channels provided additional useful information about the flash VEP in patients with localized central retinal lesions.

10. Two prospective studies were carried out in two groups of patients where flash VEPs could provide useful information for the clinician despite the inherent variability in the flash response. One group of patients had long standing cataracts, the second group had sustained recent severe penetrating eye injuries, both were waiting for a clinical decision concerning the possibility of surgery to restore sight. The dense eye opacities of all the patients prevented

any opthalmological assessment of the retina, and eliminated the possibility of the patients viewing patterns, field analysers etc. Using the VEP criteria developed from the research on normally sighted individuals and in patients with known visual defects, the flash VEP, which could be consistently recorded despite very dense opacities, was graded to predict either good postoperative visual acuity or no useful visual function remaining. There were highly significant correlations between the VEP gradings and the final visual outcome, confirming that the flash VEP can reliably identify gross visual disturbances. It was concluded that the retina was adequately stimulated with the range of light intensities provided by the Grass PS 22 photostimulator. It was evident that the more information that could be recorded concerning the electrophysiological responses of the visual system, the more reliable the prognosis. Thus in the cataract patients, multichannel recordings of the VEP were important, with the channels phase reversing the evoked potentials to the two occiputs providing the most important information with which each VEP was graded. In the major trauma series multichannel recordings were unpractical, and instead the monitoring of other electrophysiological responses (ERG) provided different information about visual function, and improved the reliability of the electrodiagnostic predictions. As had been anticipated by the work with patients who had known visual field defects, the flash VEP was particularly sensitive to localized central retinal damage, and to lesions in the optic pathways and visual cortices.

11. It is apparent that the flash VEP has an important role to play as an aid to diagnosis in the most difficult cases that the clinician is presented with, that is when the patient cannot or refuses to cooperate sufficiently to be tested using standard diagnostic procedures, and where it is impossible to control fixation and gross head movements, and to sustain constant fixation on pattern stimuli. A failure to obtain a pattern VEP because of accomodation, cooperation or acuity problems provides no information about the condition of the patient, although such results have been reported (Carrol and Mastaglia, 1978). In such conditions the flash VEP is useful provided that either the topography of the VEP is recorded, or other electrophysiological measures are included in the investigation. Undoubtedly more research is needed to improve the reliability of the flash VEP and to reduce the lengthy recording time that is usually necessary in an investigative clinic. It is likely that one area which presents the possibility for a great deal of improvement is the method of stimulation, since in this work only bright, diffuse whole field flash stimulation was used at a slow flash rate. Modern technological developments raise the possibility of a greater variety of stimulus sizes, intensities, colours, rates of stimulation etc., which may provide more subtle forms of stimulation in different clinical conditions.

In 1964, Nagata and Jacobson stated that "The clinical value to be derived from the utilization of the phenomena

of the VEP will depend upon its ability to provide diagnostic and prognostic information not obtainable by other, less complex and costly examinations .... In our hands, at this time, the method does not satisfy this criteria" (p. 246). It is hoped that the research in this dissertation has gone some way to satisfying the doubts raised by Nagata and Jacobson.

APPENDIX 1

INTENSITY INFORMATION

Grass stroboscope model PS.22(flash rate 2f/sec.)

10 μsec. flash duration. Int. 16 = x 16 Int. 1

		nit/secs.	
Intensity	1	53	
	2	68	(1363 nits)
	4	96	
	8	197	
	16	483	(9661 nits)

BIPOLAR (O2-C4)															
LATENCY								AMPLITUDE							
N1	P1	N2	P2	N3	P3	N4	P4	O/N1	N1/P1	P1/N2	N2/P2	P2/N3	N3/P3	P3/N4	N4/P4
61	61	85	101	150	-	-	-	-	5.55	4.16	4.4	13.6			
62	-	-	100	125	169	-	-	-	-	-	26.25	11.25	9.75	-	-
-	-	-	112	156	212	-	-	-	-	-	14.35	16.92	8.2	-	-
-	50	67	100	137	181	218	-	-	2127	5.45	17.27	18.63	10.22	10.00	-
62	-	-	97	139	162	206	-	-	-	-	4.46	6.6	5.17	6.78	-
-	-	89	125	175	225	262	-	-	-	12.5	33	21.5	12.5	10.0	-
50	75	94	122	190	219	256	-	-	4.64	7.14	11.42	15.53	12.14	14.64	-
62	-	-	98	156	215	268	-	-	-	-	6.45	15.62	6.04	3.95	-
56	75	83	100	125	156	194	-	-	1.1	1.2	10.6	12.8	6.0	2.6	-
58.83	67.25	83.6	106.00	150.6	194.22	234.0	-	-	3.39	6.09	13.39	12.95	9.02	7.99	-
4.91	11.84	10.18	10.11	20.66	27.01	31.82	-	-	2.05	4.19	9.69	5.38	2.78	4.45	-

APPENDIX IIa

Latency and amplitude of flash VEP recorded from bipolar electrodes.

APPENDIX IIb

Latency and amplitude of the flash VEP recorded from monopolar electrodes.

MONOPOLAR AMPLITUDE (O2→EARS)														
LATENCY								AMPLITUDE						
N1	P1	N2	P2	N3	P3	N4	P4	N1/P1	P1/N2	N2/P2	P2/N3	N3/P3	P3/N4	N4/P4
-	-	-	101	144	-	-	-	-	-	6.31	7.89	-	-	-
62	-	-	97	125	171	-	-	-	-	21.25	9.75	11.5	-	-
62	-	-	106	149	212	-	-	-	-	9.21	11.31	-	-	-
-	-	-	102	144	203	-	-	-	-	3.28	4.84	8.28	-	-
-	53	72	100	190	175	224	-	2.3	4.28	14.52	19.28	11.9	10.23	-
-	-	-	100	136	181	-	-	-	-	4.5	7.66	8.00	-	-
-	-	84	119	160	225	262	-	-	10.0	25.5	15.0	10.5	9.0	-
-	-	-	-	-	-	-	-	7.5	5.16	5.66	8.16	4.5	8.5	-
50	75	98	118	197	218	251	-	-	-	-	-	-	-	-
64	-	-	100	161	281	258	-	-	-	9.61	13.07	5.76	5.96	-
56	74	80	100	125	160	210	-	1.38	1.85	10.18	8.88	6.11	3.7	-
58.8	67.33	83.5	104.3	153.1	202.88	241.0	- MEAN	3.03	5.32	11.00	10.58	8.31	7.53	-
5.76	12.42	10.87	7.81	24.61	37.1	22.8	- STANDARD DEVIATION	2.53	3.41	7.34	4.21	2.77	2.72	-

APPENDIX III

SUBJECTS IN THE NORMAL YOUNG AGE GROUP

All subjects had normal vision, and no known clinical history or neurological defect. All the EEGs were normal.

	YEARS	MONTHS
D.L.	8	8
J.A.	6	1
T.T.	8	1
H.J.	7	2
T.W.	6	0
A.S.	9	4
K.S.	7	6
S.M.	9	11
T.J.	8	3
H.J.	6	4
L.V.	9	10
P.S.	8	1
L.W.	7	0
A.F.	7	11
A.S.	8	3
A.T.	8	1
E.K.	8	5
H.J.	9	2
T.J.	9	0

NUMBER OF SUBJECTS 20

MEAN AGE 7 YEARS 8 MONTHS

AGE RANGE 6 YEARS TO 9 YEARS 11 MONTHS

APPENDIX IV

OLD AGE CONTROLS

All EEGs within normal limits.

No clinical history or neurological findings.

All visual fields, visual acuity, and retina examined and were within normal limits for the age.

SUBJECT	AGE
M.T.♀	68
A.T.♂	73
I.L.♀	61
E.S.♂	59
D.M.♀	55
C.L.♀	67
C.M.♀	71
B.K.♂	64
F.S.♂	68
H.C.♀	62
B.D.♂	67
F.W.♂	58
M.H.♂	74
M.F.♀	46
M.M.♂	70
G.H.♂	71
M.M.♀	69
E.M.♂	72
J.W.♀	50

SUBJECT	AGE
T.H. ♀	68
J.H. ♀	66
H.C. ♀	47
C.L. ♀	69
A.M. ♂	43
E.W. ♀	78

3 SUBJECTS IN 40-49 AGE GROUP

4 SUBJECTS IN 50-59 AGE GROUP

11 SUBJECTS IN 60-69 AGE GROUP

7 SUBJECTS IN 70+ AGE GROUP

25 SUBJECTS MEAN AGE 63 YEARS.

(MINUS 40-49 GROUP) 22 SUBJECTS MEAN AGE 66.4 YEARS.

APPENDIX V OPHTHALMOLOGICAL REPORT. BMEH

Race	Place of Birth
R.V. Refraction 6/5-1	L.V. 6/5
Corrected Vision N5 6/6 N6 6/6	N5 6/6 N12 6/6
Present Condition (Ophthalmic) normal	fundi.

King White letter. 16

CHART No 650 COMP.

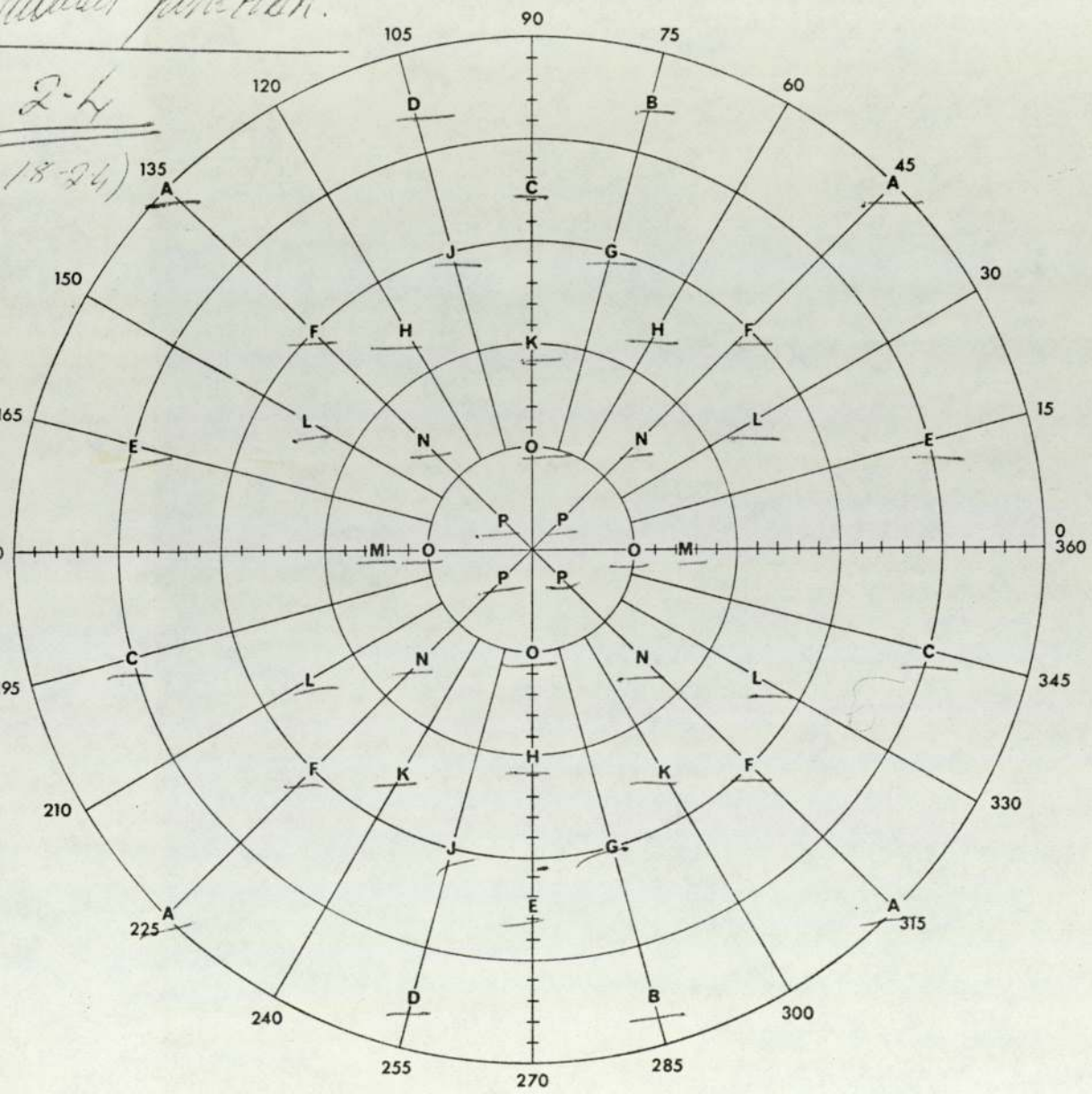
FRIEDMANN CENTRAL FIELD ANALYSER

(COMPOSITE CHART)

Macular function.

2-4

(18-24)



Name CLARK Hilda

Age 62

Date 13.6.74

Record No.

Eye – Left/Right cyls.

V.A.

CLEMENT CLARKE LTD., 16 WIGMORE STREET, LONDON W1H 0DS, ENGLAND

APPENDIX VI

The amplitude and latency of the three most consistent components of the flash VEP in the total population (6-78 years). 82 subjects.

		VEP COMPONENTS		
RIGHT EYE		N2	P2	N3
LATENCY (m.sec)	mean	88.4	116.1	163.1
	S.D.	9.1	10.4	16.4
AMPLITUDE (μv)	mean	3.4	9.3	9.1
	S.D.	3.9	4.4	5.4
LEFT EYE				
LATENCY (m.sec)	mean	87.7	115.8	162.9
	S.D.	6.9	10.2	13.7
AMPLITUDE (μv)	mean	4.3	9.1	10.2
	S.D.	5.5	3.9	5.4

		LEFT OCCIPUT								RIGHT OCCIPUT							
% OCCURRENCE	COMPONENT	PO	N1	P1	N2	P2	N3	P3	N4	PO	N1	P1	N2	P2	N3	P3	N4
	YOUNG GRP.	18	39	30	36	100	76	64	58	12	45	9	18	100	73	52	64
	ADULT GRP.	3	30	35	46	100	77	62	58	8	42	31	54	100	77	68	55
	OLD GRP.	0	19	27	76	100	76	52	22	0	19	54	78	100	71	51	22
	TOTAL GRP.	21	29	30	53	100	77	60	49	7	37	33	52	100	75	60	49

APPENDIX VII

Phase reversal of the VEP components in the normal population. The data shows the numbers of individuals that demonstrate phase reversal of each component to either occiput as a percentage of the total number of individuals recorded. (85 subjects). Binocular stimulation only.

APPENDIX VIII

BRAIN DAMAGED CONTROLS WITH NO VISUAL FIELD DEFECT

Mrs. P. A. aet 32 yrs. Pituitary tumour. Four year history of hormone disturbance. Enlarged blind spot and some reduction in vision in the periphery of the right eye, involving the right and left upper quadrants, greater involvement in the right field. Left eye N.A.D.

Mrs. E. R. aet 30 yrs. Cardiovascular accident. Oral contraceptive for 3 years. Right sided headaches and nausea. Right cerebral artery occlusion, no visual field defect.

Mrs. A. M. aet 58 yrs. Cardiovascular accident. Left posterior artery occlusion, severe memory defect and right hemiparesis. No visual field defect.

Mr. V. R. aet 41 yrs. Space occupying lesion. Right parietal glioblastoma. Left hemiparesis. No visual field defect.

Asymmetries occurred in the background EEG of Mrs. A. M. and Mr. V. R., with a greater amount of slow activity over the involved hemispheres.

Latency (m.sec.) of major VEP components.														
Binocular Stimulation														
Patients	Undamaged hemisphere							Damaged hemisphere						
Central lesions	N1	P1	N2	P2	N3	P3	N4	N1	P1	N2	P2	N3	P3	N4
E.R.	54	86	90	120	160	220	-	55	86	90	120	190	220	256
A.M.	-	70	90	125	135	225	-	-	70	90	135	165	225	-
V.R.	-	69	75	116	170	200	-	-	78	87	125	175	245	-
Pathway lesions														
P.A. R.E.	-	75	88	118	156	-	-	-	78	88	118	156	200	265
L.E.	-	-	82	119	159	-	-	-	-	83	120	162	-	-

APPENDIX IX

The latency (m.sec.) and amplitude (μv) of the major components of the VEP in four brain-damaged patients with no visual field defect.

APPENDIX X

PATIENTS WITH CENTRAL LESIONS AND KNOWN VISUAL DEFECTS

Mr. M. C. aet 54 yrs. Complete left homonymous hemianopia. Occassional headaches and loss of memory. In the background EEG the alpha rhythm was a little slow around 8c/sec., of lower amplitude on the left. Abnormalities mild and inconsistent. Only binocular stimulation used.

Mr. P. W. aet 53 yrs. Complete left homonymous hemianopia. Sudden loss of vision in left field which has persisted with sensations of flashing lights. Persistent headache right side; occlusive cerebro-vascular episode in right posterior cerebral artery. Binocular and monocular stimulation used.

Mr. H. E. aet 62 yrs. Complete left homonymous hemianopia. Cardiovascular accident one month before the VEP investigation. Only binocular stimulation used.

Mrs. E. J. aet 58 yrs. Complete left homonymous hemianopia with nystagmus to the right. Bilateral papillodoema and mild hemiparesis. Three year history of frontal headaches and flashing lights. Right parietal glioblastoma diffusely invading the cortex. Binocular and monocular stimulation used.

Mrs. M. M. aet 41 yrs. Complete right homonymous hemianopia and vision very poor in right eye. Severe memory loss and speech impairment. Suspected left parietal

space occupying lesion. EEG asymmetric with low amplitude delta and theta activity posteriorly of greater amplitude and amount on the left, and showing a tendency to phase reverse to the left parietal and posterior temporal electrodes.
Monocular and binocular stimulation performed.

Mr. J. B. aet 63 yrs. Complete right homonymous hemianopia. Loosing his sight over the past two years, and now unable to read. Very impaired vision in the left visual field. No neurological signs.
Binocular and monocular stimulation.

Miss S.C. aet 22 yrs. Bitemporal hemianopia including the central 5^{o} of vision. Pituitary tumour involving the optic chiasma.
Only monocular stimulation performed.

Mr. W. W. aet 55 yrs. Partial bitemporal hemianopia. Right visual field defect in the right eye, visual acuity 6/12. Left eye normal fields and acuity. Sudden severe occipital headache and vomitting. Both discs abnormally pale. Frontal lobe elevated on the right side, and optic nerve compressed. Pituitary adenoma compressing the optic nerve.
Only monocular stimulation performed.

Mr. S. G. aet 44 yrs. Partial bitemporal hemianopia, right visual field defect in the right eye, but with clear evidence of 5^{o} or more central sparing. Left eye no perception of light. Suprasellor meningioma compressing the optic nerve. Only monocular stimulation performed.

	Latency (m.sec.) of major VEP components													
	Undamaged hemisphere							Damaged hemisphere						
Patients	N1	P1	N2	P2	N3	P3	N4	N1	P1	N2	P2	N3	P3	N4
M.C.	-	50	62	108	162	-	-	-	-	82	108	162	-	-
P.W.	-	58	84	112	158	190	225	-	56	75	112	152	190	228
H.E.	60	75	90	105	190	-	-	-	-	75	122	180	-	-
E.J.	-	60	90	125	170	-	-	-	-	100	125	170	-	-
M.M.	50	63	80	128	175	240	-	50	63	80	125	172	230	-
J.B.	-	100	118	140	160	-	-	-	-	118	140	160	-	-
Mean Latency	-	57.8	87.3	119.7	169.2	-	-	-	-	88.3	122.0	166.0	-	-
	Amplitude (μv) of major VEP components													
Patients	N1	P1	N2	P2	N3	P3	N4	N1	P1	N2	P2	N3	P3	N4
M.C.	-	1.2	1.4	4.2	4.0	-	-	-	-	1.5	4.2	4.3	-	-
P.W.	-	3.6	1.6	4.0	1.2	4.0	4.0	-	1.8	0.6	3.8	1.6	3.4	4.2
H.E.	0.5	0.5	1.0	4.0	2.8	-	-	-	-	0.8	2.8	3.0	-	-
E.J.	-	2.0	5.3	11.2	10.0	-	-	-	-	0.5	5.0	4.5	-	-
M.M.	-	1.4	6.9	7.4	15.1	10.3	-	-	1.4	5.1	6.1	15.0	9.4	-
J.B.	-	1.2	5.0	2.8	2.0	-	-	-	-	2.0	2.4	1.5	-	-
Mean Amp.	-	1.65	3.5	5.6	5.85	-	-	-	-	1.8	4.05	5.0	-	-

APPENDIX XI

The amplitude and latency of the VEP components in patients with homonymous hemianopia. Binocular stimulation.

	Monocular stimulation - latency values													
Visual field defect	undamaged hemisphere							damaged hemisphere						
Homonymous Hemianopia	N1	P1	N2	P2	N3	P3	N4	N1	P1	N2	P2	N3	P3	N4
P.W. RE	-	-	-	105	162	189	230	-	-	-	106	160	189	225
LE	-	53	89	107	150	187	230	-	56	89	104	160	181	225
E.J. RE	-	68	90	140	-	-	220	-	72	90	145	-	-	220
LE	-	56	87	125	-	-	-	-	65	93	148	-	-	-
M.M. RE	-	50	87	131	-	-	150	-	50	87	132	-	-	150
LE	-	-	78	134	170	200	-	-	-	78	132	170	200	-
V.B. RE	-	-	118	143	168	-	-	-	-	120	145	170	-	-
LE	-	-	118	140	160	-	-	-	-	120	142	160	-	-
Bitemporal Hemianopia														
S.C. RE	-	-	75	112	150	194	237	-	-	-	112	150	190	245
LE	-	-	81	100	140	187	270	-	-	81	100	135	187	270
W.W. RE	-	-	101	135	170	-	-	-	-	110	135	170	-	-
LE	(normal)	-	(100)	(137)	(178)	-	-	-	-	(110)	(143)	(175)	-	-
Mean latency	-	56.8	92.4	124.7	158.8	-	-	-	61	96.4	127.4	159.4	-	-
Central sparing														
S.G. RE	-	-	89	130	168	200	275	-	-	100	125	164	200	275

APPENDIX XII

The mean latency (milliseconds) of the VEP components in patients with homonymous hemianopia and bitemporal hemianopia.

Monocular stimulation.

FIELD DEFECT		Monocular stimulation - amplitude values													
		undamaged hemisphere							damaged hemisphere						
Homonymous Hemianopia		N1	P1	N2	P2	N3	P3	N4	N1	P1	N2	P2	N3	P3	N4
P.W.	RE	-	-	-	4.2	1.4	2.5	3.9	-	-	-	4.6	0.8	3.0	3.5
	LE	-	3.2	3.6	1.6	3.0	3.0	3.4	-	1.2	1.0	1.8	2.8	3.0	3.7
E.J.	RE	-	2.5	10.0	12.0	-	-	8.0	-	2.5	5.5	10.4	-	-	8.7
	LE	-	4.2	10.2	10.3	-	-	-	-	3.0	4.0	9.8	-	-	-
M.M.	RE	-	6.2	7.5	15.9	-	-	3.0	-	2.4	5.0	9.6	-	-	2.5
	LE	-	7.0	16.5	5.2	2.5	-	-	-	4.7	11.2	4.8	3.4	-	-
J.B.	RE	-	-	5.8	2.5	3.1	-	-	-	-	5.0	2.0	3.0	-	-
	LE	-	-	4.5	2.0	2.4	-	-	-	-	4.0	2.0	2.0	-	-
Bitemporal Hemianopia															
S.C.	RE	-	-	2.0	4.4	4.0	4.5	5.6	-	-	-	3.0	4.5	5.0	4.3
	LE	-	-	1.5	2.0	4.3	5.0	5.6	-	-	-	0.75	2.0	6.7	1.0
W.W.	RE	-	-	3.2	10.0	9.8	-	-	-	-	4.2	9.0	10.0	-	-
	LE	(normal)	-	(2.4)	(7.0)	(6.2)	-	-	-	-	(4.0)	(9.6)	(7.5)	-	-
Mean amplitude		-	4.1	5.5	7.4	4.2	-	-	-	2.3	4.2	5.8	3.7	-	-
Central sparing															
S.G.	RE	-	-	1.9	6.2	6.0	4.7	4.9	-	-	2.0	5.0	9.2	6.4	3.0
	LE				BLIND							BLIND			

APPENDIX XII

Mean amplitude of the VEP components in homonymous hemianopia.
Monocular stimulation.

APPENDIX XIIIa

PATIENTS WITH UNILATERAL DISCIFORM DEGENERATION

Mrs. D. S. aet 58 yrs. Right eye 6/36 $\bar{c}$. less than 6/60 $\bar{s}$. Central field loss out to 20° for left field, and out to 5° for the right upper field and lower field. Left eye, N.A.D., visual acuity 6/6.

Mrs. D. K. aet 70 yrs. Right eye slight pigmentary changes around the macula, no field defect, visual acuity 6/9. Left eye, central field loss out to 20° in the left visual field, and out to 15° in the right visual field. Visual acuity hand movements.

Miss B.E. aet 65 yrs. Right eye central field loss out to 20° for the left upper field, out to 15° for the right upper field, and out to 10° for the two lower fields. Visual acuity 6/60. Left eye pigmentary changes around the macula, fields normal, visual acuity 6/6.

APPENDIX XIIIb

BILATERAL DISCIFORM MACULA DEGENERATION

PATIENTS WITH UNEQUAL INVOLVEMENT OF THE TWO EYES.

Mr. A. H. aet 72 yrs. Right eye pigmentary changes, visual acuity 6/36.Left eye long standing extensive disciform degeneration of the central 20°. Visual acuity counting fingers.

Mr. R. P. aet 64 yrs. Right eye early disciform degeneration. Visual acuity 6/60$\bar{s}$, 6/12 $\bar{c}$. Left eye long standing degeneration of the central 25° of the left visual field, and out to 5° for the right upper quadrant and 10° for the right lower quadrant. Visual acuity less than 6/60.

Mr. R. S. aet 73 yrs. Right eye extensive disciform degeneration visual acuity counting fingers. Left eye had some pigmentary changes, and the visual acuity was deteriorating very rapidly to be 6/36 on the test day.

Mrs. E. J. aet 72 yrs. Right eye long standing disciform degeneration. Visual acuity hand movements. Left eye had early disciform degeneration possibly associated with a subretinal haemorrhage. Visual acuity 6/60$\bar{s}$, corrected to 6/24.

Mr. W. E. aet 78 yrs. Right eye disciform degeneration involving central 15°, in the upper field and the central 10° for the lower fields. Visual acuity 6/60. Left eye early changes, visual acuity 6/36.

Mrs. G. G. aet 75 yrs. Right eye pigmentary changes in the macula region, visual acuity 6/60, corrected to 6/36. Left eye disciform degeneration confined almost totally to the central 20° of the left visual field. Visual acuity 1/60.

Latency in m.sec. of major VEP components														
	Less effected eye VA range 6/12 to 6/36							More effected eye VA range 6/60 to hand movement						
Patient	N1	P1	N2	P2	N3	P3	N4	N1	P1	N2	P2	N3	P3	N4
A.H.	47	60	79	124	161	198	250	50	70	110	128	175	220	275
G.G.	-	65	94	131	170	-	-	52	60	93	117	165	-	-
R.P.	-	72	98	143	179	225	-	50	75	104	138	197	-	-
E.J.	-	69	95	113	153	187	220	60	90	120	150	187	237	-
R.S.	-	75	115	134	189	225	270	-	73	107	147	189	235	-
W.E.	-	-	112	131	175	200	225	-	69	93	124	212	-	-

APPENDIX XIIIb

Bilateral macula degeneration with unequal involvement of the two eyes, six patients.

Amplitude in μv of major VEP components														
	Less effected eye VA range 6/12 to 6/36							More effected eye VA range 6/60 to hand movement						
Patients	N1	P1	N2	P2	N3	P3	N4	N1	P1	N2	P2	N3	P3	N4
A.H.	1.3	3.4	6.5	11.7	7.4	4.6	3.7	2.5	2.2	2.0	2.5	2.7	2.5	4.0
G.G.	-	9.6	13.7	6.8	3.0	-	-	1.0	5.6	10.2	8.4	5.0	-	-
R.P.	-	3.1	5.4	6.5	2.4	2.9	-	0.8	2.9	4.8	4.3	2.5	-	-
E.J.	-	6.0	8.2	3.4	6.5	5.4	3.0	0.4	5.0	10.5	2.9	1.1	4.8	-
R.S.	-	3.8	6.9	2.0	2.1	3.9	2.0	-	2.5	6.3	2.6	2.9	5.9	-
W.E.	1	1	0.8	1.8	3.2	1.0	2.1	-	7.5	2.2	2.9	3.2	-	-

APPENDIX XIIIb

Bilateral macula degeneration with unequal involvement of the two eyes.

APPENDIX XIIIc

BILATERAL DISCIFORM MACULA DEGENERATION

PATIENTS WITH EQUAL INVOLVEMENT OF THE TWO EYES.

Mr. R. P. aet 76 yrs. Right eye disciform degeneration of the central 5^{o} of both inner fields, out to 20^{o} in the left lower field, and out to 10^{o} in the right lower field visual acuity 6/60. Left eye disciform degeneration of the central 25^{o} of the left visual field, the central 5^{o} of the right upper field, and out to 10^{o} in the right lower field. Visual acuity 6/60.

Mr. R. B. aet 78 yrs. Right and left eye extensive macula degeneration involving central 20^{o}, visual acuity perception of light in both eyes. Early cataracts prevented accurate assessment of fields and visual acuity.

Mrs. A. W. 88 yrs. Right and left eye extensive disciform degeneration. Visual acuity less than 6/60 in both eyes with the beginnings of bilateral cataracts.

Miss. M. F. aet 13 yrs. Stargardt's disease with bilateral degeneration changes in the macula region. Visual acuity of right and left eye 6/36 with correction.

APPENDIX XIVa

UNILATERAL CATARACTS

REFERRALS FOR VEP ASSESSMENT PRIOR TO A CATARACT OPERATION

Patient	Age (years)	Good eye	Cataract eye	Postoperative results
N.T.	49	R. eye amblyopic 6/24.	L. eye inaccurate P.L. and glaucoma.	L. eye total retinal detachment perception of light.
O.T.	57	L. eye - 6/24, early opacities.	R. eye senile cataract count fingers.	6/9 unaided.
M.G.	78	L. eye early senile change 6/24.	R. eye. Old trauma penetrating wound. Perception of light.	6/18 unaided. Probably will improve in future.
R.C.	37	L. eye 6/6.	R. eye. Old trauma accurate perception of light.	1/36 no improvement with correction.
H.W.	64	R. eye 6/9 corrected.	L. eye high intraocular pressure perception of light.	Hand movements gross central choreoretinal degeneration.
M.S.	37	L. eye 6/6	R. eye old trauma perception of light.	Refused surgery.
B.L.	32	L. eye 6/6	R. eye squint. R. eye old trauma, when 4 years old.	Good fundus. No improvement from counting fingers, no technical reason probably amblyopic.
D.D.	22	L. eye 6/6	R. eye old trauma 8 years ago accurate perception of light.	6/5
D.E.	43	L. eye 6/4	R. eye old trauma 15 years ago accurate perception of light.	Perception of light. Old retinal detachment.
H.S.	51	L. eye 6/9	R. eye old trauma when 7 years old. Counting fingers.	6/9 - surprisingly good acuity.

Patient	Age (years)	Good eye	Cataract eye	Postoperative results
L.S.	51	L. eye 6/6.	R. eye old trauma 26 yrs. ago. Accurate perception of light.	6/9
M.H.	57	R. eye 6/9 corrected vitreous floaters.	L. eye poor vision for years some chorcidal atrophy.	6/9
I.T.	94	R. eye 6/9	L. eye trauma 3 yrs. ago	6/18 unaided Fundus normal will probably improve to 6/6.
G.A.	52	R. eye 6/9	L. eye mature cataract no injury.	6/18 $\bar{s}$ fundus 6/9 $\bar{c}$ normal
H.D.	62	L. eye 6/9	R. eye poor vision for 25 yrs. possible retina detachment when 36 yrs. perception of light.	6/12
E.R.	58	R. eye 6/6	L. eye mature cataract no injury.	6/9 fundus normal
J.B.	69	L. eye 6/6	R. eye old trauma 30 yrs. ago. Intraocular foreign body accurate perception light.	6/12 aided 3 days post op. will probably improve to 6/6.
M.R.	10	R. eye 6/6	R. eye congential caratact perception of light.	6/36 no improvement with correction, amblyopic.
R.M.	67	R. eye 6/9	L. eye cataract no history of trauma	6/6
C.E.	87	R. eye 6/9	L eye perception of light.	6/12 fundus normal.
G.B.	74	L. eye 6/9	R. eye counting fingers.	6/6 fundus normal.

APPENDIX XIVb

The Grading of Flash VEP in Patients with Unilateral Cataracts and Good Visual Acuity (6/12 or better)

	Normal/Cataract eye differences				Matched control criteria		Normal control group criteria: eye difference		Normal absolute criteria of latency		Normal criteria of amplitude		Cataract eye		VEP
	% reduction P2		P2 latency delay (ms.)		>33%	>12ms.	>50%	>12ms					Phase reversal	phase reversal	
Patient	I2	I4	I2	I4	Amp	Lat	Amp	Lat	Cataract	Good eye	Cataract	Good eye	O2	O1	Grade
M.M.	↓20	-	9	6	-	-	-	-	-	-	-	-	✓	✓	1
L.S.	↑	-	-	-	-	-	-	-	-	-	-	-	✓	✓	1
D.D.	↓52	↓34	10	16	*	-	-	-	-	-	-	-	✓	✓	1
H.S.	↑	-	7	-	-	-	-	-	-	-	-	-	✓	✓	1
G.B.	↓51	↓42	10	11	*	-	-	-	-	-	-	-	✓	✓	1
J.B.	↑	-	17	13	-	*	-	*	*.002	-	-	-	✓	✓	1
R.M.	↓40	↓35	-	-	*	-	-	-	-	-	*.05	*.05	✓	✓	1
M.G.	↓70	↓62	10	8	*	-	*	-	-	-	-	-	✓	No PR obtained	2
C.E.	↓52	↓48	13	14	*	*	-	*	-	-	-	-	✓	No PR obtained	2
E.R.	↓7	-	6	-	-	-	-	-	-	-	-	-	✓	✓	1
H.D.	↓20	-	6	11	-	-	-	-	-	-	-	-	✓	✓	1
G.A.	↑	-	16	14	-	*	-	*	*.005	-	-	-	✓	✓	1
I.T.	↑	-	-	7	-	-	-	-	*.002	*.002	-	-	✓	✓	1
O.T.	↓50	↓38	4	9	*	-	-	-	-	-	-	-	✓	✓	1

N.B. Legend for symbols see Appendix XIVc, page 360.

Patient	Normal/cataract difference				Matched control criteria		Normal group eye difference		Normal criteria latency		Normal criteria amplitude		Cataract eye		VEP Grade
	% reduction P2		P2 latency delay (m.sec.)										phase reversal	phase reversal	
	I2	I4	I2	I4	amp	lat	amp	lat	cataract	good eye	cataract	good eye	O2	O1	
D.E.	↓46	↓48	24	14	*	*	-	*	* .005	-	-	-	-	-	3
H.W.	↓65	↓79	12	12	*	*	*	*	* .05	-	-	-	-	-	3
B.L.	↓35	↓44	10	8	*	-	-	-	-	-	-	-	✓	?	2
R.C.	↓32	↓42	47	31	*	*	-	*	* .002	-	* .05	-	-	?	3
M.R.	↓60	↓56	-	-	*	-	*	-	-	-	* .05	-	?	?	3
N.T.	↓62	↓81	6	18	*	-	*	-	-	-	* .05	-	-	-	3

↑ denotes a higher amplitude in the cataract eye.
↓ denotes a lower amplitude in the cataract eye.
- denotes a similar or shorter latency in the cataract eye, or nonsignificant findings.
* significantly abnormal VEP.
✓ phase reversal obtained of the P2 component.

APPENDIX XIVc

The grading of the Flash VEP in patients with unilateral cataracts and poor visual acuity (6/24 or worse).

Bibliography

Abraham, F.A., Melamed, E., and Lacy, S. Prognostic value of visual evoked potentials in occipital blindness following basilar artery occlusion. Appl. Neurophysiol., 1975, 38, 126-135.

Adams, W.L., Arden, G.B., and Behrman, J. Responses of human visual cortex following excitations of peripheral retinal rods. Brit. J. Ophthal., 1969, 53, 439-452.

Adler, F.H. Physiology of the eye. 3rd Ed., 1959, Mosby, St.Louis.

Adler, J., Kacer, O., and Mensikova, Z. Electroencephalography and visual evoked responses in monitoring of patients conditions. Sb. Ved. Pr.Lek. Fak. Karlovy Univ., 1975, 18, 397-411.

Adrian, E.D. and Mathews, B.H.C. The Berger rhythm; potential changes from the occipital lobes of man. Brain, 1934, 57, 355-385.

Amassian, J.E., Waller, H.J., and Macy, J. Neural mechanisms of primary somatosensory evoked potential. Ann. N.Y. Acad. Sci. 1964, 112, 5-32.

Arden, G.B., and Sheoney, V.B. The assessment of visual function in patients with opacities: a new evoked potential method using a laser interferometer. In Visual evoked potentials in man: new developments, J.E. Desmedt (Ed.), 1977, Clarendon, 381-394.

Arfel, G., Albe-Fessard, D., and Walter S. Evoked potentials in coma. Electroenceph. clin. Neurophysiol., 1968, 25, 93.

Armington, J.C. The electroretinogram, the visual evoked potential, and the area-luminance relation. Vision Res., 1968, 8, 263-276.

Armington, J.C. Visual cortical potentials and electroretinograms triggered by saccadic eye movements. In Visual evoked potentials in man: new developments, J.E. Desmedt (Ed.), 1977, Clarendon, 286-300.

Armington, J.C., and Bloom, M.B. Relations between amplitudes of spontaneous saccades and visual responses. J. opt. Soc. Am., 1974, 64, 1263-1271.

Armington, J.C., Corwin, T.R ., and Maretta, R. Simultaneously recorded retinal and cortical responses to patterned stimuli. J. opt. Soc. Am., 1971, 61, 1514-1521.

Asselman, P., Chadwick, D.W., and Marsden, C.D . Visual evoked responses in the diagnosis and management of patients suspected of multiple sclerosis. Brain, 1975, 98, 261-282.

Babel, J.B., Stangos, V., Korol, S., and Spiritus, M. Ocular electrophysiology. A clinical and experimental study of electroretinogram, electro-oculogram, visual evoked response, 1977, Georg Thiene.

Barlow, J.S. Rhythmic activity induced by photic stimulation in relation to intrinsic alpha activity of the brain in man. Electroenceph. clin. Neurophysiol. 1960, 12, 317-321.

Barlow, H.B., Blakemore C., and Pettigrew, J.D. The neural mechanism of binocular depth discrimination. J. Physiol. Lond. 193, 327-342.

Barlow, J.S., and Ciganek, L. Lambda responses in relation to visual evoked responses in man. Electroenceph. clin. Neurophysiol. 1969. 183-192.

Barnet, A.B. EEG audiometry in children under three years of age. Acta Otolaryngol (Stockh), 1971, 72, 1-13.

Barrett, G., Blumhart, L., Halliday, A.M., Halliday, E., and Kriss, A. The paradoxical lateralization of the scalp-recorded visual evoked response. Electroenceph. clin. Neurophysiol. 1976(a), 41, 535.

Barrett, G., Blumhart, L., Halliday, A.M., Halliday, E., and Kriss, A. A paradox in the lateralization of the visual evoked response. Nature, 1976(b), 261, 253-255.

Bartlett, N.R., Eason, R.G. and White, C.T. Binocular summation in the evoked cortical potential. Percept. Psychophys., 1968, 3, 75-76.

Baumann, H., Baumann, R., Gurk. C.L., and Wolfer, F. Electro-physiological studies of central nervous performance during monotony. Electroenceph. clin. Neurophysiol. 1968, 24, 259-273.

Behrman, J. The visual evoked response in hysterical amblyopia. Brit. J. Ophthalmol., 1969, 53, 839-845.

Behrman, M.S., and Levi, D.M. Hysterical amblyopia: electrodiagnostic and clinical evaluation. Amer. J. Optom. Physiol. Opt., 1975, 52, 267-274.

Behrman, J., Nissim, S., and Arden, G.B. A clinical method for obtaining pattern visual evoked responses. In Experimental medicine and biology, G.B. Arden (Ed.), 1972, Vol. 24, Plenum, 199-206.

Bergamini,L. and Bergamasco, B. Visual evoked potentials in subjects with congenital anuridia. Electroenceph. clin. Neurophysiol. 1965, 19, 394-397.

Bergamini, L. and Bergamasco,B. Cortical evoked potential in man, 1967, C.C. Thomas, Illinois.

Bergamini, L. Bergamasco, B., Mombelli, A.M., and Cardiglio, G. Visual evoked potentials in subjects with congenital anuridia. Electroenceph. clin. Neurophysiol. 1965, 19, 394-397.

Berger, H. Uber das Elektrenkephalogram des Menschen. Arch. Psychiatr., 1929, 87, 527-570.

Bickford, R.G. The interaction of averaged multisensory responses recorded at the inion. Electroenceph. clin. Neurophysiol., 1964, 17. 713.

Bickford, R.G. Averaged responses and possible sources of artifact. In Averaged evoked potentials: method, results and evaluations. E. Donchin., and D.B. Lindsley, (Eds.) NASA SP-191, 1969, 279-281.

Bickford, R.G., Jacobson, J.J., and Cody, D.T.R. Nature of average evoked potentials to sound and other stimuli in man. Ann. N.Y. Acad. Sci., 1964, 112, 204-223.

Bignall, K.E. Comparison of optic afferents to primary visual and polysensory areas of cat neocortex. Expt. Neurol. 1968, 17, 327-343.

Bignall, K.E., Imbert, M., and Buser, P. Optic projections to non-visual cortex of the cat. J. Neurophysiol., 1966, 396-409.

Bishop, G.H. and Clare, M.H. Sites of origin of electric potentials in striate cortex. J. Neurophysiol., 1952, 15, 201-220.

Blakemore, C. Mechanics of the mind, 1977, Cambridge Univ. Press.

Bodis-Wollner, I. Recovery from central blindness evoked potential and psychophysical measurements. Electroenceph. clin. Neurophysiol., 1977, 42, 178-184.

Bogactz, J., Vanzulli, A., Handler, P., and Garcia-Austt, E. Evoked responses in man. II Habituation of visual evoked response. Acta Neurol. Latinoamer., 1960, 6, 353-362.

Borda, R.P. Visual evoked potentials to flash in the clinical evaluation of the optic pathways. In Visual evoked potentials in man: new developments. J.E. Desmedt (Ed.), Clarendon, 1977, 481-489.

Bostock, H., and Jarvis, M.J. Changes in forms of cerebral evoked response related to the speed of simple reaction time. Electroenceph. clin. Neurophysiol., 1970, 29, 137-145.

Bough, E.W. Stereoscopic vision in the macaque monkey: a behavioural demonstration. Nature, 1970, 225, 42-44.

Bourassa, C.M., Singer, M., Mills, L., and Lynch, M.D., and Groesbeck, R. Photic evoked cortical potentials in functional amblyopia. Canad. J. Ophthal., 1971, 6, 72-78.

Bourne, J.R., Childer, D.G., and Perry, N.W. Topological characteristics of the visual evoked response in man. Electroenceph. clin. Neurophysiol., 1971, 30, 423-436.

Brazier, M.A.B. Some uses of computers in experimental neurology. Exp. Neurol., 1960, 2, 123-143.

Brazier, M.A.B. Evoked responses recorded from the depths of the human brain. Ann. N.Y. Acad. Sci., 1964, 112, 33-59.

Brazier, M.A.B. Varieties of computer analysis of electrophysiological potentials. In The evoked potentials. W. Cobb and C. Morocutti (Eds.), Electroenceph. clin. Neurophysiol., 1967, Suppl.26, 1-8.

Brazier, M.A.B. Electrophysiological studies of the hippocampus in man with averaged response computations. Acta Physiol., Acad. Sci. hung., 1969, 26, 107-116.

Brindley, G.S., and Lewin, W.S. The sensations produced by electrical stimulation of the visual cortex. J. Physiol., 1968, 196, 479-493.

Brodman, K. Vergleichende Lokalisationstehre der Grosshirnrinde. J.A. Barth, 1909, Leipzig.

Bruner, J., and Tauc, L. Habituation at the synaptic level in aplysia. Nature (Lond.), 1966, 210, 37-39.

Buchsbaum, M., and Fedio, P. Visual information and evoked responses from the left and right hemispheres. Electroenceph. clin. Neurophysiol., 1969, 26, 266-272.

Buchsbaum, M., and Fedio, P. Hemispheric differences in evoked potentials to verbal and non-verbal stimuli in the left and right visual fields. Physiol. Behav., 1970, 5, 207-210.

Burian, H.M., and Burns, C.A. A note on senile cataracts and the electroretinogram. Documenta Ophthalmol., 1966, 20, 141-149.

Burns, B.D., and Pritchard, R. Cortical conditions for fused binocular vision. J. Physiol. (Lond.) 1968, 197, 149-171.

Callaway, E. Brain electrical potentials and individual psychological differences, 1975, Grune and Stratton.

Callaway, E., and Halliday, R.A. Evoked potential variability. Effects of age, amplitude and methods of measurement. Electroenceph. clin. Neurophysiol., 1973, 34, 125-133.

Campbell, F.W., and Green, D.G. Optical and retinal factors affecting visual resolution. J. Physiol. (Lond.) 1965, 181, 576-593.

Cappin, J., and Nissim, S. Visual evoked responses in the detection of field defects in glaucoma. Archs. Ophthal., N.Y. 1975, 93, 9-18.

Caroll, W.M., and Mastaglia, F.L. A combined clinical and VEP study of affected and asymptomatic members of a kindred with Leber's Optic Neuropathy. Paper presented at the International Evoked Potential Symposium, 4th to 6th September, 1978, Nottingham, U.K.

Castellini, C. Wandering gaze: source of VER variability. Atti. Fondazione Giorgio Ronchi, 1974, 29, 669-671.

Caton, R. The electric currents of the brain. Brit. Med. J., 1875, 2, 278.

Celesia, G.G., and Daly, R.F. Effects of aging on visual evoked responses. Archiv. Neurol., 1977, 34, 405.

Chalke, F.C.R., and Ertl, J. Evoked potentials and intelligence. Life Sciences, 1965, 4, 1319-1322.

Chang, H.T. Cortical responses to stimulation of lateral geniculate body and the potentiation thereof by continuous illumination of the retina. J. Neurophysiol., 1952, 19, 5-26.

Chang, H.T. The evoked potential. In Handbook of Physiology, Section 1., Neurophysiology, Vol.7, J. Field et al (Eds.), 1959, 299-313.

Chapman, R.M. Human evoked responses to meaningful stimuli. XVIIIth Internat. Congr. Psychol., 1966, 53-59.

Chase, R ., and Kalil, R.E. Suppression of visual evoked responses to flashes and pattern shifts during voluntary saccades. Vision Res. 1972, 12, 215-220.

Chatrian, G.E., Petersen, M.C., and Lazarte, J.A. Responses to clicks from the human brain: some depth electrographic observations. Electroenceph. clin. Neurophysiol., 1960, 12, 479-489.

Choudbury, B.P., Whitteridge, D., and Wilson, M.E. The function of the callosal connections of the visual cortex. Quart. J. Exp. Physiol., 1965, 50, 214-219.

Ciganek, L. Electroencephalographic responses (E.P.) to light stimulation in man. Electroenceph. clin. Neurophysiol., 1961, 13, 165-172.

Ciganek, L. Excitability cycle of the visual cortex in man. Ann. N.Y. Acad. Sci., 1964, 112, 241-253.

Ciganek, L. A comparative study of visual and auditory EEG responses in man. Electroenceph. clin. Neurophysiol., 1965, 18, 625-629.

Ciganek, L. The effects of attention and distraction on the visual evoked potential in man. A preliminary report. Electroenceph. clin. Neurophysiol., 1967, Suppl. 66, 70-73.

Ciganek, L. Variability of the human evoked potential: normative data. Electroenceph. clin. Neurophysiol., 1969, 27, 35-42.

Ciganek, L. Binocular addition of the visually evoked response with different stimulus intensities in man. Vision Res., 1970, 10, 479-487.

Clynes, M., and Kohn, M. Spatial VEP as physiologic language elements for colour and field structure. Electroenceph. clin. Neurophysiol., 1967, Suppl. 26, 82-96.

Cobb, W.A., and Dawson, G.D. Latency and form in man of occipital potentials evoked by bright flashes. J. Physiol., 1965, 152, 108-121.

Cobb, W.A., Ettlinger, G., and Morton, H.B. Visual evoked potentials in binocular rivalry. Electroenceph. clin. Neurophysiol., 1967, Suppl. 26, 100-107.

Cobb, W.A., Morton, H.B., and Ettlinger, G. Cerebral potentials evoked by pattern reversal and their suppression in visual rivalry. Nature, Lond. 1967, 216, 1123-1125.

Cohn, R. Evoked visual cortical responses in homonymous hemianopic defects in man. Electroenceph. clin. Neurophysiol., 1963, 15, 922.

Cohn, R. Visual evoked responses in the brain injured monkey. Arch. Neurol. (Chicago), 1969, 21, 321-329.

Cohn, R. Differential cerebral processing of noise and verbal stimuli. Science, 1971, 172, 599-601.

Cook, J.H., and Arden, G.B. Unilateral retrobulbar neuritis: a comparison of evoked potentials and psychophysical measurements. In Visual evoked potentials in man: new developments, J.E. Desmedt (Ed.), 1977, Clarendon, 450-451.

Cooper, R., Winter, A.L., Crow, H.J., and Walter, W.G. Comparison of subcortical, cortical and scalp activity using chronically indwelling electrodes in man. Electroenceph. clin. Neurophysiol., 1966, 18, 217-228.

Copenhaver, R.M., Beinhocker, G.D. Evoked occipital potentials recorded from scalp electrodes in response to focal visual illumination. Invest. Ophthal., 1963, 2, 393-397.

Copenhaver, R.M., and Perry N.W. Factors affecting visually evoked cortical potentials such as impaired vision of varying etiology. Invest Ophthal., 1964, 3, 665-673.

Cragg, B.G. The topography of the afferent projections in the circumstriate visual cortex of the monkey studied by the Nauta method. Vision Res., 1969, 9, 733-747.

Creutzfeldt, O.D. and Kuhnt, U. The visual evoked potential : physiological developmental and clinical aspects. In The evoked potentials. W. Cobb and C. Morocutti (Eds.), Electroenceph. clin. Neurophysiol., Suppl. 26, Amsterdam, Elsevier, 1967, 29-41.

Creutzfeldt, O., Rosina, A., Ito, M., and Probst, W. Visual evoked response of single cells and of the EEG in primary visual area of the cat. J. Neurophysiol., 1969, 32, 127-139.

Creutzfeldt, O.D., Watanabe, S., and Lux, H.D. Relations between EEG phenomena and potentials of single cortical cells. Electroenceph. clin. Neurophysiol., 1966, 20, 1-18.

Crews, S.J. Personal communication, 1974.

Crews, S.J., Hillman, J.S. and Thompson, C.R.S. Electrodiagnosis and ultrasonography in the assessment of recent major trauma. Trans. Ophthalmal. Soc. U.K., 1975, 95, 315-321.

Crighel, E., and Botoz, M.I. Photic evoked potentials in man in lesions of the occipital lobes. Brain, 1966, 89, 311-315.

Davson, H., and Graham, L.T. Visual functions in man, 1977, Academic Press.

Dawson, G.D. Central responses to electrical stimulation of peripheral nerve in man. J. Neurol. Neurosurg. Psychiat., 1947, 10, 137-140.

Dawson, G.D. A summation technique for detecting small signals in a large irregular background. J. Physiol., Lond., 1951, 115, 2.

Dawson, G.D. A summation technique for the detection of small evoked potentials. Electroenceph. clin. Neurophysiol., 1954, 6, 65-84.

Dawson, W.W., Perry, N.W., and Childers, D.G. Variations in human cortical response to patterns and image quality. Invest. Ophthal., 1972, 11, 789-799.

Desmedt, J.E. (Ed.) Visual evoked potential in man: new developments. 1977, Oxford Univ. Press.

De Valois, R.L. Processing of intensity and wavelength information by the visual system. Invest. Ophthal., 1972, 11, 417-423.

De Voe, R. G., Ripps, H., and Vaughan, J.R. Cortical responses to stimulation of the human fovea. Vision Res., 1968, 8, 135-147.

Dill, R.C., Vallecalle, E., and Verzeano, M. Evoked potentials, neuronal activity and stimulus intensity in the visual system. Physiol. and Behaviour, 1968, 3, 797-801.

Donchin, E.and Lindsley, D.B. Visually evoked response correlates of perceptual masking and enhancement. Electroenceph. clin. Neurophysiol., 1965, 19, 325-335.

Dow, B.M., and Gouras, P. Colour and spatial specificity of single units in rhesus monkey foveal striate cortex. J. Neurophysiol., 1973, 36, 79-100.

Dreher, B. Hypercomplex cells in the cat's striate cortex. Invest. Ophthal., 1972, 11, 355-356.

Dubner, R., and Brown, F.J. Response of cells to restricted visual stimuli in an assocation area of cat cerebral cortex. Exp. Neurol., 1968, 20, 70-86.

Duchowny, M.S., Weiss, I.P., Majlessi, H., and Barnet, A.B. Visual evoked responses in childhood cortical blindness after head trauma and meningitis. A longitudinal study of 6 cases. Neurology (Minneap.), 1974, 24, 933-40.

Dustman, R.E., and Beck, E.C. Phase of alpha brain waves, reaction times and visual evoked potentials. Electroenceph. clin. Neurophysiol., 1965, 18, 433-440.

Dustman, R.E. and Beck, E.C. The effects of maturation and aging on the waveform of visually evoked potentials. Electroenceph. clin. Neurophysiol., 1969, 26, 2-11.

Duwaer, A.L., and Spekreijse, H. Latency of luminance and contrast evoked potentials in multiple sclerosis patients. Electroenceph. clin. Neurophysiol., 1978, 45, 244-258.

Eagling, E.M. Ocular damage after blunt trauma to the eye. Brit. J. Ophthalmol., 1974, 58, 126-140.

Eason, R.G., Groves, P., White, C.T., and Oden, D. Evoked cortical potentials, relation to visual field and handedness. Science, 1967, 156, 1643-1646.

Eason, R.G., and Harter, M.R. Effects of attention and arousal on visually evoked cortical potentials and reaction time in man. Physiol. Behaviour, 1969, 4, 283-289.

Eason, R.G., Oden, D., White, B.A., and White, C.T. Visually evoked cortical potentials and reaction time in relation to site of retinal stimulation. Electroenceph. clin. Neurophysiol., 1967, 22, 313-324.

Eason, R.G., White, C.T., and Bartlett, N. Effects of checkerboard pattern stimulation on evoked cortical responses in relation to check size and visual field. Psychonom. Sci., 1970, 21, 113-115.

Ebersole, J.S., and Galambos, R. Modification of cortical click-evoked response during eye movement in cats. Electroenceph. clin. Neurophysiol., 1969, 26, 273-279.

Eisengart, M.A., and Symmes, D. Effect of eyeblink on the visual evoked response in children. Electroenceph. clin. Neurophysiol., 1971, 31, 71-75.

Ellenberger, C.J.R., and Zeigler, C. Visual evoked potentials and quantitative perimetry in multiple sclerosis. Ann. Neurol., 1977, 1, 561-564.

Ellingson, R.J. Cortical electrical responses to visual stimuli in the human infant. Electroenceph. clin. Neurophysiol., 1960, 12, 663-677.

Ellingson, R.J. Cerebral electrical responses to auditory and visual stimuli in the infant (human and subhuman). In Neurological and electroencephalographic correlative studies in infancy. P. Kellaway and I. Peterson, (Eds.), 1964, Grune and Stratton.

Ellingson, R.J. Variability of visual evoked responses in the human newborn. Electroenceph. clin. Neurophysiol., 1970, 29, 10-19.

Ellingson, R.J., Lathrop, G.H., Danahy, T., and Nelson, B. Variability of visual evoked responses in human infants and adults. Electro-enceph. clin. Neurophysiol., 1973, 34, 113-124.

Elul, R. In Data Acquisition and processing in biology and medicine, Vol. 5, 1968, 93-115, Pergamon Press.

Feinsod, M. Electrophysiological correlates of traumatic visual damage. In Head injuries. R.L. McLaurin (Ed.), 1976, 95-100, Grune and Stratton.

Feinsod, M., and Auerbach, E. Electrophysiological examinations of the visual system in the acute phase after head injury. Eur. Neurol., 1973, 9, 56-64.

Feinsod, M., Hoyt, W.F., Wilson, B.W,, and Spire, J.P. The use of visual evoked potentials in patients with multiple sclerosis. In Visual evoked potentials in man: new developments. J.E. Desmedt (Ed.), 1977, Clarendon, 458-460.

Fenton, T.B., Richards, W., and Smith, R.A. Disparity processing of spatial frequencies in man. J. Physiol., Lond., 1971. 225, 349-362.

Ferris, G.S., Davis, G.D., Dorsen, M.McF., and Hackett, E.R. Changes in latency and form of the photically induced average evoked response in human infants. Electroenceph. clin. Neurophysiol., 1967, 22, 305-312.

Fenwick, P.B.C., Dollimore, J.B., and Walker, S. Digital analysis of EEG in coma. Electroenceph. clin. Neurophysiol., 1969, 26, 535.

Fishman, R .S. and Copenhaver, R.M. Macula disease and amblyopia. Arch. Ophthal. (Chic.), 1967, 77, 718-725.

Fleming, D.E. Modified pupillary diameter and evoked potential component variation in waking cats. Electroenceph. clin. Neurophysiol., 1969, 27, 84-86.

Florentini, A., and Maffei, L. Evoked potentials in astigmatic patients. Vision Res., 1973, 13, 1781-1783.

Fox, S.S., and O'Brien, J.H. Duplication of evoked potential waveform by curve of probability of firing of single cell. Science, 1965, 147, 888-890.

Fricker, S.J. Analysis of the visual evoked response by synchronous detector techniques. 1. Patients with cataracts. Invest. Ophthalmol., 10, 1971, 340-347.

Fromm, G.H., and Bond, H.W. The relationship between neuron activity and cortical steady potentials. Electroenceph. clin. Neurophysiol., 22, 1967, 159-166.

Frolkis, V.V. Regulatory process in the mechanism of aging. Introd. Lecture verbatim report. Exp. Gerout. 1968, 3, 113-123.

Fromm, G.H., and Glass, J.D. Influence of cortical steady potential on evoked potential and neuron activity. Exp. Neurol., 1970, 27, 426-437.

Frommer, G.P., Galambos, R., and Norton, T.T. Visual evoked responses in cats with optic tract lesions. Exp. Neurol., 1968, 21, 346-363.

Frumkes. T .E., Battersby, W.S., and Storck, L.E. Spatial organization of cat visual system. I. - distribution and interaction of photic response in cortex. Electroenceph. clin. Neurophysiol. 1972, 32, 383-394.

Fukada, Y., and Saito, H. Directionally sensitive units in the cat's lateral geniculate nucleus. In The visual system. G.B. Arden (Ed.), 1972, Plenum Press, 125-136.

Gaitz, C.M. (Ed.) Aging and the brain. Advances in behaviour biol. Vol.3. 1972, Plenum.

Galbraith, G.C. The effect of prior EEG coupling upon the visual evoked response. I.E.E.E. Trans. Biomed. Engin., 1967, 14, 223-229.

Galloway, N.R. Ophthalmic electrodiagnosis. Major problems in ophthalmology. Vol. 1, 1975, Saunders.

Galun, R., Hillman, P., Parnas, I., and Werman, R. (Eds.). Sensory physiology and behaviour. Vol. 15, Adv. in behav. biol., 1975, Plenum.

Garcia-Austt, E. Influence of states of awareness upon sensory evoked potentials. Electroenceph. clin. Neurophysiol., 1963, Suppl. 24, 76-89.

Garcia-Austt, E., Bogacz, J., and Vanzulli, A. Effects of attention and inattention on visual evoked responses. Electroenceph. clin. Neurophysiol. 1964, 17, 136-143.

Garcia-Austt, E., and Vanzulli, A. Evoked responses and perceptual changes. Electroenceph. clin. Neurophysiol., 1970, 28, 518-521.

Gastaut, H., and Regis, H. Visually evoked potentials recorded transcranially in man. Symposium on the analysis of central nervous system and cardiovascular data using computer methods. NASA, Washington, Oct. 1964.

Gastaut, H., and Regis, H. The visually evoked potentials recorded transcranially in man. In L.D. Proctor and W.R. Adey (Eds.), NASA symposium on the analysis of central nervous system and cardiovascular data using computer methods. NASA, SP-72, Washington, 1965, 7-34.

Gastaut, H., and Regis, H. Le potentiel evoque visuel moyen (P.E.V.M.) chez l'homme normal dans des conditions standards. Relation avec les ondes lambda. In Les activities electrique cerebrales spontanees et evoquees chez l'homme. H. Gastaut (Ed.), 1967, Gauthier-Villare, Paris, 46-48.

Gibbs, F.A., Davis, H., and Lennox, W.G. The electroencephalogram in epilepsy and in conditions of impaired consciousness. Arch. Neurol. Psychiat. (Chicago), 1935, 34, 1133-1148.

Glickstein, M. Organization of the visual pathways. Science 1969, 164, 917-926.

Gouras, P., and Link, K. Rod and cone interaction in dark-adapted monkey ganglion cells. J. Physiol., 1966, 184, 499-510.

Grader, J., and Heller, G.L. Photic stimulation and the EEG in macula disease. Arch. Ophthal., 1964, 72, 763.

Graham, C.H. (Ed.) Vision and visual perception, 1965, Wiley, New York.

Grandstaff, N.W., and Pribram, K.H. Habituation: electrical changes in the visual system. Neuropsychologia, 1972, 10, 125-132.

Gross, E.G., Vaughan, H.G., and Valenstein, E. Inhibition of visual evoked responses to patterned stimuli during voluntary eye movements. Electroenceph. clin. Neurophysiol., 1967, 22, 204-209.

Groth, H., Weled, B., and Batkin, S. A comparison of monocularity visually evoked potentials in human neonates and adults. Electroenceph. clin. Neurophysiol.,1970, 28, 478-487.

Guerrero-Figueroa, R., and Heath, R.G. Evoked responses changes during attentive factors in man. Arch. Neurol. (Chicago), 1964, 10, 78-84.

Guvener, A.M., and Bagchi, B.K. Visual evoked responses in visual pathway lesions. J. Physiol., 1965, 31, 227.

de Haas, J.P. Electrophysiological examination of central scotomata due to pathological changes in the optic nerve. In The optic nerve, J.S. Cant (Ed.), 1972, Henry Kimpton, 79-87.

Haider, M., Spong, P., and Lindsley, D.B. Cortical evoked potentials during visual vigilance task performance. Electroenceph. clin. Neurophsiol., 1964, 17, 710-715.

Haider, M., Spong, P., and Lindsley, D.B. Attention, vigilance and cortical evoked potentials in humans. Science, 1965, 145, 180-182.

Halliday, A.M. International evoked potential symposium, Nottingham, 1978.

Halliday, A.M., Barrett, G., Halliday, E., and Michael, W.F. The topography of the pattern-evoked potential. In Visual evoked potentials in man : new developments, J.E. Desmedt (Ed.), 1977, Clarendon Press, 121-133.

Halliday, A.M., Halliday, L, Kriss, A., McDonald, W.I., and Mushin, J. Changes in pattern evoked responses in compressive lesions of the anterior visual pathways. Electroenceph. clin. Neurophysiol., 1976, 40, 41.

Halliday, A.M., McDonald, W.I., and Mushin, J. Delayed visual evoked response in optic neuritis. Lancet, 1972, 1, 982-985.

Halliday, A.M., McDonald, W.I., and Mushin, J. Visual evoked response in diagnosis of multiple sclerosis. Brit. Med. J., 1973, 4, 661-664.

Halliday, A.M., McDonald, W. I., and Mushin, J. Delayed visual evoked response in progressive spastic paraplegia. Electroenceph. clin. Neurophysiol., 1974, 37, 328.

Halliday, A.M., McDonald, W.I., and Mushin, J. Visual evoked potentials in patients with demyelinating disease. In Visual evoked potentials in man : new developments, J.E. Desmedt (Ed), 1977, Clarendon, 438-449.

Harden, A., Pampiglione, G., and Picton-Robinson, N. Electroretinogram and visual evoked responses in a form of 'neuronal lipidosis' with diagnostic EEG features. J. Neurol. Neurosurg. Psychiat. 1973, 36, 61-67.

Harden, A., and Pampiglione, G. Visual evoked potentials, electroretinogram and electroencephalogram studies in progressive neurometabolic 'storage' diseases of childhood. In Visual evoked potentials in man : new developments. J.E. Desmedt (Ed.), 1977, Clarendon, 470-480.

Hardin,W.B., and Castellucci, V.F. Analysis of somatosensory, auditory and visual averaged transcortical and scalp responses in monkey. Electroenceph. clin. Neurophysiol., 1970, 28, 488-498.

Harding, G.F.A. The visual evoked response. Adv. Ophthal, 1974, 28, 2-28.

Harding, G.F.A. The use of the visual evoked potentials to flash stimuli in the diagnosis of visual defects. In Visual evoked potentials in man : new developments. J.E. Desmedt (Ed.), 1977, Clarendon, 500-508.

Harding, G.F.A., Thompson, C.R.S., and Panayiotopoulos, C. Evoked response diagnosis in visual field defects. Proc. electrophysiol. Technol.Ass. 1970, 16, 159-163.

Harris, J.A., and Bickford, R.G. Cross-sectional plotting of EEG potential fields. Electroenceph. clin. Neurophysiol., 1967, 23, 88.

Harter, M.R. Visually evoked cortical responses to checkerboard patterns: effects of check size as a function of retinal eccentricity. Electroenceph. clin. Neurophysiol., 1970, 28, 48-54.

Harter, M.R. Visual evoked cortical responses to the on-and-off set of patterned light in humans. Vision Res. 1971, 11, 685-695.

Harter, M.R. and Salmon, L.E. Evoked cortical responses to patterned light flashes: effects of ocular convergence and accommodation. Electroenceph. clin. Neurophysiol., 1971, 30, 527-533.

Harter, M.R., Seiple, W.H., and Musso, M. Binocular summation and suppression: visually evoked cortical responses to dichoptically presented patterns of different spatial frequencies. Vision Res., 1974, 14, 1169-1180.

Harter, M.R., and Suitt, C.T. Visually evoked cortical responses and pattern vision in infants. Psychonom. Sci., 1970, 18, 235-237.

Harter, M.R., and White, C.T. Effects of contour sharpness and check size on visually evoked cortical potentials. Vision Res., 1968, 8, 701-711.

Hata, I. The study of visual evoked potential obtained by light stimulation in amblyopia. Acta Soc. Ophthal. Japan, 1966, 70, 719-725.

Heath, R.G., and Galbraith, G.C. Sensory evoked responses recorded simultaneously from human cortex and scalp. Nature, 1966, 212, 1535-1537.

Hernandez-Peon, R., Guzman-Flores, C., Alcaraz, M., and Fernandez-Guardiola, A. Sensory transmission in visual pathway during 'attention' in unanaesthetised cats. Acta Neurol. Latinoamer., 1957, 3, 1-18.

Holder, G.E. The effect of chiasmal compression on the pattern visual evoked potential. Electroenceph. clin. Neurophysiol., 1978, 45, 278-280.

Howe, J.W., and Harcourt, R.B. The effects of cerebrovascular disturbances upon visually evoked cortical responses with particular reference to cases of homonymous hemianopia. In Vision and circulation, J. Stanley (Ed.), 1976, Henry Kimpton, 22-28.

Hrbek, A., Karlberg, P, and Olsson, T. Development of visual and somatosensory evoked responses in preterm newborn infants. Electroenceph. clin. Neurophysiol., 1973, 34, 225-232.

Hrbek, A., and Mares, P. Cortical evoked responses to visual stimulation in full-term and premature infants. Electroenceph. clin. Neurophysiol., 1964, 16, 575-581.

Hrbek, A., Vitova, Z., and Mares, P. The development of cortical evoked responses to visual stimulation during childhood. Activ. nerv. sup. (Praha), 1966, 8, 39-46.

Hubel, D.H. Specificity of responses of cells in the visual cortex. J. Psychiat., 1971, 8, 301-307.

Hubel, D.H., and Wiesel, T.N. Receptive fields, binocular interaction and functional architecture in the cat's visual cortex. J. Physiol., 1962, 160, 106-154.

Hubel,D.H., and Wiesel, T.N. Receptive fields and functional architecture in two non-striate visual areas (18 and 19) of the cat. J. Neurophysiol., 1965, 28, 229-289.

Hubel, D.H., and Wiesel, T.N. Binocular interaction in the cat's visual cortex. J. Neurophysiol., 1967, 30, 1561-1563.

Hubel, D.H., and Wiesel, T.N. Receptive fields and functional architecture of monkey striate cortex. J. Physiol., 1968, 195, 215-243.

Hubel, D.H., and Wiesel, T.N. Stereoscopic vision in the macaque monkey. Nature, Lond., 1970, 225, 41-42.

Huber, C., and Adachi-Usami, E. Scotopic visibility curve in man obtained by the VER. Adv. Exp. Med. Biol., 1972, 24, 189-198.

Humphrey, D.R. Re-analysis of the antidromic cortical response. II.On the contribution of cell discharge and PSPs to the evoked potentials. Electroenceph. clin. Neurophysiol., 1968, 25, 421-424.

Jacobson, J., Hirose, T., and Suzuki, T.A. Combined recording of the ERG and visual evoked occipital responses (VER) in lesions of the visual pathways. Invest. Ophthal., 1968, 7, 279-292.

Jasper, H. Report of a committee on methods of clinical examination in electroencephalography. Electroenceph. clin. Neurophyisiol., 1958, 10, 370-375.

Jayle, G.E., and Tassy, A.F. Prognostic value of the electro-retinogram in severe recent ocular trauma. Brit. J. Ophthal., 1970, 54, 51-58.

Jeffreys, D.A. Striate and extra-striate origins of pattern related visual evoked potential (VEP) components. J. Physiol., 1971, 211, 29-30.

Jeffreys, D.A. The physiological significance of pattern visual evoked potentials. In Visual evoked potentials in man: new developments. J.E. Desmedt (Ed.), 1977, Clarendon, 134-167.

Jeffreys, D.A., and Axford, J.G. Source location of pattern-specific components of human visual evoked potentials. I. Components of striate cortical origin. Exp. Brain Res., 1972a, 16, 1-21. II. Components of extra-striate cortical origin. Exp. Brain Res., 1972b, 16, 22-40.

John, E.R., Herrington, R.N., and Sutton, S. Effects of visual form on the evoked response. Science, 1967, 195, 1439-1442.

John, E.R., and Morgades, P.P. The pattern and anatomical distribution of evoked potentials and multiple unit activity elicited by conditioned stimuli in trained cats. Communications in Behavioural Biol., 1969, 3, 181-207.

Jonkman, E.J. The average cortical response to photic stimulation. A study of normal subjects and neurological patients. Unpub. Ph D. dissertation, St Ursula Kliniek, Wassenaar, 1967.

Joshua, D.E., and Bishop, P.O. Binocular single vision and depth discrimination. Receptive field disparities for central and peripheral vision and binocular interaction on peripheral single units in cat striate cortex. Exp. Brain Res., 1970, 10, 389-416.

Julesz, B. Binocular depth perception of computer generated patterns. Bell System Tech. J., 1960, 39, 1125-1162.

Jung, R. (Ed.) Visual centres of the brain. Handbook of sensory physiology. Vol. 7/3, Part B., 1973, Springer-Verlag.

Kakigi, S., Miyazaki, M., and Mori, T. Human visual evoked response as a function of stimuli size and density of patterned stimulus. Jap. Psychol. Res., 1972, 14, 133-140.

Katzman, R. The validity of the visual evoked response in man. Ann. N.Y. Acad. Sci., 1964, 112, 238-240.

Kawasaki, K., Hirose, T., Jacobson, J.H., and Cordella, A.M. Binocular fusion: Effect of breaking on the human visual evoked response. Arch. Ophthal. (Chicago), 1970, 84, 25-28.

Kelly, D.L., Goldring, S., and Leary, J.L. Averaged evoked somatosensory responses from exposed cortex in man. Arch. Neurol., 1965, 13, 1-9.

Kennerdell, J.S. Evaluation of eyes with opaque anterior segments, using both ultrasonography and electroretinography. Amer. J. Ophthalmol., 1973, 853-860.

Kinney, J.A., McKay, C.L., Mensch, A.J., and Luria, S.M. Visual evoked potentials elicited by rapid stimulation. Electroenceph. clin. Neurophysiol., 1973, 34, 7-13.

Kitajima, H. On the cerebral evoked response in man as a function of the intensity of flick stimulation. Electroenceph. clin. Neurophysiol., 1967, 22, 325-336.

Kitasato, H. The relation between photic driving of EEG and the response evoked by photic stimulation in man. Jap. J. Physiol., 1966, 16, 238-253.

Kooi, K.A. Fundamentals of electroencephalography, 1971. Harper and Row.

Kooi, K.A., and Bagchi, B.K. Observations on early components of the visual evoked response and occipital rhythms. Electroenceph. clin. Neurophysiol., 1964, 17, 638-643.

Kooi, K.A., Guevener, A.M., and Bagchi, B.K. Visual evoked responses in lesions of the higher optic pathways. Neurology, 1965, 15, 841.

Kooi, K.A., Tucker, R.P., Danial, J., and Marshall, R.E. Foveal and extra foveal influences on the topography of the visually evoked, early negative potential in man. Electroenceph. clin. Neurophysiol., 1972, 33, 129-139.

Kooi, K.A., Yama nda, T., and Marshall, R.E. Binocular and monocular visual evoked responses in the differential diagnosis of psychogenic and disease-related visual disorders. Internat. J. Neurol., 1975, 9, 272-286.

Kopell, B.S., Wittner, W.K., and Warride, G.L. The effects of stimulus differences, light intensitv and selective attention on the amplitude of the visual averaged evoked potential in man. Electroenceph. clin. Neurophysiol., 1969, 26, 619-622.

Kurtzburg, D., and Vaughan, H.G. Electrocortical potentials associated with eye movement. Science, 1971, 146, 1325-1327.

Kurtzburg, D., and Vaughan, H.G. Electrocortical potentials associated with eye movements. In The oculomotor system and brain functions. V. Zikmund, (Ed.), 1973, Butterworths, 137-146.

Larsson, L.E. Correlation between the psychological significance of stimuli and the magnitudes of the startle blink and evoked EEG potentials in man. Acta Physiol. Scand., 1960, 48, 276-294.

Lehmann, D., and Fender, D.H. Monocularly evoked electroencephalogram potentials: influence of target structure presented to the other eye. Nature, 1967, 215, 204-205.

Lehmann, D., Kavanagh, R.N., and Fender, D.H. Field studies of averaged visually evoked potentials in a patient with a split chiasm. Electroenceph. clin. Neurophysiol., 1969, 26, 193-199.

Lehtonen, J.B. Functional differentiation between late components of visual evoked potentials recorded at occiput and vertex: Effect of stimulus interval and contour. Electroenceph. clin. Neurophysiol., 1973, 35, 75-82.

Lewis, E.G., and Beck, E.C. Cerebral evoked response similarity in monozygotic, dizogotic and unrelated individuals. Proc. Amer. Psychol. Assoc. 1970, 78, 181-182.

Li. C.L., Cullen, C., and Jasper, H.H. Laminar microelectrode studies of specific somatosensory cortical potentials. J. Neurophysiol., 1956, 19, 111-130.

Liftshitz, K. The average evoked cortical response to complex visual stimuli. Psychophysiol., 1966, 3, 55-68.

Lombroso, C.T., Duffy, F.H., and Robb, R.M. Selective suppression of cerebral evoked potentials to patterned light in amblyopia ex anopsia. Electroenceph. clin. Neurophysiol., 1969, 27, 238-247.

Mackay, D.M., and Jeffreys, D.A. In Central processing of visual information, handbook of sensory physiology, 1971, Springer Verlag.

Magladery, J.W. Neurophysiology and aging. In Handbook of aging and the individual. J.E. Birren (Ed.), 1959, Univ. of Chicago Press.

Marsh, J.T., and Worden, F.G. Auditory potentials during acoustic habituation: cochlear nucleus, cerebellum and auditory cortex. Electroenceph. clin. Neurophysiol., 1964, 17, 685-692.

Martin, J.I. Effects of binocular fusion and binocular rivalry on cortical evoked potentials. Electroenceph. clin. Neurophysiol., 1970, 28, 190-201.

Matsumiya, Y., Gennarelli, T.A., and Lombroso, C.T. Somatosensory evoked response in the hemispherectomized man. Electroenceph. clin. Neurophysiol., 1972, 33, 25-28.

May, J.G., Forbes, W.B., and Piantanida, T.P. The visual evoked responses obtained with an alternating barred pattern: rate, spatial frequency and wave-length. Electroenceph. clin. Neurophysiol., 1971, 30, 222-228.

Michael, W.F., and Halliday, A.M. Differences between the occipital distribution of upper and lower field pattern evoked responses in man. Brain Res., 1971, 32, 311-324.

Milner, B.A., Regan, D., and Heron, J.R. Theoretical models of the generation of steady-state evoked potentials: their relation to certain clinical problems. Adv. Exp. Med. Biol., 1972, 24, 157-169.

Minkowsky, K., and Sato, K. Properties and origins of photically evoked potential components in rabbit cortex. Int. J. Neuro. Sci., 1970, 1, 75-85.

Morocutti, C., Sommer-Smith, J.A., and Creutzfeldt, O.D. A study of visual evoked potentials in normal subjects and in patients with cerebral disease. Electroenceph. clin. Neurophysiol., 1964, 17, 585.

Morrell, F. Electrical signs of sensory coding. In Neurosciences: a study programme, G.C. Quarton, T. Melnechuk, and F.O. Schmitt (Eds.), 1967, Rockefeller Univ. Press, N.Y., 452-469.

Morrell, L.K., and Morrell, F. Evoked potentials and reaction times: a study of intra-individual variability. Electroenceph. clin. Neurophysiol., 1966, 20, 567-575.

Muller, W. Correlations between VER and ERG with particular consideration of clinical aspects. In Advances in electrophysiology and pathology of visual system. E. Schmoger (Ed.), 6th Iscerg Symposium, 1968, Thiene, Leipzig.

Myers, R.E. Commissural connections between occipital lobes of the monkey. J. comp. Neurol., 1972, 118, 1-16.

McAdam, D.W. Increase in CNS excitability during negative cortical slow waves in man. Electroenceph. clin. Neurophysiol., 1969, 26, 216-219.

McAlpine, D., Lumsden, C.E., and Acheson, E.D. Multiple sclerosis: a reappraisal, 1972, Churchill-Livingstone, Edinburgh.

McKay, C.L., and Kinney, J.A.S. Similarities between the cortical extracted pattern responses with bipolar and monopolar recordings. Vision Res., 1976, 16, 1510-1512.

Näätänen, R. Selective attention and evoked potentials. Am. Acad. Sci. Fin. 1967, 151, 1-226.

Nagata, M., and Jacobson, J.H. Combined ERG amd occipital response recording. In Clinical electroretinography, H.M. Burian and J.H. Jacobson (Eds.), 1964, Pergamon, 235-247.

Nash, M.D., and Fleming, D.E. The dimensions of stimulus complexity and the visual evoked response. Neuropsychologia, 1970, 8, 171-177.

Nawratzki, I. The electrical responses in the retina and occipital cortex following photic stimulation of normal and amblyopic eyes. Amer. J. Ophthal., 1966, 61, 430-435.

Ogden, T.E. and Miller R.F. Studies of the optic nerve of the rhesus monkey: nerve fiber spectrum and physiological properties. Vision Res., 1966, 6, 485-506.

Ogle, K.N. Spatial localization through binocular vision. In The eye. Vol.4, 1964, Academic Press.

Obrist, W.D., and Booth, C.E. Longitudinal study of EEG in old age. Excerpta med. Int. Congr. Series, 1965, 37, 180-181.

Ohba, N. Visual evoked responses in man by localized retinal stimulation. Jap. J. Ophthal., 1967, 2, 221-226.

Ommaya, A.K. A physiopathologic basis for non-invasive diagnosis and prognosis of head injury severity. In Head injuries, R.C. McLaurin (Ed.), 1976, Grune Stratton, 49-77.

Oosterhuis, H.J.G., Ponsen, L., Jonkman, E.G., and Magnus, O. The average visual response in patients with cerebrovascular disease. Electroenceph. clin. Neurophysiol., 1969, 27, 23-34.

Orpin, J.A., Orpin, E., and McCullogh, C. The evoked cortical potential in macula degeneration. J. Am. Geriatr. Soc., 1974, 22, 536 -537.

Otomo, R. Uber Aufbau und Gliederung der corticelen Sehsphare bei der Katze. Arch. Psychiat. Nervenkr., 1966, 202, 212-234.

Pagni, C.A., Ettorre, G., Maroserro, F., and Cassinari, V. Primary visual potentials in man during repetitive photic stimulation. Experientia, 1964, 20, 641-645.

Pampiglione, G. Some observations on the variability of evoked potentials. In The evoked potentials, W. Cobb and C. Morocutti, (Eds.), Electroenceph. clin. Neurophysiol., 1967, Suppl.26, 97-99.

Pasik, P., and Pasik, T. Extrageniculostriate vision in the monkey. V. Role of accessory optic system. J. Neurophysiol., 1973, 36, 450-457.

Peacock, S.M., and Conroy, R.C. Further considerations of the regional response to photic stimulation as shown by epoch averaging. Electroenceph. clin. Neurophysiol., 1974, 36, 171-178.

Perry, N.W., Childers, D.G., and McCoy, J.G. Binocular addition of the visual evoked response at different cortical locations. Vision Res., 1968, 8, 567-573.

Perry, N.W., and Childers, D.G. The Human visual evoked response. Method and theory., 1969, C.C. Thomas, Springfield, Illinois.

Perry, N.W., and Copenhaver, R.M. Differential cortical habituation with stimulation of central and peripheral retina. Percept. Motor Skills, 1965, 20, 1209-1213.

Perrson, H.E., and Sachs, C. Provoked visual impairment in multiple sclerosis by visual evoked responses. Electroenceph. clin. Neurophysiol., 1978, 44, 664-668.

Petrek, J., Golda, V., and Lisonek, P. Acoustic evoked potentials and the amplitude of the EEG. Electroenceph. clin. Neurophysiol., 1968, 25, 579-581.

Pettigrew, J.D. Binocular neurons which signal change of disparity in area 18 of cat visual cortex. Nature, 1973, 241, 123-124.

Pettigrew, J.D., Nikara, T., and Bishop, P.O. Responses to moving slits by single units in cat striate cortex. Exp. Brain Res., 1968, 6, 373-390.

Picton, T.W., Hillyard, S.A., Krausz, H.I., and Galambos, R. Human auditory evoked potentials. I. evaluation of components. Electroenceph. clin. Neurophysiol., 1974, 36, 179-190.

Poggio, G.F. Central neural mechanism in vision. In Medicine physiology. V.B. Mountcastle (Ed.), 1968, Vol.2., Mosby, St Louis, 1592-1625.

Pollen, D., and Ronner, S.F. Periodic excitability changes across the receptive fields of complex cells in the striate and parastriate cortex of the cat. J. Physiol. Lond., 1975, 245, 667-697.

Polyak, S. The vertebrate visual system, 1957. Univ. of Chicago Press.

Potts, A.M. and Nagaya, T. Studies on the visual evoked response. I. The use of a 0.06 degree red target for evaluation of foveal function. Invest. Ophthal., 1965, 5, 303-309.

Potts, A.M. and Nagaya, T. Studies on the visual evoked response. III. Strabismus amblyopia and hysterical amblyopia. Ophthal. Docum., 1969, 26, 394-402.

Pouliquen, A., Levillain, D., Gray, F., Samson-Dollfus, D., Rogler, M. Quatre cas anatomocliniques d'hemianopsies laterales homonymes etudies a l'aide des potentiels evoques. Oto-Neuro-Ophth., 1974, 46, 133-136.

Pritchard, J.W., Chimienti, J., and Galambos, R. Evoked responses from extracranial sites in the cat. Electroenceph. clin. Neurophysiol.. 1965, 18, 493-499.

Purpura,D.P. Nature of electrocortical potentials. Int. Rev. Neurobiol., 1959, 1, 47-164.

Purpura, D.P., and McMurty, J.G. Intracellular activities and evoked potential changes during polarization in the motor cortex. J. Neurophysiol., 1965, 28, 166-185.

Regan, D. An effect of stimulus colour on average steady-state potentials evoked in man. Electroenceph. clin. Neurophysiol., 1966a, 20, 238-248.

Regan, D. An effect of stimulus colour on average steady-state potentials. Nature, 1966b., 210, 1056-1057.

Regan, D. Evoked potentials. In Psychology, sensory physiology and clinical medicine, 1972, Chapman and Hall.

Regan, D., and Cartwright, R.F. A method of measuring the potentials evoked by simultaneous stimulation of different retinal regions. Electroenceph. clin. Neurophysiol., 1970, 28, 314-319.

Regan, D., and Milner, B.A. Objective perimetry by evoked potential recording, limitations. Electroenceph. clin. Neurophysiol., 1978, 44, 393-397.

Regan, D., Milner, B.A., and Heron, J.R. Delayed visual perception and delaved visual evoked potentials in the spinal form of multiple sclerosis and in retrobulbar neuritis. Brain, 1976, 99, 43-46.

Regan, D., and Richards, W. Independence of evoked potentials and apparent size. Vision. Res., 1971, 11, 679-684.

Regan, R., and Spekreijse, H. Electrophysiological correlate of binocular depth perception in man. Nature, 1970, 225, 92-94.

Reilly, E.L., Kondo, C., Brunberg, J.A., and Doty, D.B. Visual evoked potentials during hypothermia and prolonged circulatory arrest. Electroenceph. clin. Neurophysiol., 1978, 45, 100-106.

Remond, A. Evoked brain potentials as indicators of sensory information processing. Neurosci. Res. Prog. Bull., 1969, 7, 240-242.

Remond, A., and Lesevre, N. Variations in average visual evoked potentials as a function of the alpha phase. In The evoked potentials. W. Cobb and C. Morocutti, (Eds.), Electroenceph. clin. Neurophysiol., 1967, Suppl. 26, 42-52.

Rhodes, L.E., Dustman, R.E., and Beck, E.C. The visual evoked response: a comparison of bright and dull children. Electroenceph. clin. Neurophysiol., 1969, 27, 364-372.

Richard, W. Spatial re-mapping in the primate visual system. Kybernetik, 1968, 4, 146-156.

Richard, W. Stereopsis and stereoblindness. Exp. Brain Res., 1970, 10, 380-388.

Rietveld. W.J. The occipito-cortical response to light flashes in man. Acta physiol. pharmacol. neerlandica, 1962, 12, 313-407.

Rietveld, W.J., Tordoir, W.E., and Duyff, J.W. Contribution of fovea parafovea to the visual evoked response. Acta physiol. pharmacol., neerl., 1965, 13, 330-339.

Rietveld, W.J., Tordoir, W.E., and Hagenouw, J.R.B. Influence of attentiveness, of vigilance task difficulty, and of habituation on cortical evoked responses and on artifacts. Acta physiol., pharmacol., neerl., 1966, 14, 18-37.

Rietveld, W.J., Tordoir, W.E., Hagenouw, J.R.B., Lubbers, J.A., and Spoor, A.C. Visual evoked responses to blank and to checkerboard patterned flashes. Acta physiol., pharmacol., neerl., 1967, 14, 259-289.

Ristanovic, D., and Dokic-Ristanovic, D. A dipole representation of the human visual cortex. Acta Med. Iugosl., 1971, 25, 369-378.

Ritter. W., and Vaughan. H.G. Averaged evoked responses in vigilance and discrimination: a reassessment. Science 1969, 164, 326-328.

Ritter, W., Vaughan, H.G., and Costa, L.D. Orientating and habituation to auditory stimuli: a study of short-term changes in average evoked potentials. Electroenceph. clin. Neurophysiol., 1968, 25, 550-556.

Roth, W.T., Kopell, B.S., and Bertozzi, P.R. The effect of attention on the averaged evoked response and speech sounds. Electroenceph. clin, Neurophysiol., 1970, 29, 38-46.

Russell, M.R. and White, C.T. Evoked cortical responses to checkerboard patterns: effect of check-size as a function of visual acuity. Electroenceph. clin. Neurophysiol., 1970, 28, 48-54.

Saletu, B., Itil, T.M., and Saletu, M. Evoked responses after hemispherectomy. Confin. Neurol., 1971, 33, 221-230.

Sandberg, M.A., Berson, E.L., and Ariel, M. Visual evoked response testing with a stimulator ophthalmoscope - macula scars, hereditary macula degenerations and retinitis pigmentosa. Arch. ophthalmol., 1977, 95, 1805-1809.

Sandler, L.S., and Schwarts, M. Evoked responses and perception stimulus content versus stimulus structure. Psychophysiology. 1971, 8, 727-739.

Sayers, B.M., Beagley, H.A., and Henshall, W.R. The mechanism of auditory evoked EEG responses. Nature, 1972, 247, 481-484.

Schechter, G., and Buchsbaum, M. The effects of attention, stimulus intensity, and individual differences on the average evoked response. Psychophysiol., 1973, 10, 392-400.

Schenkenberg, T. Visual, auditory and somatosensory evoked responses in normal subjects from childhood to senescence. Unpub. Ph D. dissertation, 1970, Univ. of Utah.

Schenkenberg, T., and Dustman, R.E. Visual, auditory and somatosensory evoked response changes related to age, hemisphere and sex. Proc. Amer. Psychol. Assoc., 1971, 78, 183-184.

Schenkenberg, T., Dustman, R.E., and Beck, E. Cortical evoked responses of hospitalized geriatrics in diagnostic categories. Proceed. 80th Annual Convention, APA, 1972, 671-672.

Schreinemachers, H.P., and Henkes, H.E. Relation between localized retinal stimuli and the visual evoked response in man. Ophthalmologica (Basel) 1968, 155, 17-27.

Scott, D.F. and Bickford, R.G. Stimulus indicators of summated human lambda responses. Archiv. Neurol. Chicago, 1968, 21, 277-284.

Shagass, C. Subject factors related to variability of averaged evoked responses. Electroenceph. clin. Neurophysiol., 1966, 20, 92-104.

Shagass, C. Evoked brain potential in psychiatry 1972 Plenum. New York.

Shagass, C., Amades, M., and Roener, R.A. Spatial distribution of potential evoked by half-freed pattern reversal and pattern-onset stimuli. Electroenceph. clin. Neurophysiol., 1976, 41, 609-622.

Shagass, C., and Schwartz, M. Age, personality and somatosensory evoked potentials. Science, 1965, 148, 1359-1361.

Sharrad, G.A.W. Evoked responses - Introductory studies on their relationship to the perception of language. J. Laryng. and Otol., 1969, 83, 947-958.

Shelburne, S.A. Visual evoked responses to word and nonsense syllable stimuli. Electroenceph. clin. Neurophysiol., 1972, 32, 17-25.

Shelburne, S.A. Visual evoked responses to language stimuli in normal children. Electroenceph. clin. Neurophysiol., 1973, 34, 135-143.

Shipley, T., Jones, R .W., and Fry. A. Intensity and the evoked occipitogram in man. Vision Res., 1966, 6, 657-667.

Simmons, L.A., Dunlop, C.W., Webster, W.R., and Aitkin, L.M. Acoustic habituation in cats as a function of stimulus rate and the role of temporal conditioning of the middle ear muscles. Electroenceph. clin. Neurophysiol., 1966, 20, 482-493.

Singer, W. Brain stem stimulation and inhibition in the cat. Brain Res., 1973, 61, 55-68.

Sokol, S. An electrodiagnostic index of macula degeneration. Arch. Ophthal., 1972, 88, 619-624.

Spehlmann, R. The averaged electrical responses to diffuse and to patterned light in the human. Electroenceph. clin. Neurophysiol., 1965, 19, 560-569.

Speigel, M.R. Theory and problems of statistics, 1961. Schaum, N.Y.

Spekreijse, H. Analysis of EEG responses in man, 1966. Junk Pub., The Hague.

Spekreijse, H., Estervez, O., and Reits, D. Visual evoked potentials and the physiological analysis of visual processes in man. In Visual evoked potentials in man: new developments. J.E. Desmedt (Ed.), 1977, Clarendon, 16-89.

Spekreijse, H., Khoe, L.H., and Van der Tweel, L.H. A case of amblyopia: electrophysiology and psychophysics of luminance and contrast. In The visual system, G.B. Arden (Ed.), 1972, Plenum, N.Y. 141-156.

Sperry, R.W. Physiological plasticity. In Perceptual learning and adaptation, P.C. Dodwell (Ed.), 1970, Baltimore, 70-85.

Spinelli, D.N., Pribram, K.H., and Bridgeman, B. Visual receptive field organization of single units of the visual cortex of monkey. Intern. J. Neuroscience, 1970, 1, 67-74.

Spong, P., Haider, M., and Lindsley, D.B. Selective attentiveness and cortical evoked responses to visual and auditory stimuli. Science,1965, 148, 395-397.

Stone, J. Specialized receptive fields of the cat's retina. Science, 1966, 152, 1277-1279.

Straumanis, J.J., Shagass, C., and Schwartz, M. Visual evoked cerebral response changes associated with chronic brain syndromes and ageing. J. Gerontol., 1965, 20, 498-506.

Sutton, S. The specification of psychological variables in an average evoked potential experiment. In Average evoked potentials: methods, results and evaluations. E. Donchin and D.B. Lindsley (Eds.) 1969, NASA, Washington, D.C., 237-297.

Sutton, S., Braren, M., abd Zubin, J. Evoked potential correlates of stimulus uncertainty. Science, 1965, 26, 1187-1188.

Sutton, S., Tueting, P., Zubin, J., and John, E.R. Information delivery and the sensory evoked potential. Science, 1967, 155, 1436-1439.

Symmes, D., and Eisengart, M.A. Evoked response correlates of meaningful visual stimuli in children. Psychophysiology 1971, 8, 769-778.

Tassy, A.P., Jayle, G.E., Graveline, J. The clinical value of electroretinography, 1968, Karger, Basel, New York.

Tepas, D.I., and Armington, J.C. Properties of evoked visual potentials. Vision Res., 1962, 2, 449-461.

Thompson, C.R.S., and Harding, G.F.A. The visual evoked potential in patients with cataracts. Docum. Ophthal. Proc. Series, 1978, 15, 193-201.

Thompson, R.F., Bettinger, L.A., Birch, H., and Groves, P.M. Comparison of evoked gross and unit responses in assocation cortex of waking cat. Electroenceph. clin. Neurophysiol., 1969, 27, 146-151.

Thompson, R.F., Denny, D., and Smith, H.E. Cortical control of specific and non-specific sensory projections to the cerebral cortex. Psychonom., Sci., 1966, 4, 93-94.

Thompson, R.F., and Patterson, M . M. (Eds.), Bioelectric recording techniques. Part B. Electroencephalography and human brain potentials, 1974, Academic Press.

Thompson, R.F., and Shaw, J.A. Behavioural correlates of evoked activity recorded from assocation areas of cerebral cortex. J. Comp. Physiol. Psychol., 1965, 60, 329-339.

Trevarthen, C.B., and Sperry, R.W. Perceptual unity of the ambient visual field in human commissurotomy patients. Brain, 1973, 96,

Tsutsui, J., Nakamura, Y., Takenaka, J., and Fukai, S. Abnormality of the visual evoked response in various types of amblyopia. Jap. J. Ophthal., 1973, 17, 83-93.

Uenoyama, K. Visual evoked response produced by patterned light stimulus. Invest. Ophthal., 1971, 10, 664-671.

Umezaki, H., and Morrell, F. Developmental study of photic evoked responses in premature infants. Electroenceph. clin. Neurophysiol., 1970, 28, 55-63.

Uttal, W.R. Do compound evoked potentials reflect psychological codes? Psychol. Bull., 1965, 64, 377-392.

Van Balen, A., Denier, Th. M., Van der Gon, J.J., and Hellendoorn, E.H. The differentiation between responses of foveal and extra-foveal stimuli in the ERG and EEG. In Clinical Electroretinography. H.M. Burian and J.H. Jacobson (Eds.). Vision R es., Suppl., 1966, 255-262.

Van Balen, A.T.M., and Henkes, H.E. Recording of the occipiyal lobe responses in man after light stimulation. Brit. J. Ophthalmol., 1960, 44, 449-460.

Van Balen, A.T.M., and Henkes, H.E. Attention and amblyopia: electroencephalographic approach to an ophthalmological problem. Brit. J. Ophthal., 1962, 46, 12.

Van Hof, M.W., Van Hof-Van Duin, J., Van der Mark, F., and Rietveld, W.J. The effect of image formation and that of flash counting on the occipito-cortical responses to light flashes. Acta physiol. pharmacol. neerl., 11, 485-493, 1962.

Van der Tweel, L.H., and Spekreijse, H. Visual evoked responses. Iscerg Symp. Ghent., 1966, 83-94. Karger, Basel, New York.

Vanzulli, A., Bogacz, J., Handler, P., and Garcia-Austt, E. Evoked responses in man . I. photic responses. Acta Neurol., Latinoamer., 1960, 6, 219-231.

Vaughan, H.G. The perceptual and physiological significance of the visual evoked response. Vision Res., 1966, 6, Suppl. I., 203-223.

Vaughan, H.G. The relationship of brain activity to scalp recordings of event-related potentials. In Average evoked potentials: methods, results, evaluations. E. Donchin and D. B. Lindsley, (Eds.), 1969, SP 191, NASA, Washington, 45-94.

Vaughan, H.G. New physiological approaches to psychopathology. In Experimental approaches to psychopathology, M.L. Kietzman, S. Sutton and J. Zubin, (Eds.), 1972, Academic Press.

Vaughan, H.G., Costa, D., and Ritter, W. Topography of the human motor potential. Electroenceph. clin. Neurophysiol., 1968, 25, 1-10.

Vaughan, H.G., and Gross, C.G. Cortical responses to light in unanaesthetized monkeys and their alteration by visual system lesions. Exp. Brain Res., 1969, 8, 19-36.

Vaughan. H.G., and Hull, R.C. Functional relation between stimulus intensity and photically evoked cerebral response in man. Nature (Lond.), 1965, 206, 720-722.

Vaughan, H.G., Katzman, R., and Taylor, J. Alterations of visual evoked responses in the presence of homonymous visual defects. Electro-enceph. clin. Neurophysiol., 1963, 15, 737-746.

Vaughan, H.G., and Katzman, R. Evoked response in visual disorders. Ann. N.Y. Acad. Sci., 1964, 112, 305- 319.

Walter, W.G. The location of cerebral tumours by electroencephalography. Lancet, 1936, 2, 305-308.

Walter, S.T., and Arfel, G. Responses to visual stimuli in acute and chronic coma. Electroenceph. clin. Neurophysiol., 1972, 32, 27-41.

Ware, C., and Mitchell, D.E. On interocular transfer of various visual after effects on normal and stereoblind observers. Vision Res., 1974, 14, 731-734.

Weinberg, H., and Cole, E. Averaged evoked response to classes of visual stimuli. Psychonom., Sci., 1968, 11, 71-72.

Werre, P.F., and Smith, C.J. Variability of responses evoked by flashes in man. Electroenceph. clin. Neurophysiol., 1964, 7, 644-652.

White, C.T. The visual evoked response and patterned stimuli. In Advance in psychobiology, Vol. 2. G. Newton and A.H. Riesen (Eds.) 1974, Wiley and Sons, 267-295.

White, C.T., and Bartlett, N.R. Evoked cortical responses and patterned stimuli. Amer. Psychol., 1970, 24, 211-214.

White, C.T., and Bonelli, L. Binocular summation in the evoked potential as a function of image quality. Am. J. Opt. and Arch. Amer. Acad. Opt., 1970, 47, 304-309.

Wicke, J.D., Donchin, E., and Lindsley, D.B. Visual evoked potentials as a function of flash luminance and duration. Science, 1964, 146, 83-85.

Wildberger, H.G.H., Van Lith, G.H.M., Gaarde, W.I., and Mah, G.T.M. Visually evoked cortical potentials in the evaluation of homonymous and bitemporal visual field defects. Brit. J. Ophthalmol., 1976, 60, 273-278.

Wilkinson, R.T. Evoked response and reaction time. Acta Psychologica, 1967, 27, 235-245.

Wilkinson, R.T. and Morlock, H.C. Auditory evoked response and reaction time. Electroenceph. clin. Neurophysiol., 1967, 23, 50-56.

Wilkinson, R.T., Morlock, H.C., and Williams, H.L. Evoked cortical response during vigilance. Psychonom. Sci., 1966, 4, 221-222.

Wood, C.C., Goff, W.R., and Day, R.S. Auditory evoked potentials during speech perception. Science, 1971, 173, 1248-1251.

Woody, C.D. Characterization of an adaptive filter for the analysis of variable latency neuroelectric signals. Med. and Biol. Engng., 1967, 5, 539-553.

Wooten, B.R. Photopic and scotopic contributions to the human visually evoked cortical potential. Vision Res., 1972, 12, 1647-1660.

Worden, F.G. and Galambos, R. Auditory processing of biologically significant sounds. A report based on an NRP work session held Sept. 13-15th, 1970. Neurosci. Res. Program. Bull., 1972, 10, 1-119.

Wurtz, R.H. Visual receptive fields of striate cortex neurons in awake monkeys. J. Neurophysiol., 1968(a), 32, 727-742.

Wurtz, R.H. Visual cortex neurons: response to stimuli during rapid eye movements. Science, 1968(b), 62, 1148-1150.

Wybar, K.C. Acquired optic atrophy in early childhood. In Optic nerve. J.S. Cant (Ed.), 1972, Henry Kimpton.

Yinon, U., Jokobovitz, L., and Auerbach, E. The visual evoked response to stationary checkerboard patterns in children with strabismic amblyopia. Invest. Ophthal., 1974, 134, 293-296.

Zeki, S.M. Cells responsing to changing image size and disparity in the cortex of the rhesus monkey. J. Physiol., 1974, 242, 827-841.