AN ASSESSMENT OF THE TECHNIQUE AND CLINICAL APPLICATION OF VISUAL EVOKED RESPONSE MEASUREMENTS

by

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An Assessment of the Technique and Clinical Application of Visual Evoked Response Measurements

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SUMMARY

In this study an attempt has been made to review the clinical situation concerning the use of visual evoked response tests (VER).

The literature reviewed has been selected mainly for the clinical applications of the technique and early classical work describing physiological concepts. In addition a study is made of the various derivations from the scalp made by different authors.

In the material studied, stimulation was mainly by reversing checkerboard, but flash was used in some instances. A control series of 73 subjects, of age range 4-67 years, were divided into decades of age. Mean latencies of response and standard deviations were estimated. Amplitudes were also studied and found not to relate to age.

The patients whose VER results are reported include a series of 150 with multiple sclerosis (MS) and retrobulbar neuritis (RBN), independently classified according to McAlpine's criteria.

Reports on the VER results in 24 patients with compressive lesions affecting the visual system are divided into pre-chiasmal, chiasmal, post-chiasmal and other intra-cranial sites.

The VER of 17 patients with ischaemic disease is also reported and grouped according to the area affected by the ischaemia.

Finally, there is a discussion on the physiological basis of the VER with other electrophysiological tests, in particular the electro-retinogram (ERG), Electromyogram (EMG) and the electro-encephalogram (EEG). Above all, it is emphasised that no one test gives the whole answer, and all must be assessed with the clinical findings in order to establish a diagnosis.

Some thoughts on future developments of the technique are also presented.

Key words:- Visual evoked responses, Technique, Normal variants, Multiple sclerosis, Compressive lesions, Ischaemic lesions

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The consultants of the Division of Neurological Sciences have supported me throughout this study, and I am grateful to them for allowing me to follow their patients' progress.

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GLOSSARY OF SPECIAL TERMS AND ABBREVIATIONS

AER	Auditory evoked response
Aet	Aetate. Age at time referred to.
α rhythm	Alpha rhythm. The usual dominant rhythm of an EEG, of frequency between 8 and 14 Hz, of posterior distribution and usually responsive to stimuli.
Amp.	Amplitude, usually expressed in microvolts (uV)
Artefact	Any electrical activity recorded which is not part of the VER (Q.V.) (in this study). This might be a "physiological" artefact due to such causes as the basic EEG, eye blinks, myographic potentials or a "physical" artefact produced by 50 Hz mains interference, faulty connections or amplifier noise.
β rhythm	Beta rhythm. An EEG rhythm of over 14 Hz
CRO	Cathode ray oscilloscope
C/sec	Cycles per second, or Hertz
CSF	Cerebro-spinal fluid
CT scan	Computerised tomography scan (brain scan)
δ rhythm	Delta rhythm. An EEG rhythm of less than 4 Hz
Derivation	The electrode placements from which the recording or response is obtained.
EEG	Electro-encephalogram. A graph of the spontaneous electrical activity of the brain
EMG	Electromyogram. The recorded electrical activity of active muscle. The term is often used loosely to include the measurement of nerve conduction velocities.
ER	Evoked response
ERG	Electro-retinogram. The recording of the electrical response of the retina, usually to a flash of light.
F	Flash (in context of stimulation)
F	Female (with initials of patients)

Hz	Hertz. Cycles per second
IFSECN	International Federation of Societies of EEG and clinical Neurophysiology
International 10-20 system	The system of electrode placement for EEG recommended by the IFSECN. See Figure 1:1. The midline electrodes, F_z, C_z and P_z may be shown as F_o, C_o and P_o in some instances. This is F, C and P_{zero}.
Latency	The time interval between the stimulus and the response.
M	Male
msec	Millisecond (1/1,000 second)
MS	Multiple sclerosis (synonymous with disseminated sclerosis)
P_1 P_2 P_3 N_2 N_3	Nomenclature of positive and negative deflections of the VER used in this study. Illustrated in Figure 1:2
P/F	Patterned flash
P/R	Pattern reversal
RBN	Retrobulbar neuritis
Sample	Each individual piece of EEG taken after the stimulus
Sample time or sweep time	The duration of EEG stored in the averager after each stimulus. In this study a sweep time of 250 msec was used throughout
SD	Standard deviation
SER or SSER	Somato-sensory evoked response
θ rhythm	Theta rhythm. An EEG rhythm of between 4 and 7 Hz
uV	Microvolts (1/1,000,000 volt)
VA	Visual acuity
VEP	Visual evoked potential } synonymous
VER	Visual evoked response }
WNL	Within normal limits
XY plotter	Automatic writer of which the pen moves in a lateral direction "X" and a vertical direction "Y"

Figure 1:1 Lateral view of the electrode placement and nomenclature of the International 10-20 system (Jasper, 1958). The midline electrodes F_z, C_z and P_z denote F, C and P_{zero}, and are also written as F_o, C_o and P_o in some parts of the text and figures in this study.

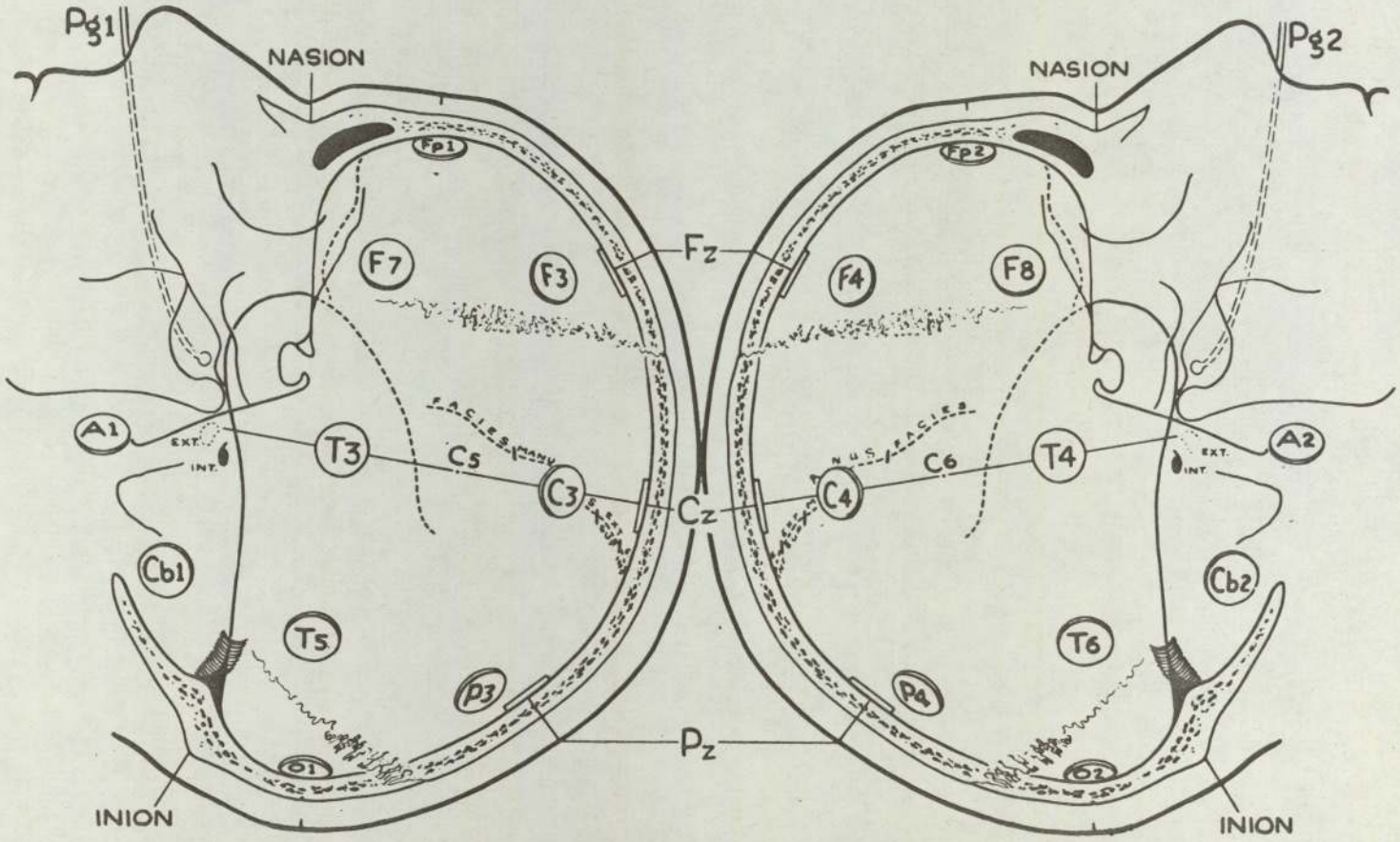
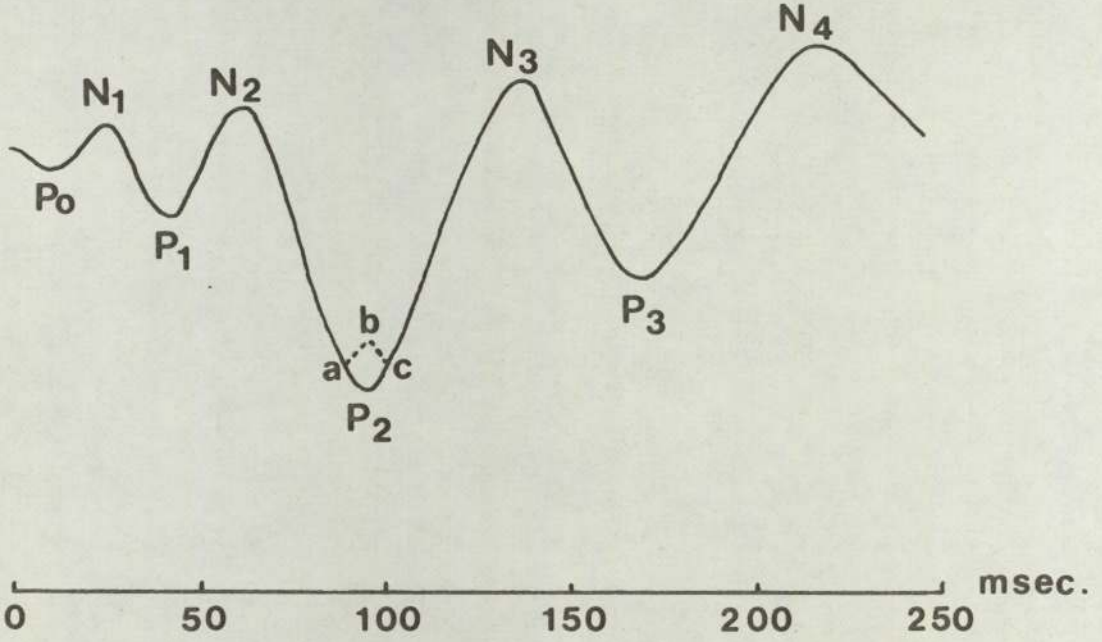


Fig. 4

The lateral view of left and right hemispheres showing all standard electrode positions, omitting intermediate positions (such as C5 and C6) which are used only for special studies with more closely spaced electrodes. These drawings were made from a series of X-ray projections with true lateral views. The location of principal fissures was determined by silver clips placed at operation and by other anatomical studies described in the text. The location of pharyngeal electrodes (Pg 1 and Pg 2) was also obtained from X-ray studies with these electrodes in place.

Figure 1:2 Stylised waveform of VER showing the nomenclature of peaks as used by Harding (1974) and used throughout the present study. A negative potential at the active electrode produces an upward deflection of the trace, according to the neurophysiology convention. The "a, b, c" variant in the P_2 peak is as described by Gastaut and Regis (1964) as Va, Vb, Vc


N1
N2
N3
N4
Po
P1
P2
P3
a
b
c
0
50
100
150
200
250
msec.

AN ASSESSMENT OF THE TECHNIQUE AND CLINICAL APPLICATION OF VISUAL EVOKED RESPONSE MEASUREMENTS

CHAPTER 1. INTRODUCTION

Since advances in electronics made it comparatively easy to detect and record cortical afferents from three types of sensory input, visual, auditory and somato-sensory, a major part of clinical and research interest has been directed towards these techniques. The amount of literature that has already accumulated on these subjects is daunting to anyone newly entering the field. The aim of the present work is to attempt to review the situation as it presently exists with regard to visual evoked responses (VER) and to assess how much this technique may now be relied upon in clinical diagnosis.

The review of the literature in Chapter 2 does not pretend to be comprehensive, but to cover mainly clinical applications of the technique and only such experimental work as appeared to be relevant to the particular subject under discussion. This is not in any way to detract from the importance of experimental work, as without this there would be no advances, but in practical terms, this study concentrates on findings which are becoming well-established, and can therefore be treated with more confidence. The obvious drawback of such an approach is that this presentation will rapidly become out of date, but this is a hazard which is inevitable in a field such as this in which so many workers are engaged and where new discoveries are being made almost daily. It is hoped to establish a platform of

reliable evidence from which further forays into the unknown may be launched.

There are already two main textbooks in English: "Evoked Potentials in Psychology, Sensory Physiology and Clinical Medicine" by Regan (1972) which covers auditory and somato-sensory as well as visual inputs, and "Visual Evoked Potentials in Man", edited by Desmedt (1976), containing important articles on clinical, patho-physiological and experimental aspects by some of the principal authors on the subject. There have also been numerous conferences and symposia, with their subsequent publications.

The present work is much more limited in its field, and attempts to approach the subject from the point of view of a worker in a Department of Clinical Neurophysiology who has experienced the demand made upon such a department by clinical neurologists, neurosurgeons, ophthalmologists and general physicians when the availability of the service became known. Undoubtedly the major impact came when it was reported that the VER could be useful in the diagnosis of multiple sclerosis (MS). In fact, so great was this impact that the demand for tests for this condition did and still does far outweigh requests for VER in other diseases. There was a danger that the test might be regarded as pathognomic for multiple sclerosis where the latency of the response was prolonged, and this was realised and countered by Halliday and other authors very rapidly. The situation is still not without risk that a remediable lesion such as a benign tumour compressing the optic nerve, causing delay in the VER, might be overlooked.

The VER will only give an indication of the situation obtaining at the time of the test. Although it may show a disruption or malfunction within the optical system, it gives no indication when

viewed in isolation of the cause of such an abnormality. Thus other factors must be considered in parallel in order to assess the situation fully. Careful attention to the history of the illness is the first priority. For instance, if a neurological deficit has been of slowly progressive onset over a number of weeks, months or even years, a progressive lesion such as a tumour should be considered. If of sudden, or rapid onset, a cerebro-vascular aetiology is possible. If symptoms, such as visual failure, develop in one eye, and recover, and then affect the other eye, with painful ocular movements, retrobulbar neuritis and possible multiple sclerosis would come to mind.

Unfortunately the situation is not so simple as the previous paragraph would imply, although the general trend in each condition is as stated. There are instances, however, where compressive lesions caused oedema which then subsided, giving the impression of an improvement in the illness. Also cerebro-vascular disease may appear to be gradually progressive, where there is atherosclerosis and a succession of minor vascular occlusions (transient ischaemic attacks) producing thrombotic accumulations over a long period. This might be difficult to differentiate from a tumour.

In the case of multiple sclerosis, a usual characteristic of the disease is that episodes of local neurological deficit occur and remit. The locality of these deficits may be widely separated throughout the whole system, so that the earlier term "Disseminated sclerosis" was probably a more accurate description. There are, however, unusual instances where the disease shows a continuously progressive course without remission.

The so-called "typical" case of multiple sclerosis is not so

difficult to diagnose on the evidence of the history and objective examination. Where further assistance is required is in the atypical development of the disease such as in the early stages before a pattern of relapse and remission becomes obvious, or where symptoms and signs relate only to one part of the nervous system.

A situation may arise that a patient complains of abnormal sensations of parasthaesia in a limb, being otherwise entirely normal This could be due to a lesion in the spinal cord, either compressive (tumour or prolapsed intravertebral disc) or ischaemic. If this is due to multiple sclerosis, the finding of a delayed response in the visual pathways, or other sensory system on objective testing, may save the patient from undergoing myelography or possibly even operative exploration, in order to exclude a compressive lesion.

This may help in establishing the disseminated nature of the condition in space. To detect its dissemination in time, only repeated examinations over a long period would cover this problem, and this is advocated where the diagnosis remains in doubt.

It is always important for the whole system to be assessed from all the evidence available, history, clinical examination and radiological evidence in addition to any functional neurophysiological tests, before a diagnosis can be made.

Arising out of considerations that the VER may be affected by other conditions than multiple sclerosis, an attempt has been made to study results in compressive and ischaemic lesions especially, and to observe whether the VER could make a useful contribution in any other condition. The results of these attempts appear in following chapters, but it is felt that the full application of this technique is still far from being realised, and it is to be hoped that many more reports of useful applications of the technique may be forthcoming.

There is also some lack of clarity about the relative value of the different diagnostic techniques, and where neurophysiological investigations as a whole fit in to the general picture. These tests are relatively new in clinical medicine when compared with radiology for instance or biochemical tests, and it is tempting in some areas to compare one with the other in a competitive light. This viewpoint shows a sad misunderstanding of the nature of the different tests and their inter-relationship and therefore an inability to use them for maximum benefit ultimately for the patient.

The true picture is that all the evidence may be assembled and used in a complementary way to build up a picture, not only of the anatomical position and displacements within the system (Xray) but also of the amount of disruption of normal function (neurophysiology). For instance, even a large benign tumour such as a pituitary adenoma may cause little visual defect. It will be revealed by computerised tomography scan (CT scan) as a space-occupying lesion, and the displacement of an optic nerve may be clearly seen. The VER then shows whether the conduction within that nerve has been disrupted, and indeed the VER can give an indication post-operatively of the amount of damage sustained by the nerve. The same applies in electro-encephalography; it is possible for a large parasagittal meningioma, for instance, to show hardly any abnormality on the EEG, but it will be shown on a CT scan. The EEG in this case is useful in showing how little the cortex has been damaged by the tumour, and gives an indication of the prognosis in terms of recovery.

It is hoped that the following work may make a useful contribution in adding more evidence in the VER in multiple sclerosis, and in showing at least some of the other conditions in which the technique

may play a part in conjunction with full clinical assessment and other tests, in the diagnosis of various conditions affecting the visual system.

CHAPTER 2. REVIEW OF LITERATURE

(i) EARLY RESEARCH AND PHYSIOLOGICAL CONCEPTS

There has been a good deal of speculation as to the nature of the visual evoked response (VER), but it is fairly generally accepted that the major positive wave which occurs at about 100 milliseconds is a summated response from a large number of neurones, and almost certainly not the primary cortical response. Brazier (1953) reported latencies of 12-25 msec in the response recorded in the calcarine cortex of the cat, depending on stimulus intensity, and earlier reports on eels (Adrian and Matthews, 1927) and frogs (Bernhard, 1940) describe similar results.

Grey Walter (1964) reported that in recordings taken from electrodes implanted in the human calcarine cortex he found a repeatable and non-adapting response to flash which occurred at an interval of about 30 msec after the stimulus. He stated that this was not distinguishable with electrodes on the surface of the scalp. The scalp VER habituates very rapidly, more so than the somato-sensory or auditory response. Cobb and Dawson (1960) reported a small wave at 20-22 msec which appeared at equipotential between electrodes at 3 cm and 6 cm above the inion, but difficult to detect as its amplitude was only about 1-1.5 microvolts (uV).

The later waves, after the 100 msec positive peak, are more variable and appear to be influenced by attention and distraction (Eason, Harter and White, 1969; Courchesne, Hillyard and Galambos, 1975).

Photopic and Scotopic Stimulation

Cobb and Morton (1952) in a paper concerning the retinogram, point out that even if a subject is dark-adapted, the first flash light-adapted them for many minutes. Armington (1964) reports on the changes in the electroretinogram (ERG) and VER with light adaptation; the first flash of a train produces the highest response, followed by diminution then some recovery. Behrman (1969) uses the dark-adapted VER to detect hysterical amblyopia, as this changes in relation to the more usual light adapted one when there is no reported subjective dark adaptation. She states that the recognisably different waveform and longer latency with the scotopic VER is further evidence that the response is obtained from the rod system. Lenman (1975, p. 163) reports that the rod system in the retina produces a longer latency response in the ERG than the cone system. De Voe, Ripps and Vaughan (1967) in studying the relation of the lowering of sensation of light as the focus is moved away from the centre of visual focus (Styles Crawford effect, 1933) state that the VER is more rapidly reduced in amplitude and concludes that this shows that the VER is mainly, if not wholly, related to cone stimulation at the fovea.

Visual Field Defects

Many studies have been carried out on the VER of patients having visual field defects (Cohn, 1963; Vaughan, Katzman and Taylor, 1963; Vaughan and Katzman, 1964; Kooi, Guvener and Bagchi, 1965; Halliday, 1967; Harding, Thompson and Panayiotopoulos, 1969) and by stimulating part of the visual field in normal subjects (Eason, Groves, White and Oden, 1967; Eason, White and Oden, 1967; Halliday and Michael, 1970; Michael and Halliday, 1971; Jeffreys and Axford, 1972; Lehmann

and Mir, 1976, and with Meles, 1977). Different stimulus and recording parameters, in particular the difference in derivation of signals between the various authors have made comparison difficult.

Vaughan et al. (1963) report a lowering of amplitude and increase in latency over the affected hemisphere in patients with visual field defects, but this was largely dependent on field defects involving the macula. Vaughan and Katzman (1964) state that the VER is a valid predictor of homonymous defects involving the central 10° of the visual field and demonstrate that a unilateral loss of Wave II (at 46 msec positive in their nomenclature) is characteristic of visual field defects. Kooi et al. (1965), in comparing their results with those of Vaughan et al. (1963), make the comment that latency asymmetries appear to be more striking with ear reference technique and amplitude asymmetry more evident with vertex reference recording. They report that slow rise times and later culmination of Waves OI (30-70 msec negative) and OII (50-100 msec positive) opposite the affected homonymous field, were most characteristic of visual pathway damage. Suppression of OV (125-190 msec negative), contralateral to the affected field, correlated both with visual system damage and the resting alpha rhythm. In the same paper they comment that their patients with a macular defect could not be differentiated from those without. Also two patients with a superior quadrantic defect had a symmetrical response (but see Lehmann and Mir, below).

Regan (1972, p. 173) comments on the great inter-subject variability in findings of visual field investigation, but remarks on the limitation of investigation to the analysis of evoked potential waveform and some consideration of amplitude over the scalp. In all these studies only flash presentation of spatially unstructured visual fields have been studied.

Later studies have extended the areas of investigation, and Lehmann and Mir's findings in multiple sclerosis subjects (1976) illustrated that fixation at the lower border of the checkerboard in pattern reversal stimulation (stimulating the upper half of the field) produces significantly longer latencies and smaller amplitudes than fixation at the upper border. They state that with fixation at the lower border, the increase in response latency may suggest reversal of polarity in extreme cases. Their reference electrode was 40% of the distance between nasion and inion (i.e. at the midline half way between Fz and Cz in the 10-20 system).

In pursuit of the differences in response obtained with stimulating vertical and horizontal meridians of the visual field, Halliday and Michael (1970), recorded from three vertical lines of electrodes over the parieto-occipital area, referred to three different sites: 10 cm above the nasion, 5 cm below the inion, and linked earlobes. The positive peak at around 100 msec was surface negative when the upper field was stimulated and surface positive with lower field stimulation. The reference did not appear to make much difference. The occipital response was largest on the contralateral side when a vertical segment 3 cm lateral to the midline was being stimulated, and very much smaller for the horizontal meridians. Michael and Halliday (1971) compare the occipital responses to upper field stimulation using linked ear reference to that with a mid-frontal reference, and find the positive response similar, but the negative wave disappears with frontal reference.

Jeffreys and Axford (1972), using a pattern appearance method of stimulation and with a midline row of electrodes from vertex to inion and reference to one earlobe, report a reversal of polarity of the waveform between upper and lower half field stimulation in most

subjects. In the same paper, using a horizontal row of electrodes across the posterior part of the head, at a level not described, they find a change in the relationship of the CI wave (negative 65-80 msec) and CII (positive 90-110 msec) relating to whether the macula is stimulated or not, and the lateral angle of the stimulus. They postulate that their CI wave represents a striate cortical response, and the CII extrastriate. This leads to their conclusion that the occipital cortex representing the upper half fields is on the inferior surface, above the cerebellum, and that of the lower half field on the upper convexity. These findings appear to agree with those of Lehmann and Mir (1976) quoted above, although in 1977 Lehmann, Meles and Mir have reported on upper and lower visual field testing with pattern reversal in a normal subject. Their findings confirmed that the main peak was at 100 msec positive on lower field stimulation and postulate that this could be due to higher receptor cell density in the upper half of the retina.

The representation of the visual field on the human cortex has been difficult to establish as the striate calcarine cortex is inaccessible for non-invasive examination. Animal studies (Whitteridge and Daniel, 1961; and others) suggest that the macula is represented at the posterior edge, and the fields spread forward so that the periphery of the visual field is at the most anterior part of the calcarine cortex. Studies from human brain injury (Holmes, 1918) support these animal findings, as does a paper by Brindley and Lewin (1968) who stimulated the calcarine cortex electrically in a conscious blind subject and recorded the subjective sensations of light "seen" in the various parts of the visual field. They report incidentally that a very high intensity stimulus appeared to invert the classical

map about the horizontal meridian. This may correlate with the findings of Werre and Smith (1964) who report changes in waveform of the flash evoked response with different derivations and changes in flash rate, and Halliday (1967) who reports marked changes in latency with alterations in stimulus intensity.

Harding et al. (1969) found a lower amplitude of response on the side opposite the defect in patients with a hemianopic field defect, using a wide-spaced bipolar technique, but Halliday et al. (1976) find the response of higher amplitude on the contralateral side to the defect, when using a midline frontal reference. He does state, however, that with a peri-occipital bipolar run, the phase-reversal occurs over the expected side, ipsilateral to the defect. In a later presentation Halliday and co-workers (1977) report the finding of a higher amplitude VER on the side opposite the field defect in a patient examined after hemispherectomy, thus illustrating that the response did not originate in occipital cortex under the electrode.

In summary of the findings relating to visual fields, then, there appears to be evidence that the occipitally recorded scalp VER is principally derived from stimulation of the lower half of the visual field, and the medial $1^{\circ}56'$ (the macula). Findings relating to lateralised field stimulation are less clear, but bipolar recording as shown in the paper by Harding et al., indicates the expected lowering of amplitude of the response contralateral to a hemianopic field defect.

(ii) PLACEMENT OF ELECTRODES AND DERIVATION

The problems of electrode placement and how they should be connected for visual evoked response observation are as complex as they are for all EEG recording. There is no reference point on the head which is indifferent to cerebral electrical activity, and any reference point below ear level on either side, or on shoulder or chest will cause contamination by cardiac potentials. There is the additional complication with flash that electrodes placed over the anterior part of the head will detect blink artefacts, which may occur as a reflex to flash or pattern reversal stimulation, and therefore at regular intervals after each stimulus.

There is considerable spread of electrical potential across the scalp. Cobb (1960) illustrated how an EEG could be obtained from the operated side of the skull after a hemispherectomy in a patient who had undergone pneumo-encephalography after operation. When the head was positioned so that half the cavity was filled with cerebro-spinal fluid (CSF) and half with air (face down), an EEG was recordable from bipolar electrodes placed one over the fluid-filled area and one over the air-filled cavity, both on the operated side. The activity was presumably conducted through the CSF from the intact cerebral hemisphere. The lowest amplitude record was obtained when both the recording electrodes were over fluid. This is consistent with both CSF and bone having a low electrical resistance. The first is not unexpected as CSF is a salty solution, and this agrees with the findings of Geddes and Baker (1967).

Halliday et al. (1976 and 1977) recorded the VER over the operated side in a patient after removal of a hemisphere.

All these findings refer, of course, to difficulties in recording

externally from the intact scalp. Direct brain recording avoids many localisation problems as recordings with intra-cerebral electrodes show that electro-tonic conduction in brain matter is minimal (Brazier, 1964), but that in the direction of axonal travel is slightly greater than when recording across fibre tracts, and an entirely different waveform may be obtained from electrodes at only 4 mm distance apart (Papakostopoulos, 1977).

The search continues for a satisfactory reference point for scalp recording. A midline reference at the vertex is obviously not inactive, as it records potentials from both hemispheres, and non-specific responses. Trials for an indifferent reference point have been made using anterior and posterior chest electrodes, with a potentiometer applied to balance out the cardiac activity. The chest cannot be regarded as neutral for brain electrical activity because it records a considerable amount from the base of the brain, to which it is connected on a broad stalk (Magnus, 1961). Many authors use linked ears as the reference point (see Table 2:I), but this can lead to false asymmetries as the ears pick up activity from the temporal lobes and there is no indication of laterality. Vaughan and Katzman (1964) use a vertex reference and explain this by stating that the use of a midline reference ensures that an observed asymmetry in response is occipital in origin, but McGillivray (1974, p. 28-29) in a chapter on EEG technique, observes that no point on the head or neck, even apart from the scalp, can be regarded as "inactive". He is critical of linked ear references as this does not indicate from which side a particular component originates.

Some authors use bipolar derivations, particularly when recording the ERG and VER simultaneously. Harding et al. (1969) uses a bipolar method, T_4 - O2 - T_5 and T_3 - O1 - T_6 of the 10-20

system in order to study asymmetries of occipital response when stimulus is applied to part of the visual field.

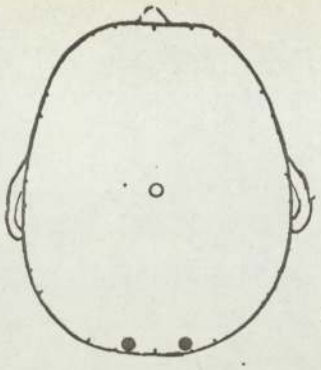
Probably the ideal would be a combination of bipolar and common reference derivations, as is recommended for full EEG recording (Recommendations of the International Committee on Standards for EEG, IFSECN, 1957).

Table 2:I gives a list of the derivations used by some of the authors who have contributed in the field of VER.

TABLE 2:I DERIVATIONS USED BY VARIOUS AUTHORS

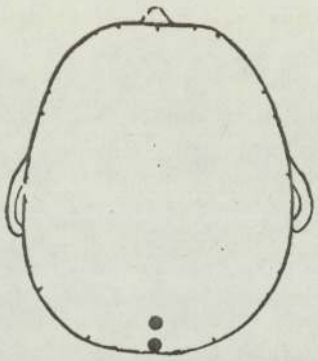
Derivation	Object of Study	Stimulus
Bipolar One electrode on the external occipital protruberance on the midline; others at 3 cm intervals in front of it and also on lines 3 and 6 cm lateral to the midline Extra electrode sometimes used 3 cm below (inion)	Area of maximum response	F
Bipolar, and midline reference O_1 and O_2 ref to F_o " " C_o " " P_o $O_1 - C_3$ $O_2 - C_4$ $O_1 - O - O_2$	Visual field defects	F
Reference: linked ears Bilateral frontal, motor, occipital, temporal electrodes, first run. Bilateral parietal, occipital posterotemporal, infraorbital, midposterocervical, second run. Bilateral occipital, posterocervical, and parietal, third run.	Normative data	F
Reference: linked ears Active electrodes: 1. Just above inion 2 & 3. Anterior midline separated by 35 mm 4 & 5. 35 mm lateral to R and L of 2 6 & 7. Lateral R) of 3 8 & 9. Lateral L) All separated by 35 mm	Variability of responses	F

Author



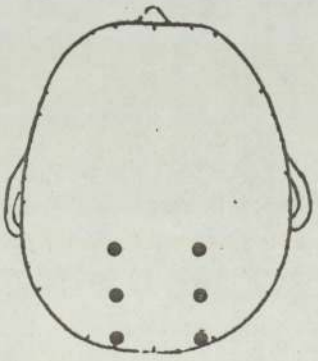
Vaughan and Katzman

1964



Copenhaver and Perry

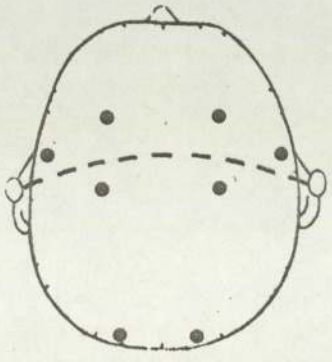
1964



Rodin, Grissell,

Gudobba and Zachary

1965

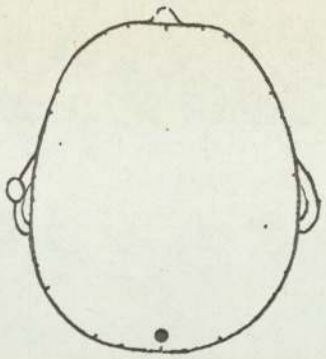


Kooi, Guvener and

Bagchi

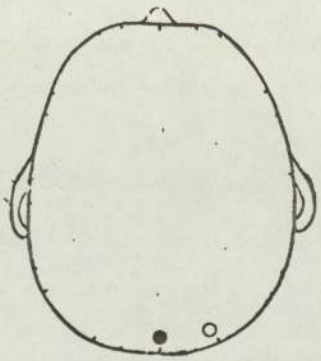
1965

Derivation	Object of study	Stimulus
Reference: Vertex Active electrodes 1 cm above and 3 cm lateral to inion	Visual disorders (with ERG, but VER claimed to show homonymous defects of the macula	F
Bipolar Electrode on inion and 2 cm above	Effects of impaired vision and change of fixation	F
Bipolar R and L occipito-parietal, and parietal to anterior-parietal	Relationship of VER with EEG background rhythms	F
Reference: Linked ears Active electrodes: frontal, motor, temporal and occipital on each side	Visual fields	F



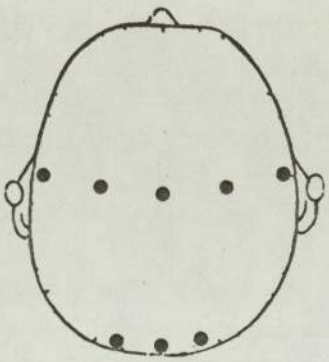
Spehlmann

1965



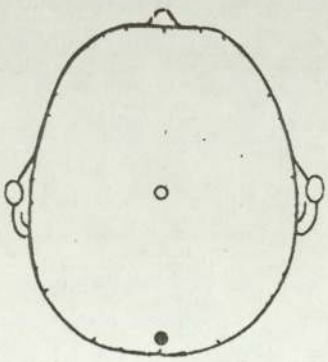
Halliday

1965



Gastaut

1967

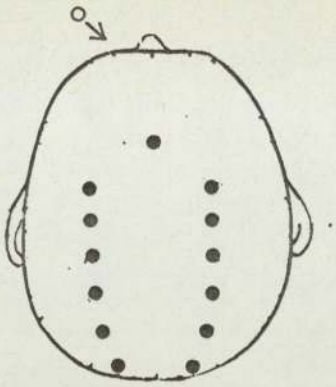


Cobb, Morton and

Ettlinger

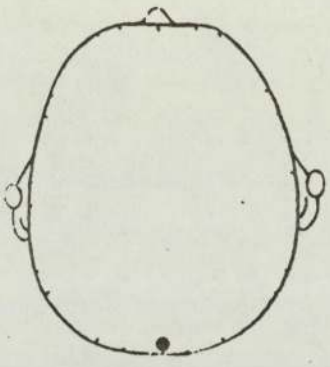
1967

Derivation	Object of Study	Stimulus
Reference: "Usually one ear" Active electrode within 3 cm of the inion	Response to diffuse and patterned flash	F
Bipolar Midline occipital to electrode to right of midline	Various lesions of the nervous system	F
Reference: Contralateral ear Active electrodes on inion, occipital, mid-temporal, rolandic and vertex	Comparison of responses from different areas (with auditory and somato-sensory also)	F
Reference: vertex or ear lobe Active electrode 3 cm above inion	Visual rivalry	P/R



Creutzfeld and Kuhnt

1967

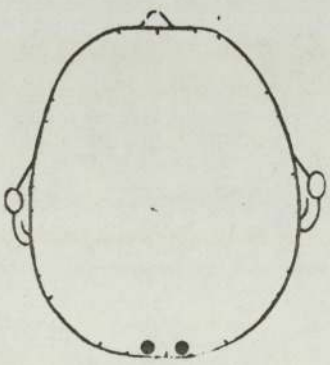


Rietveld, Tordoir,

Hagenouw, Lubbers

and Spoor

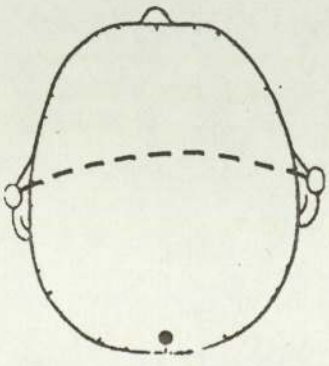
1967



Eason, White and

Odin

1967

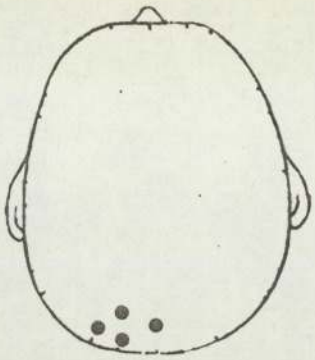


DeVoe, Ripps and

Vaughan

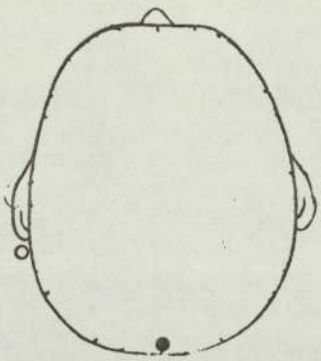
1967

Derivation	Object of Study	Stimulus
Reference: chin Active electrodes: six each side and one midline as shown	Physiological developmental and clinical aspects	F
Reference: an earlobe Active electrode 1.5 cm above inion	Effects of patterns and colours	F
Reference: ipsilateral ear Active electrodes R and L occipital 1 inch above inion and 1 inch each side midline	Upper and lower field stimulation	F
Reference: linked ears Active electrode 3 cm above inion	Narrow beam stimulation of human fovea	F



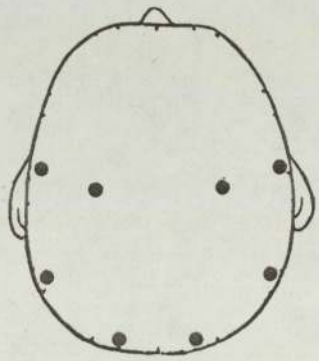
Mackay

1968



Armington

1968

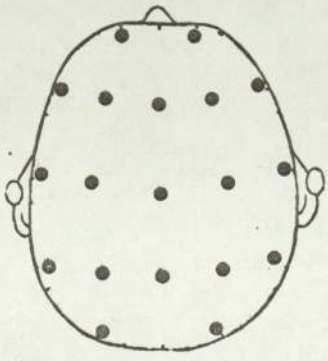


Harding, Thompson and

Panayiotopoulos

1969

1972

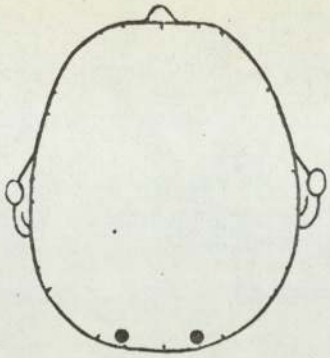


Oosterhuis, Ponsen,

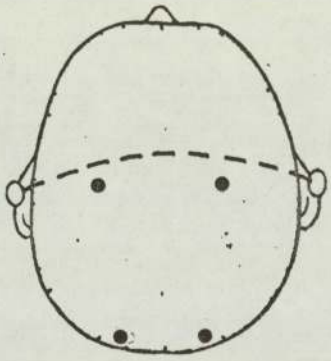
Jonkman and Magnus

1969

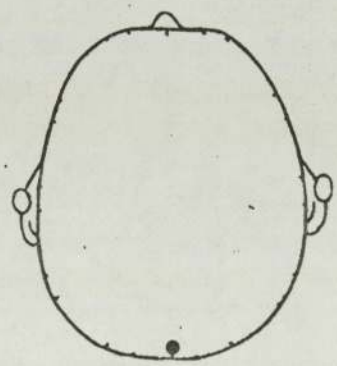
Derivation	Object of Study	Stimulus
Bipolar Longitudinal 2 cm to L of inion Transverse, midline and to L of midline	Interocular and monocular suppression (blank and patterned flash)	F
Reference: L mastoid Active electrode 1 inch above inion	Effect of vertical stripes moved horizontally	P/R
Bipolar T5 - O2 - T4 T6 - O1 - T3 O1 - C3 O2 - C4	Visual field defects	F
Bipolar 10-20 electrode positions plus one from an occipital electrode referred to as the ipsilateral ear	Cerebro-vascular disease	F



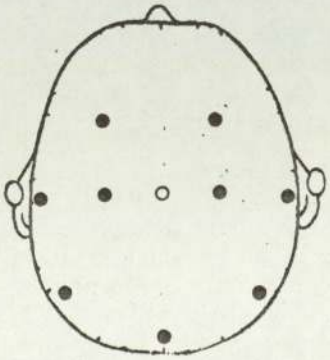
Goff, Matsumiya,
Allison and Goff
1969



Dustman and Beck
1969

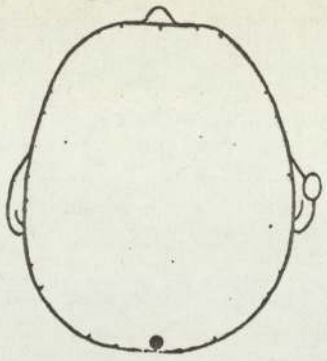


Behrmann
1969



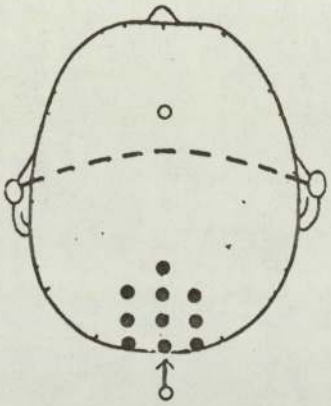
Harden and
Pampiglione
1970
1973

Derivation	Object of Study	Stimulus
Reference: Contralateral ear Active electrode occipital (final conclusion)	Pros and cons of different derivations	F
Reference: Linked ears Active electrodes O1, O2, C3 and C4	Maturation and ageing	F
Reference: One earlobe Active electrode 2 cm above inion	Hysterical amblyopia	F
Reference: Vertex or earlobe "Active electrodes placed as for usual EEG"	Disorders of vision (with ERG and EEG) Neuronal lipoidosis	F F



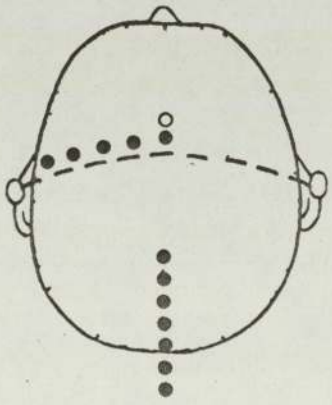
Harter and White

1970



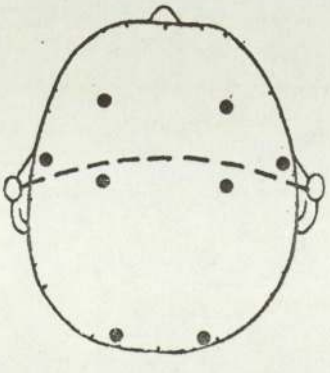
Halliday and Michael

1970



Michael and Halliday

1971

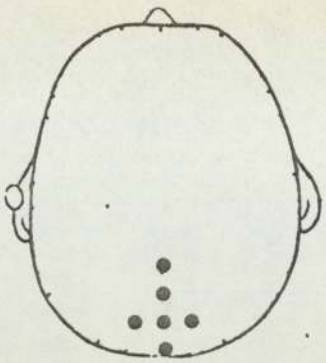


Richey, Kooi and

Tourtelotte

1971

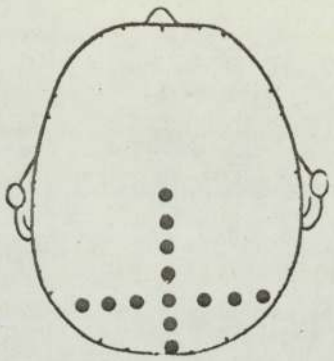
Derivation	Object of Study	Stimulus
Reference: R earlobe Active electrode 2.5 cm above inion	Effect of check size and visual acuity	P/F
Reference: Either 10 cm above nasion or 5 cm below inion or linked earlobes Active electrodes, 10 over occipital cortex at 3 cm apart laterally and 2.5 cm apart in AP direction	Vertical and horizontal meridians of visual fields	P/R
Reference: either linked ears or mid-frontal (one experiment with chain of electrodes from mid-frontal down side of head) Active electrodes in midline chain at 2.5 cm intervals from 10 cm above the inion to 5 cm below it	Topography of response with upper and lower field stimulation	P/R
Reference: linked ears Active electrodes, R and L frontal, central, occipital and temporal	Multiple sclerosis	F



Bennett, MacDonald

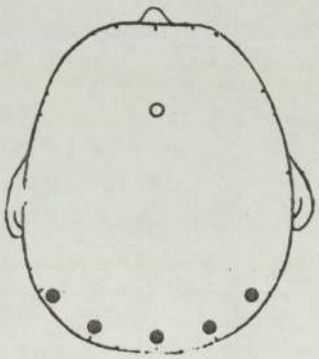
Drance and Uenoyama

1971



Jeffreys and Axford

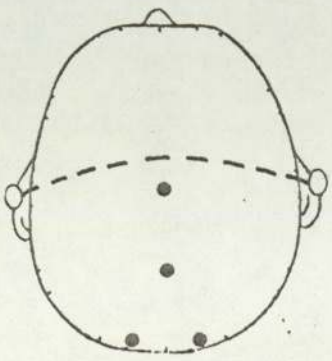
1972



Halliday, McDonald

and Mushin

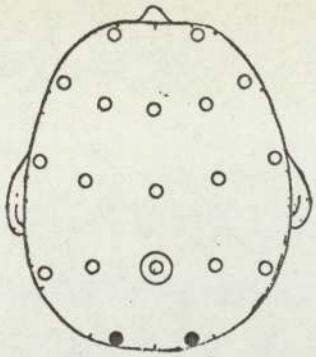
1. 1972
2. 1973
3. 1974
4. 1976 (with Halliday & Kriss)
5. 1978 (with Blumhardt



Lee and Blair

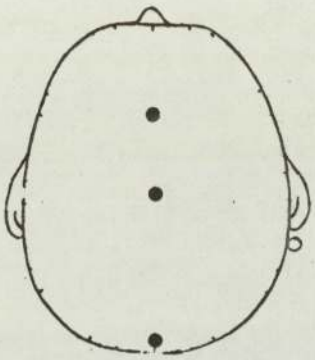
1973

Derivation	Object of study	Stimulus
Reference: L earlobe Active electrodes on inion and at 3 cm intervals above it in a vertical line Two electrodes, one each side midline electrode 3 cm above inion at 3 cm lateral to it	Statistical analysis in normals	F
Reference: one earlobe Active electrodes closely spaced in midline, 7 from vertex to inion. Also (separate study) transverse posterior line	Visual fields	P/R
Reference: mid-frontal Active electrodes in line 5 cm above inion and two electrodes each side at 5 cm intervals	1. Optic neuritis 2. Multiple sclerosis 3. Progressive spastic paraplegia 4. Compression of visual pathways 5. Visual fields Experimental scotomata in normals	F & P/R P/R P/R P/R P/R
Reference: linked ears Active electrodes O2, O1 Pz and Cz	Jakob-Creutzfeld Disease	F



Blom

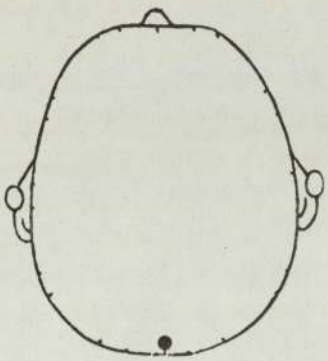
1974



Courchesne, Hillyard

and Galambos

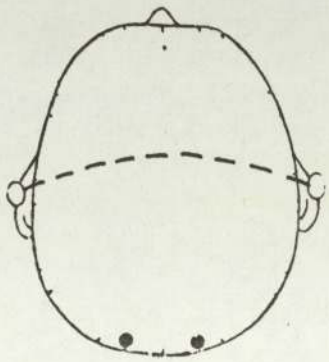
1975



Yoshida, Iwahara,

and Nagamura

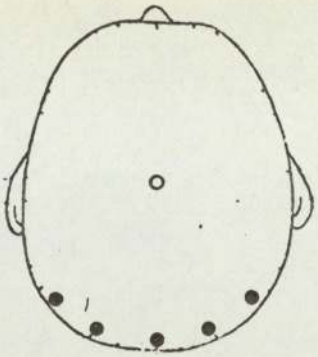
1975



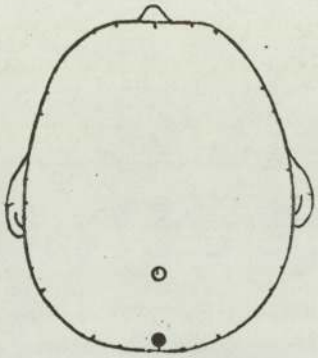
Feinsod and Hoyt

1975

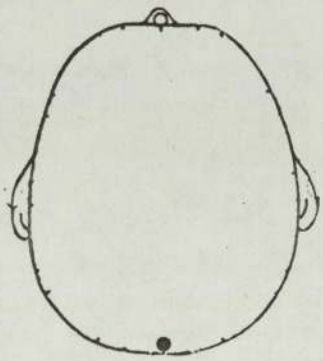
Derivation	Object of Study	Stimulus
Reference: Pz or common average (all 10-20 electrodes applied) Active electrodes O1 O2	Effects of tasks on late waves	F
Reference: R mastoid Active electrodes Fz, Cz, Oz	Effects of tasks on late waves	F
Reference: one earlobe Active electrode midline occipital	Stimulus orientation	P/F
Reference: linked ears Active electrodes O1 O2	Multiple sclerosis	F



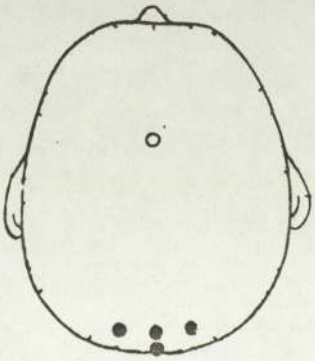
Asselman, Chadwick
and Marsden
1975



Mastaglia, Black
and Collins
1976

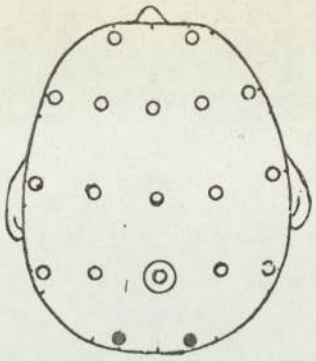


Regan, Milner
and Heron
1976

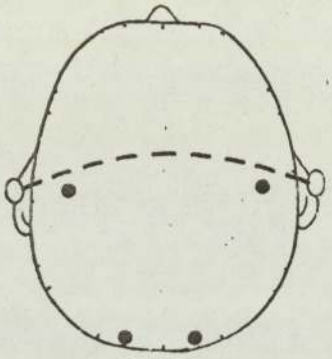


Lehmann and Mir
1976

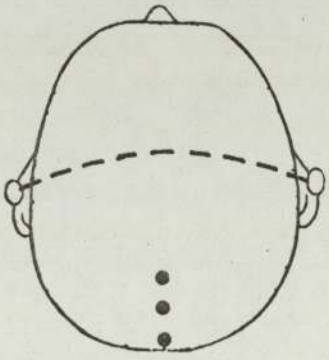
Derivation	Object of Study	Stimulus
Reference: vertex Active electrodes, 5 in ring 5 cm above inion (as Halliday)	Multiple sclerosis	P/R
Reference: Pz Active electrode Oz	Multiple sclerosis (also spinal ER)	P/R
Reference: forehead Active electrode mid-occipital	Multiple sclerosis	F P/R
Reference: 40% of distance from nasion to inion Active electrodes O1, O, O2 and midline 1 cm above inion	Multiple sclerosis and and stim. to lower half field	P/R



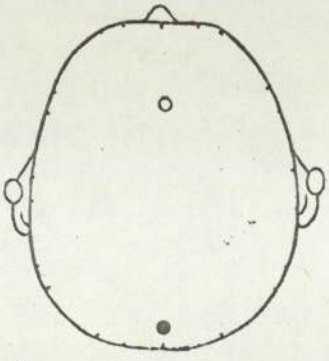
Visser, Stam,
Van Tilburg
1976



Davis and Wade
1977

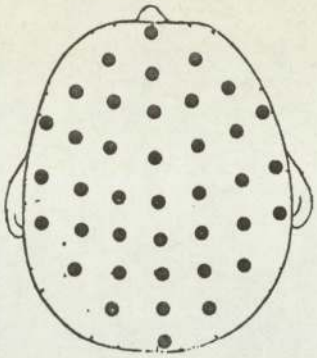


Hennerici, Wenzel
and Freund
1977



Matthews, Small,
Small and Pountney
1977

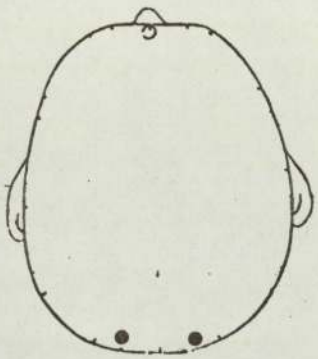
Derivation	Object of Study	Stimulus
Reference: average or Po Active electrodes O1, O2	Senile and pre-senile dementia	F (random)
Reference: linked ears Active electrodes O1, O2 C5, C6	Lateralisation of speech dominance	F
Reference: linked ears Active electrodes at midline, 3, 6 and 9 cm above inion	Multiple sclerosis Comparison of stimuli	P/R and foveal bright square
Reference: Fz Active electrode 50 mm above inion	Multiple sclerosis	P/R



Lehmann, Meles

and Mir

1977

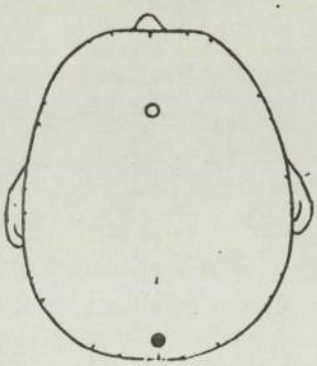


Laget, Flores-Guevara,

d'Allest, Ostre,

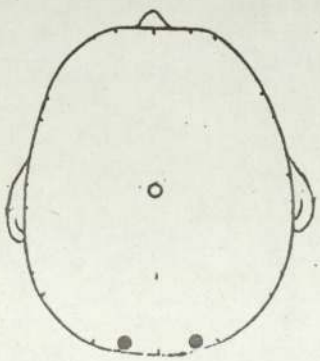
Raimbault et Mariani

1977



Hoeppner and Lolas

1978

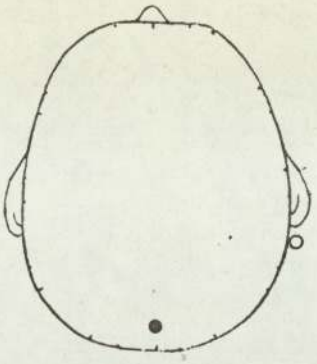


Ellenberger, Petro

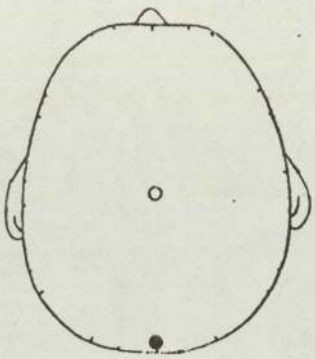
and Ziegler

1978

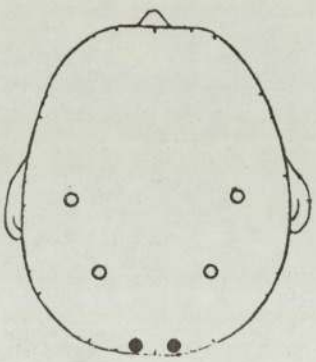
Derivation	Object of Study	Stimulus
39 gold-plated electrodes at 4 cm intervals all over head, converted to contour maps	Potential fields evoked from upper and lower hemi-retina	P/R
Reference: mid-frontal (forehead) Bilateral occipital	Maturation in normal children	F
Reference: Fz Active electrode 5 mm above inion	Multiple sclerosis	P/R
Reference: vertex Active electrode O1 or O2 contralateral to stimulated eye	Huntington's disease	F



Ashworth, Maloney
and Townsend
1978



Shahrokhi, Chiappa
and Young
1978



Holder
1978

Derivation	Object of Study	Stimulus
Reference: one mastoid process Active electrode in midline 50 mm above inion	Cerebral tumour	P/R
Reference: C_z Active electrode in midline 3 cm above inion	Multiple sclerosis and optic neuritis	P/R
Bipolar occipito-sylvian and occipito-parietal with occipital electrodes 2 cm anterior and 2 cm lateral to the inion	Effects of chiasmal compression	P/R

(iii) INSTRUMENTS FOR RECORDING, AVERAGING AND DISPLAY

Adrian (1934) first reported that a response could be seen in the occipital area to a flashing light applied to the eyes in humans, however, this response can only be seen in the scalp EEG in a small percentage of the population (Harding, 1974). It was not until Dawson (1947) devised a means of summating repeated responses by photographic superimposition and later (1954) designed an electronic averaging system, in order to extract the response from the background EEG that a more accurate assessment and measurement of the response could be made. His electronic method used a motor driving unit which delivered the stimulus and at the same time started storage of the response in sequence across a bank of capacitors. In subsequent designs the whole system has been electronically operated, but the principle of storage of samples of the response, usually at one millisecond intervals or less, still remains. The final result, or averaged signal can then be retrieved either by display on a cathode ray oscilloscope (CRO), or by the use of an X-Y plotter.

Many commercial "averagers" are now available, but in many cases there is no provision for observation of the concurrent EEG trace, or there may be a CRO display of the EEG during the test, without a permanent record. This would appear to be a serious deficit, as a very disturbed basic EEG could influence the waveform of the VER. Cohn (1964) writes on "Rhythmic after-activity in VERs"; Rodin et al. (1965) report that complexity of waveform is significantly correlated with the amount of fast activity in the record. Spehlman (1965), using patterned flash, illustrates how the response can phase-lock with the basic EEG, and Halliday (1965) reports the incidence of large cortical responses in myoclonic epilepsy (in that case to

somato-sensory stimulation). Morocutti et al. (1966) report a large bi- or tri-phasic wave evoked by flash in untreated epileptics. Harding (1976, Fig. 33:2) illustrates how the VEP may be obscured by rhythmical background activity in the EEG. Panayiotopoulos, Jeavons and Harding (1972) describe an occipital spike response, later (Jeavons and Harding, 1975, p. 26) correlated with Gastaut's "a, b and c" division of the major positive wave of the visual evoked response. Bablouzain et al. (1969) report on the detection of photogenic epilepsy in man be summation of evoked scalp potentials. Linder, Muller and Poole (1967) state that photic and cutaneous stimulation can entrain the complexes in Jakob-Creutzfeld disease and increase their occurrence, and Lee and Blair (1973) report "abnormally high amplitude" responses to flash stimulation in the early stages of this disease.

These papers are all describing either a fortuitous time-locking of EEG activity with the stimulus, or a recorded cortical discharge evoked by the flash.

Pfurtscheller et al. (1977) offered a new scheme to illustrate the relationship between evoked and background EEG activity. They expressed the view that the stimulation may influence the on-going EEG as well as producing an evoked response.

Amplifier frequency Bandwidth

Assuming, then that it is necessary to observe the concurrent EEG during the recording of the visual evoked response, there are certain hazards in taking the signal output from the EEG amplifiers and averaging it. It is obvious that the use of high frequency filters on a low setting will substantially reduce the high frequency content in the response; this is more vital in auditory and somato-

sensory work than with the visual evoked response because earlier waves are being studied, but another, less obvious hazard is the phase error, and therefore change in the apparent latency of the response produced by alteration of the time constant or low frequency filters of AC amplifiers. Attention to this has been drawn by Cobb and Dawson (1960), Kooi and Bagchi (1964), Dawson and Doddington (1973), Thornton (1975), and the basic principle is presented in "EEG Technology", Cooper, Osselton and Shaw (1974, Fig. 4:12, p. 62). This illustrates the necessity of using the same frequency response characteristics for all tests if accurate comparisons are to be made.

Cobb and Dawson (1960) advocate the use of short time constants as this reduces the effect of EEG slow waves on the evoked response, with the warning, quoted above, that this reduces the latency.

(iv) TYPE OF STIMULUS

From 1960 many authors have described the results of using a plain blue/white flash from a photostimulator. Cobb and Dawson (1960) reported that a reduction in amplitude and increase in latency resulted from a reduced flash intensity. This correlates with earlier animal experiments (Adrian, 1927; Bernhard, 1940; Brazier, 1953). Werre and Smith (1964) reported that alteration of flash rate changed the waveform of the response.

Authors may or may not state the level of flash intensity. It is difficult to measure the strength of the stimulus as this relates not only to the brightness of the light source, but the relative brightness, i.e. the contrast of the light against the ambient illumination of the room (Jeavons and Harding, 1975, p. 14 and earlier papers). Cobb and Morton (1952) describe a method of measuring light intensity, in this case in a paper on the human retinogram, in which direct measurement of the output of a tungsten filament lamp was made using a commercial photometer, and intensity variations were calculated in relation to the voltage applied to the lamp, and the duration of the flash achieved by using a rotating fan. In this paper also the subject was light-adapted, as the first flash would in any case start light adaptation and alter the ERG. Behrman and Levy (1970) illustrate an increase in VER amplitude with dark adaptation stating that in the light adapted eye, stimulation is mainly to the macula area, but with dark adaptation, the rods mainly are stimulated, situated principally in the peripheral parts of the retina (see Chapter 2 (i) final paragraph with reference to photopic and scotopic stimulation).

Bennett et al. (1971) give their subjects ten minutes' dark adaptation before recording the VER and Gastaut et al. (1967)

suggested that the a, b and c division of the major positive peak, their wave V, might be related to dark adaptation.

Many authors merely state in the "Method" that they use a well-known commercially-available photostimulator at light intensity 4 or maximum intensity, and may quote the firm's assessment of the brightness in foot candles. For instance: Grass stimulator at intensity 16 is said to produce 1,500,000 candle power for 10 microseconds at ten inches distance. Step 4 is one quarter of step 16.

Copenhaver and Perry (1964) found that the response to macular stimulation was four times greater in amplitude than when the light was only 2.5^{o} off axis. This correlates with the findings of Jeavons (1969) who reported that the following or driving response in the EEG is much reduced if the lamp is not centrally fixated. Hennerci et al (1977) and De Voe, Ripps and Vaughan (1967) also report that the response is reduced when the fixation spot is deviated from centre.

Behrman (1969) reported that the latency of the response was reduced by the use of a red flash. Rouher et al. (1969) compared red and blue flash in diagnosing various lesions of the optic nerve and claimed that loss of the early response to red flash and preservation with blue flash indicated a lesion of the macula.

Experiments with blank and checkerboard patterned flashes (Rietveld et al., 1967; Mackay, 1968) showed a greater amplitude response to pattern, a fact not unexpected in view of the enhanced photoconvulsive response seen in the EEG when a grid is placed over the light (Jeavons and Harding, 1975, p. 77-82). Spehlmann (1965) showed that the addition of a pattern can modify the form of evoked potentials with flash. Yoshida et al. (1975) reported on changes of amplitude of the VER depending on transilluminated vertical, horizontal

or diagonal lines presented as stimulus. Vertical and horizontal lines produced equal amplitude responses, but these were reduced with diagonal lines. Harter and White (1970), using a checkerboard pattern, reported a need to increase the check size when the pattern was progressively defocussed, in order to preserve the amplitude of the response.

Experiments using pattern reversal instead of flash, in order to preserve an even luminance, presented a different approach. Considerations of the nature of the pattern and size of components were entered into, and Cobb, Morton and Ettlinger (1967) in an experiment with horizontal bars moved vertically and vertical bars moved horizontally reported an equal response with either method. The amplitude of the response increased if the width of the bars increased from 56' up to $1^{\circ}52'$ but not if increased further. Armington (1968) also advocated the use of vertical stripes moved horizontally, to preserve the overall luminance of the field.

Gross, Vaughan and Valenstine (1967) introduced a reversing checkerboard. Regan and Heron (1969) advocated the use of pattern reversal stimulation in the investigation of lesions of the visual pathway, and Halliday and Michael (1970) used this form of stimulation when first studying the response from stimulation of segments of the visual fields. The pattern was back-projected on to the screen via an oscillating mirror, adjusted so that the black and white squares were reversed regularly and exactly.

The reversing checkerboard form of stimulation gained in popularity as it was found to give more consistent results than flash, although obviously not usable when the visual acuity was severely diminished (Behrman, Halliday and McDonald, 1972), or in the absence of accurate fixation.

Halliday's stimulation method was to present a checkerboard whose whole field subtended 32° at the eye, each square subtending 50' and the subject seated one metre from the screen. As against this, Asselman, Chadwick and Marsden (1975) used a smaller screen with the subject seated 50 cm away and the whole field subtending 18° from each eye. Other authors appear to have accepted these approximate criteria for pattern reversal stimulation.

Although there has been some variation between authors as to the accepted limits of normality (Halliday versus Asselman and Chadwick and others) each author appears to be able to establish his own limits by examining a series of normal controls.

Hennerici, Wenzel and Freund (1977) compare the VER obtained by a reversing checkerboard with those from flashing a foveal bright square subtending 45' from the patient's eye. This last form of stimulation produced a higher proportion of abnormal latencies in suspected multiple sclerosis. It does require a high degree of co-operation on the part of the patient in fixation, but this was monitored by observation and by a photocell to record eye movement. In a normal control series, these authors found that the variability of response to the foveal bright square was less than that obtained with pattern reversal, and there were no false positives. Billings (1978) repeated the experiment of Hennerici et al., but found that the waveform produced by the "foveal bright square" stimulus was less clearly defined than that evoked by pattern reversal.

(v) CLINICAL APPLICATIONS OF VISUAL EVOKED RESPONSES

Lesions of the visual system

Copenhaver and Perry (1964) used flash stimulation in the diagnosis of lesions anterior to the chiasm causing impaired vision in one eye, and by comparing the affected eye with the good one found more reduction in amplitude of the VER with lesions involving the macula or optic nerve than in those causing opacity. In the same year, Vaughan and Katzman (1964) produced a study of visual disorders in which the electro-retinogram (ERG) and visual evoked response (VER) were recorded simultaneously in a series of patients with various lesions of the eye and nervous system. They localised lesions to any of five levels in the visual system: 1) retina; 2) optic nerve; 3) optic chiasm; 4) retrochiasmal projections (optic tract, lateral geniculate body and geniculocalcarine tract), and 5) visual cortex. The lesions included were vascular, degenerative and space-occupying. Kooi, Guvener and Bagchi (1965) and Halliday (1967) reported inconsistent results in patients with visual field defects, but Harding et al. (1969) using a bipolar technique, found a consistent lowering of amplitude on the side opposite a homonymous hemianopia, as would be expected on physiological grounds.

Assessment of residual nervous function

Arfel (1967) carried out evoked response studies in patients in irreversible coma, and recorded an ERG from the anterior regions after the EEG was flat. Oosterhuis, Ponsen, Jonkman and Magnus (1969) made a study of the VER in patients with cerebro-vascular disease, with a discussion on the use of different derivations in recording.

Meanwhile, ophthalmologists were interested in the application of

evoked responses in the diagnosis of diseases of the eye. An absent or severely depressed evoked response during a period of cortical blindness (in children) is compatible with the ultimate return of normal or nearly normal vision (Barnet and Manson, 1970, quoted in Regan, 1972, p. 172). Normal or nearly normal responses during a period of severe visual impairment may herald the onset of rapid clinical recovery. Behrman (1969 and 1970, with Levy), using the combined ERG and VER advocated its use in the detection of hysterical amblyopia.

Localisation of lesions in the visual system.

Harden and Pampiglione (1970) appear to have been the first to describe the combined use of the ERG, VER and EEG to diagnose disorders of vision, and differentiate between diseases involving the rods and cones of the retina, the ganglion cells and cerebral lesions. They comment that because the cortical representation of the macula is so great, the cortical response (VER) is more obviously impaired with central retinal lesions than with lesions of the periphery.

Diagnosis of Multiple Sclerosis

In 1971 Richey, Kooi and Tourtelotte reported a delayed VER in patients with multiple sclerosis. This study included 50 patients and 50 age-matched normal controls. The results were abnormal in 40% of the patients and in 6% of the controls. Halliday, McDonald and Mushin (1972) reported a delayed visual evoked response in optic neuritis, with a normal ERG.

All the foregoing papers reported results using flash stimulation, and the variability of results between individuals (see Chapter 3 on Method) made this test of only limited value in clinical diagnosis,

although repeated tests might have increased its usefulness, as variability of response in each individual was found to be low. A real break-through in visual evoked response techniques was made when pattern reversal techniques were invented. This can hardly be credited solely to any particular author as it evolved from the use of patterned flash, and various types of moving stimuli as previously discussed (section iv).

The paper by Halliday, McDonald and Mushin (1973) reporting a high relationship between a delayed response to pattern reversal stimulation in patients with multiple sclerosis compared with normals aroused a great deal of clinical interest, as this disease is not easy to diagnose confidently without histological evidence. Asselman, Chadwick and Marsden (1975) published a report confirming the gist of Halliday's findings, but with slightly different absolute values. Later papers (Mastaglia, Black and Collins, 1976, combining visual and spinal evoked potentials; Regan, Milner and Heron, 1976; Lehman and Mir, 1976; Matthews, Small, Small and Pountney, 1977; Shahrokhi, Chiappa and Young, 1978) have confirmed Halliday's findings of delayed visual evoked potentials in multiple sclerosis (MS), but each laboratory has established its own limits of normality with a control series, and this is agreed to be essential in order to allow for the effects of minor variations in the technique.

Hennerici, Wenzel and Freund (1977), using a "foveal bright square" as opposed to a reversing checkerboard, have reported a greater proportion of abnormal results in MS, but this was not found to be repeatable by Billings (1978). Hoeppner and Lolas (1978) studied interocular differences and waveform in the VER of MS, and reported a greater variability of synchrony and waveform than in a control series.

McInnes (1978) reported that the "bifid" P2 wave frequently seen in MS resulted from different latencies from upper and lower half field stimulation, and recommended that these should be carried out separately and would detect a higher proportion of abnormals in MS, and Blumhardt and Halliday (1978) recommended separate lateral half field stimulation to detect sub-clinical field defects.

The method of recording and the interpretation is becoming more sophisticated and related in more detail to basic physiological principles as time passes.

Compressive lesions

Following these publications, the clinical acceptance and use of this method for the diagnosis of multiple sclerosis has threatened to swamp the use of the VER technique in any other neurological disorder, and Garfield and Neil-Dwyer (1975) and McDonald (1977) warned of the dangers of a too-early diagnosis of MS in patients with symptoms only referable to the visual system, when these could be due to compressive lesions. Halliday, Halliday, Kriss, McDonald and Mushin (1976), realising this danger, published a report of delayed VER to pattern reversal in compression of the anterior visual pathways. They report that compressive lesions cause more distortion of the waveform of the VER than is usually seen in multiple sclerosis, but this is only on average and therefore of no value in clinical diagnosis.

Other Conditions

Meanwhile some studies of other lesions involving the visual system have been continuing. Harden, Pampiglione and Picton-Robinson (1973) described the combined ERG, VER and EEG in a form of neuronal lipoidosis, in which the ERG was not usually recordable, the VER

showed a grossly enlarged form in keeping with the discharge recorded in the primary EEG. Pampiglione (1977) further develops the theme of combined ERG, VER and EEG studies in genetically determined neuro-metabolic disease and emphasises the importance of an early diagnosis where there is an effective therapy.

The published findings will be discussed more fully in Chapter 6, in relation to the results in multiple sclerosis, compressive, ischaemic and other lesions reported in Chapters 4 and 5.

CHAPTER 3. METHOD, AND RESULTS IN A NORMAL CONTROL SERIES

METHOD

In view of the wide range of stimulating and recording parameters used in the published works, it was felt that a standard procedure should be followed, which was not too much at variance with some of the major contributors in this field, and would provide a consistent standard for investigation of a variety of clinical conditions. The type of stimulus chosen, and the recording method, were limited by the funds available for apparatus, but the fact that this test may be successfully carried out with only a comparatively small financial outlay may be attractive in the present economic climate.

On analysis of the literature it was felt essential to establish criteria of normality using set parameters in our own normal control series, rather than relying on the experience of others, since many authors have shown that minor changes in the stimulus parameters will affect results. Such changes could have a marked effect on the normal range and distribution.

Stimulation

At the time of starting this study many authors were still using flash stimulation, but the reversing-checkerboard method was becoming more widely employed. It had been argued that the checkerboard maintained a constant level of luminance, thereby avoiding complications of dark and light adaptation. Also results had been shown to be more consistent than with flash and there was a clearer dividing line between normal and abnormal. For these reasons it was decided to use a reversing checkerboard as the visual stimulus where the visual

acuity and co-operation of the patient permitted. This was in the majority of cases. A small group of subjects were stimulated with both flash and pattern reversal. Flash was applied by a Grass stroboscope at Intensity 4 in a blacked-out room.

Pattern reversal stimulation was provided by a Digitimer apparatus which projects the checkerboard pattern on to an oscillating mirror, which in turn reflects it on to the back of a screen observed by the subject under test. The frequency of the oscillation and the amplitude of the movement are adjustable, and this was arranged to give an exact reversal of the black and white squares at a frequency of just under two a second. A trigger pulse is applied to the averager at the start of each one-way movement of the mirror, but not at the reverse movement. The 15 cm square screen was sited at a distance of 50 cm from the subject's eyes, subtending an angle of 8.5^{o} at the eye, from the centre to the periphery. Each check subtended 51.5' of arc at the eye. The luminance of the black squares was 2.8 lux and the white squares 88 lux incident light as measured on a standard photometer. The projector lamp was rated at 150 watts, and the room, which was normally used for visual field charting, was blacked out so that the only light came from the screen. It was hoped by this method to establish an even intensity of stimulus for all trials. It was sometimes necessary to make a small adjustment to the frequency of pattern reversal in order to avoid phase-locking with 50 Hz mains interference, or prominent beta activity in the on-going EEG.

Subject and Derivation

Before commencing the examination, the visual acuity was tested with standard reading test type. This was used in preference to the distant vision testing Schnellen chart, as the checkerboard was

relatively close to the subject's eyes and approximated more to a reading distance.

The subject was seated comfortably in an arm chair, with one eye covered and with optical correction where necessary. He was requested to fixate on a black pin head in the centre of the checkerboard, and to try not to follow the movement of the pattern. The operator was positioned so that he could observe that fixation was maintained throughout the test.

Electrodes were placed according to the International 10-20 system (Jasper, 1958). This system was worked out by Jasper in response to a request by the International Federation of Societies for Electro-encephalography and Clinical Neurophysiology (I.F.S.E.C.N.). It is based on measurements between bony landmarks on the skull, and distances of 10 and 20% of the total measurements for the placement of electrodes. The electrodes were designated according to the lobe of the brain under each of them (Fp, F, T, P and O, for Frontal Pole, Frontal, Temporal, Parietal, Occipital, etc.) and numbered so that even numbers related to the right side of the head and odd numbers to the left. The system was accepted by the International Federation, and is in use in the majority of neurophysiological laboratories world-wide.

The main advantages of this system are:

1. Inter electrode distances and distances in relation to the bony landmarks are proportional to the overall size of the head, a fact of maximum importance with children, but also in adults where there is some variation. For instance, the nasion to inion measurement may be 32 cm in a small woman, up to 38 cm or rarely, 40 cm in a large male. Circumferences of the adult head also vary between about 52 cm up to 60 cm.

2. Electrode distances are equal, which is of special importance when using bipolar derivations, so that artefactual differences in signal amplitude may be reduced to a minimum.

3. Electrode designation is clear, and relates to the part of the brain over which each is situated. The positions were found in experiments with cadavers to correspond to the brain area beneath to within one centimetre when related to the principal sulci. It is, however, recognised that a particular brain area may vary in position in relation to skull landmarks by this amount in different individuals.

The derivations used in this study were O_2 and O_1 referred to F_z throughout, although extra electrodes T_6 and T_5 were added in the latter part of the series when a four-channel averager was acquired. An earth electrode was also applied, and electrode resistances of below two kilohms were obtained.

Recording and Averaging

A Van Gogh EP8 portable EEG was used for the recording, the paper being run at 1.5 or 3 cm per second for observation of the occipital EEG on two channels, O_2 to F_o and O_1 to F_o. A gain of 5 uV per mm, time constant of 0.3 sec and an HF cut of 30% of 75 Hz, was maintained throughout all tests, as it had been found that changes in the frequency parameters would produce apparent latency differences in the results, as reported (Dawson and Doddington, 1973; Cooper, Osselton and Shaw, 1974; Thornton, 1975). An electrical output from the EEG amplifiers was connected to a two-channel "Neurolog" averager (Digitimer) where either 64 or 128 samples of 250 milliseconds duration were averaged. The higher number of samples

was used where there was excessive "noise".

This averager has 256 points or "bins" so that with a 250 millisecond sweep the sampling interval is a little shorter than one millisecond. The number of sweeps required can be set on a log scale. The "scale factor" control determines the number by which the resultant totals will be divided in order to achieve the "average". For instance, if the number of sweeps is set at 64 and the scale factor is at 64, the total value accumulated in each "bin" will be divided by 64 to give a true average of the signal applied. If, however, the "scale factor" is set at 32 (the number of sweeps still at 64), the total in each bin will be divided by 32, thus giving a result of twice the amplitude of the average. If the signal is low in amplitude and there is interference from muscle or other unwanted potentials, it is possible to add a further 64 sweeps, and if the scale factor is adjusted to 64, i.e. half the total of 128 sweeps, the amplitude will be the same as for 64 sweeps and a scale factor of 32. Increasing the number of sweeps reduces the amount of interference asynchronous with the stimulus, but considerations of fatigue on the part of the subject should impose a limit.

The system was calibrated by using the internal calibrator of the EEG machine, with the averager set at 1 sweep and the scale factor at 1, a 20 microvolt calibration signal was applied, and the system set up to give an equal deflection in the response, of two divisions on the cathode ray oscilloscope (CRO) or 2 cm on the plot.

In later results a four channel "Datalab" averager was used, which has a total of 4096 points, or 1024 for each channel when four are used, but the rest of the equipment and method remained the same so that results were comparable.

Display

At the start of the series the resultant averaged response was photographed from a CRO trace, but later an XY plotter was used to make the permanent record.

Procedure

The same procedure and order of events was used throughout the series. First the right eye was stimulated, with the left covered, and recordings made from O_2 and O_1 electrodes referred to F_o in the International 10-20 system. The test was repeated with the right eye covered. In later recordings, with the four-channel averager, electrodes T_6, O_2, O_1 and T_5 were used, referred to F_o as a short trial using a midline occipital electrode was not found to add any further information. It appeared to summate the response of the two occipital lobes, or to record the higher of the two if they were asymmetrical. By using the microprocessor on this averager, it was possible to "convert" the common reference recording into a bipolar one by subtracting channels 2 from 1, 3 from 2, and 4 from 3 respectively, to achieve T_6 to O_2, O_2 to O_1, and O_1 to T_5. Some results of these manoeuvres are shown in Chapter 5.

Normal Controls.

It is not always easy to obtain a so-called "normal subject". Volunteers are frequently accused of being "abnormal" because they volunteer, for instance in a test of this nature, a subject who is anxious about some subjective change in his vision might volunteer in order to have the system checked. This possibility should be borne in mind, but is probably not so significant in this objective test as it would be in one demanding intellectual co-operation, such

as psychometric examination.

Subjects with known lesions involving the visual pathways were not included in the normal series, but some subjects had astigmatism, myopia or other defect which could be corrected with lenses, and where this was the case, glasses were worn. No control subject suffered from a neurological disease of the brain or cranial nerves, with the exception of two migrainous subjects. In the older group, it might be assumed that some degeneration of nervous tissue had taken place, and cerebro-vascular insufficiency is another possible hazard. No overt signs of these problems were apparent.

Statistically, the greater the numbers examined, the higher the likelihood of arriving at a representation of the true population of "mean" and "standard deviation" in the measurements. Ideally, a normal series should be gathered entirely at random, and comparisons between age groups should only be made with equivalent or nearly equivalent numbers in each group. But ideal conditions rarely exist, and the normal series presented is described as accurately as possible.

The controls were mainly members of hospital staff who answered calls for volunteers, and some relatives and friends of staff. The group numbered 56. In addition, 17 patients who had spinal cord lesions proven on subsequent investigation not to be demyelinating were added to the normal control group. These last fell mainly into the 50-60 year old group.

Throughout this work the nomenclature of the various peaks which make up the visual evoked potential will be the sequential system of numbering as described by Harding (1974), negative peaks N_{1-3} and positive peaks P_{0-3}, the positive peak P_2 being that usually occurring at around 100 milliseconds after the stimulus, and designated "P_{100}" by some authors. This nomenclature was avoided as the major peak may

be considerably delayed. All illustrations show a downward deflection for positivity at the active electrode according to the neurophysiological convention.

RESULTS

Although there was a considerable variation in waveform in the control series, a definite P_2 wave was always distinguishable. In some there were little or no previous deflections, but in others it was possible to identify waves P_0, P_1 and P_2. The duration of the P_2 peak was variable, and the angle of the two sides of the peak was not always symmetrical.

Some of the variations are illustrated in Figures 3: 1-4.

It was established also that with the checkerboard so close (50 cm) from the subject's eyes, it was necessary to have optical correction in those who required it, and the possible errors obtained by omitting this are shown in Figure 3:5. This correlates with the findings of Harter and White (1970), in that instance to patterned flash, that defocussing the checks reduced the amplitude of the response. In this series it was found that latency could also be affected.

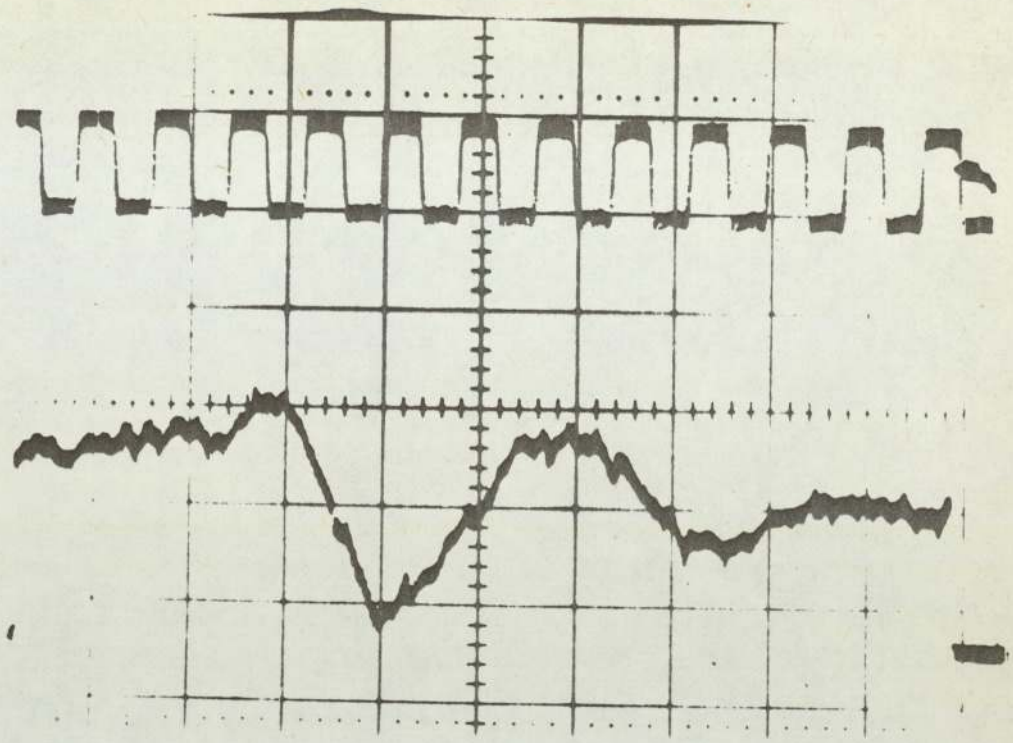
Observation of the concurrent EEG was not only useful in checking for possible artefacts, but for observation of the basic rhythm of the EEG.

The results of the visual evoked potentials in the 73 controls have been divided into decades of age, with slight adjustments in order to make convenient-sized groups. A summary of these appears in Table 3:1, showing the mean, sample standard deviation, maximum and minimum latencies in milliseconds for each age group. This is illustrated graphically in Figure 3:6.

It will be seen that latencies are considerably shorter in the 11-20 year group than in the under-tens, and between the ages of 20 and 50 years they change little. Over 50 there is a fairly sharp

Figure 3:1 Most usual waveform evoked by pattern reversal stimulation with a clear P_2 wave at 100 msec latency
Top trace 50 Hz calibration
Bottom trace VER from O_2 to F_o
Vertical scale 5 uV per division

Figure 3:2 An "a, b and c" waveform in the P_2 wave, as described by Gastaut and Regis (1964).
The "bifid" response by McInnes (1978).
Scale as above



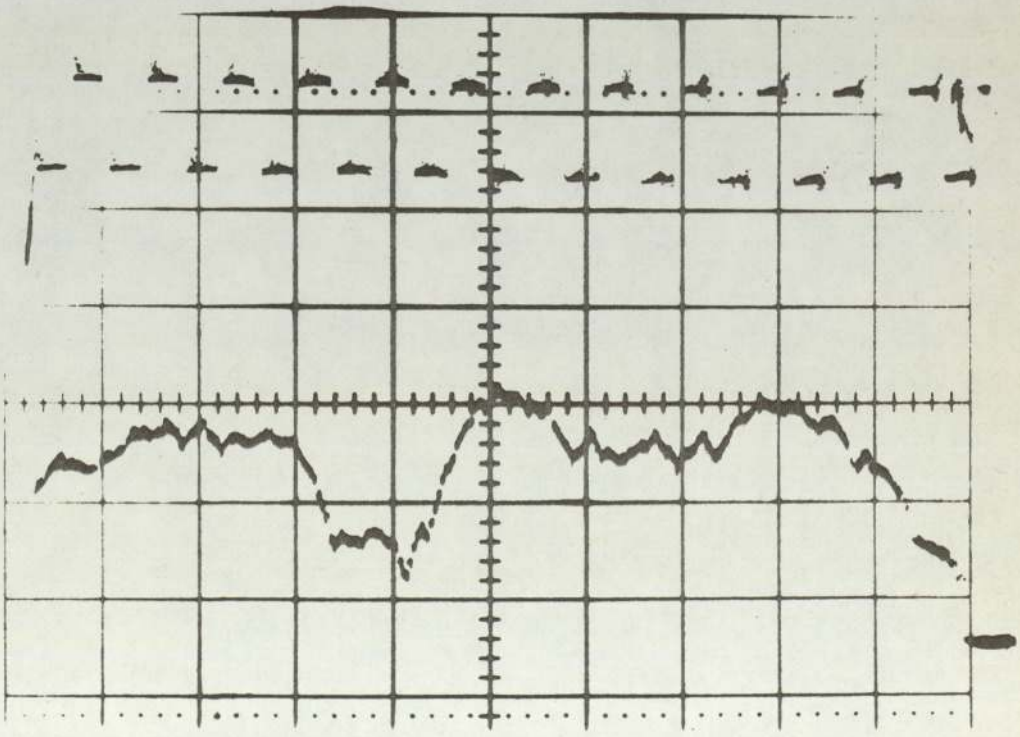
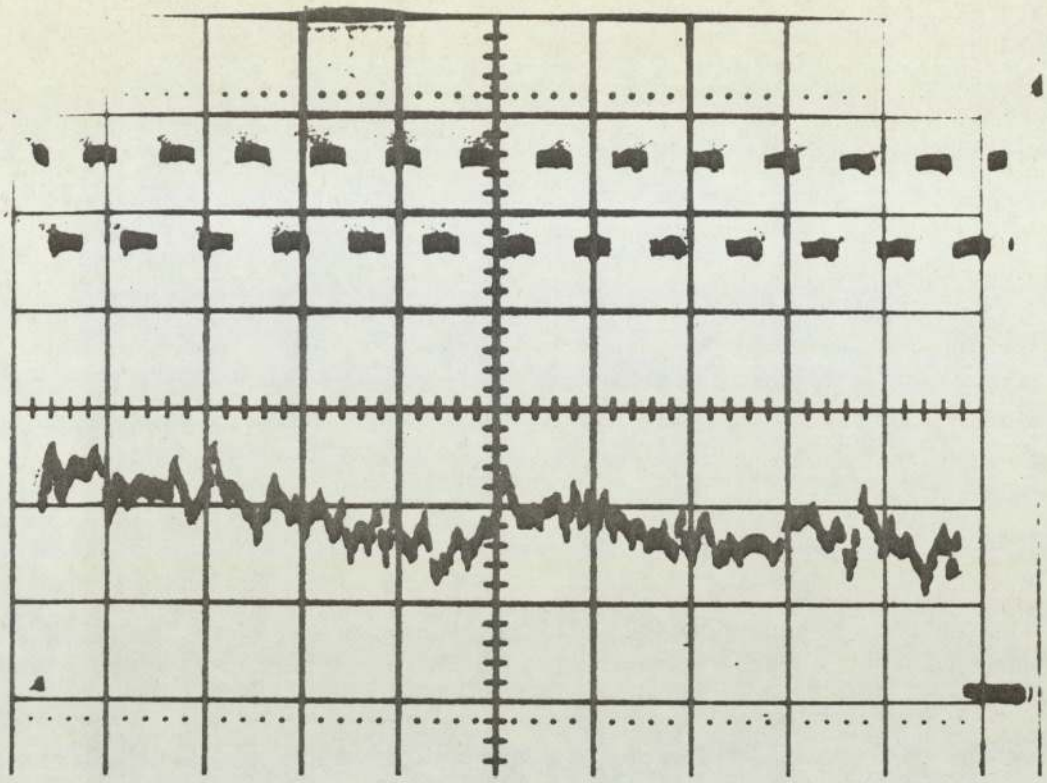


Figure 3:3 Response severely overlaid by electromyograph potentials
Vertical 5 uV per division. Horizontal 25 msec per division

Figure 3:4 An unusual waveform in the control series.
Scale as above



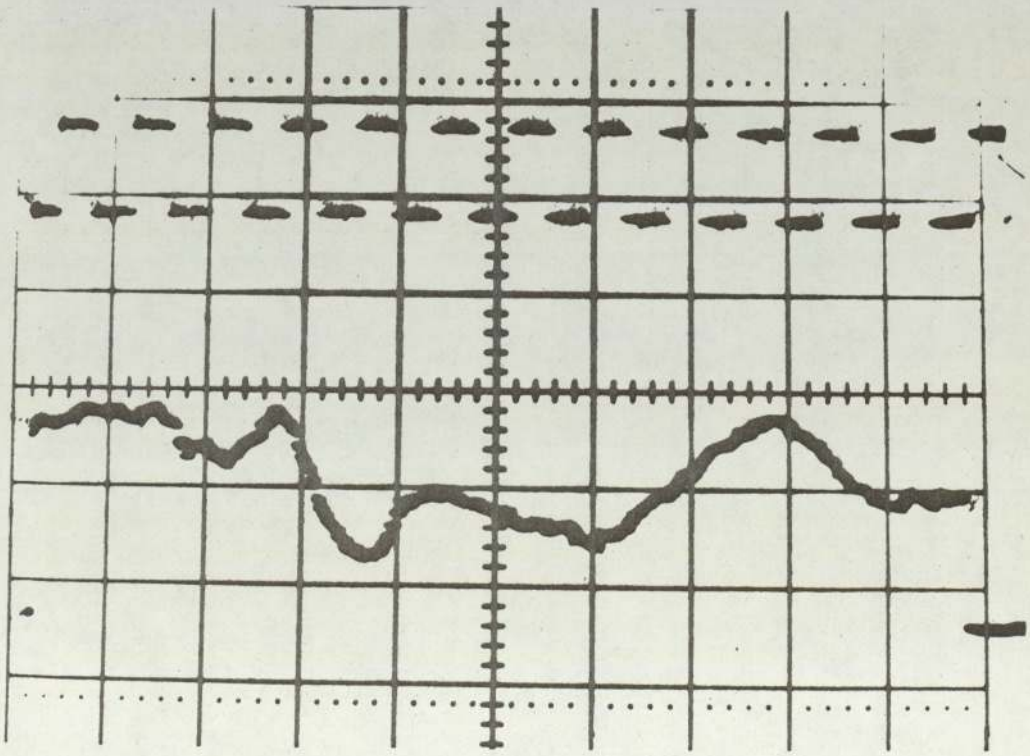


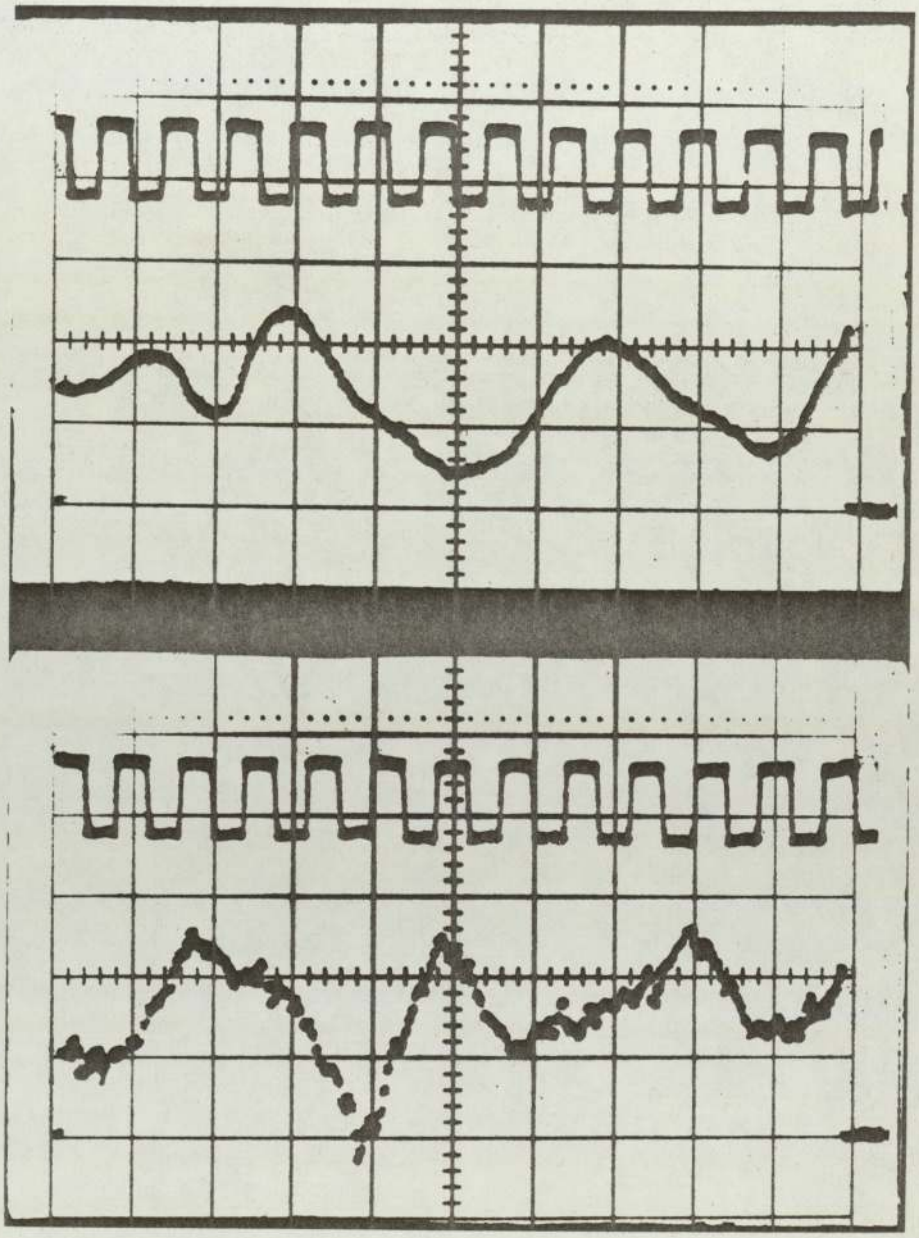
Figure 3:5 VER to pattern reversal stimulation in control subject with severe myopia

Top trace without optical correction

Bottom trace with correction

Vertical scale 5 uV/div.

Horizontal 25 msec/div



increase in latency, but paradoxically, over 60 years, in this series, that average latency has fallen somewhat.

It has also been suggested that in some cases, although all latencies fall within an accepted normal range, an asymmetry of latency between eyes, or between occipital lobes, might be significant. Accordingly, differences of latency between eyes, also differences between occipital lobes, in individuals in the seven age groups have been measured, and a summary of these appears in Table 3:2.

Amplitude

Amplitudes of the response have also been studied, and a consolidated report on these appears in Table 3:3. The amplitude of the VER has been shown to be affected by a number of factors: optical correction, defocussing of the checkerboard, luminance and contrast (which may also affect latency). All these findings were confirmed, but even when stimulus parameters were kept as uniform as possible, there was still a marked variation in amplitude between individuals, although little was seen between eyes or occipital lobes in each subject. There was a subjective impression that those individuals who were tense and unrelaxed showed a lower amplitude response, and that this correlated with a low amplitude EEG, but as tension is very difficult to measure accurately, this aspect was not pursued. It has been reported that VER amplitude directly correlates with event-related desynchronisation of the alpha rhythm (Pfurtscheller et al., 1977; Aranibar et al., 1978). Also, Rodin et al. (1965) state that the amplitude of responses (to flash) correlated with the abundance of activity in the basic EEG. As tense subjects frequently show low amplitude cerebral rhythms, this would add support to the impression that they also produce lower amplitude VER.

TABLE 3:1

Normal Controls

Mean latencies in decades of age in milliseconds (msec)
Each subject has four latencies:
R eye to R and L occipital; L eye to R and L occipital

Age 4-10 yrs	n = 36	(for 9 subjects)	Max 113 msec
	Mean = 100.86		Min 91 msec
	Sample standard deviation (SD) = 5.9		
Age 11-20	n = 24	(6 subjects)	Max 118 msec
	Mean = 98.2		Min 84 msec
	Sample SD = 9.8		
Age 21-30	n = 64	(16 subjects)	Max 109 msec
	Mean = 97.2		Min 83 msec
	Sample SD = 5.8		
Age 31-39	n = 60	(15 subjects)	Max 111 msec
	Mean = 98.1		Min 83 msec
	Sample SD = 5.3		
Age 40-49	n = 36	(9 subjects)	Max 111 msec
	Mean = 97.5		Min 88 msec
	Sample SD 7.66		
Age 50-59	n = 48	(12 subjects)	Max 117 msec
	Mean = 104.97		Min 90 msec
	Sample SD = 6.9		
Age 60-67	n = 24	(6 subjects)	Max 109 msec
	Mean = 101.6		Min 96 msec
	Sample SD = 4.3		

Mean latencies over all age groups

n = 292	(73 subjects)
Mean = 99.6	
Sample SD = 6.99	

TABLE 3:2

Normal Controls - synchrony of response

Maximum latency difference

	Between eyes	Between occipital lobes
Age 4-10 yrs	n = 9 Mean = 6.6 msec Sample SD = 3.97	n = 9 Mean = 5.6 msec Sample SD = 4.9
Age 11-20	n = 6 Mean = 8 Sample SD = 3.9	n = 6 Mean = 6.6 Sample SD = 2.7
Age 21-29	n = 16 Mean = 8 Sample SD = 4.98	n = 16 Mean = 6.5 Sample SD = 4.89
Age 30-39	n = 15 Mean = 6.22 Sample SD = 3	n = 15 Mean = 5.46 Sample SD = 3.3
Age 40-49	n = 9 Mean = 8.3 Sample SD = 4.8	n = 9 Mean = 3.4 Sample SD = 2.55
Age 50-59	n = 12 Mean = 10 Sample SD = 7.5	n = 12 Mean = 7.6 Sample SD = 7
Age 60-67	n = 6 Mean = .4 Sample SD = 2.68	n = 6 Mean = 3.16 Sample SD = 2.2

Maximum latency difference over all age groups

between eyes	between occipital lobes
n = 73 Mean = 7.15 msec Sample SD = 4.9	n = 73 Mean = 5.74 msec Sample SD = 4.6

TABLE 3:3

Normal Controls

Amplitudes

Measurement of height of N_2/P_2 Complex in microvolts (uV)

Totals

n	= 284	Max 30 uV one aet 9, one aet 38
Mean	= 10.78 uV	29 uV aet 60 yrs
Sample SD	= 5.8 uV	Min 1 uV

Amplitude difference between eyes

n	= 71	Max 10 uV
Mean	= 3.12 uV	Min Nil
Sample SD	= 2.55 uV	

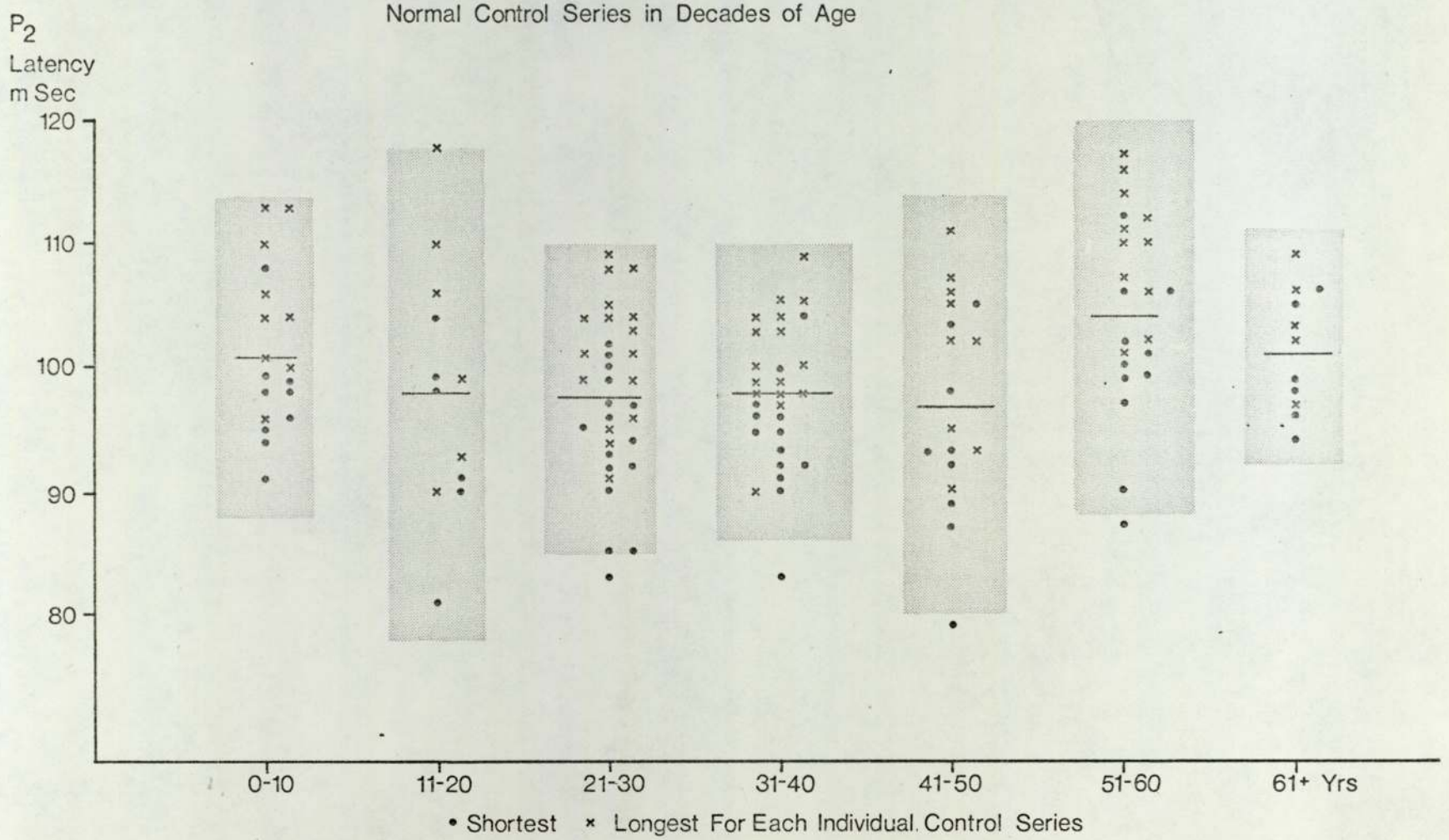
Amplitude difference between occipital lobes

n	= 71	Max 13 uV
Mean	= 3.5 uV	Min Nil
Sample SD	= 2.57 uV	

Figure 3:6 Distribution graph of individual responses in the control series. The horizontal line in each group represents the mean, and the shaded area the standard deviation x $2\frac{1}{2}$
Longest and shortest latencies in each individual arc shown as crosses and dots, respectively

VISUAL EVOKED RESPONSES TO PATTERN REVERSED STIMULATION

Normal Control Series in Decades of Age



Apart from these considerations, there appeared to be no rule about the amplitude of the VER to pattern reversal stimulation. In particular it was not related to age, and this is supported by Celesia and Daly (1977) for pattern reversal. Dustman and Beck (1969 and 1977, p. 366) report a decrease in amplitude compared with age, using flash stimulation. There were variations between 2 uV and 16 uV in the under ten year group and from 3uV and 24 uV in the 40-50 year group. There was, however, a likelihood of amplitude symmetry between eyes in each individual, and between occipital lobes, so that although the mean amplitude over the whole control series was 10.78 uV and the sample standard deviation was 5.8 uV, the mean amplitude difference between eyes was only 3.5 uV, S.D. 2.55 uV. Between occipital lobes it was 3.5 uV, S.D. 2.57 uV (for details, see Table 3:3). This would indicate that a marked asymmetry of amplitude in an individual, either between eyes or between occipital lobes, should be regarded with suspicion.

Waveform.

In none of the controls was difficulty found in identifying the P_2 wave even with the marked variation in amplitude. In the majority of subjects the P_2 wave was clearly the highest amplitude positive wave and formed a clear single peak. Figure 3:7 is a stylised illustration of the three main types of waveform seen in the normal series. Earlier waves, P_0 and P_1, could occasionally be recognised, and there was a marked variation in the amplitude of the succeeding positive peak, P_3. In no control subject did P_3 exceed the amplitude of P_2 by more than 1.5 times.

In six subjects the P_2 peak was divided into two, the "a, b and c" wave as described by Gastaut and Regis (1964), and these were

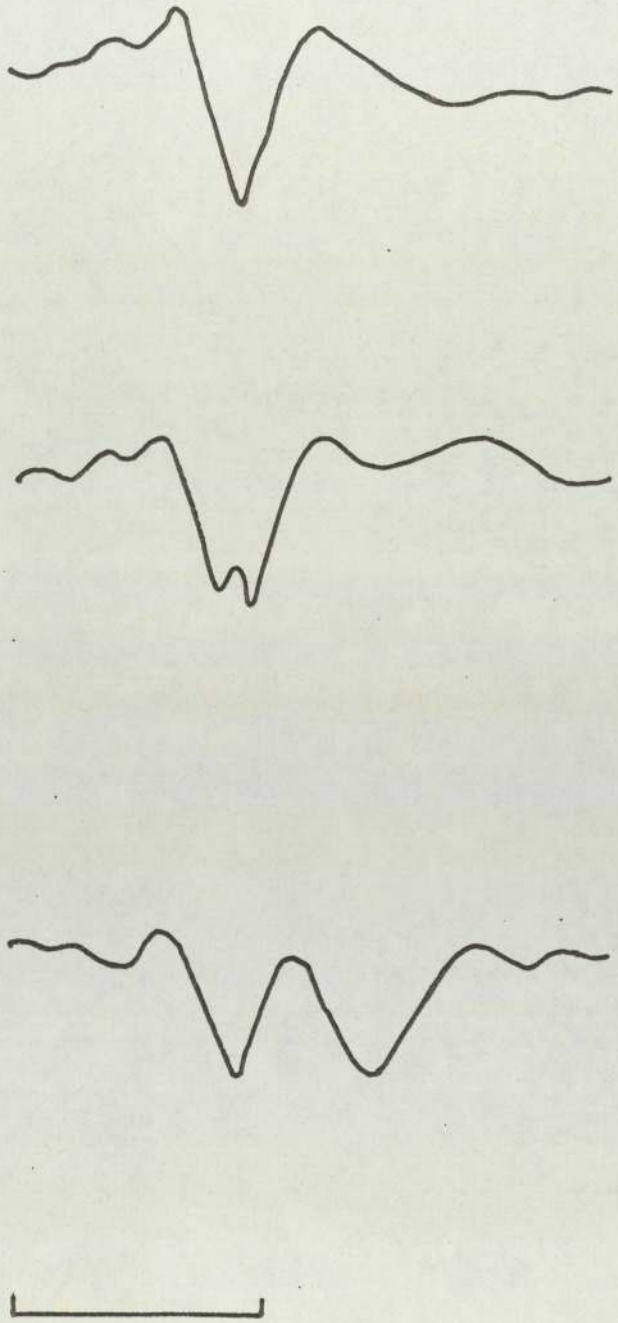
Figure 3:7 Waveforms in control series

Type I: Clear P_2 wave at about 100 msec latency
Waves P_0 and P_1 may or may not be detectable

Type II: A divided peak to the P_2 wave
The "a, b and c" response of Gastaut

Type III: Enlarged P_3 wave, equal in amplitude to P_2 or could be up to $1\frac{1}{2}$ times greater
Could be due to phase-locking with an on-going EEG rhythm

The line at the base of the figure represents 100 msec



found more often in one occipital lobe rather than from one eye. Gastaut suggests that this finding relates to dark adaptation, but this was not confirmed in the present study. If it were so, it would have appeared in one eye rather than in one occipital response.

No deliberate attempt was made to dark-adapt the subjects before performing the test, but as the right eye was invariably tested first, some dark adaptation would have taken place in the left eye by the time it was tested. No consistent difference in waveform was found between eyes over the series.

Artefacts

For the purposes of this study the usual EEG term will be extended to include any electrical activity recorded on the averaged trace which is not part of the visual evoked response. The term "physiological artefact" would include interference with the waveform caused by eye blinks, electromyograph potentials and sweating when referred to in the context of EEG. In the VER study this has been extended to include "contamination" of the response by the basic EEG.

Theoretically, any activity not occurring at a regular interval after the stimulus would "average out" of the final result, but some events may be related in time to the stimulus. For instance, it is possible that the subject may blink each time the pattern moves, so that the blink has a constant time relationship with the stimulus and will be "averaged". This occurs more commonly with flash stimulation, and results in a large electro-negative deflection in the VER appearing in the second half of the 250 millisecond sweep, so that it does not obscure a P_2 wave of normal latency. Blink artefacts can readily be seen in the "raw" EEG trace, and it is usually possible to eliminate this by simply requesting the subject to try to avoid blinking

Electromyograph (EMG) potentials are not so easy to eliminate, and may prove troublesome when the subject is sitting erect. It may be possible to reduce these by supporting the head, but a rather tense individual may still have unrelaxed neck muscles with consequent EMG contamination of the trace. Such a result appears in Figure 3:3. It should be possible to reduce this effect by increasing the number of trials, but a long test may also add to further tension in the subject.

In this situation the relatively small number (256) of sampling points or binary units (Bins) in the "Neurolog" average was a disadvantage, as the high frequency components of the EMG produced a scattering effect, and individual points could be seen. The "Datalab" averager used later, with 1024 points for each sweep, overcame the "scattering" effect, but an irregular trace was still present.

Sweat artefacts could also cause baseline variations, but were usually "ironed out" during averaging. If still present it was felt acceptable to reduce the time constant of the amplifiers to 0.1 seconds instead of 0.3 as this causes very little phase shift. This consideration has been mentioned by several authors, that is, that by altering the time constants (low frequency filters) in the amplifiers, and shift of phase occurs which alters the apparent latency of the response (Dawson and Doddington, 1973; Thornton, 1975; Cooper, Osselton and Shaw, 1974, Fig. 4:12, p. 62). With hindsight, it would probably have been advisable to carry out the whole series on the shorter time constant in order to keep exactly equal parameters.

The basic EEG was always observed while the VER was being averaged, as even in the normal subject two possibilities occur. One is that the repetition rate of the pattern change (or flash) may fortuitously phase-lock with a regular EEG rhythm, the other is that the visual stimulus may "drive" an EEG rhythm. This is more likely

with flash than with pattern reversal stimulation.

Two examples of this are illustrated in Figures 3:8 and 3:9. In the second a prominent alpha rhythm has been "averaged" as its phase has coincided with the pattern shift. In the first, a normal subject with a prominent beta component at 16 Hz also shows the effect of averaging the on-going rhythm. It is possible that wave type 3 in Figure 3:7 is the result of this. If this is suspected, the test was repeated using a slightly different rate of pattern reversal, or with flash, by randomising the incidence of the stimulus.

Of artefacts produced by electrical interference, the most common was from 50 Hz mains frequency. Obviously EEG principles obtain that electrode resistances should be reduced in order to avoid mains pick-up, but even when resistances are as low as one kilohm, electrode to electrode, mains interference can occur. It is possible to phase-lock with the 50 Hz mains cycle, so that even when the 50 Hz is invisible on the EEG trace, it is "locked-on" to the repetition rate of the pattern reversal. That is, that the start of each sweep occurs at the same part of the mains cycle, so that the 50 Hz is "averaged" with the trace. It appears as a regular rhythm with 12.5 waves in the 250 msec trace. Such a trace is illustrated in Figure 3:10. A very slight change in the rate of pattern reversal will avoid this, but it is usually more effective to cancel and re-start rather than expecting it to average-out during the remainder of the samples. It is also possible to obtain a beat frequency, where the part of the mains cycle changes slightly. This results in a periodic increase and decay of the amount of 50 Hz seen during the averaging process. Again cancellation and re-start with a minor change in repetition rate is the only solution.

Another electrical artefact can be introduced by a poor electrode

Figure 3:3 Phase-locking of the VER with a prominent beta rhythm (18 Hz) in the on-going EEG

Top two traces: EEG recorded from O_2 to F_o and O_1 to F_o, respectively

Second two lines: The average building up. These were the final eleven samples of a total of 128

Below: A plot of the final VER showing "contamination" of the picture by the EEG beta activity

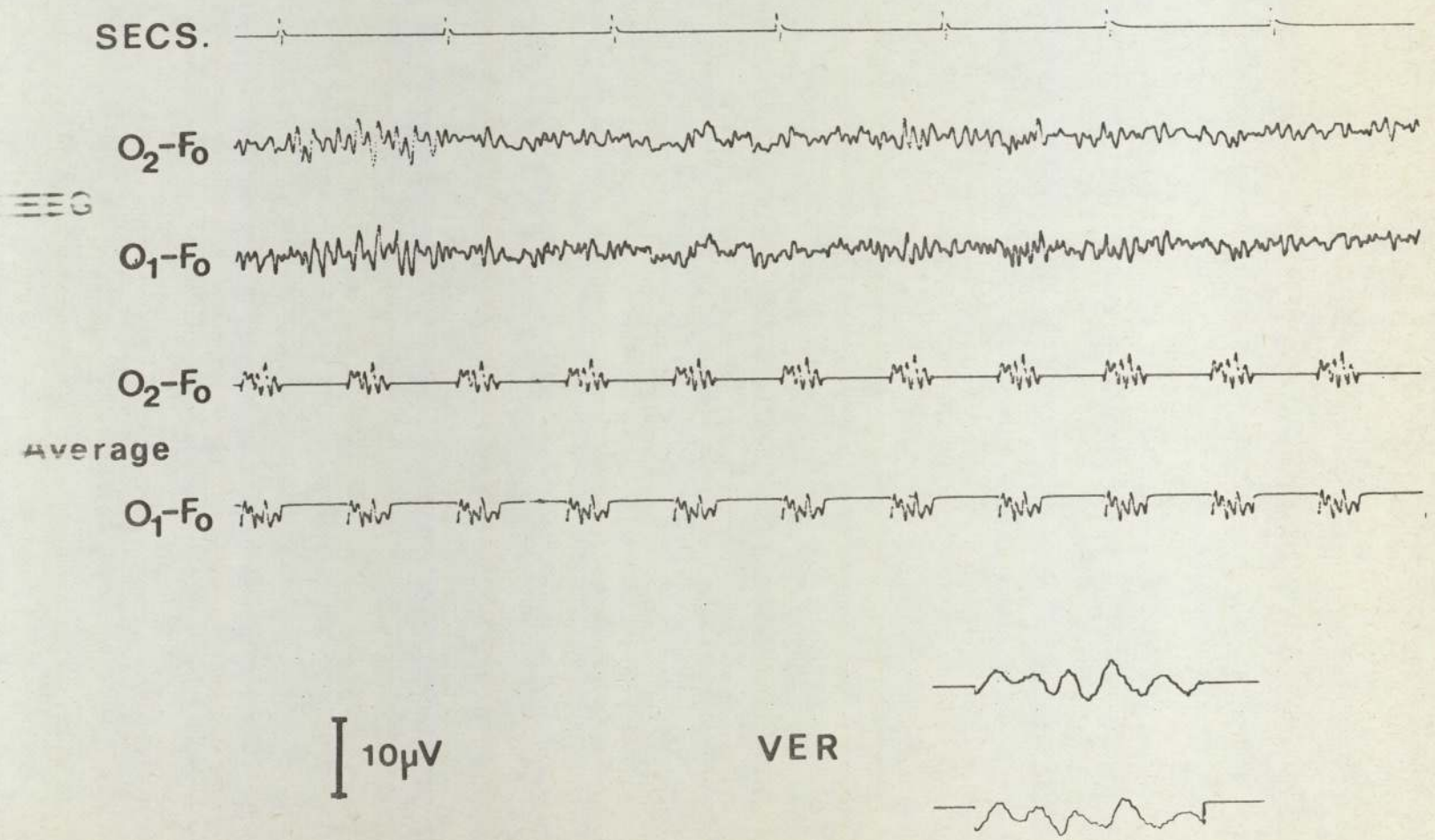

SECS.
O_2-F_o
EEG
O_1-F_o
O_2-F_o
Average
O_1-F_o
10μV
VER

Figure 3:9 "Contamination" of the VER due to phase-locking with a prominent alpha rhythm

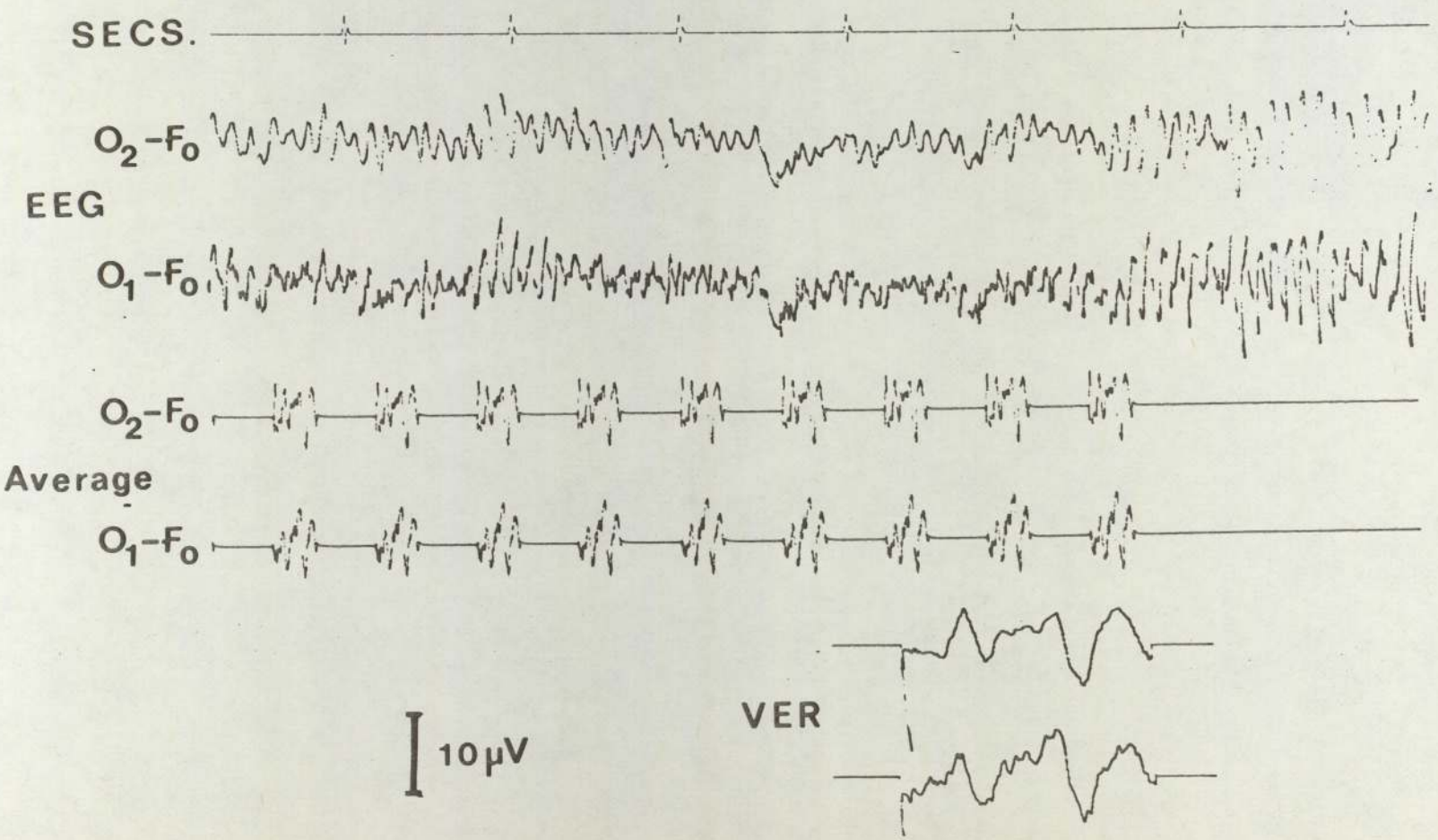
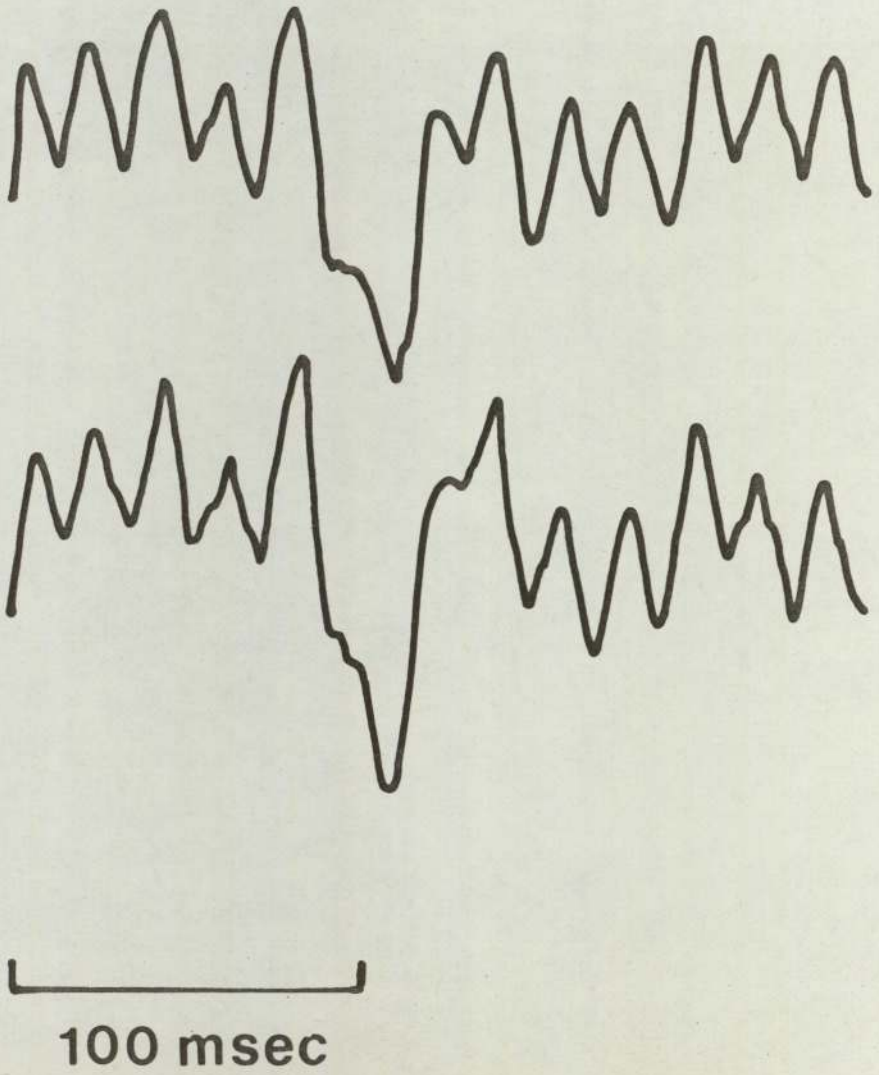

SECS.
O_2-F_o
EEG
O_1-F_o
O_2-F_o
Average
O_1-F_o
10μV
VER

Figure 3:10 Effect of phase-locking with 50 Hz mains frequency. 12.5 waves appear in the 250 msec trace. This may occur even when the concurrent EEG shows only low amplitude 50 Hz interference


100 msec

connection, either on the head or in any of the connecting plugs and contacts. This could result in amplifier blocking and consequently no signal, or only some of the samples being applied to the averager. If some of the recording were satisfactory, this would not be detectable on the averaged trace, but would falsify the amplitude measurement of the VER. This is another argument for recording the on-going EEG where the fault would immediately be obvious.

Amplifier noise level should be within the recommendations laid down by the International standards agreed by the I.F.S.E.C.N. (1958). These are that the noise level should not be above 2 uV occurring over a second or 4 uV over a minute. It is obviously essential that the noise should be random. The discrimination ratio between in-phase and out-of-phase signals should be better than 10,000 to 1.

Flash Stimulus

Twelve subjects in the normal group were stimulated with flash as well as pattern reversal, and Table 3:4 shows the results. Some difficulty was encountered in identifying the different waves with flash stimulus, and there appeared to be greater variations in latency, as reported elsewhere. Figures 3: 11, 12 and 13 show comparative VER to flash and pattern reversal in three subjects, and it is of interest to note that shorter latencies are not consistently found with one or other type of stimulus. Figure 3:14 gives a graph showing the longest and shortest latencies of response to flash plotted against the latencies in the same individual to pattern reversal. If the latencies were the same, the results would all have appeared on the diagonal line across the graph, but it will be seen that in some individuals there was a wide discrepancy, and that there was no

TABLE 3:4

Responses to flash and pattern reversal compared in the control series

Subject	Age	Sex	Longest and shortest VER to Flash msec	Pattern reversal msec	Note
R.B.	21	M	118 - 131	95 - 101	"Waterfall" response to flash
H.D.	43	F	122 - 125	93 - 95	"Waterfall" to flash
S.E.	28	F	122 - 138	90 - 99	
J.G.	18	F	96 - 106	90 - 93	
G.H.	55	M	73/138-125	96 - 106	"Waterfall" to flash
M.L.	37	F	109 - 116	92 - 100	
D.M.	37	M	91 - 104	89 - 102	
F.R.	21	M	95 - 114	101 - 109	
F.T.	54	F	80 - 86	106 - 111	
K.T.	21	F	92 - 95	92 - 104	
J.W.	25	M	68/104 - 87	90 - 94	
S.W.	20	F	84 - 106	90 - 104	

Mean and standard deviation of highest and lowest latencies:

Flash	P/R
n = 24	n = 24
Mean = 107.67	Mean = 97.58
SD = 17.25	SD = 6.67

Figure 3:11 Comparison between the VER to pattern reversal and flash stimulation in a control subject

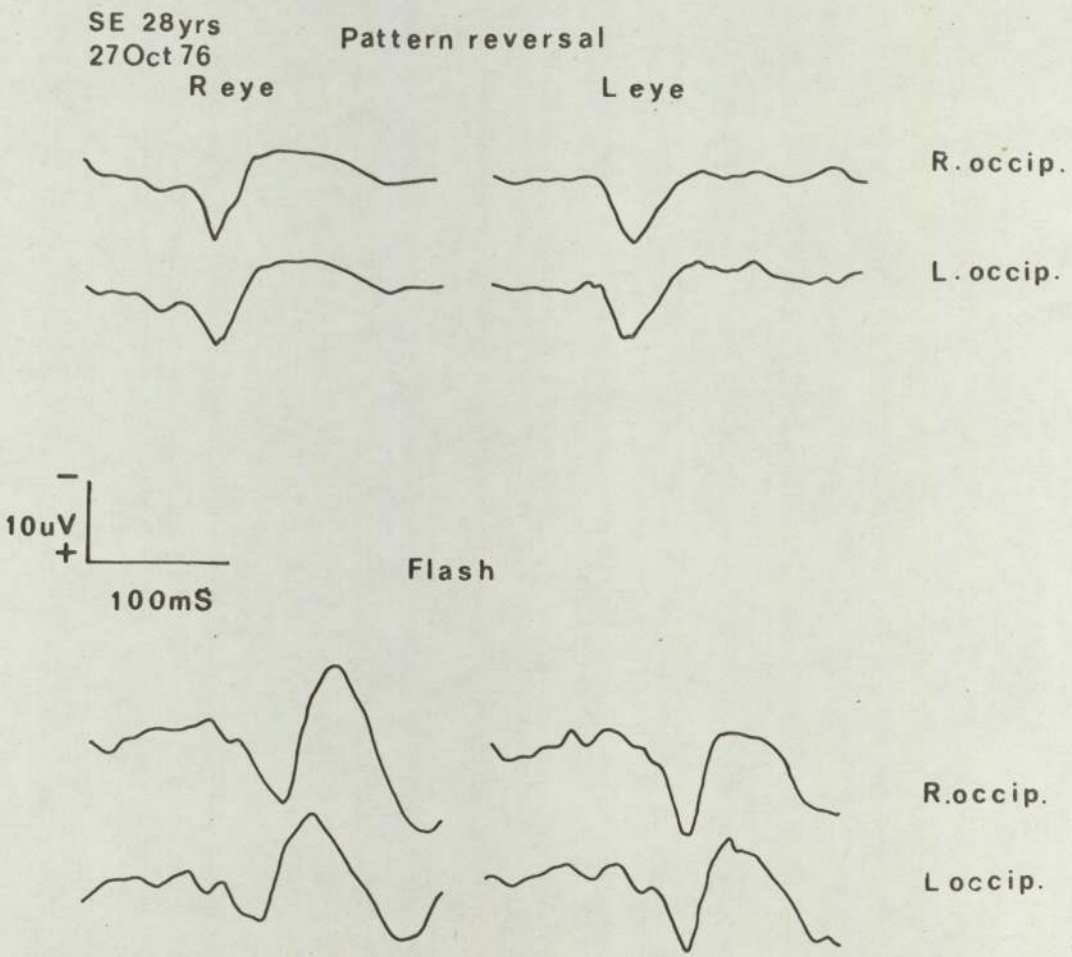

SE 28yrs
27Oct 76
Pattern reversal
R eye
L eye
R.occip.
L.occip.
10uV
100mS
Flash
R.occip.
L occip.

Figure 3:12 Pattern reversal stimulation compared with flash in a control subject

FT 53yrs
Control
7 June 76

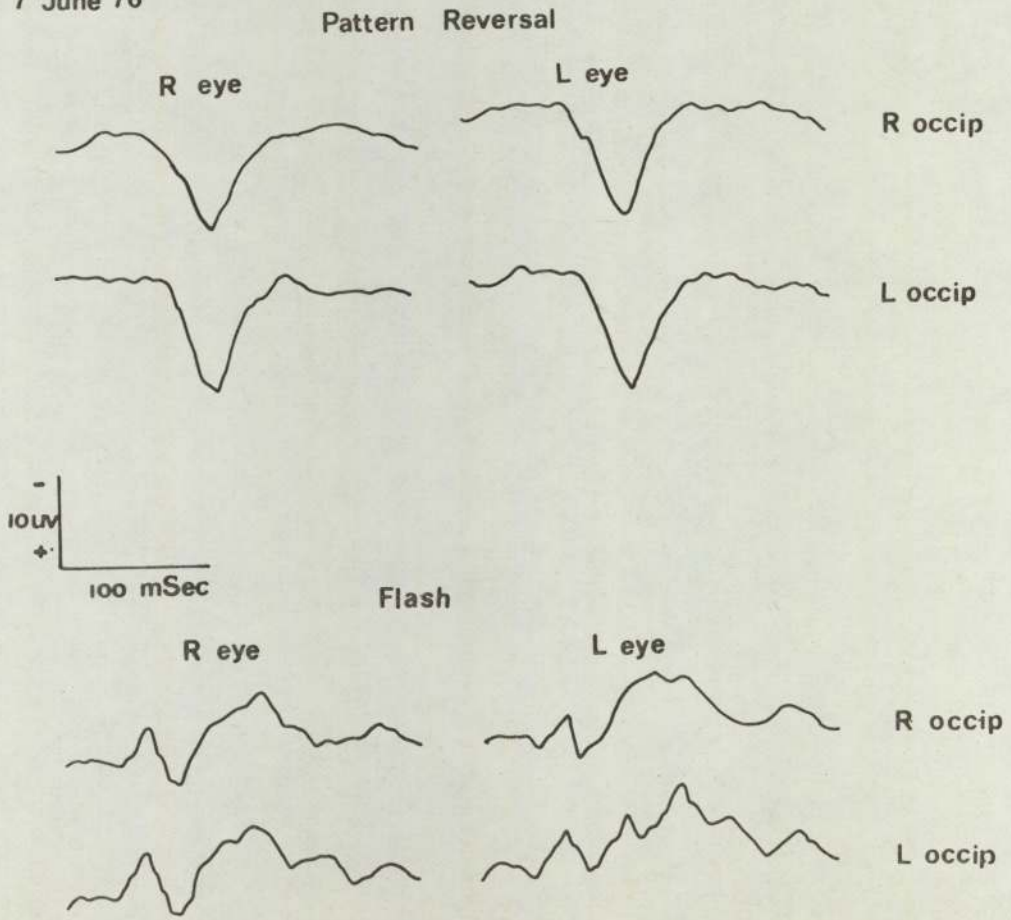


Figure 3:13 Pattern reversal compared with flash in a control subject

HS 43yrs
Control
16 Dec 76

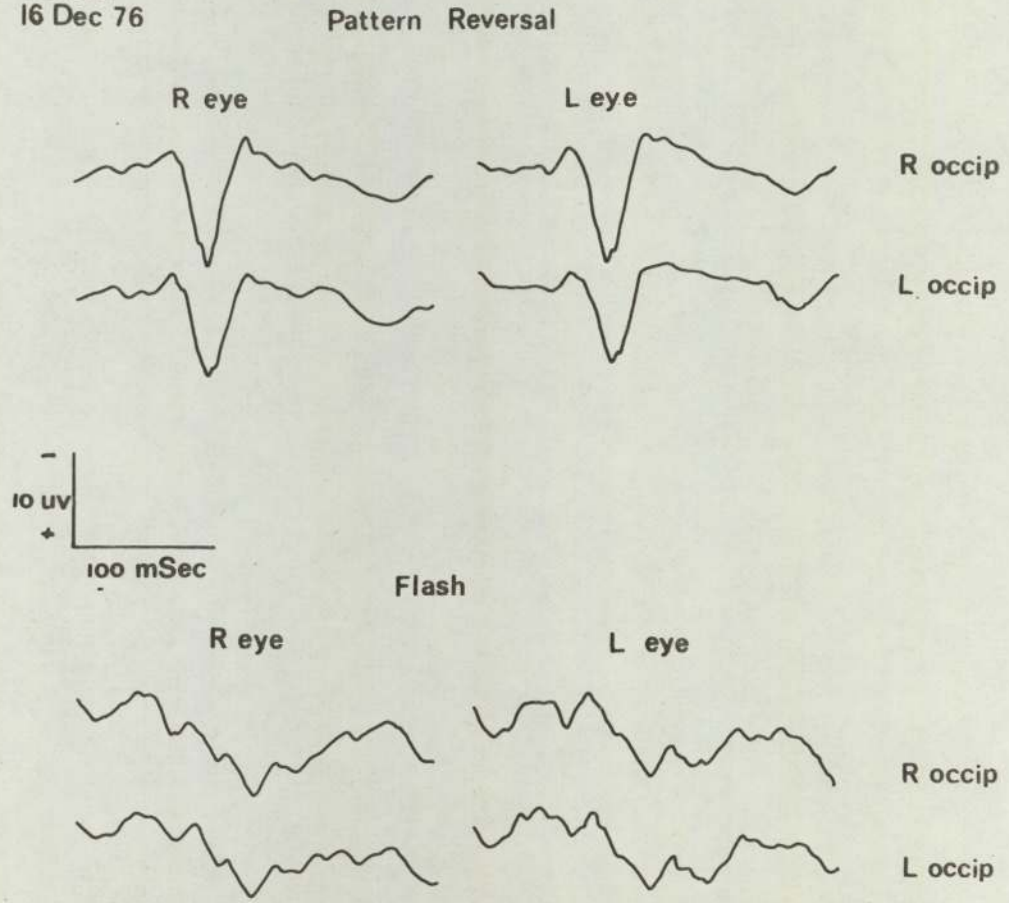
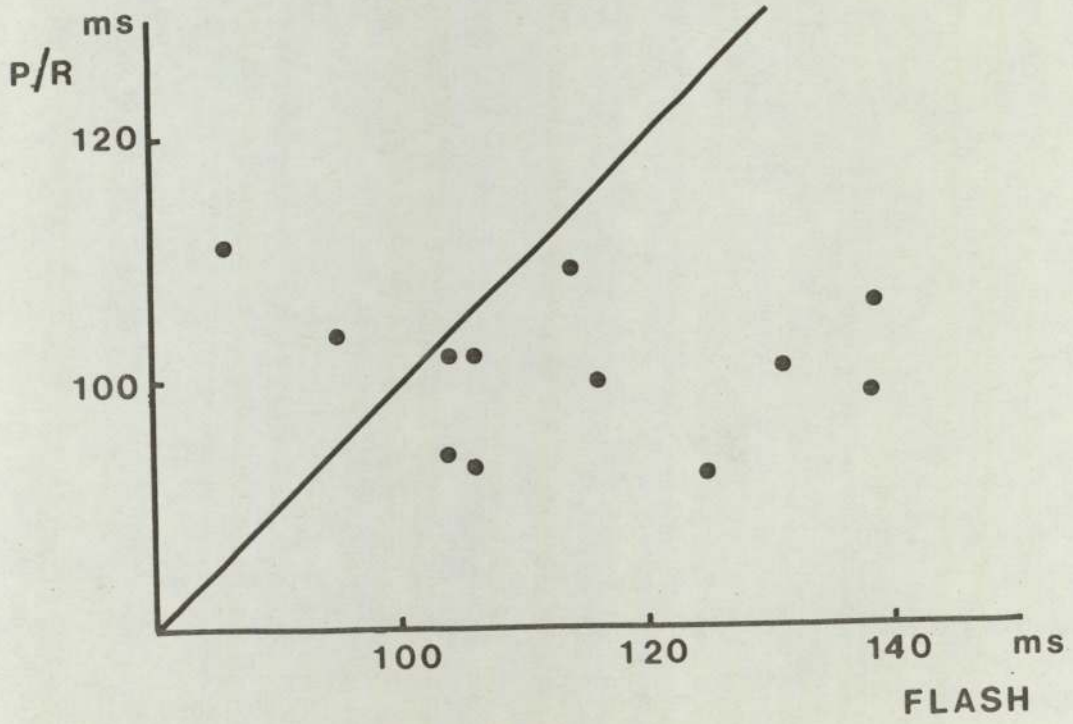


Figure 3:14 Graph to show latency of response to flash stimulation as a function of latency to pattern reversal stimulation


ms
P/R
120
100
100
120
140
ms
FLASH

consistent finding of longer latencies with either flash or pattern reversal. This graph also confirms the strict upper limit of latency in pattern reversal as against the wide variation in flash, some of which results might have been considered abnormal.

One of the difficulties in assessing the response to flash stimulation is in the identification of the P_2 wave for latency measurement. Waveforms are more variable than with pattern reversal, and in some subjects, a step-like increase in positivity in successive peaks produced a waveform which has been named a "waterfall" response. This waveform is illustrated in Figure 3:13. Authors who have had extensive experience in using flash stimulation have stated that the early waves are more reliable as an indication of prolonged latency than the later waves (Harding, 1977a; Harden, 1978).

At the end of Table 3:4 the mean latency and standard deviation is shown for flash as compared with pattern reversal stimulation in the 12 subjects. It will be noted that the mean latency is 10 msec more prolonged (about 10%) for flash and the standard deviation is 2½ times greater. Although this exercise was only carried out on a small number of subjects, it included a wide age range, and the standard deviation to pattern reversal of 6.67 msec correlates well with that to the whole normal series of 73 subjects, which was 6.99 msec.

SUMMARY OF FINDINGS IN PATTERN REVERSAL STIMULATION

The trend of increasing latency with age in the fifth decade is as expected from earlier reports (Creutzfeld and Kuhnt, 1967; Dustman and Beck, 1969, for flash; and Celesia and Daly, 1977, for pattern reversal). The shortening of mean latency in the sixty-plus age group is surprising, but could be an artefact produced by the small sample.

As the whole series shows latencies within a fairly tight compass, and an overlapping range between age groups, it was felt justifiable to establish normal limits to cover all age groups, and these consolidated results are shown at the ends of Tables 3:1 and 3:2.

Figure 3:6 shows a spot graph of the latencies related to the seven age groups, in each group the longest and shortest recorded latency of each individual is shown, with the mean of each group and two standard deviations in the shaded areas.

Establishment of Normal Limits

On the evidence obtained in the normal series, acceptable limits of latency, symmetry between eyes and between occipital lobes were established for pattern reversal stimulation. The upper limit of latency of the P_2 wave was taken as the mean plus $2\frac{1}{2}$ times the standard deviation, and no normal control fell outside this limit. In latency differences between eyes and between occipital lobes, the mean plus twice the S.D. was found to contain all except the 50-60 year age group. So that, using the stimulus parameters described, the following acceptable limits were drawn for pattern reversal stimulation:

Latency

Upper limit of latency of any of the four responses	118 msec
Maximum acceptable difference in latency between eyes	17 msec
Maximum acceptable difference in latency between occipital lobes	15 msec

with the proviso that subjects over the age of 50 years may be allowed a greater asynchrony.

CHAPTER 4. THE VER IN MULTIPLE SCLEROSIS AND RETROBULBAR NEURITIS

The material used in this study came from the neurological referrals to the Wessex Neurological Centre and Regional clinics over a period of eighteen months. In many cases the diagnosis of multiple sclerosis (MS) had been made some years previously, in some it was clinically suspected but a visual evoked response test was requested for confirmation, and in a large number the test was requested as multiple sclerosis was an outside possibility, and a painless, simple, and short-lasting test was thought to be justified, and potentially useful.

Of those patients referred the results of 150 patients' VER examinations are reported. This does not cover the entire number of patients tested in the eighteen months, but only those in whom the clinical information and follow-up were available and adequate for an accurate diagnostic classification to be made. The clinical records were analysed by an independent medical observer, without reference to the results of the visual evoked response tests, and placed in categories according to the criteria described by McAlpine and co-workers in 1972. These are summarised as follows:

Definite. 1) A history of an acute episode of a type known to occur in MS, with improvement and subsequent relapse or relapses over the course of years, with evidence in addition of signs indicative of multiple lesions in the central nervous system, on first examination or later.

2) A gradual onset of paraplegia later followed

by relapses and signs indicative of brain stem, cerebrum or optic nerve lesion.

Probable. 1) Evidence of multiple lesions suggestive of MS in the original episode. During lengthy follow-up, absence of fresh symptoms, but variability in signs.

2) A history of one or more attacks of acute retrobulbar neuritis (RBN) accompanied or followed by other signs, but no subsequent relapse.

Possible. 1) Similar history to Probable (1), but with paucity of signs or insufficient follow-up information.

2) A history of progressive paraplegia usually in early middle age without evidence of relapse or remission, other causes having been excluded.

When doubt existed, attention was paid to (1) the age of the patient; (2) any family history of the disease, and (3) the CSF findings.

In addition a separate grouping of "retrobulbar neuritis only" was made for those patients who presented with no other symptoms or signs. It was felt that some of these patients might not be suffering from MS, and indeed one of these was subsequently diagnosed as having an acute peripheral neuritis and one having had a polyneuropathy three years previously.

In view of the possible distribution of lesions, the recording method in this study was designed to show the location of defect in the visual system. One eye was stimulated, the other covered by an eye patch, and the VER was recorded from the two occipital lobes, then this was repeated with the other eye. If a delayed P2 wave occurred in both occipital responses from one eye, the lesion was presumed

to be pre-chiasmal. If it occurred in one occipital lobe from both eyes, the assumption is that the delay occurred either in the optic tracts, the lateral geniculate body or the optic radiations. Figure 4:1 illustrates this theory.

Results

The VER results have been correlated with the clinical grouping and visual history. Those cases where there were no symptoms or history implicating the visual system, such as a period of loss of acuity, restriction of visual fields or an episode of pain in the eyes, or behind the eyes with movement, have been noted as having "no visual involvement". The sole finding of pale optic discs on examination without a suggestive history or other signs in the visual system has not been included as a positive finding in the analysis of visual involvement owing to the subjective nature of this observation and the fact that the discs may appear pale for other reasons, such as in myopia.

Diplopia was noted separately, where it had occurred. This was not expected to relate to the visual evoked response, as it implicates the reflex mechanisms of the brain stem, rather than the optic nerve, tracts and radiations involved in the production of the VER.

Table 4:1 summarises the series of 150 classified results, and these are presented graphically in Figure 4:2, compared with the control series. In this graph, the longest latency found in each individual is shown, both in patients and controls, as it was thought that including all four results for each individual would be too confusing, and averages of each would be meaningless. For this reason, the "mean" line and SD are slightly higher than in the total

Figure 4.1 Model to show that a lesion in an optic nerve, anterior to the chiasm produces a delayed response to both occipital lobes when one eye is stimulated.

A post-chiasmal lesion involving the optic tract, lateral geniculate body or optic radiations produces a delayed response to one occipital lobe from each eye

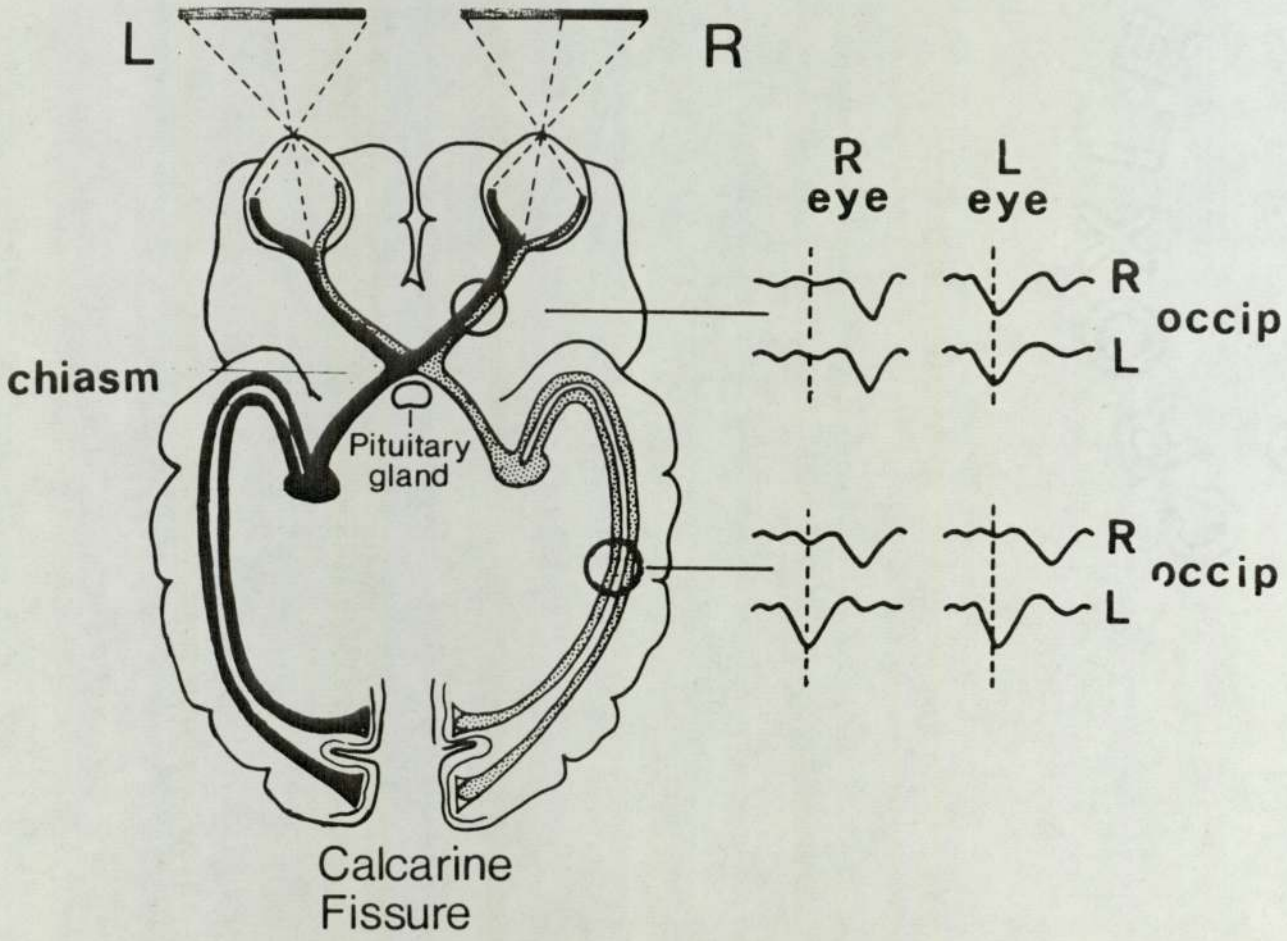

L
R
R eye
L eye
R
L
occip
chiasm
Pituitary gland
R
L
occip
Calcarine Fissure

TABLE 4:1 VISUAL EVOKED RESPONSES TO PATTERN REVERSAL STIMULATION

MS and RBN groups selected on clinical grounds only. Total 150 patients

Group	Number of patients	Delayed VER	%	Delay without visual involvement	% of Total
Definite MS	31 (17)	26 (16)	84 (97)	11	35
Probable MS	32 (5)	21 (5)	66 (100)	14	44
Possible MS	75 (12)	30 (11)	40 (92)	23	31
RBN only	12*	10+	83	-	-
	150	87	58%	48	32%

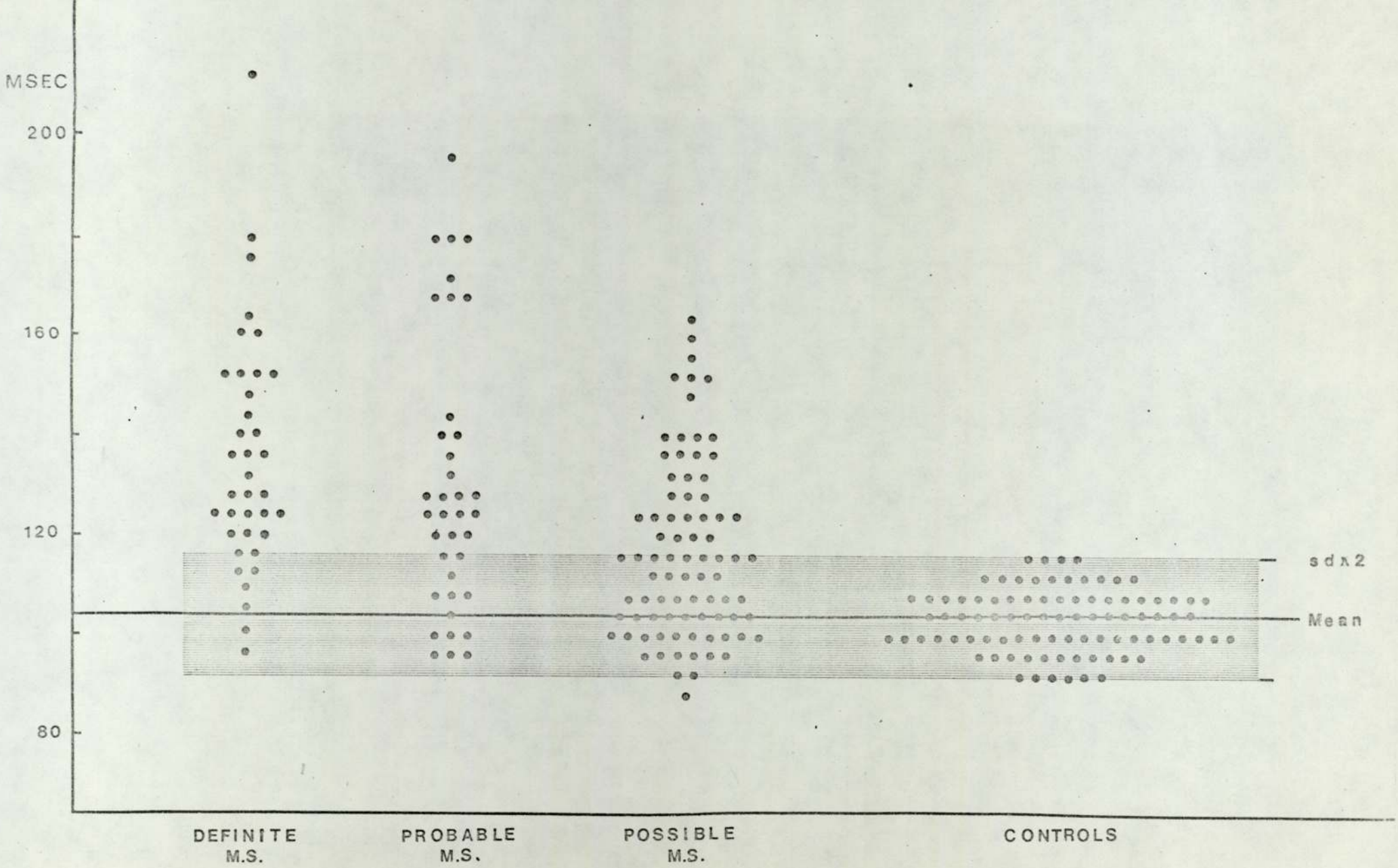
Note: Halliday's figures published in 1973 are shown in brackets

* 7 out of the 12 patients with RBN were recorded during an acute attack of retrobulbar neuritis.

\+ includes two with no detectable P_2 wave, both with acute RBN.

Out of 64 patients whose VER fell within the normal range, 7 had a history suggestive of retrobulbar neuritis

Figure 4:2 Spot graph to show the distribution of the longest recorded latency of each patient in the three MS groups compared with the longest latencies of each of the control subjects.
The mean latency of the normal control group is shown, and the shaded area represents twice the standard deviation.


MSEC
200
160
120
80
sd x 2
Mean
DEFINITE M.S.
PROBABLE M.S.
POSSIBLE M.S.
CONTROLS

results quoted earlier, when describing the series of normal control subjects.

In Table 4:1 the figures in each group have been compared with Halliday's results published in his first paper reporting delayed VER with pattern reversal stimulation in multiple sclerosis, as this is the original classic on this topic. It will be noted that Halliday's percentage of positive findings is considerably higher, but that the number of cases was smaller, particularly in the "Probable MS" group which only included five patients. Since the publication of that paper there have been others, which correlated much more closely with the present series than with Halliday's (Asselman et al., 1975; Matthews et al., 1977; Fereydoun Shahrokhi et al., 1978).

A delay in any one of the four responses obtained from each patient has been regarded as abnormal, and the various combinations of prolonged latency are summarised in Table 4:2. In three patients there was electrical evidence of separate but partial lesions in the visual system: in one the right eye to right occipital and left eye to left occipital lobes were delayed and the crossed responses were of normal latency, and in two the crossed responses were delayed and the ipsilateral responses normal, suggesting a lesion or lesions in the optic chiasm.

In two patients the prolonged latency was recorded from the opposite eye to that involved in a recent attack of retrobulbar neuritis, and repeated tests showed at times a change of the eye showing a prolonged latency, with or without clinical accompaniment of reduced visual acuity.

Some examples of the findings described above are shown in Figures 4: 3-5.

TABLE 4:2 DISTRIBUTION OF LESIONS IN MS

(Excluding patients who only presented with RBN)

Location of prolonged latency as suggested by VER	Definite MS	Probable MS	Possible MS	Total
a) Optic nerve (prolonged to both occipital lobes from one eye)	11 (5)	8 (6)	14 (10)	33 (21)
b) Post-chiasmal (Prolonged to one occipital lobe from both eyes)	2 (1)	Nil	2 (-)	4 (1)
c) Partial optic nerve or tract lesion (one response delayed out of the four)	Nil	2 (1)	5 (5)	7 (6)
d) Two separate lesions (Two incongruous responses delayed)	3 (1)	Nil	Nil	3 (1)
e) Multiple lesions (Three out of four responses delayed)	Nil	3 (2)	1 (-)	4 (2)
f) Multiple lesions (All four responses delayed)	10 (4)	8 (5)	8 (8)	26 (17)
	26 (11)	21 (14)	30 (23)	77 (48)

The figures in brackets represent those patients without symptoms or signs of diminished visual acuity, either at present or in the past.

Figure 4:3 NE - 36 yrs. WNC 29269

Prolonged latency from one eye to both occipital lobes.

The vertical hatched line is at 100 msec.

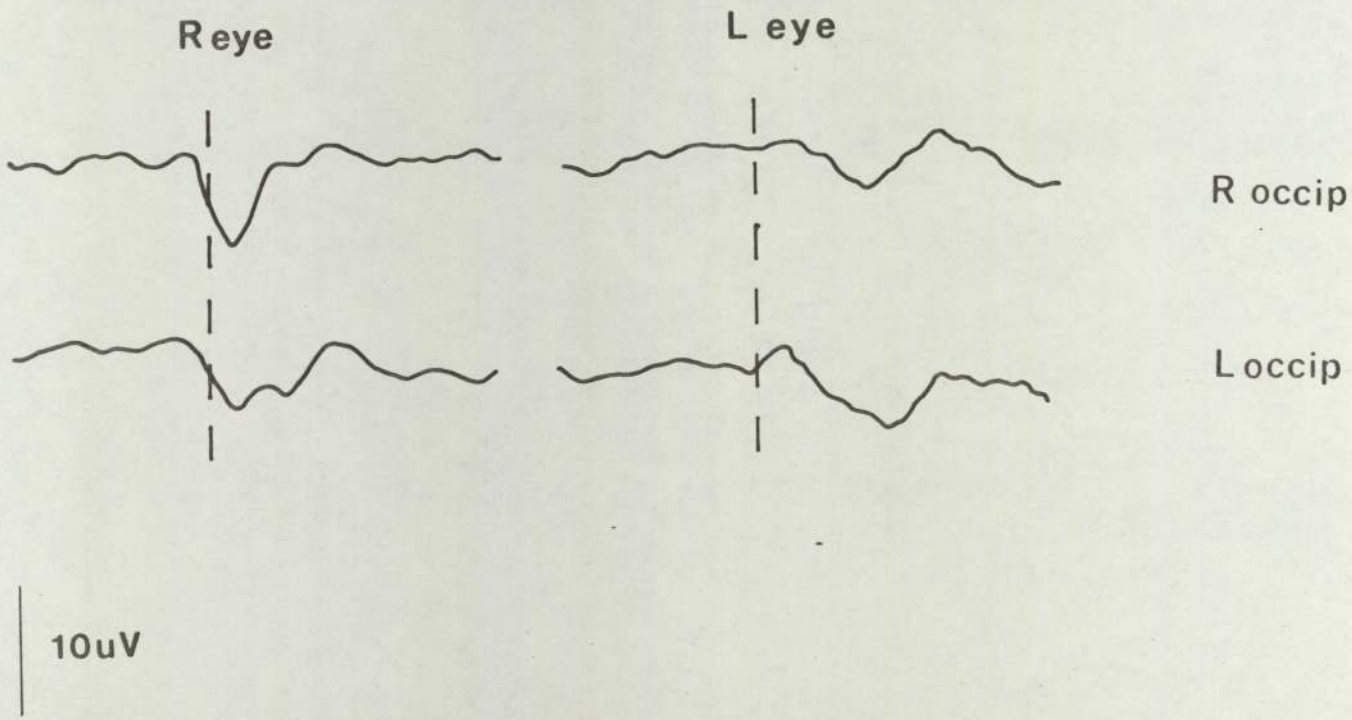


FIG.4:3

Figure 4:4 KK - 36 yrs. Bas 336302

Prolonged latency to one occipital lobe from both eyes.

Vertical hatched line at 100 msec.

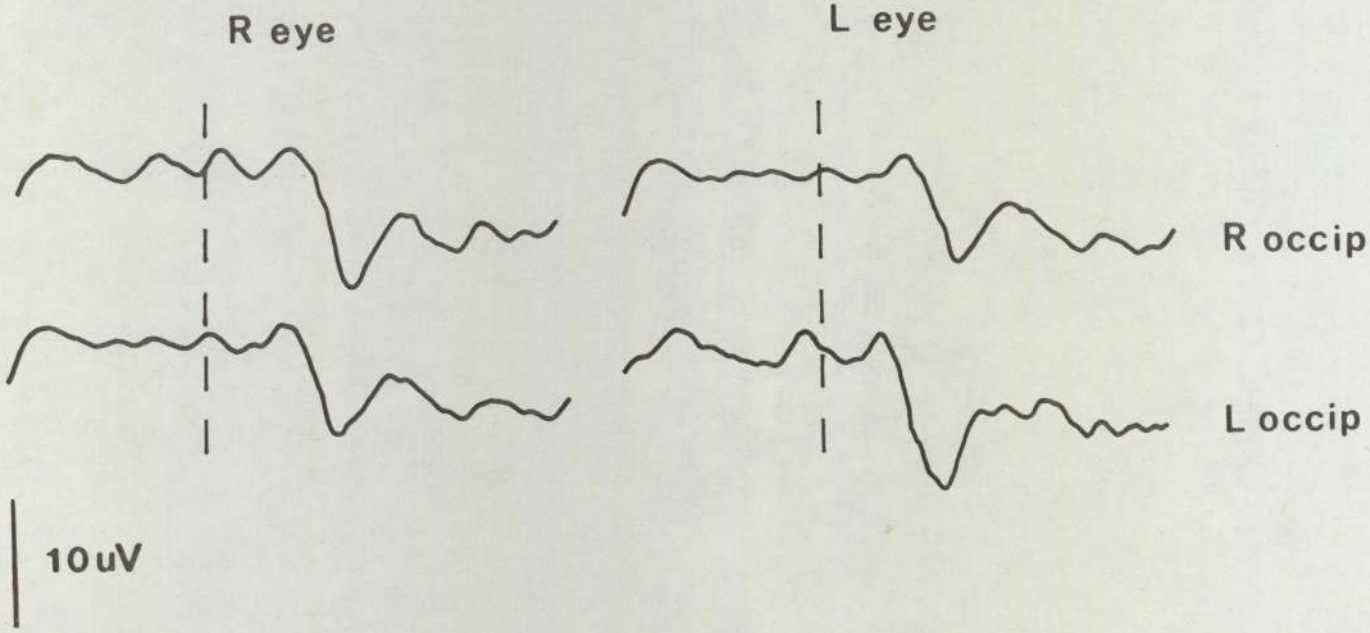


FIG.4:5

Figure 4:5 KR - 25 yrs. WNC 23065

All four responses showed a prolonged latency.

Vertical hatched line at 100 msec.

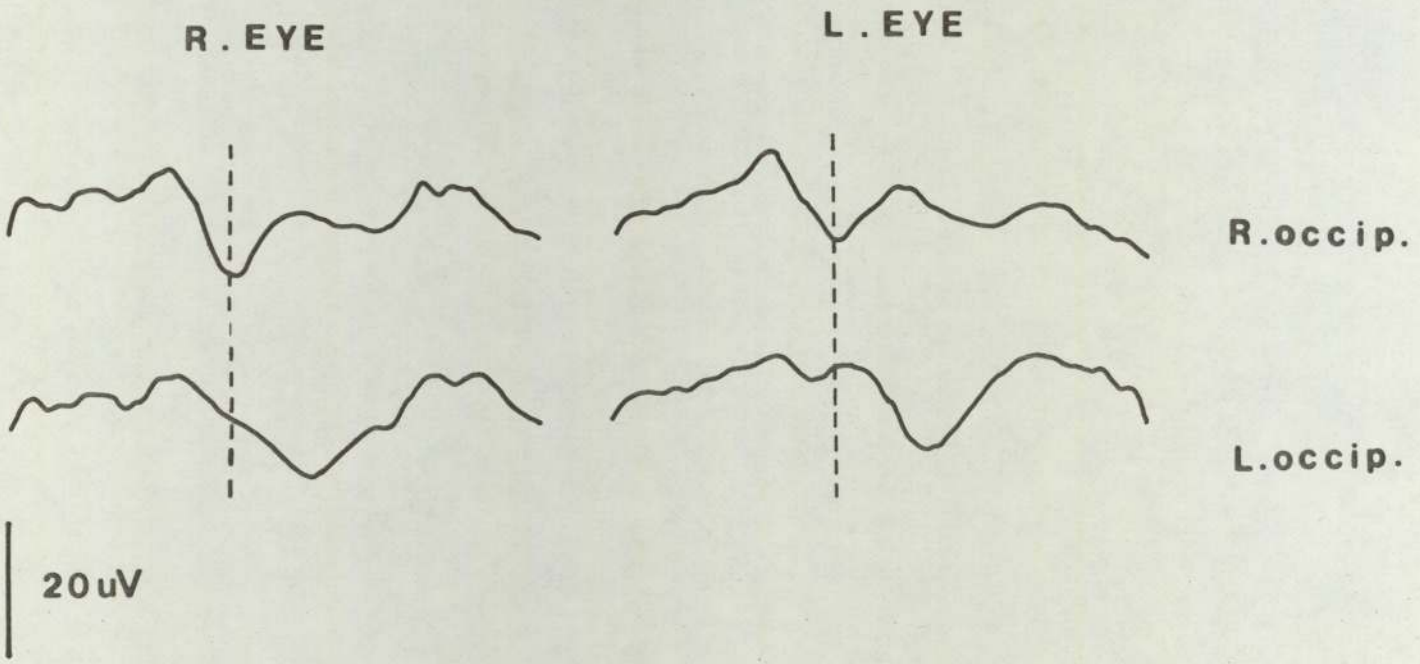


FIG. 4:4

Waveform

The VER waveforms found in the normal control series have been illustrated in Chapter 3 (Fig. 3:7). It was suggested that a single positive peak (P2) with a clear maximum point and with or without early peaks should be designated Type 1. A positive peak with a double point ("a, b and c" wave of Gastaut, or "bifid" wave of McInnes, 1978) should be Type 2, and a P2 wave followed by a similar after-wave of equal amplitude and form to the P2 wave, should be Type 3.

In MS any of these waveforms might be seen, with or without a prolonged latency of response. In addition, in MS, other waveforms were observed, and designated as follows:

Type 4. A clear positive wave at about the expected P2 latency of around 100 msec followed by a later positive wave (P3) of amplitude more than 1.5 times that of the P2 wave. On occasion it appeared that the relative emphasis of these two waves changed during the course of the development of the averaged response. This waveform was always regarded as abnormal and the latency of the major peak was reported in the results.

Type 5. An early, P_1 wave at about 40 msec followed by an increasing negativity, without a clear positive peak. This was seen in patients with a macular defect during an acute episode of retrobulbar neuritis.

Type 6. A "fragmented" response, when a succession of waves at approximately equal amplitude occurred, and in which it was difficult to determine which represented the P_2 wave. Such a response was only seen in severely-affected long-standing MS patients.

Type 7. A small positive peak at about the expected P_2 latency, followed by a high amplitude N_3 wave. This waveform was not only seen in MS patients but also in some compressive lesions reported in Chapter 5.

Type 8. An absent response. No wave of over 1 microvolt in amplitude.

These waveforms are illustrated in Figure 4:6.

The "Retrobulbar Neuritis Only" group showed a greater distortion of waveform, but many of these patients (7 out of 12) were recorded during an acute attack, when visual acuity was considerably reduced, and some had areas of amblyopia. These patients have not been included in the analysis in Table 4:2 owing to the difficulty of establishing which wave represented P_2, and therefore arriving at a figure for its latency.

Repeated visual evoked responses

Twenty-one of the patients included in this study had VER examinations carried out twice. An analysis of the findings and changes between the two trials is shown in Table 4:3 and these are summarised in Table 4:4. It will be seen that the VER results in these patients showed a lability not always related to the clinical evidence of involvement of the visual system. Neither did the length of history of the disease appear to bear any relation to the stability of the response.

Four of the twenty-one had received treatment with steroids in between the tests, and one of these patients was pregnant. One had a short trial of electrical stimulation to the spinal cord. In none of the cases with treatment did the VER show any obvious improvement.

Figure 4:6 Variations in waveform seen in patients

Type 4. A low amplitude wave at about 100 msec followed by a larger peak of prolonged latency

Type 5. An early P_1 wave at about 40 msec followed by an increasing negativity, without a clear positive peak

Type 6. A "fragmented" response in which it was difficult to identify the P_2 wave

Type 7. A low amplitude positive wave at about 100 msec followed by a high amplitude negative peak (N_3)

Type 8. An absent response. No wave of over 1 microvolt in amplitude

The vertical hatched line represents 100 msec

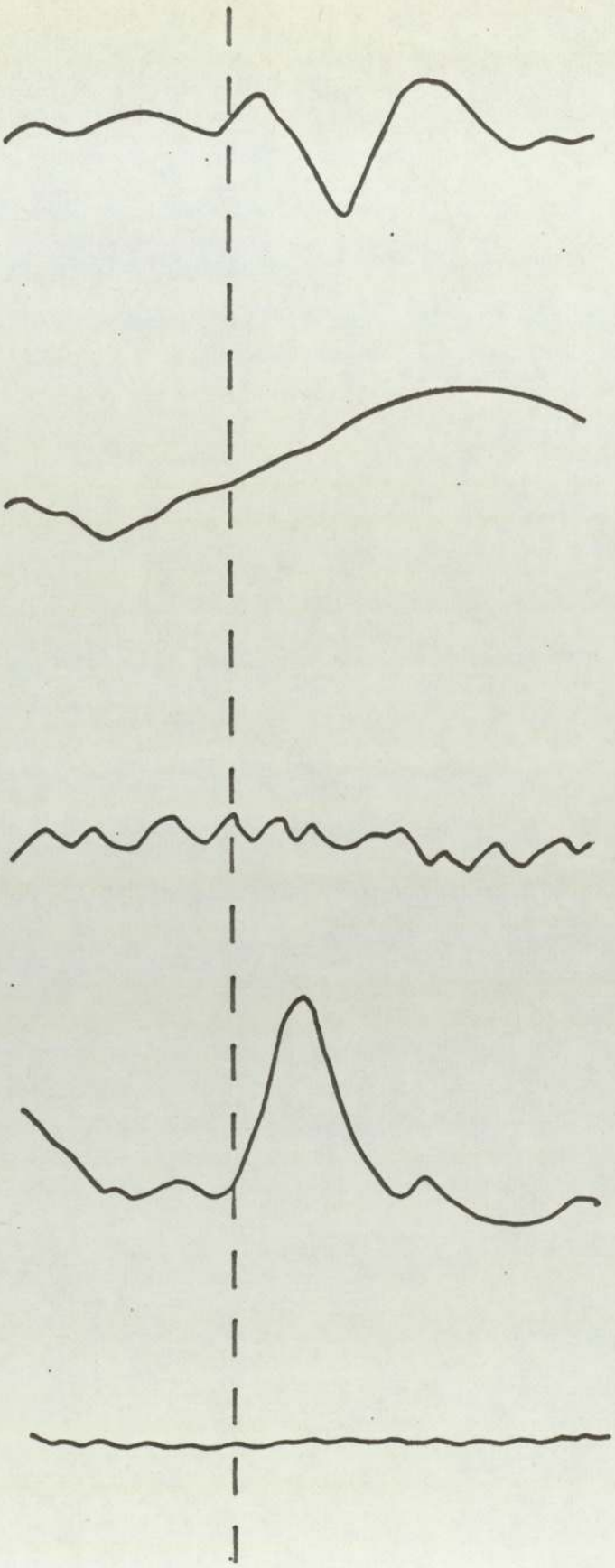


Table 4:3 REPEATED VER

1. Definite MS 7 patients. The P_2 latencies on the first and second occasion are shown.

Patient	Time interval between VERs	P_2 latencies msec		Difference	
		1st	2nd		
F.H. WNC 27037	3 mth	* 102	110	+8	
		104	107	+3	
		107	106	-1	
		109	103	-6	
				Total +4	(Algebraic)
				Av. +1	
J.J. WNC 24799	6 mth	205	179	-26	
		87	87	+0	
		122	125	+3	
		83	123	+40	
				Total +17	
				Av. +4.2	
D.G. WNC 24511	15 days	99	112	+13	
		123	115	-8	
		110	103	-7	
		84	80	-4	
				Total +17	
				Av. +4.2	
M.H. WNC 26623	14 mth	100	93	-7	
		98	94	-4	
		124	125	+1	
		124	126	+2	
				Total -8	
				Av. -2	

Table 4:3 (1)

Patient	Time interval between VERs	P_2 latencies msec 1st	2nd	Difference
G.C. WNC 25727	13 days	175	160	-15
		155	160	+5
		175	160	-15
		161	160	-1
				Total -26
				Av. -6.5
J.R. WNC 24751	2 years	114	111	-3
		106	104	-2
		122	129	+7
		120	130	+10
				Total +12
				Av. -6.5
G.S. WNC 512	1 mth	101	114	+13
		101	114	+13
		94	97/140	+46
		101	97/140	+39
				Total +111
				Av. +27.7
A.W. WNC 25105	$4\frac{1}{2}$ mth	127	98	-29
		103	93	-10
		103	115	+12
		104	115	+11
				Total -16
				Av. -4

* In each result the order of presentation is the same

R eye to R occipital lobe
R eye to L " "
L eye to R " "
L eye to L " "

Table 4:3(2) Repeated VER

2. Probable MS Clinical Group

Patient	Time interval between VERs	P_2 latencies msec		Difference
		1st	2nd	
C.C.	8 mth	109	130	+21
WNC 26180		112	122	+10
		119	113	-6
		122	124	-3
				Total +22
				Av. 5.5
M.F.	3 weeks	178	168	-10
WNC 27377		178	163	-15
		125	145	+20
		131	131	0
				Total -5
				Av. -1.2
S.M.	2 mth	100	101	+1
WNC 26808		106	100	-5
		94	106	+12
		101	101	0
				Total +7
				Av. +1.75
T.V.	15 days	76	179	+103
W'mth		76	168	+92
P90176		81	92	+11
		78	91	+13
				Total +219
				Av. +54.75

Table 4:3 (3) Repeated VER

3. Possible MS

Patient	Time interval between VERs	P_2 latencies msec 1st	2nd	Difference
H.B. WNC 25131	10 days	120	125	+5
		117	125	+28
		120	125	+5
		140	138	-2
				Total +36
				Av. +9
R.C. WNC 25677	7 weeks	107	111	+4
		109	113	+4
		103	106	+3
		103	106	+2
				Total +13
				Av. +3.25
R.C. WNC 25355	3½ mth	141	156	+15
		112	130	-18
		128	141	-13
		122	156	+34
				Total +18
				Av. +4.5
C.E. WNC 23118	1 yr 9 mth	106	120	+14
		109	117	+18
		122	123	+1
		115	126	+11
				Total +44
				Av. +11

Table 4:3 (3) Repeated VER

Patient	Time interval between VERs	P_2 latencies msec		Difference
		1st	2nd	
K.M. WNC 25907	3 mth	130	128	-2
		127	130	+3
		109	99	-10
		110	97	-13
				Total -22
				Av. -5.5
J.R. WNC 27088	2 mth	117	101	-16
		115	106	-9
		103	161	+58
		98	159	+61
				Total +94
				Av. +23.5
G.R. WNC 24843	7 mth	97	100	+3
		101	97	-4
		91	105	+14
		97	106	+9
				Total +22
				Av. +5.5
B.T. P'smth 300122	7 weeks	87	151	+64
		90	149	+59
		131	146	+15
		135	90	-45
				Total +93
				Av. +23.25

Table 4:3 (4) Repeated VER

4. Retrobulbar Neuritis only. 1 patient

Patient	Time interval between VERs	P_2 latencies msec		Difference
		1st	2nd	
P.S. WNC 26605	6 days	106	Absent	
		91	120	+29
		112	94	-18
		99	93	-6
			Total	+5
			Av.	+1.25

Analysis of results of repeated VER

Prolongation of latency

n = 16

Mean = 11.46

S.D. = 14.38

Shortening of latency

n = 5

Mean = 3.84

S.D. = 2.25

TABLE 4:4 SUMMARY OF FINDINGS IN REPEATED VER IN MS

First VER \ Second VER	Normal	Unchanged prolonged latency	Deterioration	Changed waveform	Incongruous Results
Normal	4		1		
Prolonged latency		6	4	2	3

Total 20

The figures represent the number of patients whose responses fell into each group.
For instance, four results which were normal on the first occasion remained normal.
Six who showed a prolonged latency were unchanged when seen again.
One normal became abnormal (under "deterioration"), etc.

In the "Definite MS" group one (JJ) showed an apparent post-chiasmal delay on the first occasion, and six months later a delay was found in three out of the four responses. There had been a previous history of retrobulbar neuritis in each eye, one three years and the other two years before the first VER. An episode of diplopia preceded the second VER and she had undergone treatment with Prednisone between the two tests.

DG showed a variation in waveform and improvement in latency after 15 days as an acute attack of RBN resolved. There remained an asynchrony of response between the eyes.

MH, who had suffered RBN in the left eye 45 years previously, showed a persisting left eye delayed response at an interval of 14 months.

In GC, although all four responses remained prolonged (illustrated in Fig. 4:8), the only symptom of visual involvement was some difficulty in reading and in colour appreciation eight years before the first VER.

In another repeat test, JR showed a persisting delay of response from one eye, and Type 4 waveform, even though the other eye had recently shown symptoms of retrobulbar neuritis. This had not occurred prior to the first VER.

AW showed one response delayed from one eye on the first occasion, and after four and a half months, a delay from the other eye, even though there was no clinical evidence of visual deficit.

In the "Probable MS" group one (CC) showed three out of the four responses delayed on the second occasion and there had been a progressive restriction of the visual fields in the interim period of eight months. The first VER was carried out eight months after an attack of RBN in the right eye, but the left eye showed the prolonged

latency. One showed an unchanged delay in all four responses after three weeks (MF) and one (SM) a continuing normal result after two months. The remaining one (TV) showed a marked delay on the second occasion, fifteen days after the first, even though there had been no clinical RBN.

In the "Possible MS" group NB had a prolonged latency in all four responses on two occasions at a 10-day interval, but the waveform changed from Types 1 and 2 to one of Type 4.

Out of the abnormal results remaining, in RC (WNC 25355) and CE a three out of four results showing prolonged latency became all four results prolonged three months and 21 months later respectively, without visual symptoms.

In JR, a mildly increased latency in the right eye improved two months later but the left eye developed a prolonged latency, without clinical RBN.

BT showed a fragmented (Type 6) response on both occasions with a six week interval, but with changes in emphasis of components. No retrobulbar neuritis had occurred at any time.

PS, with retrobulbar neuritis only, showed a marked difference in the Type 6 response when repeated six days later. This became Type 5 (No P_2 wave) during an acute RBN in the right eye.

Comparison of results using pattern reversal with those using flash stimulation

In some patients the visual acuity is so poor owing to presumed active retrobulbar neuritis that pattern reversal (P/R) stimulation is not possible. It was felt that some experience should be gained in the use of flash stimulation in a group of patients who had sufficient acuity for both, in order to find out whether the two modes

of stimulus had related results. Sixteen patients had both flash and pattern reversal evoked responses at the same visit. The results are summarised as follows:

Delay from one eye to both P/R and flash: 3 patients

Delay from both eyes to both P/R and flash: 1 patient (but one occipital response was normal in both)

Delay with flash stimulus, and normal to P/R: 9 patients.

In considering these results it is important to note the wide variations in response to flash in the control series.

The waveform of the flash response was frequently double or treble-peaked, and sometimes showed successive peaks of progressively more positive bias, a "waterfall" waveform (see Fig. 3:10) in the control series. This presented a problem in the identification and therefore the measurement of latency of the major positive peak. In some cases flash stimulus applied to both eyes simultaneously appeared to establish a more definite waveform than flash applied to each eye separately. Some examples of these results are shown in Figures 4: 7-9.

Discussion

It is interesting to conjecture on the pathological basis for the abnormal results, and to attempt to correlate them with the known histological findings in the disease. Lumsden (1970 and 1972, p. 318) has reported on a predilection of multiple sclerosis process for the optic pathways and cord. He reports an almost invariable presence of plaques of demyelination in the optic system in postmortem examination in this disease, even more so than in the cord. Also, he has observed the equal distribution of plaques bilaterally in individuals in his whole series of 36 cases in which full studies were made. He

Figure 4:7 DG - 31 yrs. WNC 24511

Recording during an acute attack of retrobulbar neuritis.

Scattered scotomata in R eye and central scotomata in

L eye.

Comparison between P/R and flash stimulation

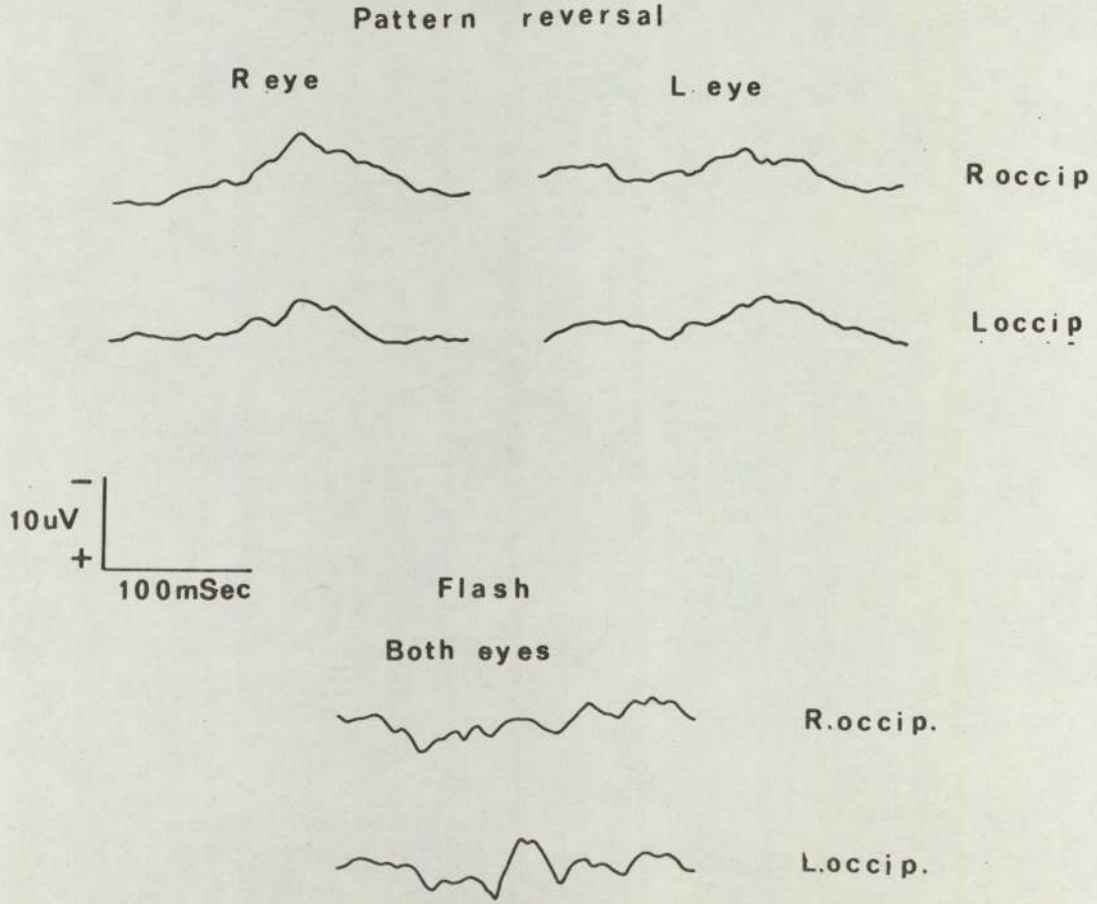

Pattern reversal
R eye
L eye
R occip
L occip
10uV
100mSec
Flash
Both eyes
R.occip.
L.occip.

FIG.4:7

Figure 4:8 GC - 48 yrs. Definite MS.

Clearer waveform to flash than P/R.

Bilaterally pale optic discs but visual acuity

R eye 6/12, L eye 6/9

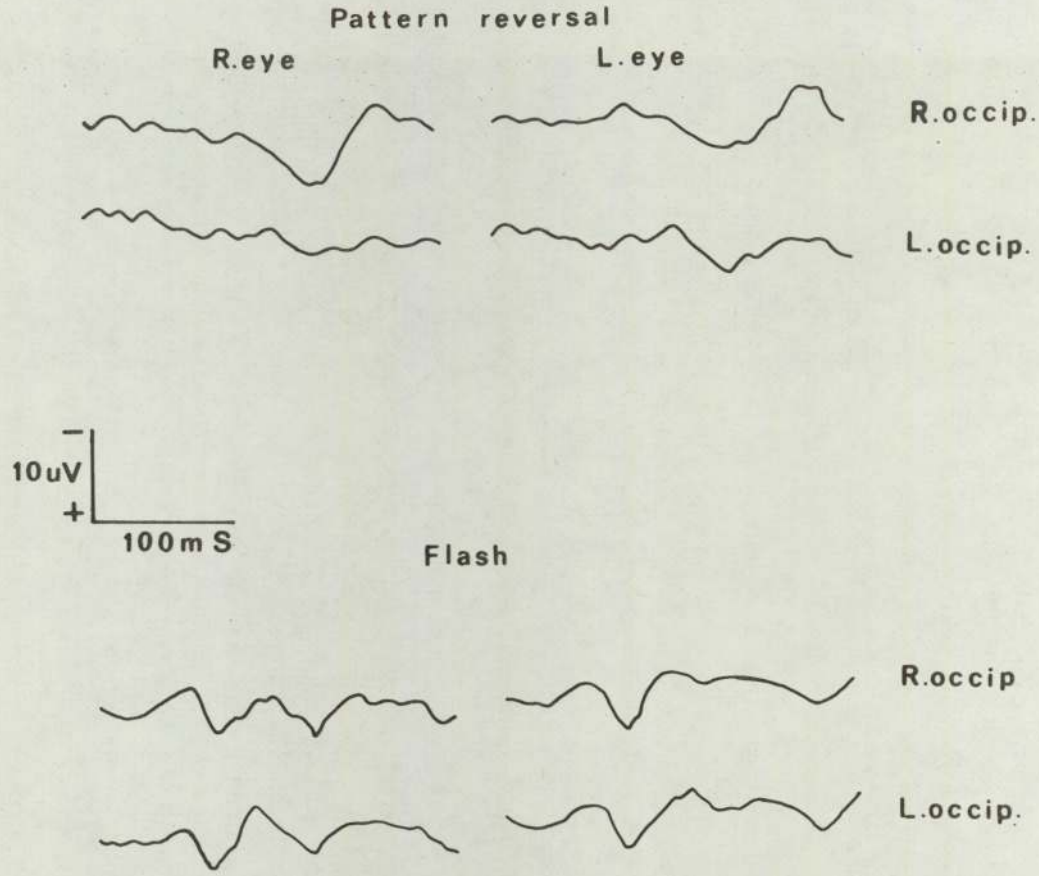

Pattern reversal
R.eye
L.eye
R.occip.
L.occip.
10uV
100m S
Flash
R.occip
L.occip.

FIG.4:8

Figure 4:9 HB - 44 yrs. Possible MS.

All four responses delayed to P/R stimulation.

Flash response less clear. No visual defect.

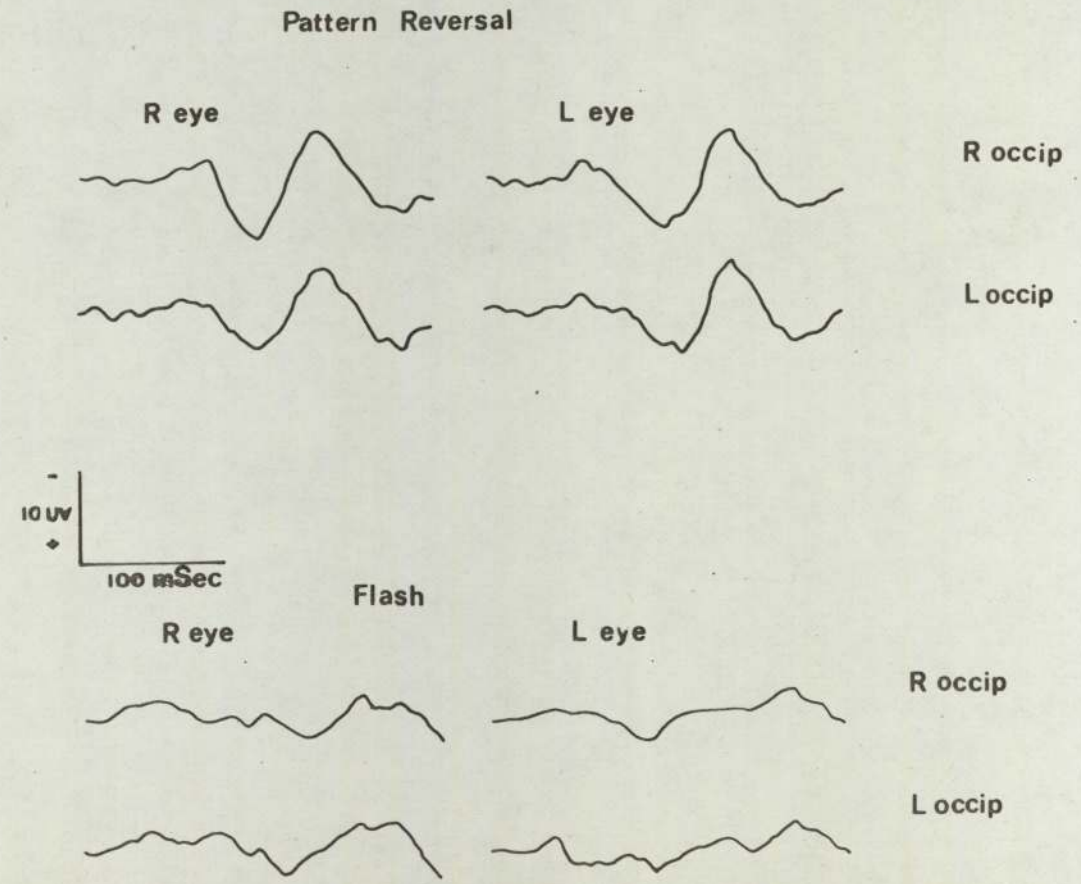

Pattern Reversal
R eye
L eye
R occip
L occip
10 UV
100 mSec
Flash
R eye
L eye
R occip
L occip

FIG 4:9

illustrates the presence of plaques in the optic nerves, chiasma, optic tracts and cerebral cortex. In the cortex, a higher proportion of plaques occur in the frontal lobes in relation to other lobes, even allowing for their larger size.

He also shows that some bundles of axons may be affected by a plaque, while others are left intact.

In view of the fact that pathological studies of this disease are on postmortem material, and that the disease may continue over many years, it has to be remembered that postmortem studies usually show the advanced stages of the disease. The majority of patients referred for VER are in the early stages, before a firm diagnosis has been made, and lesions may be assumed not to have reached the extent of distribution seen later.

This would explain the frequent lack of bilateral synchrony and symmetry of responses in the VER, in spite of the fact that Lumsden reports a symmetry of lesions in his studies. Repeated VER examination illustrates a tendency to a "balance" of acute episodes between the two sides over longer periods, either with or without clinical accompaniment. It would be tempting to assume therefore, that a static condition of prolonged latency of response from one eye over a number of years without other signs or symptoms, was not characteristic of MS, and some other lesion should be considered.

This highlights the desirability of carrying out more longitudinal studies in multiple sclerosis, in order to observe variations in latency and distribution of abnormalities.

The findings on repeated VER appear to support other evidence that a continuously changing situation occurs in this disease, and that axons may change their rate of conduction from one trial to the next, and sometimes during the course of averaging the VER. This

correlates with experimental studies by McDonald (1977, p. 430) in an inter-costal muscle nerve filament of the cat, that with demyelination there can be a progressive block in conduction with repeated stimulation, even with a repetition time as long as one second. This might account for some of the variability in the VER in MS and also for the fact that where the response is fragmented, a repeat trial with a slower rate of stimulus may produce an improved definition of the waveform. A clearer single maximum peak may emerge, rather than a "fragmented" response, although the major peak may still be abnormally delayed.

CHAPTER 5. RESULTS IN COMPRESSIVE AND ISCHAEMIC LESIONS

Compressive Lesions. Introduction

The case records of patients with compressive lesions whose visual evoked responses were recorded in a neurological centre, where the final diagnosis and follow-up is readily available have been reviewed. Most of the lesions were diagnosed by some or all of the following methods: arteriography, pneumo-encephalography, computerised tomography scan, by direct view at operation or, in one case by post mortem examination. The diagnosis was frequently made within a few days of the VER test, so that the findings may be assumed to relate closely to the radiological or operative determination of tumour site.

Some of the tests were carried out post-operatively, and this has been noted in the tables, and these provided further anatomical evidence for the effect of cortical excision, or release of pressure on the optic nerves and chiasm, on the VER. In every case the results have been correlated with the clinical evidence of visual defect, either in acuity or visual fields.

For clarity of presentation the compressive lesions have been divided into four groups:

1. Pre-chiasmal - 10 patients
2. Chiasmal - 6 patients
3. Post-chiasmal - 4 patients
4. Various intra-cranial sites - 4 patients

Total 24 patients

The grouping was made on the clinical evidence, i.e. a pituitary tumour in which the patient only showed a visual deficit affecting one eye was placed in the pre-chiasmal group. Where the visual fields

were incongruously affected in each eye or showed a bitemporal hemianopia, the patient was included in the chiasmal group, whereas a patient in whom homonymous defect occurred was classified as post-chiasmal. The "various" group includes three space-occupying lesions within the cerebrum but outside the visual cortex, and one pituitary tumour with no clinical visual defect.

The individual results are set out in Tables 5: 1-4 following.

Pattern reversal stimulation was used throughout, except where it is noted that flash stimulation was employed. Flash stimulation was only used where the visual acuity was too low, or where the patient was too ill to concentrate on the pattern.

In the tables clinical details have been kept to a minimum, and symptoms and signs outside the visual system have only been included where this might have had a bearing on the abnormalities observed. Actual P_2 latencies and amplitudes have been included for each case, and they are invariably shown in the same order:

1. Right occipital from right eye
2. Left occipital from right eye
3. Right occipital from left eye
4. Left occipital from left eye

The amplitudes shown on the right side of each result are a peak to peak measurement of N_2 to P_2. Where a result is shown as a figure followed by an oblique line and another figure, this indicates that there are two peaks of more or less equal amplitude, which could be an enlarged "a, b and c" complex, but appear more spread out than is usual for this.

A full EEG was not always carried out, but where this was so, a precis of the findings has been included. A concurrent EEG was

Table 5:1 PRE-CHIASMAL LESIONS

	Patient M or F	Final Diagnosis	Objective visual signs	VER		EEG	
	CD (F) 30 yrs	Neurofibromatosis	Fixed dilated pupil (L) with phakoma visible in L fundus (clinical evidence of multiple lesions VAR 6/9 VAL HM only	96 ms 99 80 83	15 uV 14 6 5	L temp theta and sharp waves	(1)
	BE (M) 56 yrs	L sphenoidal ridge meningioma. CT scan shows meningioma of inner third of sphenoidal ridge extending in anterior and middle fossae	Visual field full in R eye. L eye central defect spreading nasally where vision is misty	99 106 122 125	10 12 1.5 1.5		(1)
*	BG (M) 41 yrs Fig. 5:1	Pituitary tumour. At excision (after VER) the tumour was "passing upwards and to the R and causing some elevation of the R optic nerve	VAR and L N5 uncorr. Visual fields full except that in the R eye a red pin looked brownish in the temporal field and lower nasal quadrant, "but he is an unreliable witness"	122 122 109 102	6.5 6.5 6.5 6	Slow dominant rhythm with delta runs R>L anteriorly	(1)

* Indicates that this result is illustrated

Table 5:1 Pre-chiasmal lesions

Patient M or F	Final Diagnosis	Objective visual signs	VER	EEG
MJ (F) 52 yrs	Suprasellar meningioma. At operation four months after VER "both optic nerves were distorted....right in particular appeared to be crammed into the outer third of the optic foramen"	R eye field reduced to lower nasal quadrant, not extending to the macula. L eye vision normal, full field	Fragmented " 88ms 10uV 97 17	(1)
OM (M) 68 yrs	Left orbital mass (refused operation but improved on steroids)	VAR N5 VAL cannot perceive light	Flash VER 125 9 122 10 164 8 159 7	(1)
IM (F)	Right suprasellar meningioma. Operation - firm tumour removed which lay beneath and medial to a severely stretched R optic nerve which was displaced laterally and upwards	VAR 6/5 VAL 6/5 Marked reduction in right visual field sparing upper nasal quadrant and macula	P1 but no P2 " " " " 99 18 99 19	(1)
MP (F) 34 yrs	Suprasellar meningioma. At operation, findings of complete destruction of the R optic nerve and the tumour was attached to the chiasm	R eye no P/L L eye normal	Absent " 93 13 90 14	(1)

Table 5:1 Pre-chiasmal lesions (continued)

Patient M or F	Final Diagnosis	Objective visual signs	VER	EEG	
EP 58 yrs	Neurofibroma (Schwannoma) of L optic nerve	VAR 6/4 corr with full field. L eye no perception of light	88 msec 88 Absent "	2.5 uV 5	(1)
ST (M) 35 yrs	Pituitary adenoma At operation the right optic nerve was splayed and displaced laterally. Left optic nerve not seen	R eye J1 with temporal hemianopia but sparing central 4° L eye no P/L	100 100 Absent "	3 6	(1)
MW (F)	Pituitary tumour 8 years post-operative	R eye 6/5-3 with full field L eye 6/9 Global restriction of L visual field (this eye was blind pre-operatively)	105 105 130 130	8.5 9.5 3.5 2.5	(1)

(1) VER result consistent with the clinical defect

invariably run on the channels being averaged.

In the figures, where the visual fields are shown, the usual presentation is reversed so that the VER for each eye appears below the appropriate field chart.

The ten pre-chiasmal lesions all show a reduced amplitude response and/or a prolonged latency from the clinically affected eye. In five cases the VER was absent from the affected eye. Out of these, three had no perception of light in that eye. Of the remaining two, one (MJ) had a visual field in the right eye reduced to the lower nasal quadrant, not extending to the macula. The VER was fragmented and designated "absent". In the other absent VER (IM) the right visual field was reduced to the nasal quadrant and macula, the VER showed a P_1 wave at 47 msec, clearer to O_1 than to O_2, but no P_2 wave. Where the lesion was within the globe of the eye (CD) the latency was normal although the response was much reduced in amplitude.

In all cases the unaffected eye showed a normal response, except that in one (EP) the waveform was unusual in that the N_3 wave was enlarged.

In one patient with neurofibromatosis (CD) the EEG showed theta and sharp wave focal disturbances, but there was clinical evidence of multiple lesions. In another (BG - Fig. 5:1) the EEG dominant rhythm was slow, with added theta and delta activity, and the possible metabolic complications of a pituitary lesion should be considered. The VER showed a prolonged latency from the right eye and the VA was normal bilaterally but a "red pin looked brownish in the temporal field and lower nasal quadrant in the right eye.

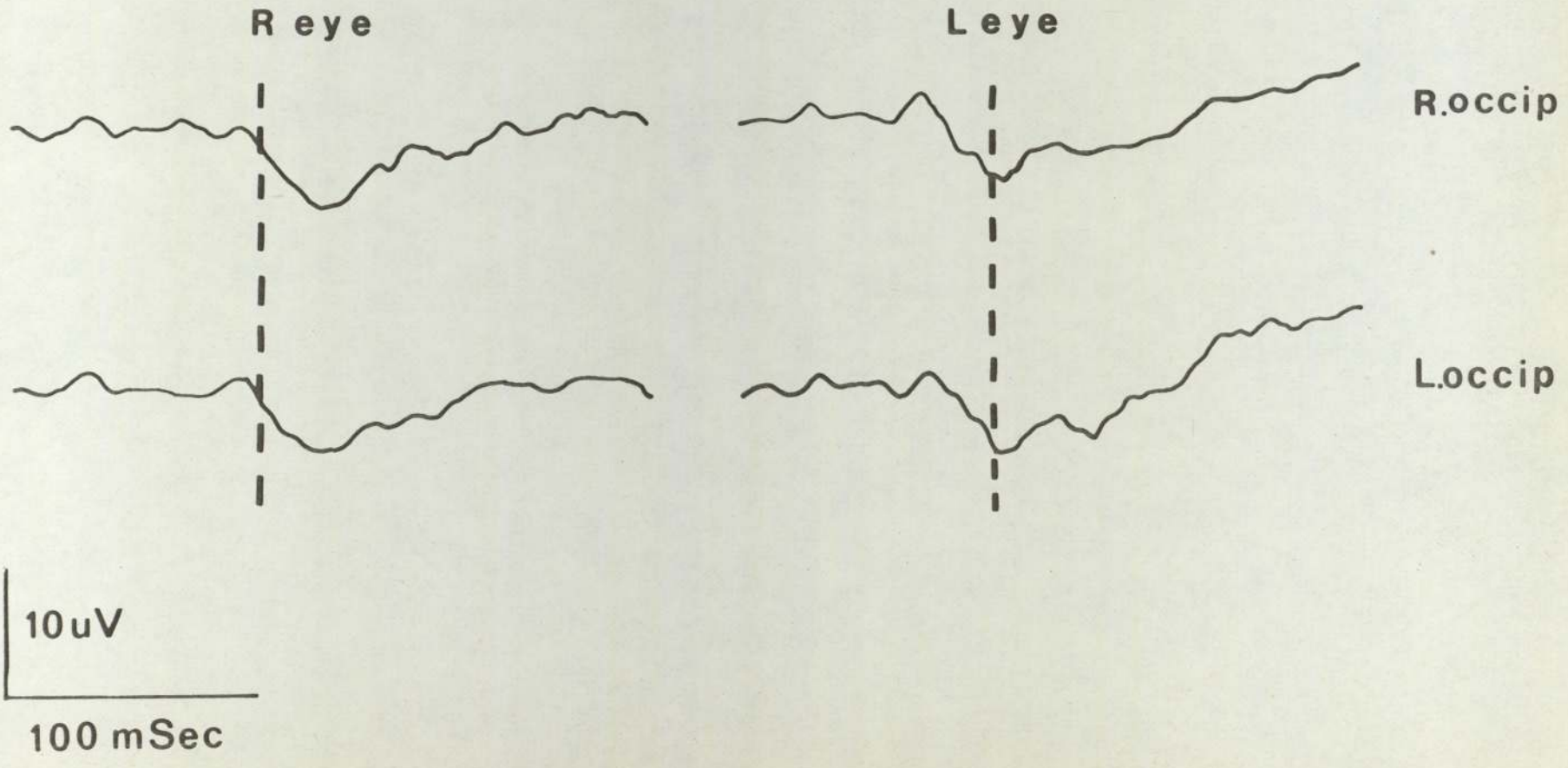
In BE, with a left sphenoidal ridge meningioma, the visual field

Figure 5:1 Pre-Chiasmal lesion. BG (M) - 41 yrs.
Pre-operative VER of a patient with a pituitary tumour "passing upwards and to the right and causing some elevation of the right optic nerve" - from operation note.

Latencies	R eye	122 msec to R occipital lobe
		122 msec to L occipital lobe
	L eye	109 msec to R occipital lobe
		109 msec to L occipital lobe

BG 41yrs
WNC 25417
2 Mar 77

Pattern reversal



was normal in the right eye and acuity N5. In the left eye vision was misty in the central part of the field spreading nasally. The VER from the right eye was normal, at 10-12 microvolts. From the left eye the response was of low amplitude and P_2 delayed to 122 msec.

In MW also the response was both of prolonged latency and lowered amplitude from the affected eye eight years after operation for a pituitary tumour. There was a global restriction of the field in this eye (left), which had been blind before operation. On formal testing the right eye with full field showed an acuity of 6/5-3, left eye 6/9.

The six lesions affecting the chiasm itself, identified by visual field charting and operative findings, did not show such consistent results as the pre-chiasmal lesions. Two of these are illustrated (Figs. 5:2 and 3, EA and HF). In EA where there was an absent temporal field in the left eye and the defect spread into the lower nasal quadrant, the right eye produced a normal VER. From the left eye to right occipital, the P_2 wave occurred at 93 msec, but the N_2 wave preceding it was more pronounced than the homologous response from the right eye. The left eye to right occipital response showed an apparent phase shift and apparent reversal of waveform, peaks occurring at positive 75 msec negative 120 msec and positive 183 msec respectively. At operation the left optic nerve was found to be "densely adherent to the tumour which overlay the nerve".

In two cases, HF and ES, there were VER changes even though the central 3° to 5° of vision was preserved, but temporal defects were present in both. In HF both right and left occipital responses from the right eye were delayed (125 and 125 msec) where the nasal field of the right eye was reduced to a short strip 3 to 5 degrees from the

Table 5:2 CHIASMAL LESIONS

Patient	Final Diagnosis	Objective visual signs	VER		EEG
* EA (F) 56 yrs Fig. 5:2	Suprasellar tumour. At operation "tumour...clearly displacing the R optic nerve laterally...L optic nerve...densely adherent to the tumour which overlay the nerve"	VAR 6/5. Slight nasal defect VAL 6/9. Absent temporal field and defect in lower nasal quadrant	95 ms 88 93 75/183	2.5 uV 3 3 2	(1)
* HF (F) 52 yrs Fig. 5:3	Parasella meningioma. At operation "calcified meningioma compressing the right side of the chiasm and right optic tract from below"	VAR 6/9. Field restricted to most of upper temporal quadrant and part of lower temporal quadrant. Central 3-5° preserved VAL 6/5. Field defect in peripheral upper temporal quadrant only, sparing central 11° of vision	125 125 100 107	10 12 20 17	(1)
EG (F) 22 yrs	Probable pituitary adenoma with "pus" inside it. CT scan and exploration. Pituitary infarction.	VAR 6/24 N12. R temporal hemianopia, crossing macula VAL 6/12 N8. L upper nasal quadrantanopia, slightly impinging on lower quadrant	130 112 Absent 125	6 3 6	(1)
WH (M) 53 yrs	Craniopharyngioma. (post-operative Has a Rickham reservoir inserted which is aspirated at intervals)	VAR 6/5. R peripheral temporal defect, sparing central 10° VAL worse than 1/60. Not possible to plot field	145 105 115 120	6 4 3.5 3.5	(1)

Table 5:2 Chiasmal lesions (continued...2)

Patient	Final Diagnosis	Objective visual signs	VER		EEG
ES (F) 29 yrs	Pituitary tumour. Tumour seen to be lying medial to R optic nerve	VAR 6/36 N10. R. lower temporal quadrant field defect, sparing central 5° VAL 6/36 N18. L peripheral nasal defect, sparing central 14°. Tested with 10 mm white object	97 130 99 99	2.5 2 6 5	(1)
PT (F)	Pituitary adenoma. (post-operative) At operation 9 years ago a cystic mass was seen between the optic nerves and under chiasm. Tumour excised.	Bitemporal hemianopia, with the left eye defect spreading over the midline. Not recently charted but said not to have changed in last four years	114 111 114 123	6 1 5 7	(1)

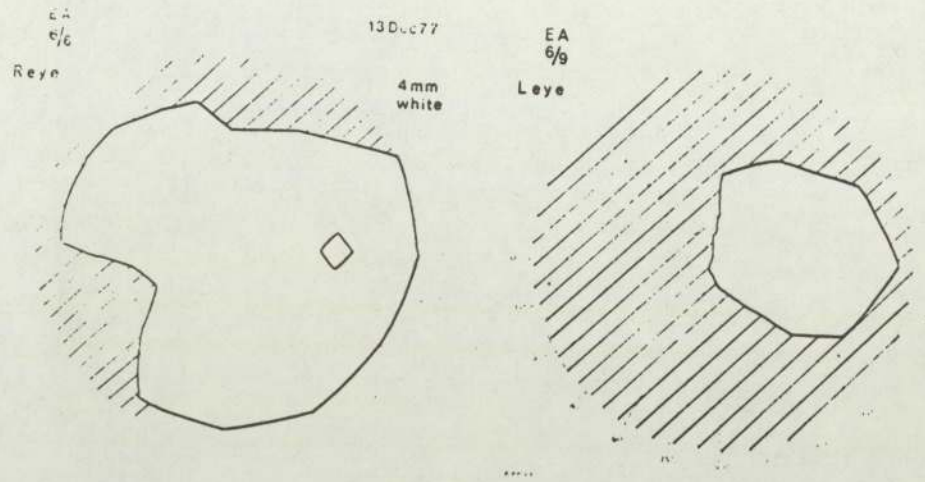
* indicates that this result is illustrated

(1) VER result consistent with the clinical defect

Figure 5:2 Chiasmal lesion. EA (F) - 56 yrs.
Pre-operative visual fields and VER of a patient with a suprasellar tumour. At operation "...tumour clearly displacing the right optic nerve laterally....left optic nerve....densely adherent to the tumour which overlay the nerve."

Latencies R eye 95 msec to R occipital lobe
88 msec to L occipital lobe
L eye 93 msec to R occipital lobe
75 & 183 msec to L occipital lobe
two positive peaks, possibly indicating a reversal of polarity of the P_2 wave

In the visual fields the central 11° of vision is preserved in the R eye, and in the L the defect includes most of the lower half field.
Note that in this and all illustrations including the visual fields, the plot of each field has been shown above the VER of the same eye



EA 56yrs
14 Dec 77

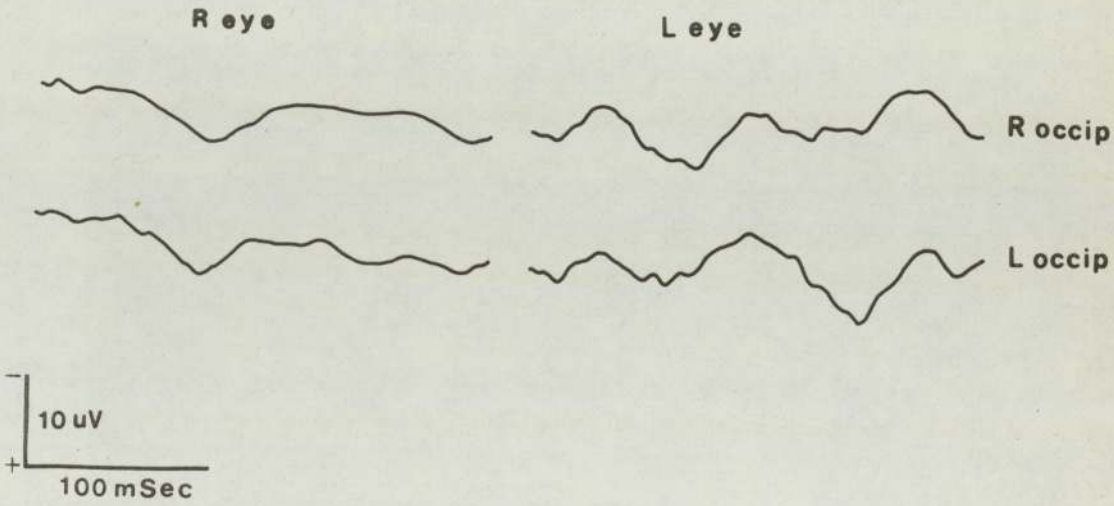
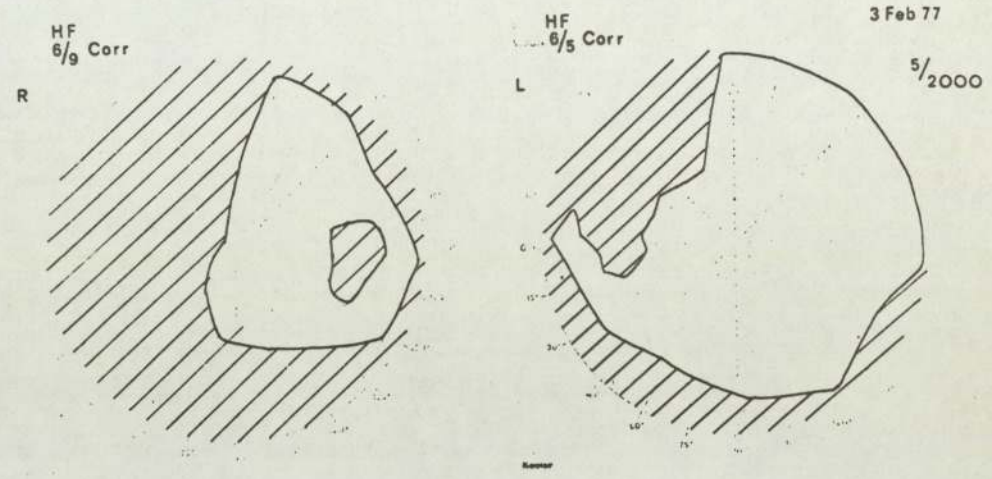


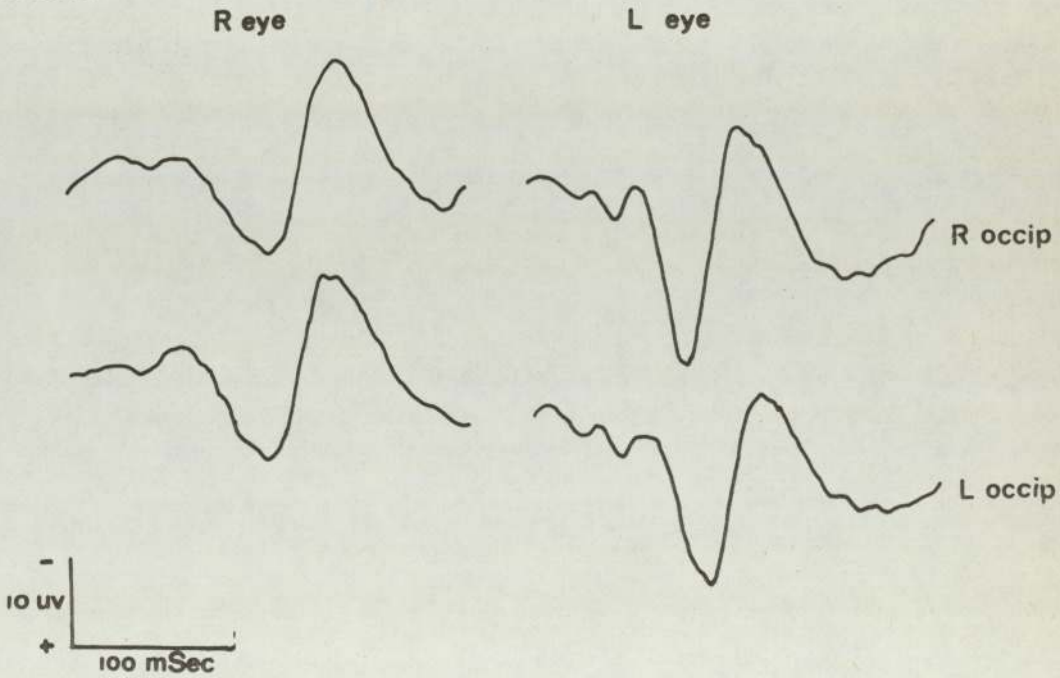
Figure 5:3 Post-chiasmal lesion. HF (F) - 52 yrs. Parasellar meningioma. Pre-operative VER delayed to both occipital lobes from the R eye, where a substantial defect is present in the lower half field. Normal in the left eye where the defect only encroaches as far as 11° of vision from the centre.

Latencies R eye 125 msec to R occipital lobe
125 msec to L occipital lobe
L eye 100 msec to R occipital lobe
107 msec to L occipital lobe



HF 51yrs
WNC 26115
16 Feb 77

Pattern Reversal



midline and the defect spread across to the lower part of the temporal field 15° below the macula.

In ES the right eye responses were ill-defined, particularly right eye to right occipital, and the right eye to left occipital response was delayed. The left eye response was of normal latency. Her visual fields showed a right homonymous defect but sparing the central 14° in the left eye and the upper temporal quadrant in the right eye. In this eye the lower temporal quadrant defect spread up to the central 5° of vision.

In one (WH) repeated aspirations for the relief of pressure had been made from a Rickham reservoir previously inserted. This patient's right visual field showed a temporal defect to within 8° of the macula. The visual acuity in the left eye was too poor to allow the visual field to be tested. The VER showed a delayed but clearly defined P_2 wave at 145 msec to the right occipital lobe from the right eye, and a regular repetitive peak waveform (Type 3) response to the left occipital lobe whose first major positive peak was at 105 msec. The response from the left eye was very low in amplitude but at the upper limit of normal latency (115, 120 msec).

Another patient (PT) showed results consistent with the clinical evidence, although the VER was carried out nine years after operation. She had a bitemporal hemianopia with the left eye defect spreading over the midline. The only markedly prolonged latency was left eye to left occipital, which reflected the extension of the hemianopia over the midline in that eye.

EG, who had an unverified pituitary tumour, showed a poorly defined VER, with the abnormal responses ipsilateral to the field defect.

In the post-chiasmal lesions two had undergone right occipital lobectomy for neoplasia (SH and WT). SH showed an enlarged N_3 wave in all results, and an indistinguishable P_2 at the right occipital electrode in the first test carried out six days after operation, and a clear phase reversal on the left occipital electrode on a bipolar derivation. When this was repeated six months later the VER appeared normal, although on bipolar derivation a residue of left occipital focus remained (contralateral to the preserved field and the occipital lobectomy). WT had a reduced amplitude P_2 at the right occipital lead, although all latencies were normal. The bipolar derivation, in this instance obtained by subtraction, again showed a left occipital phase reversal of the P_2 wave.

These two cases show the maximum amplitude of the P_2 wave over the intact occipital lobe and a greatly reduced response on the operated side. The phase reversal of the P_2 wave over the intact hemisphere confirms the laterality of the response.

One pituitary tumour (RG) placed into the post-chiasmal group on the grounds of a right homonymous hemianopia showed a slower response to the left occipital lobe from both eyes, although this still fell within the normal range. The EEG showed left-sided delta activity with alpha suppression and slowing, which was further evidence of extra-sellar extension.

The remaining post-chiasmal tumour (JM) was a large intrinsic glioma of the right hemisphere, invading the right lateral ventricle and producing a left homonymous hemianopia, and other right hemisphere signs. The waveforms were all distorted, but no distinguishable P_2 wave appeared at the right occipital electrode from the right eye. The EEG was grossly disturbed with irregular right-sided delta activity and bilaterally synchronous stereotyped "peaked" waves.

Table 5:3 POST-CHIASMAL LESIONS

Patient	Final Diagnosis	Objective visual signs	VER		EEG	
RG (M) 43 yrs	Pituitary tumour (previously treated with radiation)	R homon. hemianopia sparing central 5° with peripheral defect also, more in R eye	108 115 92 115	1 2 1.5 1.5	L sided delta activity with alpha suppression and slowing	(1)
* SH (F) 50 yrs Fig. 5.4	R occipital oligodendroglioma (6 days post-op)	L homonymous hemianopia sparing central 2° There had been a pre-op history of flashing lights and formed visual hallucinations in the L half field plus headache	P2 absent enlarged N3 90 P2 absent enlarged N3 90	1.5 7	Alpha rhythm was reduced in amplitude in the R occip area in the first record but symmetrical in the second	(1)
Fig. 5.5	Repeated 6½ months post-op	L homonymous hemianopia	98 98 105 105	6 5.5 6 6		
JM (M) 64 yrs	Extensive R hemisphere tumour replacing R lateral ventricle	L homonymous hemianopia	Absent P_2 Distorted waveform 97 101 98	 7 4 3	Irregular slow waves throughout R hemisphere and rhythmic synch runs of sharply formed delta waves bilaterally	(1)

Table 5:3 Post chiasmal lesions (continued)

Patient	Final Diagnosis	Objective visual signs	VER		EEG
WT (M) 47 yrs Fig. 5.6	R occipital fibrosarcoma (10 days post-op)	L homonymous hemianopia sparing central 10° in the R eye and 5° in the L eye	108 110 103 110	2 3.5 1 3.5	8 Hz alpha rhythm (1) reduced in amplitude in the R occipital area in peri-occipital derivation

Figure 5:4 Post chiasmal lesion. SH (F) - 50 yrs.

VER six days after a R occipital lobectomy for an oligodendroglioma. This shows an absence of P_2 wave in the R occipital area but an enlarged N_3 wave in all responses. A clear phase reversal of the P_2 wave appears about the L occipital lead on bipolar montage. The patient had a left homonymous hemianopia.

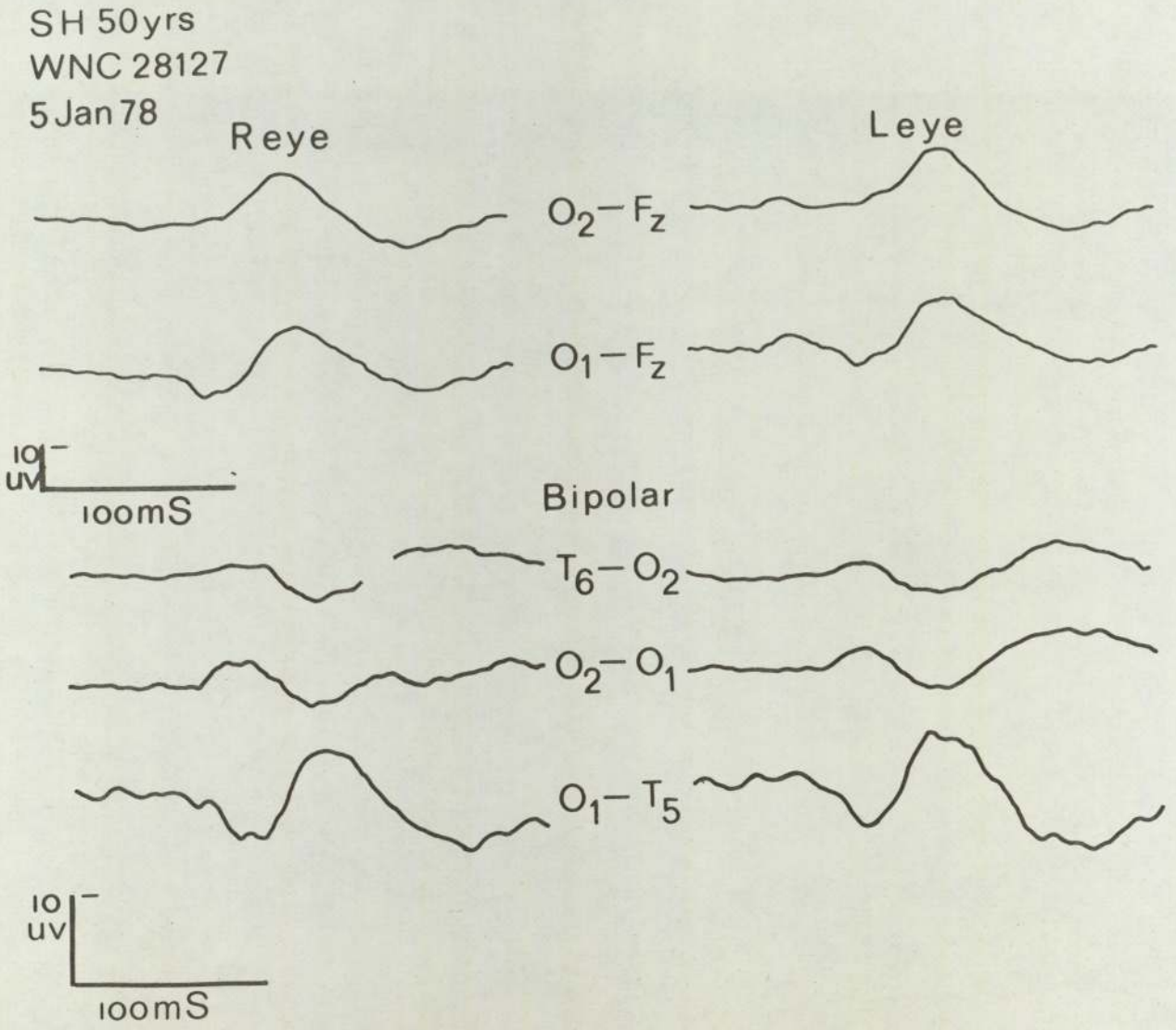
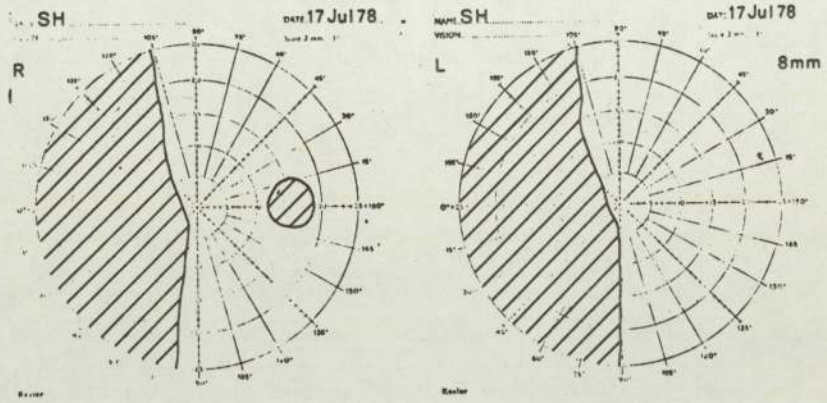
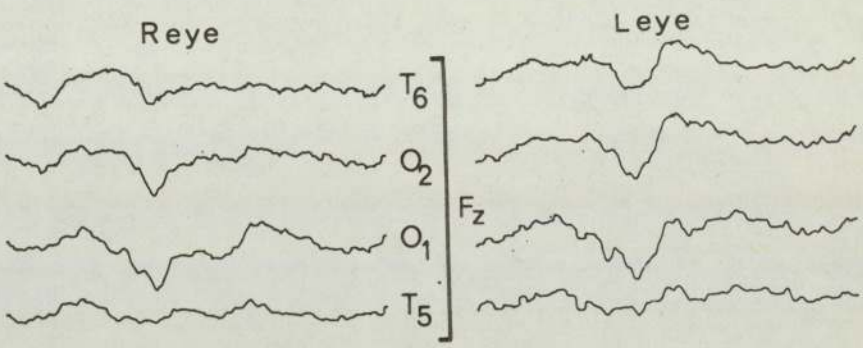

SH 50yrs
WNC 28127
5 Jan 78
Reye
Leye
O_2-F_z
O_1-F_z
10 uv
100mS
Bipolar
T_6-O_2
O_2-O_1
O_1-T_5
10 uv
100mS

Figure 5:5 SH (F) - 50 yrs.

The same patient as in Figure 5:4. The VER repeated six months after operation shows an almost-symmetrical P_2 wave in the occipital leads, but the bipolar derivation by subtraction still suggests a left occipital focus of the response. The enlarged N_3 wave seen previously has now resolved. The visual field plot shows an almost-complete left homonymous hemianopia





Bipolar by subtraction

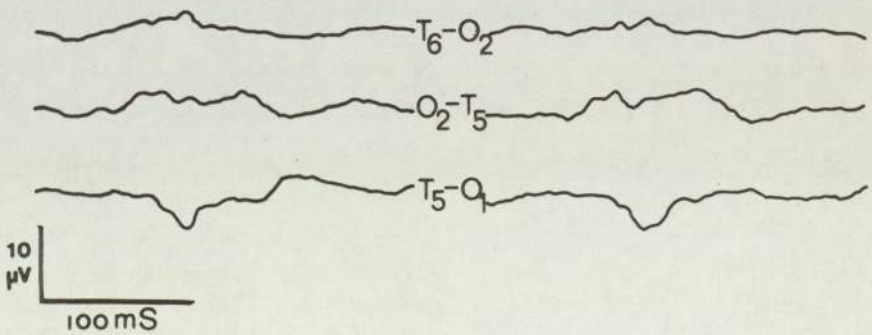
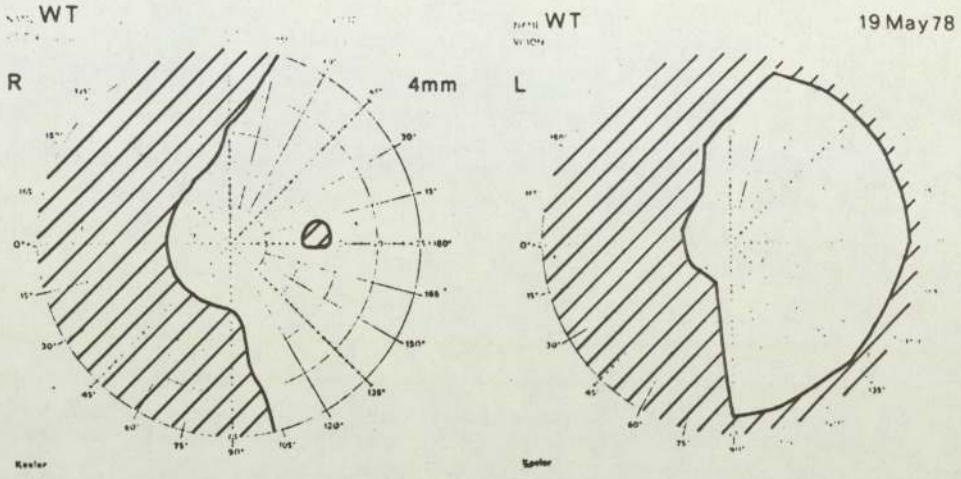


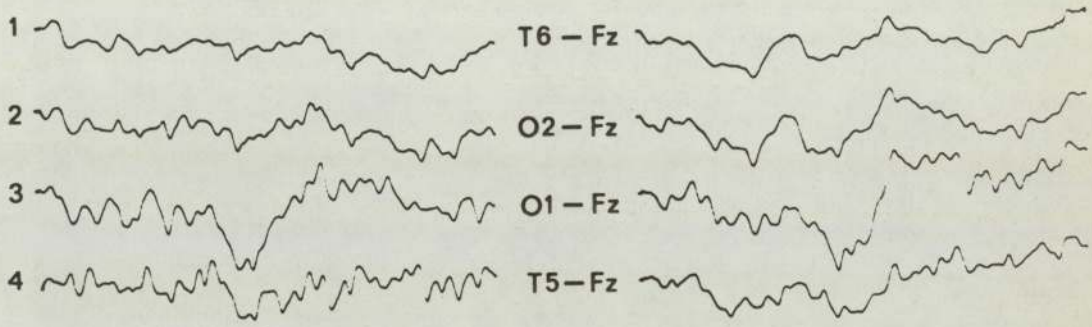
Figure 5:6 WT (M) - 47 yrs.

VER amplitude reduction on the operated side 10 days after a R occipital lobectomy for fibro-sarcoma. The bipolar derivation (by subtraction) shows a clear phase reversal of response in the L occipital area. The visual fields were plotted six days after the VER was recorded and show preservation of the central 10^{o} of vision in the R eye and 5^{o} in the L eye. Otherwise there is a L homonymous defect



R eye

L eye



Bipolar (by subtraction)

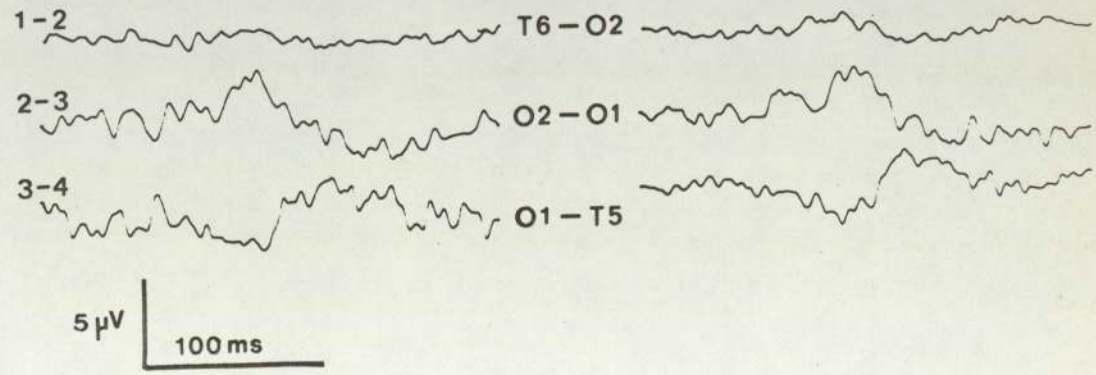


Table 5:4 VARIOUS LESIONS

Patient	Final Diagnosis	Objective visual findings	VER		EEG
WF (M) 53 yrs	Unverified suprasella meningioma shown by CT scan and angiogram	VAL normal, fields full (3rd nerve palsy is the only clinical sign	102 101 105 99	13 10.5 7 5.5	
DL (F) 29 yrs	Pituitary tumour. (post-op 22 mths) CT scan: no evidence of extrasellar extension but a small density seen within the sella itself	VAR and L 6/9 corrected. Visual fields full. The vision in the R eye had been slightly impaired pre-operatively	127 93 87/131 90	6 8 5 (2 peaks) 8	dominant rhythm of 10 Hz
EP (M) 38 yrs	Unverified hypothalamic glioma. $2\frac{1}{2}$ mth post op (exploratory op finding: both optic nerves were seen not displaced. There was a space between them and the surface of a capsular structure beneath)	VAR less than 6/60. VAL 6/12 Both visual fields grossly constricted with a bitemporal hemianopia, bisecting the macula in the L eye and eliminating the central 1^{o} in the R eye	101 98 106 107	3.5 3.5 5 6	
MS (F) 41 yrs	4th ventricle ependymoma. Died on day following op, 11 days after VER. P.M. findings: marked generalised gyral compression. Herniation of cerebellar tonsils. Medulla enlarged Mass filled 4th ventricle. Severe hydrocephalic dilation of aqueduct, 3rd and lat ventricles. Floor of 4th ventricle traumatised and trauma extends into vermis and cerebellar hemispheres. Discolouration of pons; haemorrhagic infarction due to secondary displacement	VA 6/24 bilat (corr) (Horizontal nystagmus to R and L, also vertical nystagmus)	80 78 77 76 Large negative wave at 135 msec	6 5 2.5 4	9 Hz alpha rhythm, showed occasional runs of 4Hz as a component

An unverified suprasellar tumour (WF) producing a third nerve palsy showed a normal VER although the amplitude was reduced on the side of the palsy. The eyelid had to be held open as there was a complete ptosis, but there could have been some focussing difficulty due to the possible involvement of the ciliary muscles with the third nerve, although this did not show on formal testing of visual acuity.

In another patient (DL) twenty-two months after operation for a pituitary tumour, the VER showed a prolonged latency from right eye to right occipital lobe, and a "Type 4" waveform from left eye to right occipital, even though no field defect had ever been demonstrated. There was a note, however, that there had been some impairment of vision in the right eye pre-operatively.

The VER was within normal limits in a suspected hypothalamic glioma (EP) even though the visual fields were severely constricted, with a bitemporal hemianopia including the macula in both eyes and eliminating the central 1^{o} in the right eye. The only asymmetry was a reduction in amplitude of the responses from the right eye; latencies were normal. The remaining patient (MS) with a verified fourth ventricle ependymoma showed short P_2 latencies but an enlarged N_3 wave in all responses, at about 135 msec. This tumour spread upwards between the two cerebellar hemispheres, and an additional complication was evidence of severe hydrocephalus.

Summary of findings in compressive lesions

In the ten compressive lesions affecting pre-chiasmal structures, all ten showed VER results consistent with the clinical evidence in that the affected eye produced either a delayed or low voltage response or both, or an absent response. Out of these two showed a slight response although vision was reduced to no perception of light

Table 5:5 SUMMARY OF FINDINGS IN COMPRESSIVE LESIONS (Affecting visual pathways only)

Figures in the boxes represent numbers of patients with prolonged latency of response

Location of Lesion	Normal VER	One eye	One occipital	One result	Two incongruous results	Total
Pre-chiasmal	1 (amp asymm one eye)	9	-	-	-	10
Chiasmal	-	1	1	3	1	6
Post-chiasmal	1 (amp asymm one occip)	-	2	1	-	4
Totals	2	10	3	4	1	20

in one, and to the periphery of the lower nasal quadrant in the other.

In the six chiasmal lesions, three showed a response consistent with the field defect, that is a lowered response in the occipital lobe contralateral to the major defect. In two the response was inconsistent in that the lower amplitude appeared in the occipital lobe contralateral to the intact field. One (EG) showed a consistent response from one eye, inconsistent with the other but the waveforms were all poorly defined.

The four post-chiasmal lesions all showed responses whose asymmetry was consistent with the site of the lesion in that the lowered amplitude appeared contralateral to the field defect.

Conclusions

In lesions involving the globe of the eye and the optic nerve, the VER shows an abnormal response consistent with the localisation of the lesion to the affected eye. That the VER is reduced in amplitude where the acuity is reduced is well established. An interesting finding, also reported, is that the latency of response can be prolonged where there is a compressive lesion and this lends support to experimental evidence that demyelination may occur as a result of compression of a nerve while leaving the axon itself intact (Gledhill et al., 1973). Thus in effect the same result occurs as with the demyelination of MS.

Lesions involving the chiasm tend to produce incongruous field defects, that is a partial defect in one eye, with a defect in the other eye not corresponding to the homonymous field, or only partly consistent. This may be due to compression of only a part of the complex bundles of axons passing through the optic chiasm, either

ipsilaterally or crossing to the opposite side.

The clinically post-chiasmal lesions all showed the occipital asymmetry of response expected on physiological grounds. That is, that a patient with a left homonymous hemianopia showed a reduced amplitude response in the right occipital lead and vice versa.

In the reports of post-chiasmal lesions the EEG findings have been included where relevant, as this gave a good indication of whether there was cortical involvement.

A discussion on the physiological basis of these findings relating to recording parameters appears in Chapter 6 (i), including comparisons with the findings of other authors.

Ischaemic Lesions. Introduction

The VER findings in a group of 17 patients with ischaemic lesions affecting the visual system are described.

Many of the patients whose final diagnosis established or suggested a vascular lesion were referred as suspected multiple sclerosis, as these might show recovering sensory or motor symptoms, and in some cases, visual changes, possibly associated with this disease. In some MS was only an outside possibility, but the VER was requested as a check. In others the VER was carried out not strictly for diagnostic purposes, but as a deliberate exercise in order to establish the finding, particularly in patients showing visual field defects. In Table 5:6, presenting these results, a column headed "referral diagnosis" has been included, to show how these problems were presented to the Neurophysiology Department.

The ischaemic lesions do not have the benefit of actual observation of the brain and optic system at an operation, as had many

of the compressive lesions, but many were diagnosed by means of cerebral angiography. In some ways this may be more accurate than operative observation, as occlusion of a main cerebral artery, for instance, would suggest the presence of ischaemia in its territory, which might be more clearly definable than the extent of the effects of a tumour. Some were diagnosed on the grounds of clinical findings in history and examination only, and where possible, the evidence for reaching each diagnosis has been stated.

When investigating ischaemic lesions the practice of recording the EEG whilst carrying out averaging of the VER was thought to be additionally important. The general principles determining this practice have been outlined previously (Chapter 3. Method: "Recording and averaging" and "Artefacts"). Another advantage is to enable the EEG itself to be studied. With ischaemic lesions, the whole cerebral circulation may be affected, or at least a large part of it, related to a particular arterial supply. Therefore, the on-going EEG would serve as a likely indicator of evidence of local or general deficiency of blood supply.

A visual defect may result from local ischaemia, such as is caused by an ophthalmic artery thrombosis. It is also possible that it may be a part of a much wider lesion, such as caused by a basilar artery ischaemia. The EEG is unlikely to be affected by the former, but may be disturbed in the latter case.

Most of the patients in this group were over 39 years of age, and the average age was 46.64 years, youngest 14 and oldest 74 years. Of the two youngest, at 14 and 16 years, the ischaemic episode was secondary to intracranial tumour, but neither tumour directly affected the visual system.

In view of the more complex situation often arising from

ischaemic lesions, the full EEG, where recorded, is described in Table 5:6 with the results of the tests.

Results in Ischaemic lesions

An analysis of the ischaemic lesions showed that four patients with clinically-diagnosed brain stem vascular lesions showed normal VER and EEG, except for slight theta excess in some EEG (DA, MB, GG and RM).

Three patients with ischaemic optic nerve lesions showed reduced amplitude and prolonged latency of response from the affected eye, the other being normal (RP*, BV and JW*), but one of these (BV) subsequently developed defective visual acuity in the previously unaffected eye, with a corresponding increase in P_2 latency, and was considered to be suffering from MS in addition to the proven arteriovenous malformation.

Of five patients whose visual deficit was due to ischaemic impairment of cortical function, three showed prolonged latencies with waveform distortion, and all of these three had a marked EEG abnormality with delta range slow waves in the occipital region (SR, AS and MW). In one (BS) the VER was entirely normal although there was a left homonymous upper quadrantic field defect resulting from a right occipital thrombosis. The EEG showed some right posterior theta activity. In the remaining patient (EW, Fig. 5:9) who had suffered a right occipital infarct, the VER was lower in amplitude from the left eye to the right occipital lobe, with some waveform distortion. There was a left homonymous hemianopia but this had bisected the macula in the left eye and spared the central 2° of vision in the right eye. The latencies were all within the normal range.

The remaining five patients had normal vision and a normal VER,

* Figs. 5:7 and 5:8

TABLE 5:6 ISCHAEMIC LESIONS

Patient M or F	Referral diagnosis	Final diagnosis	Objective visual signs	VER		EEG
D.A. (M) 48 yrs	? MS	Brain stem vascular insufficiency	VA normal (scattered sensory and motor deficits)	106 mS 107 115 115	8 uV 9 7 8	Low amplitude with some diffuse theta components
M.B. (F) 57 yrs	? MS	Brain stem vascular episode. (Previous neurosyphilis)	VAR 3/7-5) corrected VAL 3/4) A red pin appears pinker and duller on R than L	91 109 106 103	7 7 9 10	Beta dominant Slight excess of theta in temporal areas
G.G. (F) 43 yrs	? MS	Possible brain stem vascular disturbance	CA 6/5 bilaterally (Recent diplopia and internuclear ophthalmoplegia)	94 94 93 93	12 12 12.5 12	Normal
R.M. (F)	? inflam atory ? vascular ? demyelinating	Brain stem vascular lesion	VAR 6/9 L 6/6	111 96 103 98	2.5 3 5.5 4	
*R.P. (M) 52 yrs	Ischaemic optic neuropathy	Ischaemic optic neuropathy (L carotid angiogram)	VAR 6/6 N5 VAL less than 6/60 N36	96 99 122 128	9 11 2 2	8-9 Hz alpha rhythm. Low amp. Theta and slower components in temporal leads, more on the right

Table 5:6 Ischaemic lesions (continued)

Patient	Referral diagnosis	Final diagnosis	Objective visual signs	VER		EEG
B.V. (F) 43 yrs	? MS ? arterio-venous malformation	A-V malformation at beginning of L middle cerebral artery (angiogram) Note: This patient is now thought to bave MS in addition to her A-V malformation	VA normal 4 Jan 77 28 April 77 VAR now reduced to hand movements only	103 100 106 103 93 91 116 107	9 7.5 1.6 2 3 2.5 7 8.5	
*J.W. (M) 74 yrs Fig. 5:8	? MS ? compressive lesion of L optic nerve	Ischaemic lesion of optic nerve in area of chiasm (ophthalmologist)	VAR N5 Field full VAL N18 disc pale L lower nasal quadrantanopia	116 113 166 162	13.5 19.5 2 4	
S.R. (M) 16 yrs	Visual blurring after L vertebral angiogram	1. Occipital ischaemia 2. R acoustic neurinoma	Vision improving Fields full at time of VER	120 111 120 114	7 1 8 4	Alpha rhythm at 8-9 Hz was preserved but bilateral occipital delta activity, slower in the left side was present
A.S. (M) 14yrs	Cortical blindness	Ischaemic lesion secondary to colloid cyst of the 3rd ventricle	"some return of vision in past two weeks"	110 105 107 131	4.5 3 3 2.5	Some alpha range activity, but mainly large irregular delta waves

Table 5:6 Ischaemic lesions (continued...3)

Patient	Referral diagnosis	Final diagnosis	Objective visual signs	VER		EEG
B.S. (F) 54 yrs	Migraine with infarct	R occipital thrombosis with migraine. CT scan shows R occip ischaemia	VAR and L J1 Left homonymous upper quadrant defect spreading slightly into lower quadrant (confrontation only)	98 mS 93 94 96	6 uV 8 8 9.5	R parieto-temporal theta abnormality
M.W. (F) 56 yrs	Basilar artery ischaemia	Basilar artery ischaemia Angiograms: Int car art stenosis on L, less marked narrowing on R. R vertebral and R postr inf cerebellar art not seen	Improving cortical blindness One month before VER had a series of fits followed by blindness	Flash VER only both eyes simultaneously 109/192 7/10 103/186 5/1 Small positive peak seen around the expected P_2 latency, followed by a much larger delayed peak		Gross bilateral delta activity, maximal posteriorly, improving on second occasion after an interval of 25 days
*E.W. (F) 62 yrs Fig. 5:9	R occipital infarct	R occipital infarct (CT scan)	VA 6/5 bilat L homonymous hemianopia, through macula in left eye but sparing central 2° in R eye	112 108 115 117	11 11 3 8	(limited to occip leads) appears normal with 9-10 Hz alpha rhythm

Table 5:6 Ischaemic lesions (continued....4)

Patient	Referral diagnosis	Final diagnosis	Objective visual signs	VER		EEG
J.A. (M) 48 yrs	? retrobulbar neuritis ? vascular ?? tobacco amblyopia	Probable vascular lesion	Blind R eye since industrial injury. L eye P/L only; progressive loss. Improved to 6/6 by time of VER (also temporal lobe epilepsy	Absent " 112 116	 5 5	(3) L temporal discharges, one recorded during an attack
R.B. (F) 32 yrs	? MS	R middle cerebral artery occlusion (Carotid angiogram and CT scan)	VAR and L 6/5 (L orbital bruit)	96 96 99 102	10 9 12 9	Mild theta excess bilaterally
P.C. (F) 60 yrs	Transient ischaemic attacks in vertebral artery	L carotid stenosis (angiogram)	VA J1 bilat corr	87/106 93 90/106 93	10 a,b & c 11 10 a,b & c 7	3-5 Hz theta activity in the L fronto-temporal region, increased on OB
P.D. (F)	? MS	Possible angioma "unusual for MS"	VA normal bilat	93 92 96 95	13 12 13 11	Rather fragmented alpha rhythm with theta excess, more on the left side
J.P. (F) 49 yrs	Cerebro-vascular disease ?? MS	Suspected cerebro-vascular insufficiency (serum cholesterol high)	VA normal (R sided sensory changes)	90 96 90 90	9 6 8 8	Normal

Figure 5:7 RP (M) - 52 yrs

Ischaemic optic atrophy diagnosed by L carotid angiography

VAR eye - N.5 VAL eye - N.36

Latencies R eye 96 msec to R occipital lobe

99 msec to L occipital lobe

L eye 122 msec to R occipital lobe

128 msec to L occipital lobe

The VER from the L eye shows a reduction in amplitude as well as a prolongation of latency of the response

RP 52yrs
wnc 24877
14Jly76

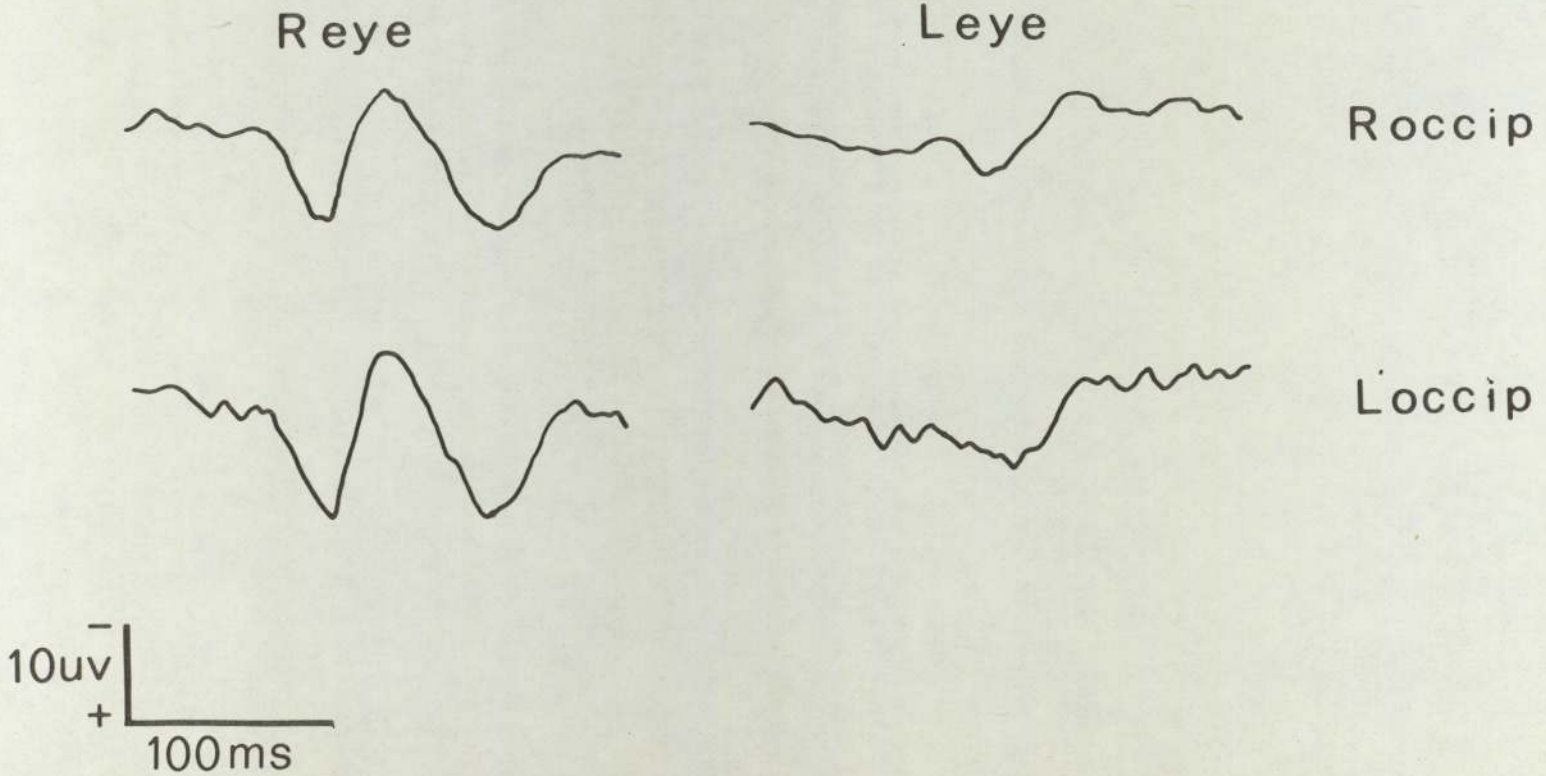


Figure 5:8 JW (M) - 74 yrs

Reduction in amplitude and prolonged latency of response from the L eye in a patient with an ischaemic lesion affecting the optic chiasm

VAR - N.5 VAL - N.18 witha L lower nasal quadrantanopia

Latencies	R eye	116 msec to R occipital lobe
		113 msec to L occipital lobe
	L eye	166 msec to R occipital lobe
		162 msec to L occipital lobe

JW 74yrs
WNC 26256
30 Mar 77

Pattern Reversal

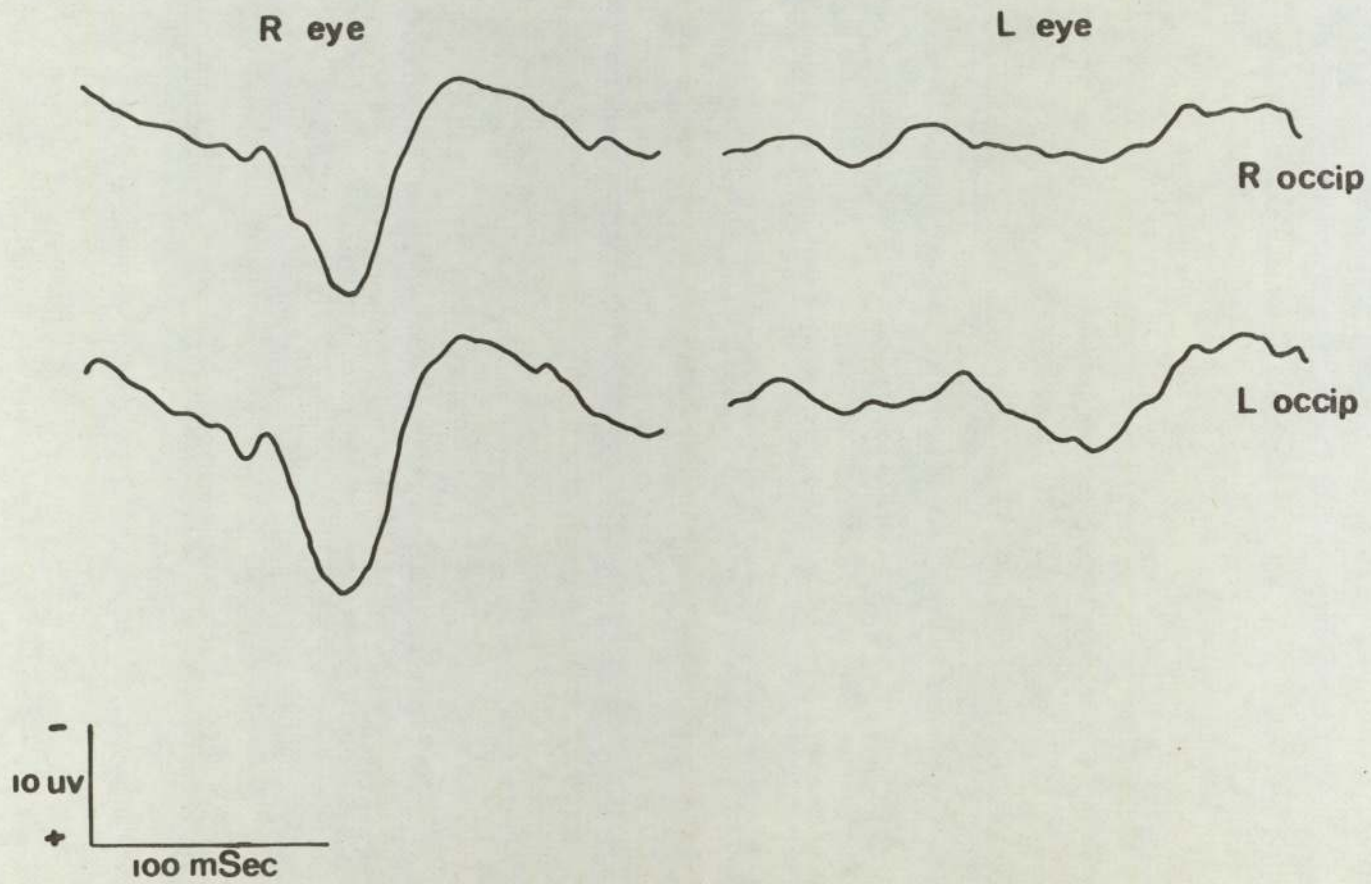
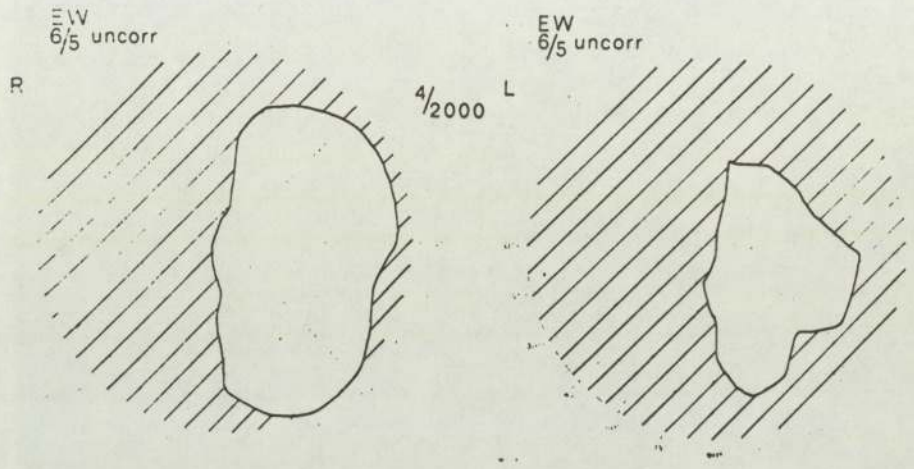


Figure 5:9 EW (F) - 62 yrs.

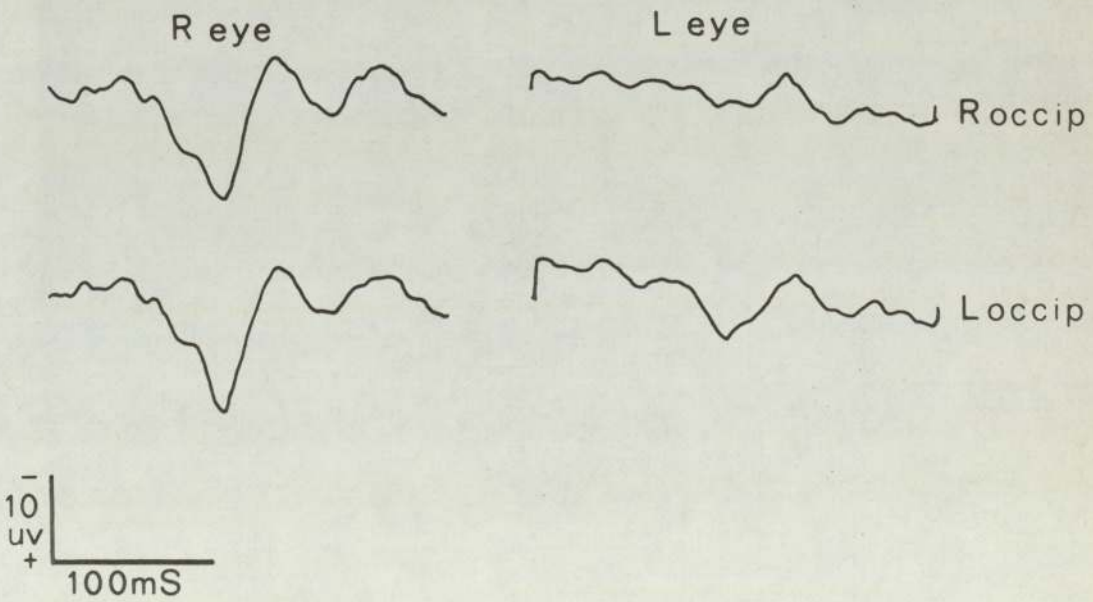
R occipital infarct, demonstrated by CT scan. A normal VER appears from the R eye where the central 2^{o} of visual field is preserved. A reduced amplitude VER from L eye to L occipital, and reduced P_2 wave, L eye to R occipital is recorded.

The L temporal hemianopia divided the macula.

Latencies R eye 112 msec to R occipital lobe
108 msec to L occipital lobe
L eye 115 msec to R occipital lobe
117 msec to L occipital lobe



EW 62yrs
11 Feb 77



and the clinical history and EEG of these are described:
JA's vision had deteriorated and then improved in his left eye. The right had been blind since an industrial injury. The EEG showed a temporal lobe discharge accompanying a clinical attack with automatic behaviour. The diagnosis is still not fully established, but the underlying cause of the symptoms is thought to be cerebro-vascular disease.

RB had a left middle cerebral artery occlusion, in which the EEG showed a slight theta excess. Her vision was normal, but she had a left orbital bruit.

PC, with a left carotid stenosis, showed some excess slow activity in the left fronto-temporal region on the EEG. Her vision was normal.

PD, diagnosed as possibly having an angioma, showed some excess slow activity in the left fronto-temporal region on the EEG. She also had normal vision.

JP, with suspected cerebro-vascular insufficiency, had both EEG and VER within normal limits, as was her vision, but she had right-sided sensory changes.

Summary of findings in seventeen patients with ischaemic lesions

1. In four cases where the lesion was confined on clinical grounds to the brain stem the VER was normal, as was the visual acuity, although one of these had a reduced appreciation of a red pin in one eye and another had a history of diplopia.
2. Three patients with ischaemic optic nerve lesions showed a reduced amplitude and prolonged latency of response from the affected eye, the other being normal.

3. Out of five patients with ischaemic impairment of cortical function, three showed prolonged latencies with local delta waves on the EEG. One had a normal VER and lateralised posterior theta activity on the EEG. The fifth showed a low amplitude VER from the eye in which the field defect bisected the macula, but the latency was longer in the ipsilateral occipital lobe to the left homonymous hemianopia. A limited EEG run concurrently with the VER appeared to be normal.
4. The remaining four patients had normal vision at the time of testing, and normal VER. Their diagnoses were: (1) Left middle cerebral artery occlusion; (2) left carotid stenosis; (3) suspected angioma; (4) suspected cerebro-vascular insufficiency. In these first three the EEG showed excess slow or intermediate slow activity over the affected area. It was normal in the fourth. These findings are presented in table form in Table 5:7.

Conclusions in Ischaemic Lesions

The ischaemic lesions, like the compressive lesions, show VER changes related to the area affected, and the most consistent finding is an abnormal VER from the affected eye in optic nerve lesions. They may also show a prolonged latency and distorted waveform (JW, Fig. 5:8) as with compressive lesions, where the chiasm is affected.

In occipital cortex lesions three out of five showed a prolonged latency of response, all with local EEG abnormality. In one (EW) where there was a right occipital infarct shown on the CT scan, the field defect was more extensive in the left eye than the right and split the macula on the left. The VER from the left eye that was

TABLE 5:7 SUMMARY OF ISCHAEMIC LESIONS. Numbers of patients whose VER fell into each category

Location of ischaemic lesion	VER normal	Latency prolonged in: One eye	One occipital lobe	One response out of the four	All four responses	EEG	Total
Brain stem	4					Normal or minor theta only	4
Left carotid stenosis	1					L fronto-temporal theta	1
Right middle cereb. occln	1					Mild bilat theta excess	1
Diffuse vasc. disease	3					Normal, or mild theta excess	3
Optic nerve		2				Normal 1 ipsilat theta in 1	2
Optic radiations	1		* 2	1	1	3 out of 5 showed occip delta activity 1 theta, 1 normal	5
Total	10	2	2	1	1		16

* One (EW) showed an amplitude asymmetry in the occipital responses and distortion of waveform in the eye in which the field defect bisected the macula

Note: Case BV, with an arterio-venous malformation at the beginning of the left middle cerebral artery, has been omitted from this table as subsequent events have suggested MS in addition to the proven vascular lesion.

distorted and reduced in amplitude and the response to the right occipital area showed a very small P_2 wave and a larger N_3. It could be postulated from both the clinical and VER findings that this ischaemic lesion had affected the part of the right occipital radiations representing the left eye more than that representing the right eye.

The normal VER with the patient with an upper quadrantic defect (BS) from a right occipital thrombosis is not unexpected in view of the known greater sensitivity of the scalp recorded VER to lower half field defects. Compare this with JW (Fig. 5:8) whose VER was grossly affected from the eye with a lower nasal quadrant-anopia.

As with the compressive lesions, a distorted or incongruous VER waveform results from partial lesions of the optic pathways. In both, where there is involvement of the occipital cortex, there is likely to be an EEG slow wave abnormality. This, combined with a prolonged P_2 latency is more likely to be found with ischaemic lesions than with tumours, but this finding is not sufficiently conclusive to be helpful diagnostically.

CHAPTER 6. DISCUSSION AND CONCLUSIONS

(1) THE PHYSIOLOGICAL BASIS OF THE VEP

When recording a physiological event such as an evoked response, it is more satisfactory to know, or at least to be able to conjecture intelligently, on the origin of the potential recorded. That there is a response in the occipital cortex which is time-related to a stimulus to the eye, whether this be in the form of a flash or pattern, has been established beyond any reasonable doubt since Adrian first reported it (1927) in eels and frogs. Brazier (1953) found a response in the calcarine cortex of cats and Grey Walter (1964) found a repeatable and non-adapting response to flash with electrodes implanted into the human calcarine cortex. These responses were of a latency after the stimulus ranging from 12-25 milliseconds in cats to 30 msec in humans. It can be seen with direct cortical electrodes and is repeatable and non-adapting, but cannot be seen individually on scalp recording.

Assuming that the distance from the retina to the calcarine cortex is about 15 cm, and that the synaptic delay in the retinal bipolar and ganglion cells, the lateral geniculate bodies and at the cortex amount to 6 msec, a response in 30 msec from the stimulus would mean a conduction velocity of almost 0.2 metres per second, which is equivalent to the conduction velocity in the slowest C fibres of the sensory system, slow pain, possibly heat and post-ganglionic autonomic efferents. Even this latency is hard to accept, as the optic nerves are myelinated, unlike C fibres, and this would lead one to expect a higher conduction velocity.

The question arises as to whether the measurement of the latency of the response from the time of the flash or other stimulus is valid for measurement of the conduction velocity through the whole visual system. Allowance should be made for the time taken in processing the signal within the retina, as this is a structure of complexity almost like cerebral cortex, in which many interactions occur. The signal evokes a response in the receptor cells, rods and cones. These activate the bipolar cells, which in turn synapse with the ganglion cells. There are also inter-related influences with horizontal cells and other structures, so that it is conceivable that a considerable delay may occur between the flash of light or other signal, and the commencement of the conduction of the impulse at the distal end of the optic nerve.

These considerations were reviewed by Brazier (1953) in which she quoted Adrian and Matthews (1928), who showed that both increase in luminance intensity and the area of retina stimulated had the effect of shortening the latency of cortical response in the eel. They concluded that the delay was due to interaction at retinal synapses. Similar findings were reported by Bernhard (1940) in the frog. Brazier placed recording electrodes across the globe of the eye in a lightly anaesthetised cat, one on the retina and the other on the cornea. She demonstrated that the ERG latency was prolonged by reduction in the intensity of flash stimulus and the "b" wave of the electroretinogram showed a slow rise time with low flash intensity.

Incidentally, in this paper, the electrodes were connected so that when the retina became negative, an upward deflection occurred on the trace. The illustrations show that the ERG appears with a

similar waveform and the same polarity as shown for the human ERG by Galloway (1975). As vertebrate retinae show a similar spatial arrangement of receptor cells, bipolar and ganglion cells (although different proportions of rods and cones), this raises doubt as to the accepted polarity of human ERG. Galloway and other authors regard the corneal electrode as the "active" one, and place a "reference" usually on the zygoma lateral to the outer canthus of the eye. Most of the ophthalmological reports of ERG use the convention of an upward deflection of the trace for a positive potential at the "active" electrode. The direct recordings from the globe of the eye of the cat reported by Brazier would suggest that the corneal electrode should be regarded as the reference, and the zygomatic electrode is more likely to be recording from the retina, possibly due to the bony connection with the back of the orbit.

The result is that apparently fortuitously, these animal and human studies show an ERG of the same polarity.

Returning to the cortical evoked response, it is accepted that the positive response occurring at 100 msec after the stimulus is of the highest amplitude and most easily recognised part of the complex. Adrian (1941, 1951) quoted by Brazier (1953) identified the repeating response of 100 to 140 msec at the cortex with repetitive activity in thalamic neurones. He found that it could be recorded in the optic radiations after removal of the cortex. Records on man (Cohn, 1952) show a 110 msec positive cortical response to flash at 4 Hz but absent at 7 Hz. This is further developed by Brazier and distinguished from the "driving" response seen in the EEG with photic stimulation.

Early oscillatory potentials

Further evidence as to the spread of electrical activity through the visual system has been presented by Cracco and Cracco (1978), who review previous animal work. They report on oscillatory potentials in humans at 100-160 Hz over anterior head regions and 80-170 Hz over posterior head regions. The former appear to relate to the ERG and the latter to the occipital cortex.

The latencies of onset for the anterior potentials was from 9 to 17 msec and over the central-parietal-occipital regions, 13 to 24 msec. These oscillations persisted after the flash for over 100 msec in some subjects.

The potentials were best seen with the stroboscope at maximum flash intensity (Grass intensity 16. 1,500,000 candle power at 10 inches distance).

It is postulated that some of these potentials originate in the region of the lateral geniculate body, but the precise physiological basis of them has yet to be determined.

Harding (1979) reports on potentials recorded from central areas, independent of the anterior ERG and the posterior VER, which may relate to activity in the lateral geniculate body.

This evidence is quoted to illustrate that the electrical response in the visual system does not consist of a simple throughput of action potential, but a complex arrangement of reverberating circuits. These appear to be active within the retina itself, in the brain stem and possibly between brain stem and calcarine cortex.

When averaging methods were developed, Cobb and Dawson (1960) found a response at 20-22 msec equipotential between midline electrodes 3 and 6 cm above the occipital protruberance. This was difficult to detect, but varied between subjects and was of only

1 to 1.5 microvolts in amplitude.

It seems likely that this response was the primary signal arriving at the cortex, and that the major positive wave which follows at around 100 msec (the P_2 wave) is a complex response involving other structures. This potential is much easier to detect, in fact it may at times be seen in the "raw" EEG, as it is of the order of 2 to 30 microvolts in amplitude, and it has been established that its latency is affected by lesions of the optic nerve, chiasm, tract and radiations. Therefore it appears to be acceptable to measure the latency of this wave in order to assess conduction time through the optic pathways, even though this is almost certainly not the primary impulse.

Rod and Cone reception

There has been some discussion as to whether the VEP is from rod or cone reception in the retina. DeVoe, Ripps and Vaughan (1967) conclude that the response to flash results almost entirely from cone stimulation at the fovea on his evidence that the response diminishes in amplitude and increases in latency rapidly as a narrow beam of stimulus is moved outward even 10 minutes of visual angle from the centre. Behrman, on the other hand, postulates that VEPs to flash originate from the rod system as the responses have a recognisably different waveform and longer latency in a dark-adapted VEP than the more usual light adapted one. It was stated by Cobb and Morton (1952), however, that the first flash would light adapt subjects for many minutes, in an experiment on the human retinogram, and this finding seems likely to apply to the VEP also.

The introduction of the reversing checkerboard avoided the problems of a changing light intensity, but it was still important

for fixation to be maintained at the centre. Variations in fixation have been found by this author to produce a more "rounded" waveform of the P_2 wave on the VEP. It would seem more likely that the principal reception of response, and the production of a P_2 wave, depend on foveal stimulation, and this is supported by evidence quoted in the MS section (Chapter 4) that patients with macular field defects show absence of the P_2 wave. A finding also reported by Halliday (1978). As there are no rods at the fovea in humans, and only cones, this further supports the theory that the P_2 wave of the VEP is a result of cone cell activity.

Visual fields

On arrival at the striate calcarine cortex, the central point of vision is represented at the extreme posterior tip of the occipital lobes, and the macula, that is the central 1.5^{o} of visual angle, is represented over about one third of the entire calcarine cortex, the more peripheral part of the field situated anteriorly. In a vertical direction, the upper half field has its sensory nuclei in the lower part of the calcarine cortex, possibly below the inion and curving under the occipital lobe over the tentorium (Jeffreys and Axford, 1972) and the lower half field is projected to the upper part of the visual cortex. Lehmann and Mir (1976 and 1977) also report longer latencies and smaller amplitude with upper half field stimulation. This is supported by the evidence in Chapter 5: Compressive and ischaemic lesions, in that greater distortions of waveform and changes in latency were seen in subjects with lower half field defects.

The findings in homonymous lateralised field defects have been more confusing. Halliday (1977) has consistently found a higher amplitude VEP on the side opposite to a homonymous defect, even in a

post-hemispherectomy patient. In this series (Chapter 5) the reverse has been found, except in two patients with chiasmal compressive lesions. The findings of a lower amplitude response contralateral to the field defect, when using 10-20 placements, have been found by many authors: Harding et al. (1969), using a bipolar montage; Eason et al. (1967). Kooi et al. (1965) found distortions of waveform but used a linked-ear reference. More recently Holder (1978) supported this and found an even greater occipital asymmetry, with reduced amplitude contralateral to a half-field defect, using electrodes 3 cm above the inion and 2 cm out from the midline, and demonstrated the reverse finding (1978 meeting) using Halliday's montage in simultaneous recordings on a patient after occipital lobectomy. He reports an even greater asymmetry of response when using a smaller check size as stimulus.

It appears likely that it is mainly the difference in recording technique which accounts for the apparent contradiction in results.

There are two major differences in technique, one is that Halliday uses a checkerboard which subtends 16° at the eye, from centre to periphery, as against the 8.5° of this author. The other is in electrode derivation. Halliday places five active electrodes, one in the midline occipital area 5 cm above the inion and two each side, lateral to this at 5 cm intervals. This author has used the O_1 and O_2 placement of electrodes as described in the International 10-20 system of recording, which on a usual adult head is from 3.2 to 3.8 cm above the inion, and 2.7 to 3 cm lateral to the midline on each side. Thus the two active electrodes are about half the distance out from the midline and about 1.5 cm lower than Halliday's. Both use a midline frontal reference. Harding uses, in addition, two electrodes between O_1 and T_5 and O_2 and T_6, which he designates O_3

and O_4 respectively. Early experiments by Halliday and Michael (1970) showed that with 10 scalp electrodes placed over the occipital cortex at 3 cm intervals lateral to the midline and 2.5 cm intervals in an A-P direction, stimulation of a segment of a circle, the response was greatest on the contralateral side to that stimulated, but much reduced on stimulating the horizontal meridians (presumably due to the fact that mainly the peripheral field was being stimulated which, as discussed above, has a much reduced representation, in the anterior part of the calcarine cortex). In the same experiment, upper field stimulation produced an apparent reversal of the response in that the major peak at 100 msec was negative, and became positive with lower half field stimulation.

This reversal of polarity confirms Jeffreys and Axford's (1972) findings, quoted above.

The response is of very much higher amplitude in the midline occipital area, presumably due to a summation effect from the two sides of the calcarine cortex.

Considerations of the theoretical physiology of the visual evoked potential, and both the published and personal experience of practical findings, led to the choice of recording parameters.

(ii) ESTABLISHMENT OF PARAMETERS FOR RECORDING

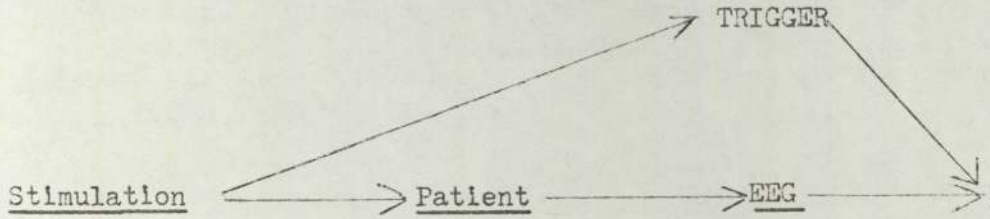
It has already been shown in Chapters 2 (Review of Literature) and 3 (Method and Results of a Normal Control Series) that the recording technique has a substantial influence on the results obtained. Many authors have emphasised that it is necessary for each laboratory to establish its own acceptable limits of normality by recording from a control series. Table 6:1 shows some of the factors which influence the findings.

One of the advantages of starting rather late in the visual evoked response scene was that benefit could be gained from the experience of other workers, and also that commercial manufacturers were beginning to produce suitable apparatus. In fact, the availability of funds and the commercially-obtainable apparatus had a considerable influence on the choice of method.

We will take the stimulus first. It had to be determined in the first instance what information was desired from the test. Where there was a question of whether the retina was receiving light and the optical pathways were intact, then flash stimulation was needed, and a commercially available stroboscope with a triggering facility was used. If any qualitative assessment of visual function was needed, it was essential to standardise the light intensity and ambient lighting, and the distance of the light from the subject's eyes.

With pattern reversal it has been shown that the pattern edges must be in focus, so that if optical correction is necessary, this should be employed. Each square of the pattern should not subtend a visual angle of more than about 50', as it has to be remembered that

TABLE 6:1 VARIABLE FACTORS WHICH MAY INFLUENCE THE VISUAL EVOKED RESPONSE



Stimulation	Patient	EEG	Averager	Display
Pattern reversal (P/R) or flash	Right or left or both eyes	Derivation Gain	Number of Trials	Plot
Distance from eye(s)	Corrected or uncorrected	Time constant	Scale factor	C.R.O. (Settings variable)
Angle subtended (P/R)		HF filters	Sweep time	
Square size (P/R)				
Frequency of change (P/R)				
Frequency of flash				
Relative brightness (P/R or flash)				

the macula only covers the central 1.5° of visual angle (3° from side to side) and a much larger square would occupy most of macular vision. Harter and White (1970) report that small checks of 10-20' subtense give a greater amplitude of evoked response to patterned flash. A short trial by this author with a 20' square size in the checkerboard for pattern reversal stimulation produced no marked change in latency. The whole area of pattern stimulation should not be too large, as stimulation of a wide field would spread the response forward in the visual cortex and might complicate the waveform at the occipital electrodes. The brightness and contrast of the screen affect latency as well as amplitude of the response, and this is also relative to the ambient lighting in the room, and the pattern reversal stimulator which uses a projected image reflected by an oscillating mirror is more likely to keep a constant stimulus intensity than a television type pattern reversal stimulator, although the latter is more flexible for experimental work.

These considerations determined the chosen stimulus parameters described in Chapter 3, of a reversing checkerboard 15 cm square, subtending 8.5° at the eye with the subject at 50 cm distance, each square subtending an angle of 54'.

In the choice of electrode site and derivation, the International 10-20 system has established that O_1 and O_2 are on the occipital lobes, and this system has the added advantage that the electrode distances adjust to the size of the head as they are proportional to the whole measurement. Although adult heads do not show a marked variation in size, this becomes important when recording from children and infants. The reference to be used may also be important, and the same considerations as for EEG recording apply. It is not possible to find a truly indifferent reference point on the head, and many

devices have been used to overcome this difficulty.

It seems appropriate at this point to discuss the dipole concept.

The Dipole Concept

Originally the term "dipole" used in physics is applied to a bar which has a positive charge on one end and negative on the other. Movement of the bar near a conductor will induce a current in the conductor.

In the experience of this author the first encounter with the term "dipole" was in very high frequency radio and radar (Admiralty Handbook of Wireless Telegraphy, 1937 edition). In that context the term described an aerial whose length corresponded to the wavelength of the signal. By "tuning" the aerial, i.e. altering its effective length, so that one end of the aerial was at minimum and the other at the peak of the wave, as the speed of electricity is 3×10^8 of a second, an HF signal of, say 150 megaHertz would have a wavelength of 2 metres, which would be a convenient length for an aerial. If we apply this to the alpha rhythm, however, a true dipole for this would be 150,000 kilometers long. So this radar term is obviously not applicable in neurophysiology.

If, however, the term is used merely to describe the two sampling points of a potential gradient across the brain, or skull, it only indicates the difference in potential between those two points. It has to be remembered that this is the extent of the information to be gained from this method of measurement, and no indication is given of possible rise or fall in potential between the two points, or their relationship to adjacent areas.

Magnus (1961) uses the term when describing opposite poles

(negative and positive) across the thickness of the cortex, and postulates that in the superficial cortex the cumulative effect of large numbers of neurones firing synchronously can be picked up by using surface electrodes. The positive and negative poles within the depths of the sulci are situated in opposition to each other and therefore cancel out in surface recording. He illustrates the changing sign of a spike discharge as depth electrodes are inserted deeper into the brain.

In a session at the EEG Society meeting in January, 1977, the dipole theory was thoroughly aired. Henderson, Butler and Glass approach the problem from a mathematical angle and maintain that meaningful results can be obtained in spite of the complexity of the brain which has "sheets" of dipoles working in unison. Macgillivray also finds ways of simplifying the situation of complex inter-connectivity of cell populations, but Dawson states that particular rhythms, such as the alpha rhythm cannot be ascribed to a single generator source, and states that the term can only be used in relation to a fixed moment of time, when existing potential differences at that moment may be plotted.

The whole question of the dipole is highly relevant to recording the VER, and the choice of electrode placement and derivation obviously influences the waveform of the response, even to producing a reversal of polarity or confusing lateralisation of responses in half field stimulation.

No totally satisfactory solution to the derivation problem has so far been achieved.

The choice of recording parameters depends on the information to be gathered. If the object of the test is solely to find out whether there is a delayed response, some authors have found it

adequate to use a single channel connected to two midline electrodes, one parietal and one occipital. The published results in these seem to correlate quite well with other authors as to the percentage of positive findings in multiple sclerosis. This method cannot, however, give any information as to the site of a lesion, apart from the fact that if one eye at a time is stimulated, and one only shows a delay, it is likely to be pre-chiasmal. Reference to one ear lobe is likely to produce a reduced amplitude response on the ipsilateral occipital electrode, and some authors have used the ipsilateral ear as reference on each side. This would appear to be preferable to using the contralateral ear, as it is reasonably certain that the ear is not electrically inert as far as cerebral activity is concerned, and it would not be clear from which side any activity originated. The same argument applies to the common practice of using linked ears or linked mastoids. There may be a relative "equipotential" with one occipital lobe, leading to a false appearance of amplitude increase on the opposite side.

If a single reference point has to be used, a midline frontal electrode seems least likely to produce false asymmetries as the argument is that it is well away from the occipital cortex. Even this may not be true, as the longitudinal sinus contains a channel of blood and CSF, both of which are very good conductors of electricity (Geddes and Baker, 1967).

Probably a more accurate picture of the distribution of the response could be gained by using an average reference derivation with the usual 22 electrodes of the 10-20 system, or a bipolar system spanning both hemispheres as used by Harding, or a combination of common reference and bipolar systems as reported by Blom (1974) and Oosterhuis et al. (1969).

The method chosen, as stated above, is limited by the apparatus available, and as only a two-channel averager was used at the start of this series, recordings were made from O_1 and O_2 referred to F_z.

With four channels, acquired later, some experience was gained in using a midline occipital electrode, but this appeared only to record the waveform from the occipital lobe showing the highest amplitude response. Finally, with four channels, electrodes T_5 and T_6 were used, referred to F_z, in addition to O_1 and O_2, and with the microprocessor facility on the averager, it was possible to convert the result into a bipolar derivation by subtraction, and therefore confirm the side emphasis of response in patients with lateralised visual field defects.

Concurrent EEG

It is felt that it is very important to record the ongoing EEG while carrying out Visual Evoked Potential tests, as the result may be affected by spontaneous EEG activity, or the stimulus may "drive" the cerebral electrical activity and produce an apparently enlarged response. The first has been illustrated by Figure 3:8, where a marked 16 Hz beta component in the EEG appears as four equal amplitude waves in the 250 msec VEP trace, and Figure 3:9, where the P/R has synchronised with a prominent alpha rhythm. This may be fortuitous synchrony of the repetition frequency of the pattern reversal with a particular phase of a regular rhythm. Similar findings have been reported by Goldstein and Sanders (1970) and Pfurtscheller et al. (1977). It is also possible that the EEG may be "driven" by the stimulus; more likely with flash than with pattern reversal, and Figure 6:1 illustrates this occurrence in a patient with the repetitive complexes of Jakob-Creutzfeld disease. This can

Figure 6:1 The complexes of Jakob-Creutzfeld disease apparently evoked by regular flash stimulation. The complexes revert to a slower repetition rate when flash is discontinued.

VER averaged from $C_3 - O_1$ derivation

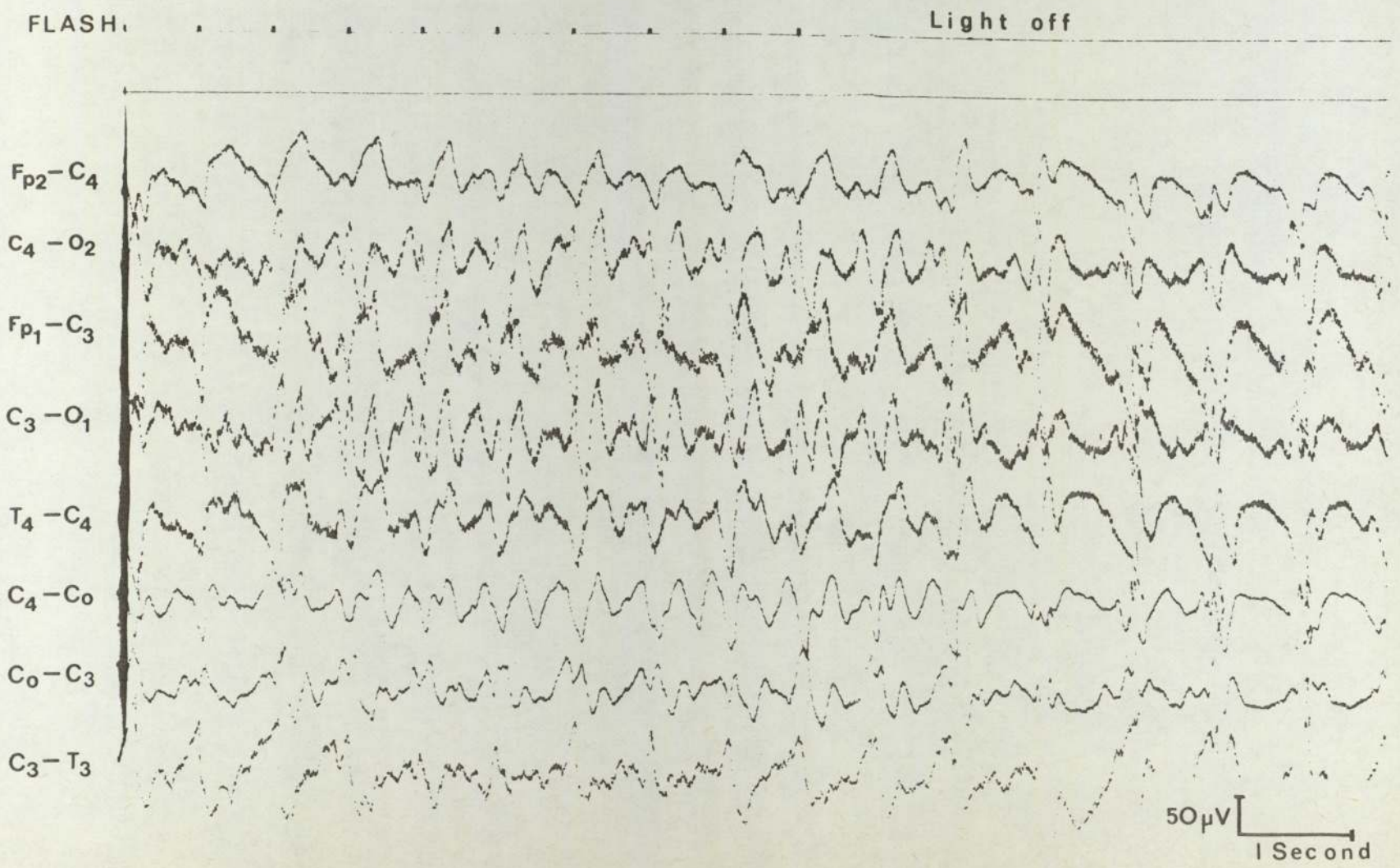
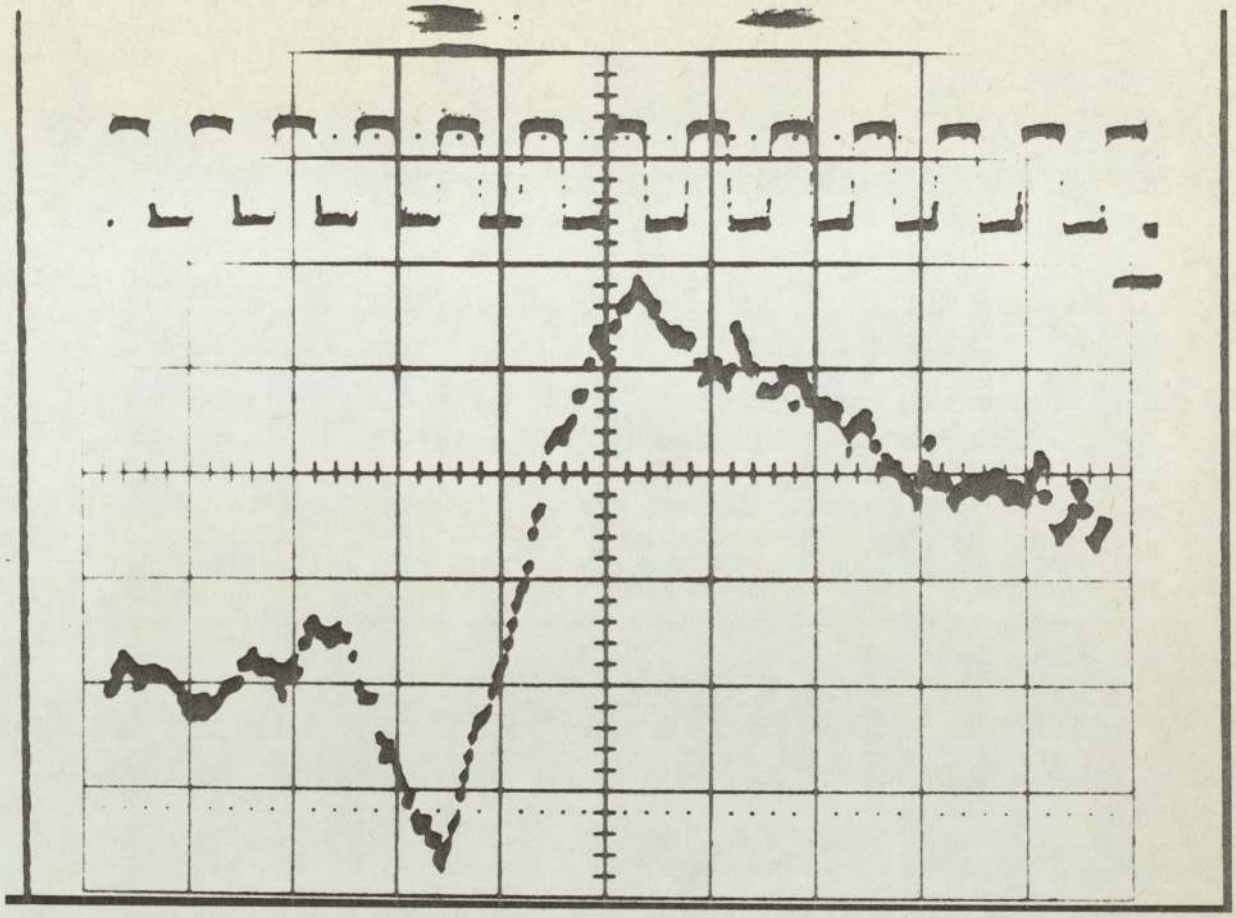
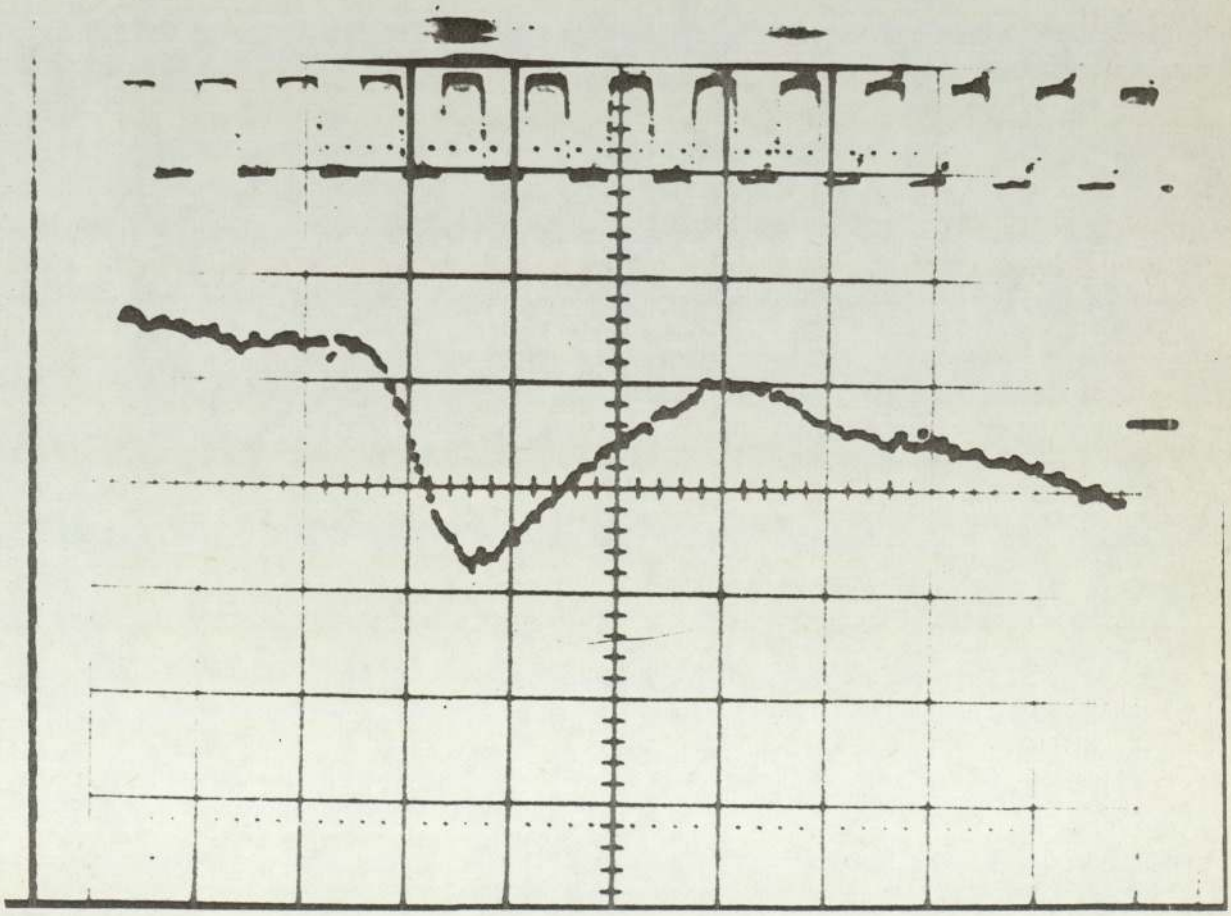

FLASH
Light off
$F_{p2}-C_4$
C_4-O_2
$F_{p1}-C_3$
C_3-O_1
T_4-C_4
C_4-C_o
C_o-C_3
C_3-T_3
50μV
1 Second

Figure 6:2 VER to regular flash stimulation in a patient with Jakob-Creutzfeld disease (A piece of the on-going EEG at this trial is illustrated in Fig. 6:1)
Vertical scale 5 uV per division.
Horizontal scale 25 msec per division

Figure 6:3 VER in the same patient with randomised flash.
Same scale





usually be avoided by randomising the flash incidence. Subjects with a photo-convulsive response to flash may also exhibit the same phenomenon. Harding (1970) illustrates the relationship of occipital spikes with the flash evoked response in photosensitive epilepsy.

Another advantage of seeing the on-going EEG is in the detection of artefacts, as high amplitude transients, if occurring during the 250 msec sweep period, may contaminate the result. Blink artefacts as a reflex response to a flash usually occur in the second half of the 250 msec trace, but electrode or static generated artefacts may occur at any time and falsify the results, if they are of sufficient amplitude to survive averaging.

Also, if there is an amplitude asymmetry in the VER, it is useful to note if the EEG also shows such an asymmetry. Provided, of course, the electrodes are symmetrically placed, an amplitude asymmetry in the EEG could be due to a cortical lesion, but if the EEG is symmetrical and the VER asymmetrical, the optic tract on the side of the lowered response would be implicated.

Need for Standardisation

Although the use of different recording parameters has extended the knowledge of the subject, it creates difficulties in the comparison of results by different authors. It would seem that the time is now approaching for an international meeting of prominent clinical workers in the field to discuss some sort of standardisation of technique for clinical use. This would be similar to the meeting in 1957 which recommended standards for EEG recording (IFSECN, 1958). This would then simplify comparisons of clinical material, and would provide a forum for discussion of the relative merits of each system.

(iii) PRESENT CLINICAL VALUE OF THE VER

As in other electrophysiological tests, i.e. EEG, EMG, evoked response techniques may be of value in detecting defects which are not clinically apparent. The technique of visual evoked responses, which is relatively recent in clinical use, is going through the same process in general appeal as did ECG and EEG in their early development. They were each hailed as a major breakthrough in diagnostic potential, and possibly too much emphasis was laid on their reliability at the outset. It is only with time that the advantages and limitations of the technique reach a true balance.

Multiple sclerosis

The undoubtedly important discovery that the VER detected sub-clinical conduction defects in the visual system in multiple sclerosis led to the assumption that an abnormally prolonged latency in the response was pathognomic for MS. This danger was rapidly realised, and many papers were published to show that latencies could be prolonged in compressive lesions. There have also been reports of an effect on the VER of metabolic disorder, in myxoedema, and a brief report of the effects of ischaemia.

Although the findings that the VER can be affected by other lesions tends to detract from its usefulness in the diagnosis of MS, it is still a valuable tool if used in the context of the whole clinical picture. Its greatest value in MS is where the clinical signs and symptoms are confined to a spinal cord level, and there is no clinical evidence of involvement of the visual system. An abnormal finding in the VER in this situation is much stronger evidence of MS than where the visual system is alone affected.

It is still not an open and shut diagnostic aid even in this situation, as other conditions may result in disseminated lesions. Among these are: neurofibromatosis, vascular degenerative disease and metabolic disorder.

If the diagnosis continues to be in doubt, repeated examinations may clarify the position in regard to MS, as there may be considerable variation in the reults even after a few weeks, as shown in Chapter 4.

There are other respects also in which abnormalities may be seen in MS, as compared with a control population. It has to be remembered that in the visual system signals are conducted through large trunks of axons in the optic nerves, chiasm, tracts and radiations. Each optic nerve contains at least a million axons, and since the development of the electron microscope, has been shown to contain many smaller fibres not visible with the previously-used light microscope.

While the characteristic plaques of MS are caused by groups of fibres becoming demyelinated, there is nevertheless the possibility that areas within a given section of the optic nerve may become demyelinated, leaving other axons intact. This theory is supported by the following evidence:

1. Blumhardt and Halliday (Oct. 1978, EEG Soc) have shown that sub-clinical field defects may be revealed by stimulating the lateral half fields separately in MS, and finding an absent response on one side.

2. McInnes (Sept. 1978, Nottingham) recommends stimulation of the upper and lower half fields independently, and this may divide an "a, b and c" wave response. They postulate that this type of waveform is produced by different conduction times in fibres from the upper

and lower retinae.

3. In Chapter 4, it is reported that some MS patients showed a "fragmented" response (Waveform Type 6, Chap. 4), or a small peak at the expected latency (around 100 msec) and a higher amplitude peak occurring later (Waveform Type 4, Chap. 4). There could also be a change in emphasis of amplitude during the course of the build-up of the averaged response.

It could be postulated from this that as some groups of axons became "blocked" by a standing charge unable to produce nerve conduction, the signal was bypassed through other bundles of axons.

4. There is also some evidence that the rate of change in pattern reversal may be critical in diagnostic testing for MS (personal observation), and while a relatively slow pattern reversal (1000 msec intervals) produced a normal response, a reversal frequency of 600 msec would result in a delay or a distorted waveform.

The MS patient, while possibly producing a normal latency of response to full field stimulation, may have an abnormal response with any of the following changes of parameter:

1. Lateral half field stimulus
2. Vertical half field stimulus
3. A faster rate of pattern reversal
4. Repeated examinations over a period of time.

With all these variations of test, normal controls have been shown to maintain responses with acceptable latency ranges.

It could be argued therefore that patients suspected of having multiple sclerosis and having a normal VER on full field testing should also be tested with half field stimulation, either lateral or vertical. It would be necessary, however, for normal control limitations to be established when using these altered stimulus parameters.

Compressive Lesions

The findings of abnormal VER in other conditions encourage the diagnostician to search for clinical applications of these findings.

The computerised-tomography scanner is obviously now the best indicator of space-occupying lesions, but only demonstrates an actual presence. The VER detects function of a nerve, and may be used to determine the effect of a known compressive lesion, or to assess residual damage after surgical removal of such a lesion. It has been shown in Chapter 5 (Case BG) that the VER is more sensitive than clinical examination to optic nerve damage by a compressive lesion.

In tumours affecting the chiasm and post-chiasmal structures, some confusing results have been reported. As far as compressive lesions of the chiasm itself, it may not be valid to use these as evidence for VER correlation with visual field defects, as the area of compression is uneven. A tumour may impair the function of some axons travelling through the chiasm while leaving others intact This is illustrated by the findings of incongruous visual field defects. Also the findings at operation, where the optic nerves are clearly visualised, might not correlate entirely with the VER. See Case EA in Chapter 5 where both optic nerves were displaced but only the left produced an abnormal VER, and more central visual field defect. In Case HF, in Chapter 5, the tumour was seen to be compressing the optic chiasm and the right optic tract from below, but the VER only showed a delay from one eye (the right), and central vision was preserved in the left eye.

It would appear preferable to study lesions posterior to and not impinging upon the chiasm, in order to correlate these with symmetry and synchrony of the VER. In this respect it is interesting to compare cases SH and WT in the post-chiasmal group. Both these

patients had undergone a standard right occipital lobectomy and therefore could be assumed to have identical lesions (although the tumours were of different pathology). Both showed a VER of higher amplitude and phase reversing over the intact occipital lobe. The interesting fact is that the visual field in one (SH) showed an almost-complete left homonymous hemianopia, sparing the central 2° of vision. In the other patient (WT) the left homonymous hemianopia was incomplete, sparing the central 10° of vision in the right eye and 5° in the left eye. It could be postulated from these findings that the representation of the visual fields in the calcarine cortex varies slightly between individuals.

Ischaemic lesions

There have been few reports so far on the effect of starvation of the blood supply on the VER. Theoretically it did not seem likely that ischaemia would produce a delay in the response, as it does not cause demyelination (Weller, personal communication). Rather would it be expected that there would be a reduction in amplitude of the response through axonal degeneration, thus reducing the signal. In fact, the VER may be reduced and also prolonged on the affected side, whether this be pre- or post-chiasmal. This leads to the postulation that the delay occurs at the synapses, either within the retina itself, or in the lateral geniculate bodies. Another possibility is that ischaemia may damage a section of axons within the optic nerve or parts of the occipital cortex, leaving others intact, resulting in a change of polarity in the response, or a change in waveform. This is illustrated in Figure 5;9, Case EW, where the waveform appears to have reversed polarity between the right and left occipital responses from the left eye with an

occipital infarct.

This is an important finding, as the clinical symptoms and signs of ischaemic disease may be similar to early evidence of MS, i.e. sensory loss, hyperaesthesiae, reduced visual acuity. They may also affect more than one system, and may improve, like a remission in MS.

A full EEG examination may assist in the diagnosis, as ischaemia may affect the cerebral rhythms also, but this is not certain as the vascular insufficiency may be confined to the ophthalmic branches of the internal carotid artery only.

Again, repeated tests over a period may assist in the differentiation. The VER in ischaemic lesions affecting one optic nerve is likely to remain unchanged, or improve only slightly. In MS, changes are more likely, and it has been reported that the lesions in MS found in post-mortem studies, have a symmetrical distribution, so that repeated VER studies would be likely to show either bilateral prolonged latencies, or a change of lateral emphasis.

It might be concluded from this that in repeated studies over several months or years, if the VER remains delayed from one eye only it is more likely to be due to an ischaemic or compressive lesion than MS.

Metabolic disease

Reports of the effects of metabolic disease are as yet infrequent, but it has been shown (Cooper, 1977) that myxoedema produced a prolonged latency in the VER as well as slowing of the dominant rhythm in the EEG. On treatment with thyroid, both the EEG and the VER showed an improvement in frequency and latency respectively.

More recently, Hamel et al. (1978) reported that the VER latency is prolonged in patients with renal failure, and improves after dialysis. Lewis, Dustman and Beck (1978) found that both the visual and somatosensory evoked potentials tended to show a longer latency and increased amplitude in patients before renal dialysis or transplantation. The EEG dominant rhythm was also slowed. All their findings showed improvement after successful kidney transplant. They comment that the VER, SER and EEG may be a more sensitive indication of early renal failure than clinical observation or biochemical tests.

A possible further advantage of evoked response measurements over study of the EEG is that they provide a simpler and more exact indication of nerve function. In studying small changes of EEG dominant rhythm, an electronic frequency analyser would be required on the one hand. On the other hand, the EEG is influenced also by the state of awareness of the subject under test, and it would be difficult to ensure exactly comparable conditions of recording on every occasion.

Reports of other metabolic conditions have been slow in appearing but it may be assumed that metabolic disorders will show a global change whereas those due to a compressive lesion or local vascular deficit will be lateralised. They may be further differentiated from MS in that the delays are symmetrical, whereas in MS, although delays may be seen bilaterally, there are frequently changes in waveform, and other variations between eyes or occipital lobes. Again, repeated tests over a period may add further elucidation.

Other Conditions

It is conceivable that many other conditions affecting the nervous system may also show changes in the VER. One such unexpected finding was experienced with a patient referred as possibly suffering from MS. The VER showed a prolonged latency in one post-chiasmal result, but the EMG was characteristic of a polyneuropathy. The eventual diagnosis was sarcoidosis.

Diseases of the eye

Many eye diseases are detectable by direct examination with an ophthalmoscope, but where there is an opacity of the lens such as in cataract or glaucoma, or inflammation and effusion of blood due to direct injury, the ERG and the VER may give a valuable indication of the function of the retina (Harding, 1977, p. 507-8; Crews, Thompson and Harding, 1978).

The ERG shows a response to a light flash, and this normally increases in amplitude with dark adaptation. In rod degeneration, where night vision is impaired, the ERG amplitude does not increase. These results are of value, but only give a global indication of retinal function. If a more localised assessment of retinal dysfunction is required, the VER, with electrodes strategically placed over the visual cortex, should show local differences at the receiving end, and may show the effect of, for instance, local reduction in blood supply to part of the retina or optic nerve.

Another application is in detached retina. Subjective visual appreciation may be lost, but if the VER is present, this is evidence that the pathways are intact and surgery may be worthwhile.

Hysterical Blindness

The diagnosis of hysteria is always a last resort where no objective signs or clinical tests have shown evidence of disease. It still remains a last resort, and must do until some positive finding makes the diagnosis.

In patients complaining of loss or diminution of vision, both the ERG and the VER may be of considerable value. The presence of an ERG goes a long way towards excluding retinitis pigmentosa, and a normal VER in the presence of a claimed reduction in visual acuity makes a lesion in the optic pathways unlikely.

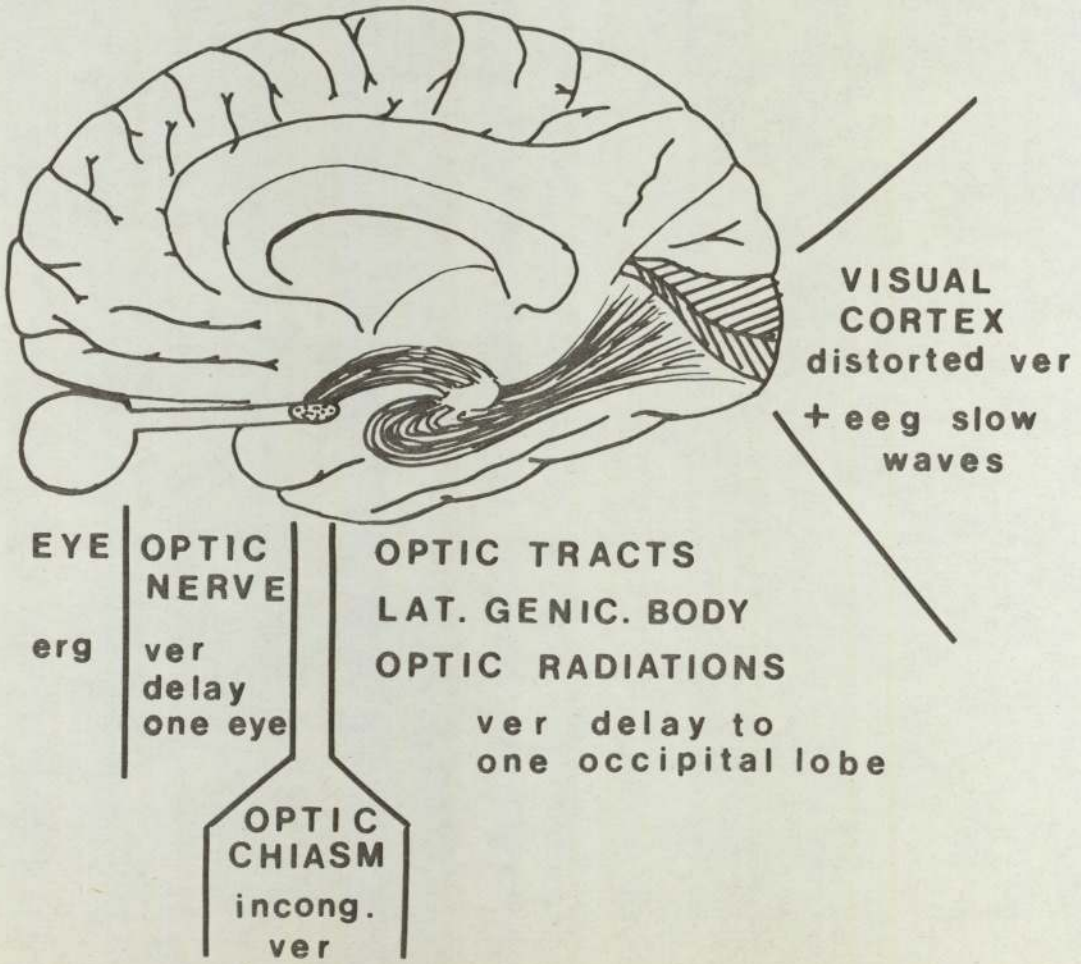
The normal findings may be used to reassure the patient whose symptoms are, after all, a cry for help. Further enquiries and efforts should be made to reach the seat of the problem.

Conclusions on present clinical value of the VER

The clinical value of electrophysiological tests of the visual system is widening rapidly as more applications and results are reported. It is becoming increasingly obvious that, like other electro-physiological examinations, the VER cannot be taken in isolation, and the results must be assessed in the context of the clinical history and results of examination.

Figure 6:4 shows a model for the use of the electrophysiological tests in clinical medicine. If the lesion is in the globe of the eye, the ERG and direct examination are most likely to make a diagnosis. If in one optic nerve, the VER response from stimulating one eye should reveal the defect when compared with stimulating the other eye. If in the optic chiasm, incongruous waveforms are likely to result, in any combination of the four responses. Lesions posterior to the chiasm, in the optic tracts, lateral geniculate bodies or

Figure 6:4 Model for demonstration of the possible localisation of lesions by the VER.
The medial surface of the right hemisphere is shown.
For explanation, see text.


VISUAL
CORTEX
distorted ver
+ eeg slow
waves
EYE
erg
OPTIC
NERVE
ver
delay
one eye
OPTIC TRACTS
LAT. GENIC. BODY
OPTIC RADIATIONS
ver delay to
one occipital lobe
OPTIC
CHIASM
incong.
ver

optic radiations would produce a delayed or distorted VER to one occipital lobe, and visual cortex lesions may show EEG abnormalities, sometimes with a normal VER latency, or with waveform distortion. Metabolic disorders, if producing any change at all, might be expected to result in global changes over the whole system, and longitudinal studies with treatment could be helpful. This has been shown in myxoedema (Cooper et al., 1977) and renal failure (Hamel et al., 1978).

It has also to be borne in mind that patients may be suffering from more than one condition. Although statistically rare, it is possible for a patient to have both a space-occupying lesion and MS. In the author's recent experience, one patient had both MS and neurofibromatosis, and another was suffering from an arterio-venous malformation and MS.

It has been shown that the response to flash stimulation is very variable between individuals, but highly consistent when repeated on the same person. This means that as a qualitative test compared with the norm it is not reliable, but that on-going tests, or comparisons between the eyes it can yield valid results.

The physiological basis of the VER should also be appreciated, when attempting to assess any defect, and with pattern reversal, the area stimulated has an important bearing on the findings. For instance, no change will be seen where there is a visual field defect affecting the peripheral field, outside the central 10° of visual angle, if a checkerboard subtending a smaller angle is used.

Likewise, it has been shown that where the field defect is in the upper half field, the VER is not so readily altered as when it is in the lower half field, as the representation on the cortex of the lower half field of vision (upper retina) is more easily accessible

to scalp electrodes, and also the choice of reference could have a bearing in this situation.

One major drawback with the pattern reversal VER is that it requires some co-operation of the patient, unlike the auditory evoked potential, and somato-sensory evoked responses which can be carried out on totally uncooperative subjects and young babies. Even flash stimulation should be applied to central vision if possible, and although some response is obtained where it is off-centre, it could show a reversal in polarity.

Pattern reversal stimulation requires a good deal of concentration and co-operation in order to achieve a meaningful result, but its potential as a diagnostic tool is only just emerging.

One difficulty is that the criteria of normality have been established in relation to the latency of a particular wave, the P_2, or positive wave normally occurring at about 100 msec after the stimulus. This is quite acceptable where this wave is readily recognisable, and indeed with MS patients it may still be recognisable although delayed (Figs. 4:3 and 4:5). The difficulty of reporting an exact latency figure arises when there is waveform distortion, even apparent reversal of polarity (Figs. 5:2 and 5:9), and it is difficult to establish whether the result shows P_2 delayed, absent or reversed.

These problems arise primarily from the established methods of measurement and the desire to produce a numerical result for data analysis. This is essential for agreeing on normal criteria, but it would appear to be an over-simplification of the situation when asymmetrical demyelination or compressive effects within nerves or tracts cause distortions of the waveform.

(iv) POSSIBLE FUTURE DEVELOPMENTS

Where multiple sclerosis is concerned the actual placement of electrodes seems to be of less significance than in other conditions. Authors who have used a single channel, with a midline occipital electrode referred either to an anterior midline position, one ear or both ears seem to have obtained similar results in their percentage of positives according to McAlpine's criteria.

A possible advancement in the VER in MS would be an increase in the number of longitudinal studies on individuals over a period.

In patients showing visual field defects there appear to be many more openings for advancement. Most authors, the present one included, are using a very simple system of recording the VER, and two or even four electrodes over the posterior part of the head are quite inadequate for studying the situation where a field defect exists. There are complications presumably due to electrotonic conduction through electrolytic fluids, blood and CSF, and the later part of the response relates to inter-neuronal connections in the cortex or even between the cortex and the brain stem.

It is likely that a highly complex system of amplitude gradients in the response is present over the posterior part of the head, and this is suggested by the findings of authors using comparative common reference, average reference and bipolar derivations. One potentially rewarding series of studies would be to place multiple electrodes at no greater than 2 cm intervals all over the posterior third of the head, also covering 3 cm below the inion, and to record the response as a contour map for stimulation of different parts of the retina. This should bear a more consistent relationship to visual field defect as although the primary visual

reception area is deeply situated along the midline, it has already been shown that it is possible to study amplitude gradients over the surface of the scalp which show some sort of relationship to the part of the field stimulated. This view is expressed by Spekreuse (VEP in Man, 1977). A similar technique as that outlined above has recently been described by Ragot and Rémond (1978) on a normal subject, showing sequential maps at 1 millisecond intervals after a visual stimulus, by using 48 electrodes evenly distributed over the whole head.

At the optical end, it might be possible, with ophthalmological co-operation, to develop a method of stimulating isolated points on the retina by means of optical lenses, so that in the future, a more objective plot of the visual fields was obtainable than by relying on the patient as witness. This could be particularly valuable where the patient's attention span was limited or there was some mental confusion, but at present the VER is no substitute for the conventional methods of visual field plotting.

Further advances may also be made in the study of metabolic disorders or other illnesses affecting the whole system. Although some authors have been using combined electrophysiological techniques for many years (Vaughan and Katzman, Harden and Pampiglione), and obtaining useful diagnostic information by the concurrent view of the ERG, VER and EEG, this practice is by no means common. The division of medical specialty between ophthalmology and neurology should not deter the neurophysiologist from looking at the visual system as a whole, in order to assist in clinical diagnosis and monitoring of treatment.

The employment of combined studies of the ERG, VER and concurrent EEG can assist in the differentiation between many lesions

affecting the visual system from eye to brain, or between an organic and non-organic condition. It can also provide objective evidence of dysfunction in subjects who are unable to co-operate, either young children or for other reasons, but it has to be remembered that the presence of an electrical response does not necessarily mean that the subject perceives the sensation in such a way as to influence behaviour. Also the absence of a response does not necessarily preclude eventual recovery, and in many cases longitudinal studies could be of value, so that the effectiveness of treatment or the progress of the disease may be monitored.

It would appear important in this relatively new technique to keep an open mind about future applications. When the patient presents in person at the clinic, the evidence is a collection of history, symptoms, signs and results of tests. Reports that the VER is abnormal in a certain percentage of cases of a particular disease are of limited value in the clinical situation, as the particular patient may fall into one of the groups of negative findings.

The clinician needs not so much to know that 58% of patients with MS have an abnormal VER, as that an abnormal VER may indicate MS, compressive lesion, ischaemic lesion or metabolic disorder, and that a normal VER excludes none of these.

It may, by its nature, offer further elucidation of the problem, but the final answer is only arrived at by a comprehensive study of all the evidence, clinical and investigative, and possibly follow-up studies in addition.

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