A Study of Short Latency Photically Evoked Potentials in Man

Martin Parsons Rubinstein BSc.FBCO.

Thesis Submitted for the Degree of

Doctor of Philosophy

Clinical Neurophysiology Unit
Department of Ophthalmic Optics
The University of Aston in Birmingham

July 1981

THE UNIVERSITY OF ASTON IN BIRMINGHAM

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SUMMARY

The VEP and ERG are reviewed and a hypothesis is proposed that short latency early components of the VEP may originate in structures of the visual pathway intermediate between retina and visual cortex.

Under conventional conditions for generating and recording the cortical VEP (VECP) these short latency potentials are of inconsistent presentation and a technique has been developed to accentuate a number of early components.

A triphasic complex of early components was detected in 95% of normal subjects and scalp topographical studies revealed this to be of maximal amplitude around the upper mastoid process. The mean latencies (in m.secs.) of the peaks of the complex were P21.0, N26.2, P33.6. Monocular stimulation produced bilateral reduction in amplitude of the complex indicating a post-chiasmal origin and this evidence in conjunction with the scalp site of its maximum amplitude led to its title the "Visually Evoked Subcortical Potential" (VESP).

A topographical study of the ERG showed wide distribution over the face and scalp, but at posterior temporal sites only a vestigial 'b' wave remnant existed in some subjects, the VESP therefore not being a volume-conducted ERG signal.

A subcortical origin for the VESP was confirmed by findings in patients with lesions at selected sites along the visual pathway which showed a) in unilateral retinal detachment, abolition of ERG from the affected eye but bilateral preservation of VESP; b) in unilateral non-demyelinating optic nerve lesions preservation of ERGs but reduction or abolition of VESP and VECP; c) in chiasmal compression, abolition of the VESP contralateral to the stimulated eye; d) in hemianopia of subcortical origin, reduction or abolition of the VESP over the affected hemisphere; e) in hemianopia of cortical origin bilateral preservation of VESP with reduced or abolished VECP over the affected hemisphere.

The VESP may, with further work, supplement the ERG and VECP in ophthalmic electrodiagnosis.

Evoked Potentials; Visual Pathway; Far-Field; Topography; Visual Evoked Subcortical Potential.

ACKNOWLEDGEMENTS

To Professor Graham Harding for introducing me to the subject and for his continued advice, encouragement and help during the work. To Neville Drasdo and Lesley Jones for frequent, useful discussions. To my Father for his expert clinical guidance. To Margaret Geddes and Ann Davies for their speed and expertise in producing the manuscript.

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CHAPTER 1

INTRODUCTION

1.1. GENERAL INTRODUCTION

Electrophysiological examination of the visual system has become an established part of modern neuro-ophthalmic practice, visual function being objectively assessed by the use of the Electroretinogram (ERG) and the Visually Evoked Potential (VEP).

The ERG gives information regarding retinal function in the form of a potential change in response to photic stimulation while the VEP is a measure of the functional integrity of the visual pathways also in the form of electro-potential changes due to photic stimulation.

By combining both methods of examination it is frequently possible to detect and locate lesions at different levels of the visual system with some accuracy.

Such procedures are supplementary to the more conventional and routine clinical methods and are rarely used exclusively. They provide an objective assessment of function and are eminently suitable to situations in which subjective responses are unreliable or other objective observations are in doubt.

Studies of the "resting potential" of animal eyes began in the first half of the nineteenth century (DuBois-Reymond, 1849) and the ERG was demonstrated a few years later (Holmgren, 1865). Some years after this, electrical

currents of the brain were discovered (Caton, 1875) and being distinctly different to the ERG initiated two areas of study. Work in both areas flourished and established the ERG and the so-called Electroencephalogram (EEG) as useful clinical measures of electrical activity. However, the isolation of the VEP from the ongoing EEG was a much later development and in man was first studied by electrophysiologists in the mid 1930's (Adrian and Matthews, 1934). Rapid technological advances aided the understanding of the VEP and by the early 1960's systematic studies were being published. Normative clinical data were gradually established, using rather simple, unstructured flash stimulation which was intrinsically rather crude. Some few years later however, with the introduction of structured stimuli the precision with which the VEP could be generated and analysed was greatly improved and studies of the visual system using the VEP have since become rather more accurate.

The ERG is clearly an overall response from the whole retina and more posterior structures are not involved in its generation. The major portion of the VEP used clinically is generally accepted as reflecting the arrival of afferent volleys at the occipital cortex via the visual afferent fibres, most of the response being generated by the foveal fibres, thus representing a measure of central visual function. However, the concept that the response at the level of the retina frontally and the visual cortex posteriorly are totally isolated

would seem unlikely and indeed proposals have occasionally been made that the initial components of the VEP recorded in the area of the visual cortex might reflect remnants of the ERG being conducted along the visual pathway or independent potentials generated in other parts of the pathway.

Systematic studies of such photically evoked activity generated at sites intermediate between the retina and visual cortex are poorly documented and the work described in this thesis has been an attempt to delineate such activity using scalp electrodes in man. Normative studies have been carried out and scalp distributions of the various photically evoked activities plotted. The behaviour of such intermediate potentials in a variety of focal pathological conditions has been observed, in an attempt to assess the clinical utility of these potentials and as an aid to identifying their origin.

1.2. THE VISUAL PATHWAY AND ORGANISATION OF THE VISUAL SYSTEM

The visual pathway is a sensory tract, and as such conforms to the generalised form of afferent tracts carrying impulses to the brain. It begins at the sentient layer, the retina, and more posteriorly is divided into six parts (Wolff, 1975): the optic nerve; the optic chiasma; the optic tract; the lateral geniculate body; the optic radiation; the visual cortex (Figure 1.2.1.). In the visual system the end-organ is the sensory epithelium of the rods and cones in the retina and the afferent neuron of the first order is the bipolar cell. The second order neurons are the ganglion cells of the retina, the axons of which cross the nerve fibre layer, the optic nerve, chiasma, optic tract and terminate in the lateral geniculate body. The lateral geniculate body serves as a relay-station, from which the third order neurones carrying impulses via the optic radiation to the visual cortex.

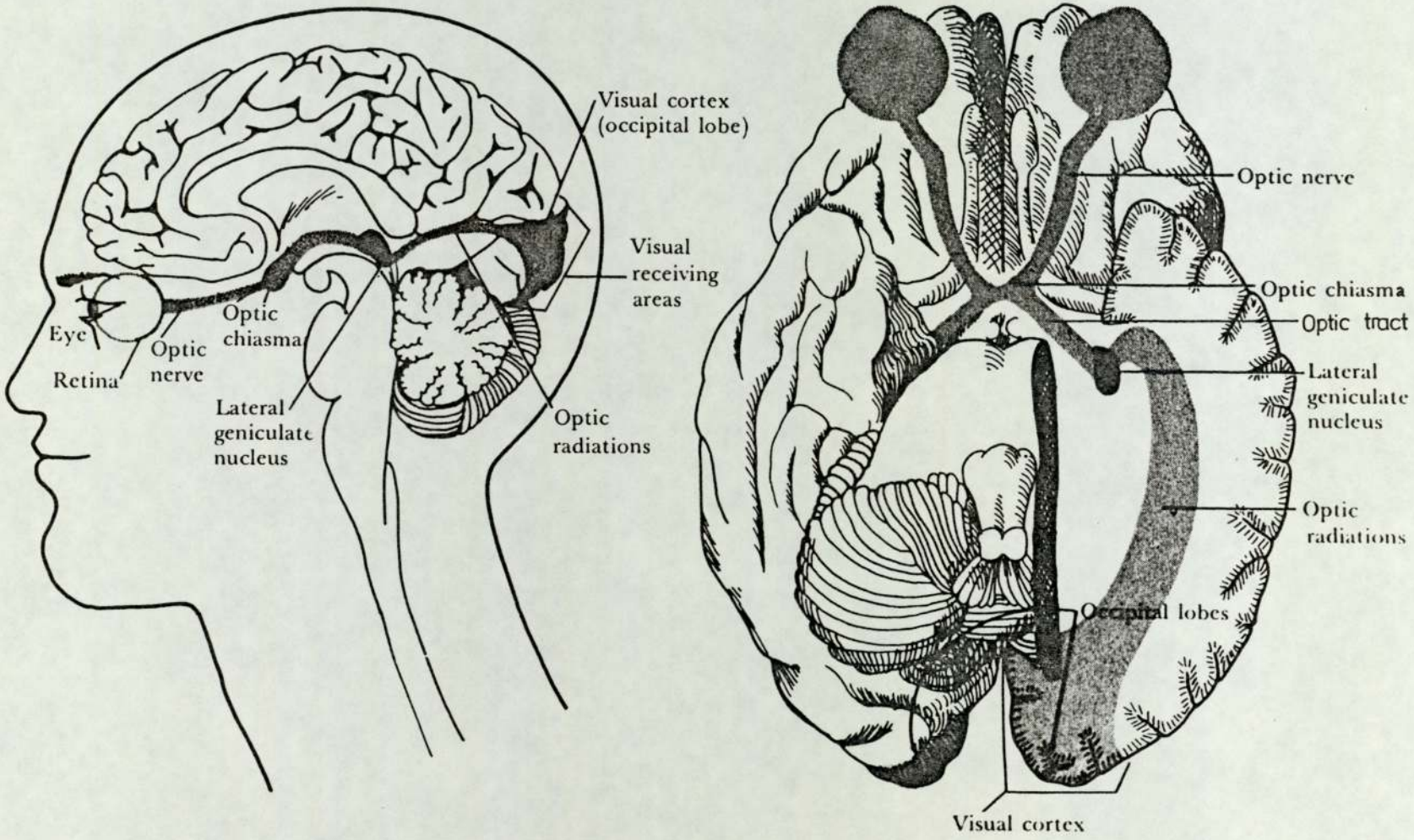
Bruesch and Arey (1942) revealed that about 38% of all fibres carrying information to and from the brain are within the optic nerves.

The Retina

The retina is bounded anteriorly by the vitreous and posteriorly by the pigment epithelium and is firmly secured to the eye only at the optic nerve head posteriorly

FIGURE 1.2.1.

Diagrammatic representation of the human visual pathway (after Lindsay and Norman, 1977)


Visual cortex
(occipital lobe)
Visual
receiving
areas
Optic
radiations
Eye
Retina
Optic
nerve
Optic
chiasma
Lateral
geniculate
nucleus
Optic nerve
Optic chiasma
Optic tract
Lateral
geniculate
nucleus
Optic
radiations
Occipital lobes
Visual cortex

and at the ora serrata anteriorly. The most peripheral portions of the retina are devoid of function, which is remarkable since the histological structure of these areas is similar to that of the remaining retina, except that the elements are smaller and more sparse (Saltzmann, 1912).

During life the retina is transparent and of a purplish red hue due to its content of visual pigment, and it is curious that the orientation of the retina is "inverse" in that light has to penetrate the whole thickness before reaching the photo-sensitive receptors. It is suggested that this is to ensure that the rods and cones are close to the pigment epithelium and the choriocapillaris from which the supply of photo-sensitive pigment is derived (Duke-Elder, 1961).

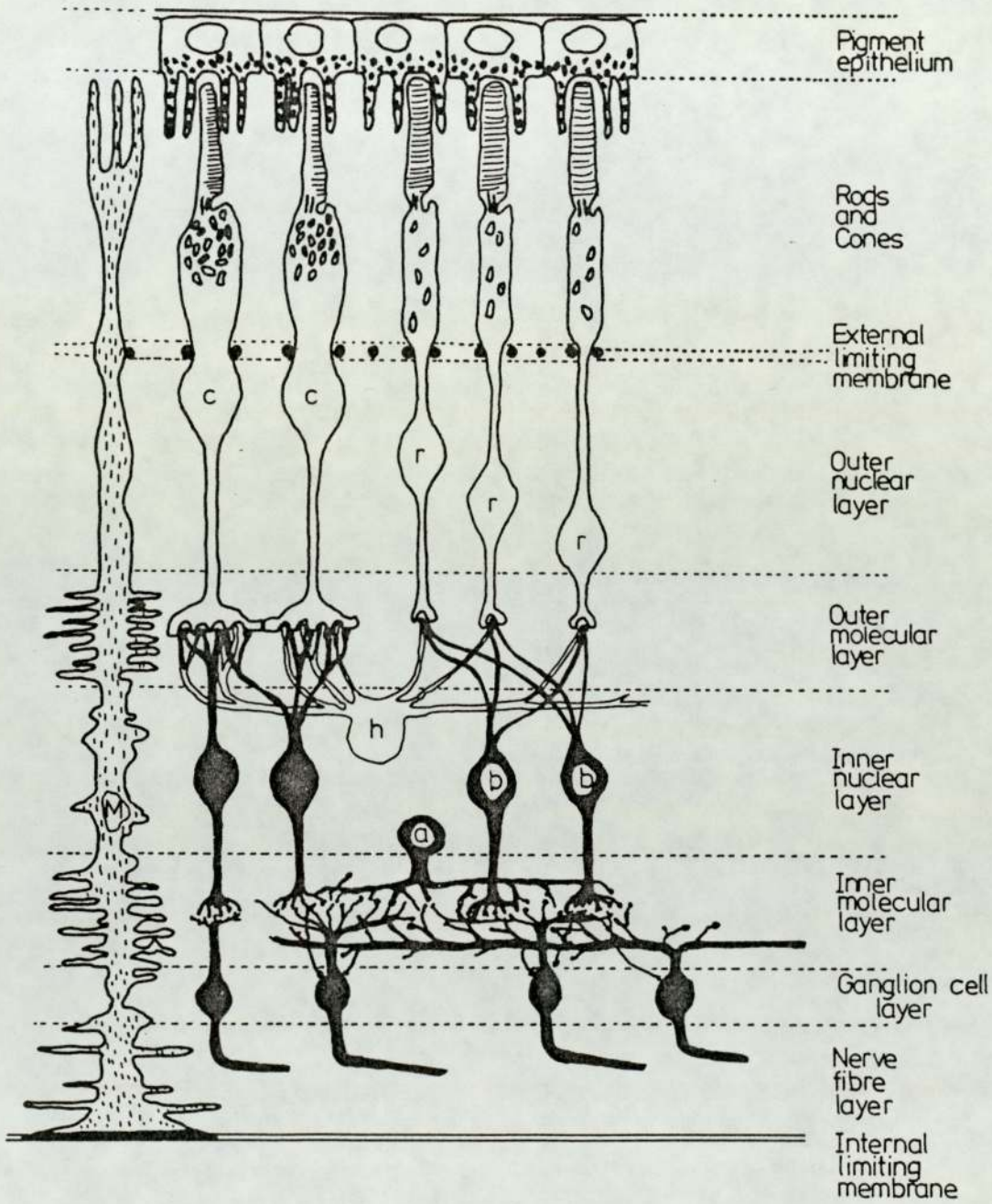
The retina comprises ten distinguishable layers (Polyak, 1957) which from the outside inwards are:

1. The pigment epithelium
2. The layer of rods and cones
3. The external limiting membrane
4. The outer nuclear layer
5. The outer molecular (plexiform) layer
6. The inner nuclear layer
7. The inner molecular (plexiform) layer
8. The ganglion cell layers
9. The nerve fibre layer
10. The internal limiting membrane (See Figure 1.2.2.).

The pigment epithelium is a single, regular layer of cells whose bases are firmly adherent to the choroid. From their apices, numerous processes containing melanin and other pigments extend into the layer between the outer

FIGURE 1.2.2.

Diagrammatic representation of the human retina (see text for details)



c - cone r - rod
h - horizontal cell
b - bipolar cell
a - amacrine cell
M - Müller cell

segments of rods and cones. At the optic disc (where the optic nerve enters the globe) the pigment epithelium does not reach as far as the choroidal basal lamina and the cells may be depigmented in appearance, producing the so called 'choroidal ring' around the edge of the disc.

The palisade of thin rods and thicker cones constitutes the true receptive part of the retina and lies just outside the external limiting membrane of the retina, their cell bodies lie just internal to it. The more fragile outer segments of the rods and cones contain hundreds of protein plates separated by lipid membranes. The photosensitive pigments rhodopsin and iodopsin responsible for absorption of the light stimulus are contained in these segments. The inner segments appear thicker and contain an abundance of mitochondria packed into a zone called an ellipsoid. The ellipsoids are larger in cones than rods and this gives the receptors their characteristic and different shapes. The mitochondria content of the ellipsoid suggests that they are the 'power generators' of the photo chemical stimulus into a neural discharge.

The external limiting membrane is described by Wolff (Wolff, 1975) as having the form of 'wire netting' since it comprises a membrane consisting of a series of cytoplasmic strands separated by large fenestrations, the fenestrations taking up a larger area than the strands themselves. It is through the fenestrations that the processes of the rods and cones pass.

The outer nuclear layer consists of the rod and cone nuclei. Since the cone fibres are short their nuclei usually lie immediately adjacent to the external limiting membrane, but the nuclei of the larger rods lie further within the outer nuclear layer. The fibres of the rods and cones continue beyond the nuclei ending in the outer molecular (plexiform) layer. The terminations of the rods and cones differ in that the rod has a small 'knob' at its end, while the cone has a larger end with several lateral processes or feet.

The rods have long been correlated with scotopic vision and the cones with photopic vision (Duke-Elder,1961) and since both types of sensory receptor are possessed in man, the type of retina is often described as being of a 'duplex' nature (Davson, 1972). Photopic vision is characterised by low sensitivity, high acuity and colour vision, whilst scotopic vision is characterised by high sensitivity, low acuity and absence of colour vision and thus the proportion of rods and cones in an area of retina determine its threshold in relation to these parameters.

The processes of the Horizontal cells and Müller fibres make up the remainder of this layer and a fine interlacing synaptic network between the components and the processes of the rods and cones is established.

Within the inner nuclear layer are several types of cells, namely the sensory Bipolars, the Horizontal cells, the

Amacrine cells, the nuclei of the Müller fibres and capillaries of the central retinal vessels. The bipolar cells are the first order neurones and have their synapses with the dentrites of the ganglion cells in the inner macular (plexiform) layer. The horizontal cells are flat and have processes directed horizontally, paralleling the retinal surface. As such, they have synapses with the rod and cone cells giving horizontal connections and also have certain metabolic functions. The Amacrine cells, of which there are five types, have a simple shape and a single process passing inwards and ending in the inner molecular (plexiform) layer, some of the cells making direct contact with the fibres of the optic nerve. The processes of these cells also have a horizontal orientation and provide similar horizontal associations between adjacent rods and cones.

The inner molecular (plexiform) layer consists of the end portions of the bipolar cells and the dendrites of the Ganglion cells. Also, in this layer are the distal processes of the amacrine cells, Müller fibres and capillaries of retinal vessels.

The cells of the Ganglion cell layer are distinctive in having abundant cytoplasm to serve the long axons which they possess, extending back to the brain. There are five types of these cells, which constitute the second order neurons of the visual pathway and it is only their cell bodies which are actually included in this layer.

Accompanying these cell bodies are further parts of the Müller fibres, neuroglia and further retinal capillary branches.

The axons of the ganglion cells are found in the nerve fibre layer, tightly packed and non-myelinated (although occasionally they may be seen in a myelinated form around the optic disc) and leaving the globe via the lamina cribrosa and then the optic nerve. The fibres are arranged in parallel-running bundles and anastomose with each other forming a network amongst which are the 'feet' of the Müller fibres. The Internal Limiting Membrane is an optically homogeneous layer between retina and vitreous covering the entire inner surface of the retina except at the disc.

The Müller fibres which have been described as passing through all layers of the retina from Internal to External limiting membranes are considered as providing mechanical support to the retina and serving to hold the retinal layers together (Cogan, 1976). Metabolic functions are also suggested for these fibres (Kuwabara and Cogan, 1961). The Macula Lutea (yellow spot) is a shallow ill-defined oval depression at the posterior pole of the eye, lying temporal to and having approximately the same size as the optic disc and is supplied with an abundance of ganglion cells in laminar arrangement. At its centre is the fovea, being about the size of a pin-head and is formed anatomically by the local attenuation

of the inner layers of the retina. This is the thinnest part of the retina since there are no Müller fibres, ganglion cells or bipolar cells and the axons of the photoreceptors assume a skewed orientation by radiating obliquely rather than vertically, being given the special name, Henle's layer (Henle, 1866).

There are no rods at the fovea, only cones, and these are more slender and longer than elsewhere in the retina. In the retina generally large numbers of rods and cones are connected to each ganglion cell, but the cones at the fovea are individually connected to simple ganglion cells and this results in the impulse being generated and the signal received by the brain being much clearer from this area. Graham (1965) suggests that there are about 100,000 single receptor channels within the fovea, which, covering approximately the central 2^{o} of the visual field is the point of most acute vision.

The retinal nerve fibres arising from ganglion cells nasal to the optic disc pass directly to it, but on the temporal side are arranged differently. The fibres from the macular area from a spindle-shaped bundle - the papillo-macular bundle, which comprises one-third of all retinal fibres (Reed and Drance, 1975) and corresponding to that part of the visual field known as the centro-caecal area lying between the blind-spot and the fixation point. A horizontal raphé exists between fovea and

the temporal periphery and is a functional boundary between the superior and inferior retinal halves.

Four different retinal quadrants - upper temporal, lower temporal, upper nasal and lower nasal - may be considered from the anatomical viewpoint. An imaginary vertical line bisecting the fovea results in nasal and temporal hemi-retinae, and an imaginary horizontal line bisecting the fovea results in upper and lower hemi-retinae. In each of these four quadrants there are also fibres subserving central vision from the appropriate parts of the macula and fovea. This is a useful sub-division in visual field assessment, although it differs from the conventional ophthalmoscopic division of the retina into its quadrants by lines bisecting the centre of the optic nerve head.

The Optic Nerve

In man there are approximately 1 million axons leaving the eye, (Arey and Bickel, 1935 and Oppel, 1963) as the optic nerve, which has been described as a solid cylindrical mass which is extensively penetrated by many tunnels (Cohen, 1967), extending from the globe anteriorly to the chiasma posteriorly via the optic foramina at the rear of the orbit. Its length in toto is of the order of 5 cm. and its intracranial diameter between 4 - 7 mm.

Having passed through the lamina cribrosa at the optic

disc in an unmyelinated form the fibres then acquire a myelin coating. The sheaths of the optic nerve are continuous with the meninges of the brain and are composed of a mixture of collagenous and elastic tissue which also make up the septa of the meshwork of the nerve.

In addition to the visual fibres in the optic nerve there are pupillary, autonomic and probably centrifugal fibres. The anatomical evidence concerning efferent fibres to the retina has been reviewed by Granit (Granit, 1947) who considers the positive evidence overwhelming, although there is not complete agreement on this subject.

The distribution of axons within the optic nerve is important. The papillo-macular bundle enters the temporal edge of the optic nerve head and this is therefore its initial position in the nerve, but the macular fibres gradually sink towards the centre of the nerve after the first centimetre or so along its length with the peripheral fibres being distributed around them (Figure 1.2.3.).. The extramacular temporal fibres enter the nerve both above and below the papillomacular bundle and the nasal fibres tend to be concentrated in the nasal side of the nerve. Proceeding posteriorly towards the chiasma a 45 degree nasal rotation of the location of the peripheral fibres develops such that on entering the chiasma the inferior nasal fibres originally lying on the inferior nasal side of the nerve now lie in the whole of the inferior aspect of the nerve (Figure 1.2.3.)..

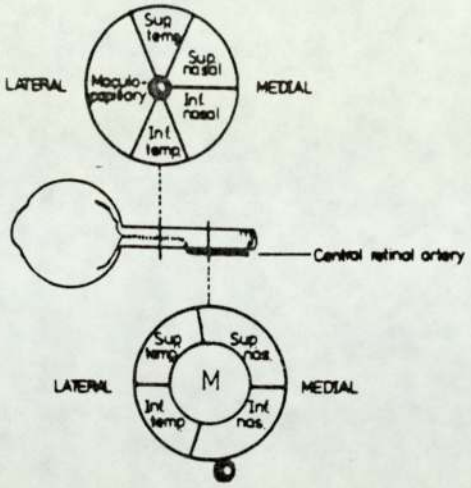
FIGURE 1.2.3.

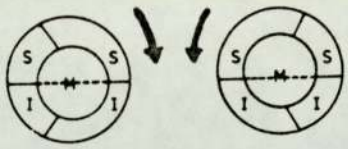
Diagrammatic representation of afferent fibres in different regions of the human visual pathway (see text for details)

M = maculo-papillary fibres

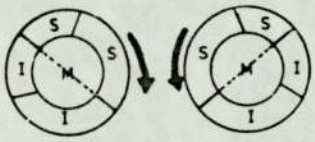
I = inferior fibres

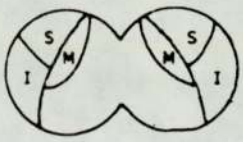
S = superior fibres



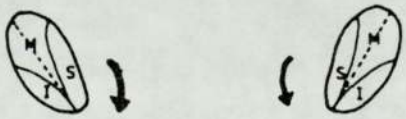


Optic nerve



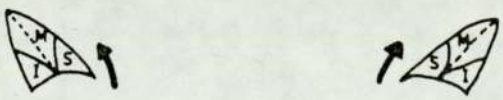


Chiasma



Optic tract

Lateral geniculate body



Optic radiation

The Chiasma

The two optic nerves unite at the chiasma which is a flattened tablet-like structure some 12 mm. in transverse diameter and 8 mm. from front to back. Its position is extremely variable (Whitnall, 1921) and accounts for variations in visual field defects produced by tumours in this area. In the majority of cases it lies above the pituitary fossa, such that a part of the fossa is in front of it, and generally does not actually rest upon the structures beneath it, but is separated from them by the basal cistern of the subarachoroid space which constitutes between 1 to 10 mm. (Traquair, 1916 and Cope, 1916). It has been suggested that the position of the chiasma may be related to the shape of the skull (Walsh and Hoyt, 1969).

The chiasma is unique in that it is the site at which half the information output from each eye crosses to the contralateral optic tract emerging from the chiasma. The nerve fibres from the nasal half of each retina cross to mix with uncrossed fibres from the temporal half of the retina of the other eye. Some of the more inferior peripheral decussating fibres form a short loop which extends into the optic nerve of the opposite side, before passing backwards into the optic tract, forming the anterior Knee of Wilbrand, and some of the superior peripheral decussating fibres form a similar loop passing a short distance into the optic tract of the same side,

before crossing, forming the posterior Knee of Wilbrand (see Figure 1.2.4.).. The macular fibres decussate in a similar manner, in the postero-superior part of the chiasma (Hoyt and Luis, 1963).

The fibres from the temporal parts of the retina do not decussate, but continue backwards through the chiasma into the ipsilateral optic tract. According to Kupfer, Chumbley and Downer (1963) the ratio of crossed to uncrossed fibres is about 53 to 47, indicating a slightly higher proportion of uncrossed fibres in the human visual system than previously reported.

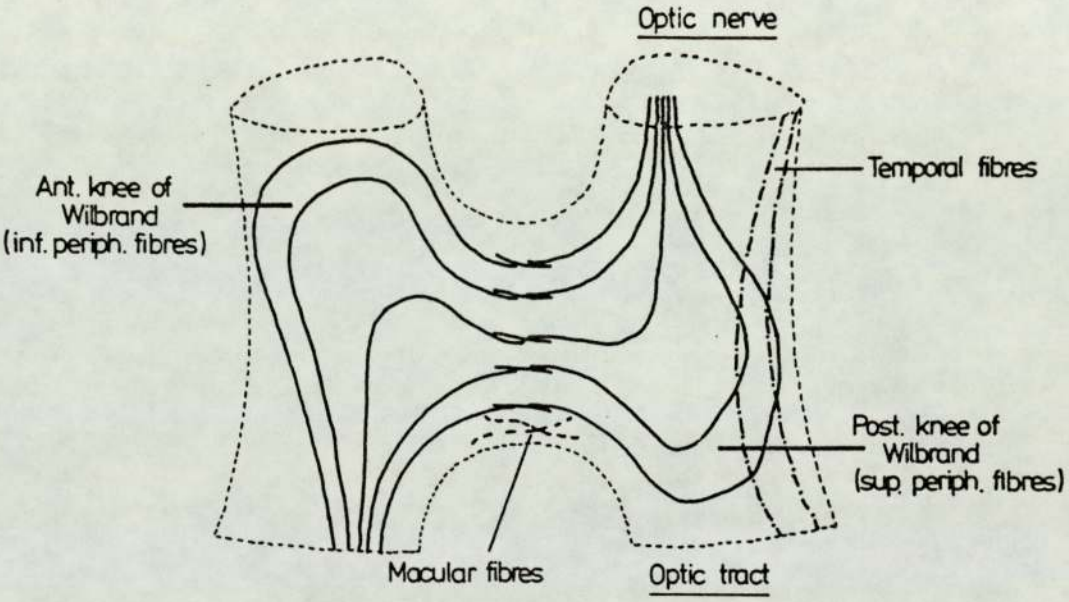
The Optic Tract

The optic tract extends from each postero-lateral corner of the chiasma to the lateral geniculate bodies posteriorly. It has the form of a flattened band, and is composed of fibres from the ipsilateral temporal retina and contralateral nasal retina, the uncrossed fibres lying dorso-laterally and the crossed fibres lying ventro-medially. The macular fibres lie on the medial chiasma, but as they pass backwards along the tract assume a more dorsal position (Figure 1.2.3.) and the fibres from the inferior quadrants of the retina rotate medially, while those from the superior quadrants simply rotate to become situated laterally in the tract. As the nerve fibres pass backwards, those from corresponding areas in the two retinae become more closely associated until

FIGURE 1.2.4.

Diagrammatic representation of nerve fibre arrangement within the chiasma (after Wolff, 1975).

Nerve fibres from the nasal half of each retina cross to mix with uncrossed fibres from the temporal half of the retina of the other eye. Some inferior peripheral decussating fibres form a short loop (Anterior Knee of Wilbrand) passing forward to the optic nerve of the opposite side. Some of the superior peripheral decussating fibres form a similar loop (Posterior Knee of Wilbrand) passing into the optic tract of the same side before crossing. Macular fibres decussate in the postero-superior part of the chiasma.


Optic nerve
Ant. knee of Wilbrand (inf. periph. fibres)
Temporal fibres
Post. knee of Wilbrand (sup. periph. fibres)
Macular fibres
Optic tract

in the lateral geniculate bodies an accurate relationship is established.

The Lateral Geniculate Body

When the optic tract reaches the postero-lateral aspect of the thalamus it splits into two - 1) a lateral and larger portion ending in the lateral geniculate body , 2) a small medial portion ending in the medial geniculate body. The visual pathway fibres are in the lateral route. Brindley (1970) proposed that about 80% of the visual fibres from the optic tract enter the lateral geniculate body itself, the rest passing through or round it to reach the surface of the pulvinar and superior colliculus.

The lateral geniculate body is part of the thalamus and marks the termination of the second order neurone. It constitutes a neuronal relay station since it is the only synapse between the retina and the visual cortex. It is a small, rather triangular shaped body appearing on the postero-lateral part of the pulvinar of the thalamus. Its name - geniculate or 'knee-like' - is derived from the fact that its appearance is such that it is bent up upon itself, its dorsal surface being convex medially and concave laterally. The optic tract fibres enter at its antero-ventral surface and efferent fibres (in the optic radiation) leave at its dorsal surface.

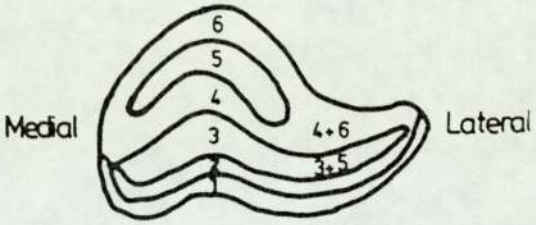
Within the lateral geniculate body are six laminae of cells which are numbered from 1 to 6 from within outwards (Figure 1.2.5.). Layers 1 and 2 contain large cells (the magnocellular layers) and the other layers contain smaller cells (the parvocellular layers), (Duke-Elder, 1961). Laminae 1, 4 and 6 receive inputs from crossed nerve fibres and laminae 2, 3 and 5 receive inputs from uncrossed nerve fibres (Figure 1.2.5.) (LeGros Clark, 1949). Each retinal point is represented in several laminae (Kupfer, 1962) and small corresponding areas of the retinal of the two eyes are represented in a linear manner in all six laminae of one lateral geniculate body. In effect, the projection from the retina on the lateral geniculate body is not 'point-to-point', but rather each point area in the retina is represented by a wedge-shaped area in the lateral geniculate body, thus producing a 'point-to-sector' representation (Duke-Elder, 1961). Each nerve on entering its laminae divides into a number of extensions, each ending in a 'bouton' (Davson, 1972), which is applied to a lateral geniculate body cell, each cell having only one bouton applied to it.

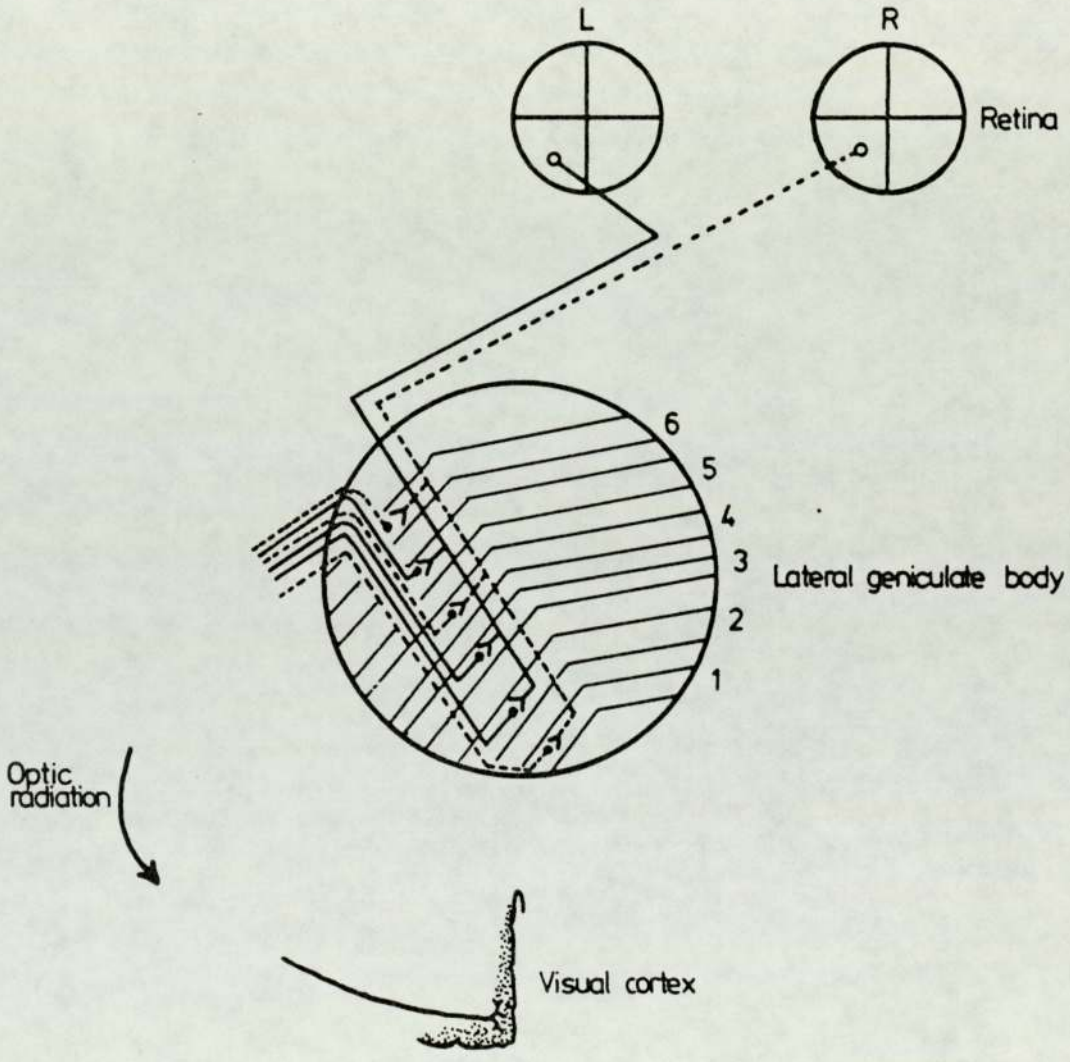
Synapses are made via the lateral geniculate cells with the terminations of the optic radiation fibres. The complexity in fine structures of the lateral geniculate body tends to suggest that it serves more function than simply a neuronal 'relay-station' and there is strong evidence (Snodderley, 1972) that it is actively involved

FIGURE 1.2.5.

Diagrammatic representation of the human lateral geniculate body

The upper part of the figure illustrates the laminar arrangement of the right lateral geniculate body as viewed from behind. The lower part of the figure illustrates the neuronal connections and relations within the lateral geniculate body (see text for details)


6
5
4
3
Medial
4+6
3+5
Lateral


L
R
Retina
6
5
4
3
2
1
Lateral geniculate body
Optic radiation
Visual cortex

in colour processing.

The Optic Radiation

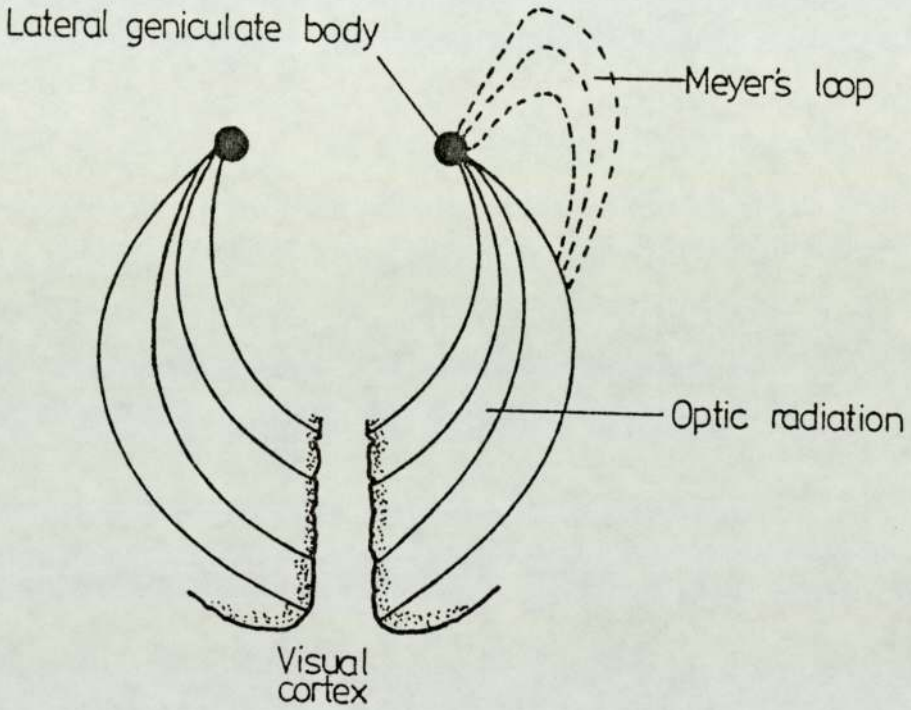
The new relay of fibres that carries impulses from the lateral geniculate body to the striate cortex of the occipital lobe is termed the optic radiation. After leaving the lateral geniculate body the optic radiation ascends for a very short distance in the retrolentiform portion of the posterior limb of the internal capsule. Temporal rotation of the component bundles of fibres in the optic radiation occurs such that the previous nasal rotation of the fibres which occurs between the eye and the lateral geniculate body is now corrected (Figure 1.2.3.). Meyer (1907) showed that the inferior bundle of fibres swings anteriorly towards the pole of the temporal lobe while arching over the inferior horn of the lateral ventricle (Meyer's loop), although the degree of anterior looping of fibres is considerably variable between individuals (Figure 1.2.6.).

The superior bundle of fibres carries impulses from the medial group of cells in the lateral geniculate body, conveying information from the extramacular area of the corresponding upper quadrant of each retina to the visual cortex above the calcarine fissure and the anterior end of the post-calcarine fissure. The middle bundle (constituting nearly half the total number of optic radiation fibres) conveys macular impulses to the

FIGURE 1.2.6.

Diagrammatic representation of Meyer's Loop

The inferior bundle of fibres in the optic radiation loops anteriorly before passing backwards from the lateral geniculate body to the visual cortex.


Lateral geniculate body
Meyer's loop
Optic radiation
Visual cortex

posterior pole of the occipital lobe and ending both above and below the post-calcarine fissure. The inferior bundle ends in the visual cortex below the post-calcarine fissure.

Within the occipital lobe the optic radiation is spread out in a dorso-ventral direction so that its lower margin lies close to the inferior surface. The fibres leave the radiation abruptly and at right-angles and run medially in the white matter of the striate area before entering the grey matter to reach their terminations.

The Visual Cortex

The occipital lobes comprise the posterior portions of the cerebral hemispheres. According to one popular convention devised by Brodmann (1909), each lobe may be divided into 3 areas namely Brodmann's areas 17, 18 and 19 according to the cellular organisation of each area.

Mapping of the human visual cortex first became possible (Holmes, 1919), after the First World War in healthy brain-injured adults and later in patients in whom visual field defects could be related to cortical damage defined at post-mortem (Holmes, 1931). Studies were performed during the Second World War by Spalding (1952a, b) who produced similar cortical 'maps' and gave the first estimate of cortical area associated with the central $8 - 10^{o}$ of the visual field. Brindley and Lewin (1968)

devised a new approach by the implantation of an array of electrodes and separate stimulating circuits over the calcarine cortex in a blind subject, results produced being remarkably consistent with the previously established visual maps.

The visual projection area (Area 17) is situated along the superior and inferior lips of the calcarine fissure and extends around the posterior pole of the hemisphere for a distance of 1 - 1.5cm.

The cell bodies of the cerebral cortex are arranged in layers separated by relatively cell-free areas containing mainly the dendritic and axonal processes of the cells and on the basis of differences in appearance of these layers, the visual cortex is divided into cyto-architectonic areas, the most distinctive area being that which in section reveals a myelinated band, the line of Genari from which the area gets it other name, the striate cortex. This is Brodmann's Area 17.

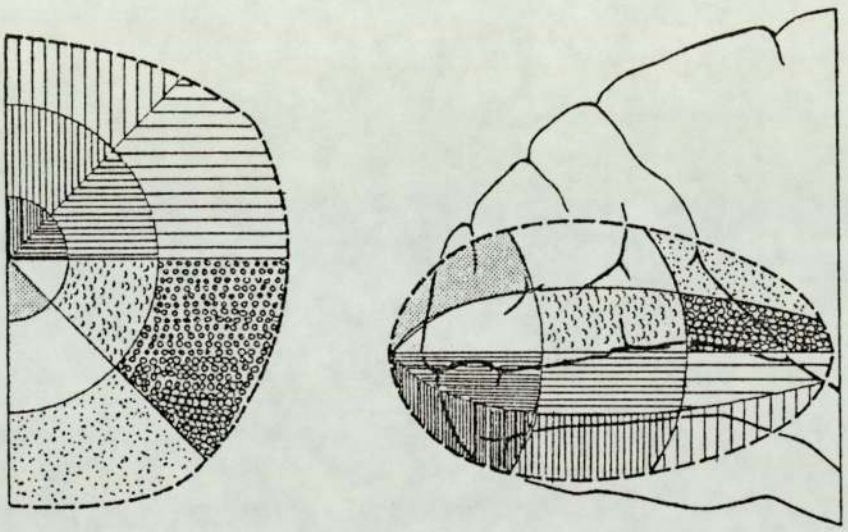
Area 18, the Parastriate area, lies just outside Area 17 while Area 19, the pre-striate area separates Area 18 from the parietal and temporal lobes.

The basic pattern of visual field representation is well known (Figure 1.2.7.). The macula is represented at the occipital pole in a wedge-shaped area, extending slightly onto the lateral surface of the occipital lobe,

FIGURE 1.2.7.

Diagrammatic representation of visual field projection at the cortex
(Guillery, 1976)

The visual field representation is shown as it would appear if the cortex within the calcarine fissure were flattened out on the surface of the brain. The lower field is represented in the upper banks and the upper field in the lower banks.



with the apex of the wedge being 2 - 3 cm. anterior to the occipital pole. The retinal periphery is represented further anteriorly within the calcarine fissure, the upper fields below the fissure and most of the lower fields above the fissure (Spalding, 1952a,b).

The primary visual stimulus is received at Area 17, Area 18 probably serving to integrate visual impulses and Area 19 serving as co-ordinator of visual impulses with other sensory and motor activities (Cogan, 1976). The central macular area has a disproportionately large cortical representation. The magnification factor (i.e. the number of millimetres of visual cortex per degree of visual field) is roughly proportional to the ganglion cell density in the corresponding portion of retina (Whitteridge, 1973) and is therefore largest for the central foveal region of the retina, decreasing with increasing retinal eccentricity.

Visual field plots following suprageniculate lesions have repeatedly shown that the macular area tends to be spared more commonly than other regions and this may be partly due to the relatively large macular representation. The concept of 'macular sparing' remains an enigma - one proposal suggests projections from one lateral geniculate nucleus to both hemispheres (Duke-Elder and Scott, 1971), whilst others argue that a differential blood supply to different parts of the optic radiation may account for

the phenomenon (Stephens and Stilwell, 1969).

Conclusion

The visual pathway is clearly a complex system and investigations into the fundamental problems and mechanisms of the eye, pathway and vision per se are dependent on a thorough understanding of the structure (and function) of the constituent portions of the system. In any clinical determination of the localisation of lesions of the visual pathway or indeed in the localisation of sources of photically evoked potentials, an accurate knowledge of the disposition of the afferent visual fibres is of the utmost importance.

1.3. HISTORICAL OVERVIEW

Bioelectric potentials were recognised as early as 2000BC by Egyptian society when discharges from "electric" fish were accidentally encountered by children (Ripps, 1978). More systematic approaches to electrophysiology paralleled the studies of electric circuitry itself and the experiments of Benjamin Franklin in the 1760's with lightning potentials and his accidental demonstration that the human body received an electric shock when placed in contact with a charged Leyden jar, led towards a more scientific interest in bioelectric phenomena in the latter part of the eighteenth century. In 1791, Luigi Galvani published a paper reporting experiments on frog legs - the nerve of a partially dissected frog was connected to a lightning rod with one wire and its foot was grounded with another wire, and he observed that the leg muscles contracted whenever there was a flash of lightning, thus establishing a definite connection between electrical currents and muscular contraction. Similarly he found that contraction of the muscle could be initiated when the circuit from foot to nerve was completed with two wires of different metals (Galvani, 1791). His experiments although demonstrating that animal tissue may be stimulated by an electric current did not actually prove that the tissue produces a current. He had however demonstrated the first moist battery using two metals and the frog's tissues providing the electrolyte and he introduced the term "Galvanic Current" to describe the

phenomenon. Volta (cited by Boring, 1942) demonstrated between 1792 and 1800 that a brine-soaked piece of paper could be substituted for the frog muscle and an electric current would still flow through the wires provided that they were dissimilar metals and the development of the voltaic pile followed in 1800. However, an anonymous publication (cited by Brazier, 1968) three years after Galvani's original contribution described muscle contraction in the absence of metals. The first galvanometer was made in 1811 and the first one sensitive enough to be practicable for measurement in 1821 (Boring, 1942). Johannes Müller in 1834 dismissed the ancient theory that nervous conduction was related to animal spirits and suggested an electrical origin on the basis that the speed of the impulse was too rapid even to be measured (Müller, 1834). Matteucci (1841) showed that a galvanometer indicated a current when connected between the surface of a muscle and a wound in the muscle, a current which he later called the 'current of injury' or the 'current of rest', for it flowed without observable muscular contraction.

The Electroretinogram

The cornerstone of electrophysiological research in ophthalmology was laid in 1849 by DuBois-Reymond, professor of physiology in Berlin. In his study of potentials from various parts of the nervous system he discovered that the eye demonstrated a potential

difference between its anterior and posterior surfaces and this led to the concept of the 'resting potential' of the eye (DuBois-Reymond, 1849). Using a simple galvanometer with one electrode in contact with the cornea and one on the optic herve he found that the anterior surface was positive with respect to the posterior surface and measured a potential difference of 6 millivolts between anterior and posterior poles of an enucleated tench eye. The 'resting potential' was most easily seen in fish, but would also be seen in frogs and turtles. It was not until sixteen years later that a Swedish physiologist, Frithiof Holmgren, conducting similar experiments on intact and enucleated frog eyes, showed that using a recording procedure similar to that of DuBois-Reymond, the 'resting potential' could be modified by the action of light shining on the eye. His galvanometer gave one deflection when the eye was illuminated and another when the light was cut off (Holmgren, 1865). He had described what is now known as the Electroretinogram (ERG). Apparently unaware of Holmgren's work, Dewar and McKendrick were carrying out similar experiments in Edinburgh (Dewar and McKendrick, 1873 a,b,c). The sudden admission of light into a frog eye produced a small deflection on the galvanometer with a pair of electrodes on anterior and posterior poles of the eye, indicating that the cornea had become positive relative to the posterior pole, the galvanometer drifting back to its original position when the light was extinguished. It was soon discovered that the same responses could be initiated in the intact organism under

a form of anaesthesia, and they showed that the response to light could also be recorded between the cornea and the exposed brain, allowing the eye to be left in situ. Dewar (1877) found that the same electrical changes could be recorded in frogs using a wire electrode placed on the cornea and a reference electrode inserted into a small abraded area in the skin of its back or indeed any other part of its body. In the same publication he described his observations (and in fact the first ever to be published) on the human eye - a clay trough filled with saline was constructed around the orbital margin and into this solution was placed one of the electrodes, the other electrode being placed in a second saline-filled trough into which one of the hands was placed. His recordings were poor and subject to considerable eye movement artifact. He concluded that his method was "too exhausting and uncertain to permit quantitative observations being made".

At this time it was generally thought that the ERG and the 'resting potential' were related. Holmgren (1880) mapped out the spatial distribution of the 'resting potential' of the enucleated frog eye, showing that the largest voltage existed between opposite poles of the eye and between other areas of the eye no difference in potential was measurable. Kühne and Steiner (1880) demonstrated that the direction of the current was from the back to the front of the eye via the vitreous and a year later succeeded in recording from across the isolated retina, indicating that the retina was polarised

(Kühne and Steiner, 1881). The early view that the ERG was simply an increase in the 'resting potential' due to light, gradually changed and reports that the 'resting potential' of an excised eye could rapidly diminish and eventually change polarity but that the response to illumination recorded simultaneously did not reduce or change sign, suggested independence of the two potentials (Kühne and Steiner, 1881).

By far the biggest problem in the early development of electroretinography was technical and advances in instrumentation produced rapid advances in the research into the ERG. After attempts to partially automise the recording technique (Dewar and McKendrick, 1873 a,b,c), a major and important technical advance was made by Gotch (1903). Earlier workers had stimulated the eye using a candle or sunlight but Gotch used an arclamp which allowed much more control over the illumination. He also introduced the use of the capillary electrometer instead of the galvanometer which because of its more rapid response rate permitted a more accurate recording of the ERG. A complex apparatus was constructed incorporating a photographic mechanism to produce a permanent detailed record of the waveform with a simultaneous time scale, and recordings showing several of the now characteristic features of the ERG were published, for example the high amplitude positive deflection preceded by a very much lower amplitude negative deflection.

The invention of the string galvanometer (Einthoven, 1903) enabled more delicate and precise recordings to be made and Einthoven and Jolly (1908) working on frogs were the first to show the presence of three distinct components to the ERG, termed "a", "b" and "c" substances and hence their work formed a firm basis for subsequent researchers. With the introduction of the valve amplifier an increased range of sensitivity was introduced and was first used for ERG recording by Chaffee, Bovie and Hampson (1923) who produced extremely well defined recordings and demonstrated the superimposition of ripples on the basic response, mainly on the "b" wave. These oscillations had been noted previously by Einthoven and Jolly (1908) but their suspicion that they might be artifactual led to their exclusion from the analysis. Similar oscillations had also been seen by Fröhlich (1914) who, working on cephalopods, noted that their frequency increased with increase in flash stimulus intensity. Progress in human recordings was still slow and responses could only be obtained when conditions were favourable, great difficulties being encountered due to artifacts related to corneal sensitivity and eye movements. Kahn and Lowenstein (1924) began more serious attempts at human recordings but still presented a rather pessimistic viewpoint. Hartline (1925) used a more sophisticated version of Dewar's corneal electrode by enclosing a conducting fluid in tightly sealing goggles around the eyes. He was able to produce much more consistent responses by making the subject as comfortable as possible and showed clearly that human

responses were of similar outline to other vertebrates. In addition, he proved that the response from intact eyes was identical to that from excised eyes and that the response amplitude increased (as in other species) with increased stimulus intensity. Sachs (1929) used a 'wick-type' electrode placed in light contact with the limbus and in conjunction with the use of local anaesthesia found that longer recording sessions were possible.

By this stage an ERG waveform could be accurately recorded and analysed and it was clearly recognised that although the response was recorded via the cornea it reflected retinal activity. Investigations into the precise retinal origins of the various components were inevitable and by far the greatest contributor to electrophysiological research on the retina during this century was Ragnar Granit, whose numerous publications are best summarised by referring the reader to his classic text "Sensory Mechanisms of the Retina" (Granit, 1947).

Recordings of the human ERG became more common (Cooper, Creed and Granit (1933) and Groppel, Haas and Kohlrausch (1938). with the improvements in technology - the use of the directly coupled DC amplifier was introduced (Karpe, 1945) in conjunction with an oscillograph, recording being made with the subject enclosed in an electrically shielded room to minimise artifact. Riggs (1941) reported the use of a silver disc electrode embedded in a haptic contact lens filled with physiological saline and

with a painted fixed-size entrance pupil to control the amount of light entering the eye. A reference electrode consisting of a cup filled with saline was fixed to the skin over the cheekbone. This arrangement allowed recordings to be performed over a period of 1 hour or more. Karpe (1945) described a similar method of recording, eliminating much of the interference due to background noise. In recent years numerous further technical improvements have been made - the use of the superimposition technique for direct recording of an average waveform and the present use of computers has simplified and improved the clinical technique.

An International Society for Clinical Electroretinography (ISCERG) was founded in 1962 and standards for Clinical Electroretinography established. Advances in the clinical use of the ERG over the past 20 years have been immense but the author regards a description of these to be beyond the scope of this thesis. The reader is referred to the texts of Armington (1974); Galloway (1981) and Babel, Stangos, Korol and Spiritus (1977).

The Visual Evoked Potential

Although photically evoked electrical activity of the eye has been studied for some 130 years in animals and almost 100 years in man, that of the brain and the visual pathway has a considerably shorter history.

In a communication to the Royal Society in 1874, David Ferrier presented a paper entitled "The Localisation of Function in the Brain" in which he recorded the effects on animals of ablation by cautery and of electrical stimulation of the cerebral cortex. He mapped out those areas of the cerebral cortex which gave focal movement on electrical stimulation of the cortex and noted how these corresponded to the sites of paralysis following ablation of specific cortical areas (Ferrier, 1874). This was followed by two further follow-up papers both entitled "Experiments of the Brain of Monkeys" (Ferrier 1875a, b) and it was Ferrier's first paper which led Richard Caton to imagine that electrical currents might be detected in the brain even at rest.

In February 1875 Caton presented a report of some of his work on the electrical activity of the nervous system to the Medical Institution of Liverpool in a paper entitled "On the electrical relations of muscle and nerve" and also gave a demonstration of the effects he had described. The work was performed on frogs and he showed muscle currents evoked by stimulation of nerve as well as by direct stimulation of the frog's triceps muscle and how the passage of a constant current could increase or decrease excitability in a nerve. The first report of electrical activity in the brain was given later that year (Caton, 1875) at the Annual Meeting of the British Medical Association in a paper entitled "The Electric Currents of the Brain". In this extremely

short paper a vast amount of information was communicated. Caton experimented on the brains of rabbits and monkeys and proved conclusively that in all animals studied, the galvanometer used indicated the existence of electric currents, the external surface of the grey matter being positive relative to the surface of a section through it. He concluded that the currents of the grey matter were related to its function and indeed he concluded his paper by stating that the currents of a rabbit's brain which Ferrier had previously shown to be related to eye-lid movements were also markedly influenced by stimulation of the opposite retina by light. His technique of localisation of sensory function being so conclusive overshadowed another major contribution to his paper - he described the placement of electrodes at two points on the external surface or one electrode on the grey matter and one on the surface of the skull and the demonstration of "feeble currents varying direction" - this was spontaneous electrical activity of the brain (later called the electroencephalogram). Two years later he published a much fuller account of his work on cats, monkeys and rabbits, describing experiments principally directed towards sensory localisation (Caton, 1877). He demonstrated that the current became feebler if both electrodes were applied to the external skull surface, that the strength of the current varied at different points, that the current was in constant fluctuation and that it usually fell to near zero after death. A point was found on the posterior lateral part

of the cerebral hemisphere in which variation of the current occurred when the retina was stimulated by a bright light. This he observed in three out of seven rabbits examined. A similar experiment to localise a variation due to auditory stimulation by a loud bell produced no results and he reflected that the rather unproductive outcome of his experiments on sensory stimuli was due to problems of swelling, congestion and haemorrhage of the exposed brain producing an accompanying disturbance of the electrical currents.

After ten years of further work, Caton reported his findings at the Ninth International Medical Congress in Washington. Having applied his electrodes to any region of the exposed brain, the animal was tethered loosely but generally unrestrained. Some experiments inevitably failed for technical reasons but under favourable conditions he could obtain evidence of electrical currents of high energy and again reported that externally placed electrodes gave feebler currents than those placed in direct contact with the brain. Having placed electrodes on the region stimulation of which caused eye movement, he found that light caused 'negative variation' almost immediately and that if the light was partially shaded the current was diminished. He concluded that the light may have excited the visual centre or it may have acted generally on the whole brain (Caton, 1887).

Beck (1890) performed two series of experiments, the

first on the spinal cord of frogs and the second on the currents of the cerebral cortex in warm blooded animals (rabbits and dogs). Using electrodes placed at pairs of points on the cortex the current between them was observed with and without afferent stimulation. On visual stimulation of one eye (using a burning magnesium ribbon) he described an 'electro-negative tension' arising in the contralateral occipital lobe, more localised in dogs than rabbits. He was unsuccessful in finding an electrode position where auditory stimulation produced a measurable response, largely due to the difficulty of placing electrodes on the inner surfaces of the temporal lobes. Claims as to the original discovery of such brain activity thrived. Fleishl von Marxow (1890) in a letter stated that during the year 1883 he had performed experiments on different animals - when two electrodes on the surface of the cerebral hemispheres were convected via a galvanometer little or no deflection occurred, but stimulation of a sense organ which had its central projection in the area of 1 electrode would cause the needle to turn in a definite direction (and the needle would turn in the opposite direction if activity occurred under the other electrode instead). Such a galvanometric deflection had been conclusively shown on stimulation of either eye and recording from the area of the visual cortex. No mention was made in this letter of ongoing brain activity but only that in response to sensory stimulation.

After several communications between Von Marxow and Beck both claiming originality in discovery of the brain's

electrical activity, Caton (1891) published a letter as a form of reminder some 16 years after his first report, that he could claim to be the original discoverer of the phenomenon.

Danilevsky (1877) in his doctoral thesis confirmed many of Caton's original observations and some years later (Danilevsky, 1891) described his experiments in detail but expressed uncertainty as to how the results should be interpreted, especially since some of the reactions to sensory stimuli appeared to be very variable.

Napoleon Cybulski a teacher and collaborator of Beck was the first to use two galvanometers stimultaneously in order to trace an electrical change across the cortex in response to a peripheral stimulus. Using one galvanometer on other areas of the hemisphere from the area being tested gave them clear evidence of localisation of function but they warned that cortical areas did overlap and were not totally separate (Cybulski and Beck, 1891).

Kaufman (1912) repeated and reinforced the arguments of many of the earlier experiments, using technically improved equipment and although not successful in evoking cortical responses to peripheral nerve stimulation did succeed in recording a response to photic stimuli and compared this with the response to direct optic nerve stimulation. Neminsky (1913) with a technique combining the use of an Einthoven string galvanometer and a moving

photographic paper, worked on dogs and published a paper which was the first in the literature to contain such a permanent record of the brain's electrical activity. The spontaneous fluctuations, which he termed the 'electrocerebrogram' could even be recorded from the unopened skull, although they were greatly attenuated. A similar photographic technique was used by Cybulski (Cybulski and Jelena - Macieszyna, 1914). The first attempts to make recordings of brain electrical activity in humans were by a German psychiatrist, Hans Berger. In 1924 his experiments began and in 1925 the first recording was made. He first used as electrodes fine platinum wires inserted into the scalp, soon modifying these to zinc-plated steel needles. Later still he began using large plate electrodes of various metals which were strapped to the forehead and back of the head. In the same year he made recordings in brain-injured men, but did not publish until 4 years later (Berger, 1929). He found in man similar categories of waves (seen originally by Neminsky in animals) which he termed the alpha and beta ranges and used the word 'Elektrenkephalogramm' to describe the phenomenon (now known as the electroencephalogram, or EEG). Berger observed (like Caton in 1875) that sensory stimulation appeared to reduce the spontaneous brain activity and concluded that this was related to attention and he demonstrated that when a subject's eyes were closed an alpha rhythm was seen in the EEG which disappeared when the eyes were opened (Berger, 1932). Adrian and Matthews (1934) working first on anaesthetised rabbits and later

on humans) suggested that the alpha originated in the occipital lobe and despite considerable contention from Berger they were later proved correct. In their pioneering work on humans they demonstrated that responses 'following' regularly repeated flashes of light could be recorded in the EEG (Adrian and Matthews, 1934). This was to be the first human Visual Evoked Potential (VEP) and it is of interest to note that this was recorded some 57 years after the first human recording of the ERG.

The 'following' response was not observed in all normal subjects and it is most likely that it was simply obscured by the much higher amplitude background EEG. These responses were shown to be generated by the visual projection areas of the brain. Cruickshank (1937) in her work on the human alpha rhythm showed firstly that the rhythm became blocked when the eyes were illuminated and secondly the production of 'on' effects or evoked potentials (EP) which varied with the intensity and duration of the stimulus, the implicit time (measured to the peak of the first EP) varying between 60 and 115 m.secs. depending on the stimulus intensity. Adrian (1944) suggested that with the then present technical facilities the EEG could only be useful in detection of gross defects and detailed brain analysis could not be possible, basically because of the attenuating effects of skull and scalp. Walter, Walter, Dovey and Shipton (1946) commented that the two technical difficulties in studying EPs were that an adequate bright light source of sufficient functional

flexibility had not been available and that the EPs (like the spontaneous EEG) were often too complex to be interpreted by the unaided eye. With the use of a newly designed 'high power stroboscope' capable of producing a flash duration of the order of 10 μ.sec. and frequency analysis of the resulting records, vast improvements in interpretation were claimed.

In 1947, Monnier began a series of publications on the 'conduction time' of the optic pathways from retina to cortex. He suggested that a light stimulus would suppress the alpha rhythm after a latent period (called the 'blockage interval') which included the time taken by the nervous impulses initiated in the retina to reach the cerebral cortex. The 'conduction time' of the optic pathways could be calculated if the latency of the peak of the ERG 'b' wave (the 'retinal latency') was subtracted from the 'alpha blockage interval', the average normal conduction time being of the order of 124 m.sec. (Monnier and Jeanneret, 1947), this being longer than the 'implicit time' as above.

In the same year (Dawson, 1947) the major technical advance of photographic superimposition was introduced, and in 1951 the first averager was reported (Dawson, 1951) and later its application to EPs (Dawson, 1954). Both superimposition and the superior averaging techniques require that the EP will be "time-locked" to the stimulus whereas the background noise of the EEG will be random in its relationship. Thus, on repeated stimulation, if

the EEG is stored the common features will gradually summate producing a clearer EP whilst the random noise containing all possible phases of waves will decrease as the root of the sample. Subsequent work with the averaging technique (although now technically more refined with the advent of computers) which has become the standard method used in EEG and EP laboratories has proved its worth.

Monnier published further work proposing that the variability of the blocking time was chiefly due to variations in the retinal part of the process, that the pre-retinal time and central period of the blocking time decrease with increase in stimulus intensity and that the blocking time decreased when the subject was more alert. He claimed that the long latency of the blocking of the alpha rhythm depended on perceptive mechanisms in the visual association areas (Monnier and Meier, 1949). Cobb (1950) using Dawson's superimposition technique recorded cortical responses to short light flashes and again noted considerable intersubject variability in form, latency, number of phases, polarity of the first phase and overall duration of the response. In some subjects the response started as little as 35 m.sec. post-stimulus in others it was at least 60 m.secs.

The use of high frequency flash stimulation was often found to produce a troublesome photo-electric artifact at some scalp electrodes and the use of a periodically altered pattern of much lower brightness was advocated

(Marshall and Harden, 1952). This consisted of the presentation on a cathode ray tube of a circle of expanding diameter starting as a dot and increasing at constant speed to a maximum diameter, then returning to the dot configuration almost instantaneously. With good fixation a 'pattern driving effect' could be observed in the occipital derivations even with very low illumination levels, provided that the pattern was just visible. Although no EEG traces were illustrated in this paper, it was claimed that the flash artifacts were also circumvented.

Using a combined ERG and VEP recording technique Monnier (1952) reported in a comprehensive paper that a series of alternating potentials could be recorded at the occiput, the first of which since its latency almost matched that of the ERG 'b' wave was termed potential 'b', a surface positive component beginning 35 m.sec. after stimulation and peaking after 48-62 m.secs. 'c', 'd' and 'e' potentials followed, with alternating polarities. Component 'c' (100 $\pm$ 10 m.sec. latency) was considered the most consistent component and the 'b' component was described as being the only one to be a specific response of the occipital cortex. Almost identical recordings were made by Van Hof (1958) and Van Balen and Henkes (1960).

Jayle, Camo and Boyer (1955) recorded EPs in the EEG of all their normal subjects provided that a sufficiently

bright flash was used and proposed in explanation for the wide inter-individual variability of the response that each individual has a stimulation threshold which must be reached and beyond which photic stimulation has no augmenting effect on the electrical activity of the occipital cortex. Calvet, Cathala, Hirsch and Sherrer (1956) using a complex method of integration employing a cathode-ray oscilloscope recorded clear VEP waveforms when subjects received between 50 and 150 successive photic stimuli at both fast and slow rates of presentation.

Further variations and improvements on the method of averaging were developed during the next few years (Barlow, 1957; Remond, 1958; Buller and Styles, 1959 and Cooper and Warren, 1961). The first digital computer used was the Average Response Computer (Clark, 1958 and Clarke, Brown, Goldstein, Molnar, O'Brien and Zieman, 1961) and with the implementation of transistorisation, the Computer of Average Transients was developed (Clynes, 1961).

The first systematic studies of the VEP were published in the early 1960's. Four main components (positive component at 20-25 m.secs., negative at 40-50 m.secs., positive at 55-65 m.secs., negative at 90-100 m.secs.) were recorded by Cobb and Dawson (1960) using a closely spaced bipolar montage around the occiput and supra-occipital region. Repeatability of components over a period of time was good although amplitude appeared to be variable and reduction in flash intensity resulted

in reduced amplitude and increased latency of the response. Visual fixation seemed to be a determinant of form and size of the response. A more thorough analysis (Vanzulli, Bogacz, Handler and Garcia-Austt, 1960) investigated the effects of stimulus intensity, arousal and eye closure and again stressed the wide inter-individual variability of the VEP, probably due to the folded areas of visual projection in the medial surface of each hemisphere. Tepas and Armington (1962) while performing combined ERG and VEP recordings, stressed that the VEP was a more variable phenomenon than the ERG.

A more systematic study of the morphology of the human VEP (Ciganek, 1961) using a bipolar midline occipital-parietal montage specified a series of waves of alternate polarity with average latencies of approximately 40, 55, 75, 95, 116, 135 and 195 m.secs., which he designated I-VII, wave I being surface negative at the occipital electrode. The first three waves were called the primary response, representing the response specific to area 17 of the visual cortex. The secondary response (waves IV-VII) was suggested as being due to a non-specific, more diffusely organised system. A later rhythmic after-discharge was also described, best demonstrated when the eyes were closed.

Vaughan, Katzman and Taylor (1963) whilst investigating changes in the VEP in cases of homonymous hemianopia made recordings by means of computer averaging using

occipital electrodes referred to the vertex. Waves I-III of Ciganek were examined and the latencies were slightly different, the difference being attributed to variation in electrode placement and stimulus parameters.

In a critical review of several major workers' findings, Rietveld (1963) attempted to account for some of the many discrepancies between their results, concluding that variations in recording montage and stimulus and analysis parameters were the factors having a significant effect on the VEP. A similar problem still exists (Halliday, Harding and Holder, 1980).

Kooi and Bagchi (1964) using the same component designations as Ciganek (1961) evaluated the VEP from a morphologic and topographic viewpoint. Wave III recorded between occipital and parietal electrodes was the most consistent component, having a latency of between 80 -120 m.secs. Test-retest reliability during the same session was high ($r = 0.87 - 0.97$), and slightly lower ($r = 0.88$) for longer periods of time. Differences in individual response configuration were attributed to 'minor procedural variations' or related to neural differences between subjects.

Since alterations in the ERG may be associated with photoreceptor pathology, alterations of the VEP were increasingly considered to be associated with alterations in the visual pathway in patients with non-retinal

visual disorders (Vaughan and Katzman, 1964) and combined ERG and VEP recordings were made in a number of different visual pathway pathologies. Alterations in the VEP were closely correlated with the anatomical site of the pathology only in a moderate percentage of cases (Copenhaver and Bienhocker, 1963; Vaughan and Katzman, 1964 and Copenhaver and Perry 1964).

Gastaut and Regis (1964) again described a VEP of similar outline to that of Ciganek (1961) and with the most consistent component being a positive deflection at 100 - 150 m.secs.

The use of an electronic stroboscope producing brief flashes of light delivered stimulation to both rods and cones to a mixed and unknown degree. Van der Tweel and Verduryn-Lunel (1965) suggested using a TV projection tube to deliver sinusoidally modulated light as a stimulus. Even at low levels of illumination occipital responses, often large, could be elicited. At higher frequencies (9 - 15 cycles per second) the VEP reproduced the shape and amplitude of the stimulus. It is not clear however, how this system could further differentiate between rod and cone function.

The marked consistency in results of many workers of a major wave occurring between 80 - 150 m.secs, led to the investigation of the possible site of origin of this component. Rietveld, Tordoir and Duyff (1965) investigating foveal and parafoveal contributions to the VEP

concluded that the major positive component (Wave IV of Ciganek) and its preceding negative component were related to the central region of the fovea. Preservation of the major positivity was found with extinction of earlier components when a small foveal stimulus target was used (Potts and Nagaya, 1966) and the component was considered to be better regarded as part of the primary response rather than the secondary response (Jonkman, 1967).

The presence of this major component has since been further documented by a multiplicity of authors (e.g. Dustman and Beck, 1969; Harding, 1974 and Sokol, 1976) using different stimulation and recording techniques and a composite schematic diagram of the normal VEP to diffuse flash stimulation is shown in Figure 1.3.1., with the component designations of several authors.

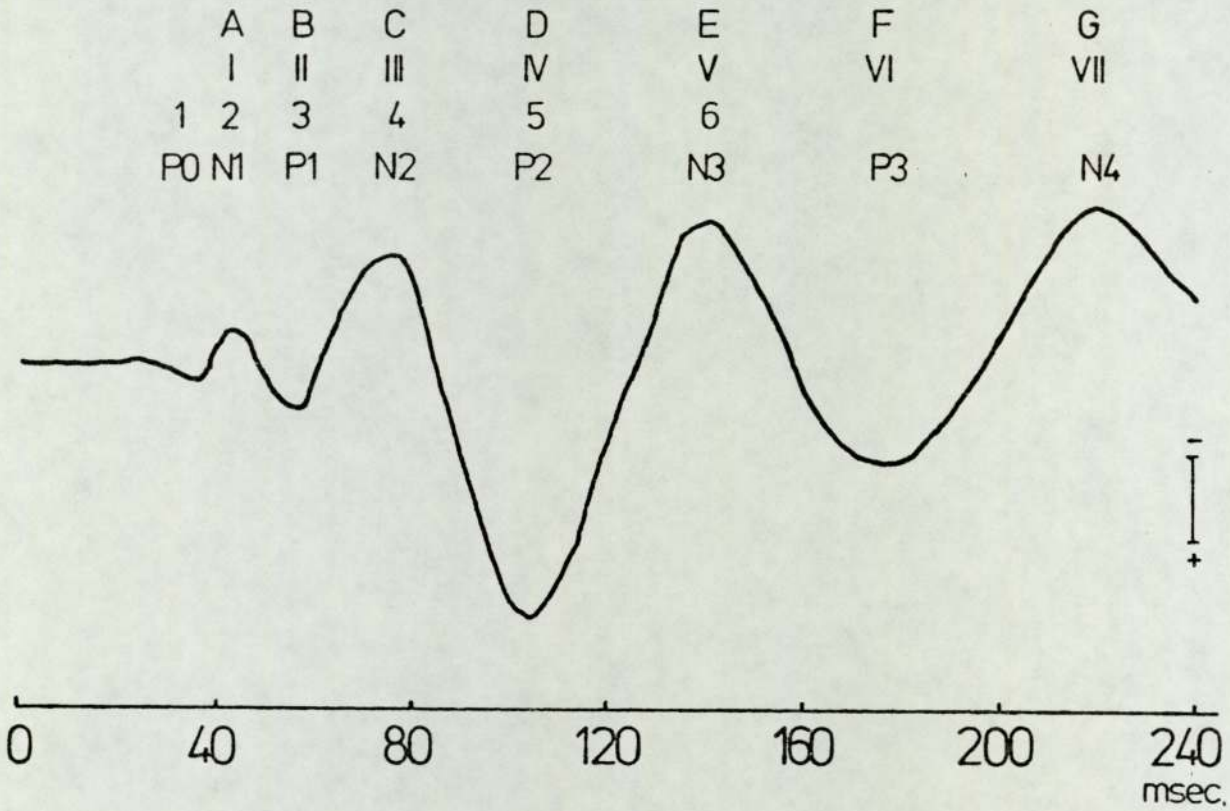
By the end of the 1960's, VEP techniques using flash stimulation had been found to be useful for basic research and for a limited number of well selected clinical problems, but it lacked the precision and sensitivity for wider clinical use (Rouher, Plane and Solé, 1969 and Halliday and Mushin, 1980).

It was gradually realised that a more appropriate method of generating the VEP might be to use a structured stimulus (e.g. a pattern) which changed periodically either by alternately appearing and disappearing ('pattern-appearance') or by alternately reversing ('pattern-reversal').

FIGURE 1.3.1.

Schematic representation of normal VEP to diffuse flash stimulation

Schemes of component labelling are shown above the waveform. The first row (letters) is that of Dustman and Beck (1969); the second row (Roman numerals) is that of Ciganek (1961); the third row is that of Gastaut and Regis (1965); the fourth row is that of Harding (1974). (after Harding, 1974)


A B C D E F G
I II III IV V VI VII
1 2 3 4 5 6
P0 N1 P1 N2 P2 N3 P3 N4
0 40 80 120 160 200 240
msec.

This form of stimulation differs from unstructured flash stimulation in that it produces a VEP which is due to contrast modulation, or local luminance changes, the mean overall luminance of the stimulus remaining constant. Clearly, unstructured flash stimulation presents only luminance changes to the visual system.

Early investigation of the influence of introducing structural factors into the visual stimulus was made by Spehlmann (1965) who used a technique best described as 'flashed pattern', in which cardboards of different patterns were illuminated by a stroboscope and observed by the subject. The most effective pattern in evoking a VEP was a checkerboard, and the major positive component normally seen at around 100 m.secs. appeared to occur much later at 180 - 375 m.secs. The amplitude of this wave depended on the contrast between black and white components of the pattern and was much higher than the amplitude of the largest component elicited in the same subject by unstructured flash stimulation. An earlier negative component at about 100 m.secs. was also normally seen.

Spekreijse (1966) in stressing the importance of separating luminance and pattern stimulation devised a method in which the total luminous flux of the stimulus was maintained at a constant level. This contrasted with the technique of Spehlmann (1965) in which the pattern luminance varied.

Cobb, Morton and Ettlinger (1967) and Cobb, Ettlinger and Morton (1968) using a pattern-reversal system showed that a VEP could be generated without change in total retinal illumination and inferred that pattern information and intensity change might be processed differently by the visual system.

Harter and White (1968) investigated the relationship between contour sharpness, stimulus check size and amplitude of VEP using various ophthalmic lenses before the subjects eyes to vary the sharpness of focus of the stimulus. Both the previously described negative and positive peaks (Spehlmann, 1965) were found to be sensitive to focus and size of checks, the amplitude of both components decreasing with increasing blur of the checks. This feature has now become established as a characteristic determinant to the successful use of the pattern VEP.

Following these early discoveries, rapid advances were made in normals (e.g. Halliday and Michael, 1970; Michael and Halliday, 1971; Regan, 1972 and Arden, 1973) and in a variety of pathological conditions of the visual system (e.g. Regan and Heron, 1969 and Halliday et al.1973).

Two well defined methods of pattern stimulation have now evolved, namely 'pattern-appearance' and 'pattern-reversal', producing two distinct types of VEP with differing scalp distributions (Jeffreys, 1977) and the latter

technique, until recently, has received wider acclaim as a clinically useful stimulus, producing a waveform similar to that of the flash VEP, but with a major component often of higher amplitude. Generally, patterned stimuli are considered more precise VEP generators than unstructured flash since fixation and retinal locus stimulated can be precisely determined and entoptic stray-light is minimised.

An overwhelming number of publications on the VEP in the normal and abnormal visual pathway has since been produced (see Desmedt, 1977 and Barber, 1980).

The technique of pattern stimulation is clearly a much more sensitive technique than flash in terms of its utility in the localisation of pathology, but it must be remembered that the success of the technique depends to a large extent on the co-operation of the subject (Halliday and Mushin, 1980 and Rover, Shaubele and Fuchs, 1980). Flash stimulation is a more robust technique, ideally suited to unco-operative patients or those with impaired abilities of fixation and with the combined use of phase-reversal techniques over either occipital lobe (Harding, Thompson and Panayiotopoulos, 1970), a reasonable degree of accuracy may be achieved.

Some laboratories have abandoned the flash stimulus in favour of pattern, but in others combined techniques survive.

There still exists a wide inter-laboratory variation in types of stimuli, computational hardware and electrode montages and this leads to differences in results in both normals and abnormals. However, the common feature is a major component of latency around 100 m.sec. (polarity varying depending on recording technique) and a number of earlier and later components within a fairly well defined latency zone. The clinically useful latency zone is usually between approximately 80 m.secs. and 150 m.secs. and components outside this zone are rarely taken into consideration. The major component at the centre of this zone is the one most closely related to central visual function monitored at the occipital cortex (Regan, 1972; Harding, 1974 and Potts, 1981), and thus probably the most important one in determining the integrity of the central visual pathway.

1.4. EARLY COMPONENTS OF THE VEP - DEFINITION AND RESEARCH HYPOTHESIS

The most consistent and repeatable component of the VEP during clinical assessment of the visual pathway using flash or pattern-reversal stimulation is the so-called 'major component', usually being of positive polarity and assuming the designation P_2 or P100 (Harding, 1974; Halliday and Mushin, 1980) although, depending on recording convention used, the polarity may be reversed and the component then assumes the designation N_2 (Sokol, 1976 and Glaser and Laflamme, 1979). This occurs at a latency of approximately 100 m.sec. with pattern reversal stimulation and at approximately 120 m.secs. when diffuse unstructured flash stimulation is used.

However, several other components are also often seen preceding and following the major component and the latency range within which these occur is between approximately 60 and 140 m.secs.

In reports of the VEP technique, components occurring outside this latency envelope are poorly documented, although later ones, for example the P300 component, are well established in other clinical and non-clinical contexts (Halliday, 1980a, b). This lack of documentation may be due partly to the successful clinical applications of the well established components and partly due to the relative consistency of such components within and between laboratories compared with the relative

inconsistency of other components.

The components of the VEP studied in this thesis are generally referred to as 'early components' and in this context will refer to those components occurring before 50 m.secs. post-stimulus.

Such components have been known for many years, but are under normal conditions for recording the VEP, rather variable and unreliable. They are not regularly demonstrated in conventional VEP recordings although they are relatively more common in the records of early workers who used rather crude flash stimuli of high intensity (Cobb, 1950; Cobb and Dawson, 1960 and Ciganek, 1961). The more recent innovation of pattern stimulation in which luminance is maintained at a constant level and contrast changes only are presented (Spekreijse, Estevez and Reits, 1977) produces recordings in which such components are more rarely seen.

The ERG is extremely stable and repeatability is good. The origins of the various components are well documented and are clearly all retinal (Babel, et al. 1977; Galloway, 1981; Norden, 1979 and Ripps, 1978). The VEP recorded at the occiput is less stable than the ERG but the most repeatable major components are thought to be of cortical origin (Goff, Allison and Vaughan, 1978 and Riggs, 1969).

Although data from different laboratories varies, the

photopic ERG 'a' wave has an average peak latency of around 10-20 m.secs., and the 'b' wave has one around 35-50 m.secs. (Kooi, 1979). However, early deflections of the VEP recorded at the occiput have been demonstrated with latencies of between 20 and 30 m.secs. (e.g. Ciganek, 1961; Cobb and Dawson, 1961 and Cracco and Cracco, 1978). This would imply that after the afferent volley has travelled the length of the visual pathway, a response might still be recorded at the occiput before the major component (i.e. 'b' wave) of the ERG is recorded from the retina and would suggest distinctly different modes of neural transmission and processing of the ERG and VEP.

Postulates as to the origins of these early components of the VEP are diverse. Several authors favour the electro-retinogram in view of its high amplitude and its domination of the anterior portions of the scalp (e.g. Allison, Matsumiya, Goff and Goff, 1977) whereas others, in fact, strongly deny this possibility (Perry and Childers, 1969 and Vaughan, 1966). The visual cortex is also suggested as the source of such waves (e.g. Nakamura, 1978). However, several of the intervening structures of the visual pathway between retina and cortex are also considered likely sites of origin. Possible optic nerve potentials have been studied (Honda, 1977 and Siegfried, 1980), and shown to have different morphological characteristics to the well established ERG and VEP. The optic tract has been suggested (Riggs, 1969) and more posterior structures

namely the lateral geniculate body or geniculo-calcarine tract considered more likely sources by other authors (Picton and Hink, 1974 and Cracco and Cracco, 1978).

Support is lent to the latter suggestions by several surgically orientated studies. In a survey of the effects of surgical lesions at a variety of sites along the visual pathway of unanaesthetized Rhesus monkeys, Vaughan and Gross (1969) found changes in the EPs suggesting that early wavelets in the VEP were diminuted by ipsilateral section of the optic tract suggesting that the wavelets reflect the geniculo-calcarine input to the striate cortex. Corletto, Genitilomo, Rosadini, Rossi and Zattoni (1967) made depth recordings of the VEP before and after ablation of the occipital pole of an epileptic patient and noted persistence of initial components having peak latencies of less than 45 m.secs. Spire and Hosobuchi (1980) made depth recordings of a photically evoked potential of around 22 m,secs. latency from a site slightly anterior to the lateral geniculate body region in a patient undergoing cranial surgery.

Clearly therefore, opinions as to the origins of such early components are diverse. Most of the constituent portions of the visual pathway have been advocated as possible generators, but the reports from depth recordings generally imply that the responses are produced by those parts of the visual pathway intermediate between retina and visual cortex, and most probably the post-chiasmal segments.

Such VEP early components may be likened to the auditory system Brainstem Auditory Evoked Potential (BAEP). Acoustic nerve and brainstem potentials are volume-conducted to surface recording electrodes and form a composite series of up to seven waves constituting the BAEP. The BAEP was discovered by Sohmer and Feinmesser (1967) and finally established in several definitive studies published a few years later (Jewett, Romano and Williston, 1970 and Jewett and Williston, 1971). In these latter studies a number of extremely low amplitude components produced in response to clicks were recorded between the mastoid and vertex using surface electrodes, with latencies as short as 1.4 m.secs. to the first peak and up to 5.1 m.secs. The peak-to-peak amplitudes of the scalp recorded BAEP are of the order of 0.6 - 1.4uV. (Jewett and Williston, 1971) and easily occluded by the higher amplitude spontaneous EEG (Stockard, Stockard and Sharbrough, 1980). The term "far field" was applied to the technique of recording at a distance from the generator site and a large number of averages performed in order to improve the signal to noise ratio and hence facilitate recording of an evoked potential from the deep brainstem structures (Jewett and Williston, 1971).

The hypothesis upon which the work described in this thesis has been based is that the early components of the VEP possibly originate at generators anatomically intermediate between the retina and occipital cortex. Since the location of these structures is deeper within the skull than the retina or occipital cortex and the

few reports in the literature of early components consistently indicate their minute amplitude and variability, when surface-recorded, conventional parameters for generating and recording the VEP have been considerably modified in an attempt to accentuate and facilitate production of these components, to determine their scalp distribution and possible source(s) of origin.

CHAPTER 2

DEVELOPMENT OF TECHNIQUES

2.1. REVIEW OF SHORT-LATENCY POTENTIALS

Although the present work is concerned with an examination of early components of the VEP, short latency EPs may also be generated by structures other than the visual pathway. They may be recorded as a manifestation of muscle activity around the scalp and such potentials may often be a source of contamination when recording EPs of neurogenic origin. Similarly, the auditory system is a generator of several types of EP some of which are of short latency, as already mentioned in Section 1.4.

To put into perspective the early VEP components a brief review of other short-latency potentials will be included in this section.

Evoked Myogenic Potentials

A variety of reflexes are generated in the muscles of the face and scalp in response to sensory stimuli (Goff, Allison and Vaughan, 1978). All the muscles of the body are considered to react to sound (Bickford, Galbraith and Jacobson, 1963a; Bickford, Jacobson and Galbraith 1963b) and although those of the extremities require high intensity stimulation to produce consistent reflexes, the muscles of the scalp are more sensitive and react to lower intensities (Gibson, 1978). Averaged responses to clicks recorded by Geisler, Frishkopf and Rosenblith (1958) were considered to be neurogenic and originating in the auditory cortex, but Bickford, Jacobson and Cody (1964) contended this, suggesting

that these supposedly neurogenic potentials were in fact of a 'sonomotor' origin, producing a widespread activation of the muscular system in response to clicks. Latencies ranged from 6 m.sec. for cranial responses to 50 m.sec. for a response in the leg. Using an inion to ear derivation a number of waves was consistently recorded with the negative components at 12, 26 and 54 m.secs., with a more variable negative component at 75 m.secs. The waveforms were of considerably better resolution when a large number of averages (around 1000) was used. Flexion of the neck forwards increased the response amplitude and further studies of the effects of variation in tension of the neck muscles verified the conclusion that such responses arose mainly from neck muscles, which have insertions near the inion. Observation of a curarised subject showed almost complete suppression of the response to vertex and inion regions. Finally, in three deaf patients with normal vestibular function Bickford et al. (1964) managed to record responses from the inion.

Since this time further categorisation of auditory myogenic EPs has been developed.

The inion response, recorded using an active electrode on or near the inion is probably derived from the cervical muscles (Gibson, 1978) and the largest component is negative with a latency of around 30 m.sec. Correlations between the inion response and hearing

defects have proved poor and its clinical utility is therefore rather limited (Gibson, 1978).

The parietal response is a mixture of myogenic and neurogenic components (Mast, 1965; Vaughan and Ritter, 1969) with latencies ranging between 8 and 60 m.secs. and differs from the inion response in that it is recordable under forced neck traction and is generally of rather different characteristics (Mast, 1965). The neurogenic components of this response may be derived from the auditory areas of the thalamus and the primary auditory cortex (Picton, Hillyard, Krausz and Galambos, 1974).

The post-auricular response is recorded using an active electrode placed over the post - auricular muscles immediately behind the pinna and first reported by Kiang, Crist, French and Edwards (1963). It is a rather variable response between and even within subjects (Picton et al. 1974) and is very sensitive to electrode placement, the response amplitude reducing dramatically if the active electrode is displaced more than 2 cms. from its optimal site (Vaughan and Ritter, 1969). The main components are a negative peak at 12-13 m.sec. and a later positive peak at 16-17 m.sec, and its presence is often dependent on muscle tone (Jones, Harding and Smith, 1980).

An analogous myogenic potential initiated by visual stimulation, the photomyoclonic response is also

well known.

Bickford, Sem-Jacobsen, White and Daly (1952) investigated the so called photomyoclonic and photoconvulsive responses in a series of patients and normals. The differentiation between the two types of response was clear, for example the photomyoclonic response was frequently recorded in normals, muscle tension was increased, the response was recorded mainly around the face and frontal scalp and was clinically accompanied by fluttering of the eyelids. The photoconvulsive response however, was rarely recorded in normals, did not produce change in muscle tension, could be recorded over the whole scalp and was often accompanied by eye movements and arrest of speech. Generally the photomyoclonic response was not distressing to the patient whereas the photoconvulsive response produced major disturbances of cerebral function and if photic stimulation was continued a generalised seizure always ensued. The EEG patterns paralleled the differences in clinical manifestations - the photomyoclonic response consisted of high voltage spike discharges following each light flash and maximal in the frontal derivations; the photoconvulsive response appeared as a diffuse synchronous spike-wave discharge triggered by the light, but its rate of repetition was unrelated to the light stimulus and continued as an after-discharge when photic stimulation ceased. The latency of the photomyoclonic response was measured

in one normal subject and two psychiatric patients and in all instances varied between 50-60 m.sec. The amplitude of the response was found to be approximately proportional to the brightness of the photic stimulus and demonstrated an 'all-or-none' characteristic when the frequency of the flash was varied, the usual effective range being between 6-15 flashes per second. The effects of facial muscle tension were investigated and it was found that a larger photomyoclonic response could be produced if the tension was increased and vice-versa. In conclusion they postulated a number of pathways by which the two types of responses might be mediated and stressed the importance of a stretch-reflex mechanism affecting scalp and facial musculature involved in the photomyoclonic response. Pathways for the photoconvulsive response were rather more hypothetical but suggested a cortical origin.

Bickford, White, Sem-Jacobsen and Rodin (1953) reported that the photomyoclonic response had at least three components with latencies of 40-70 m.sec., 70-80 m.sec. and 105-115 m.sec., the first response always being present but the later ones being more variable.

Cobb and Sears (1957) in a brief abstract commented that the blink reflex to flash and the photomyoclonic response might have some similar characteristics as the pathway serving both were incompletely known, and suggested that from their measures of latency of response there was time for the blink and photomyoclonic responses to travel

"by way of the visual cortex". This contrasts with the hypothesis of Bickford et al. (1952) that the shortness of latency and frequent absence of recordable response at the cortex favoured the concept of a short subcortical pathway for the photomyoclonic response.

Harlan, White and Bickford (1958) studied the electrical activity produced by eyelid flutter. A rhythm sometimes having the appearance of alpha activity could occasionally be observed in EEG recordings from frontal and temporal derivations, particularly from electrodes near the eyes. It was usually inhibited when the eyes were open or by holding closed eyelids motionless. The response generally appeared as rhythmic activity of 4-14 cycles per second and although of lower frequency than the myogenic responses of Bickford et al. (1953) it might be considered as a scalp recorded response to photic stimulation, since eyelid flutter is often observed in subjects undergoing such stimulation. The authors however suggested that its origin might be the oscillation of the electric field of the eyes produced by rapid ocular movements associated with eyelid flutter.

Bickford, Jacobson and Cody (1964) again stressed the importance of the photomyoclonic response and noted the possible hazard of using averaging techniques which might summate the photomyoclonic response and contaminate the recording of the VEP proper. In the case of forced neck tensioning the waveform of the VEP was considerably altered with several high amplitude components of

latencies between 50 - 100 m.secs. superimposing on the basic VEP. They suggested that precautions such as suitable head position and maximal muscle relaxation would reduce the photomyoclonic response.

The term 'microflex' was applied to the myoclonic response to the sensory stimuli averaged by computer (Bickford, 1966) and the use of such short-latency microflexes in neurological assessment was advocated.

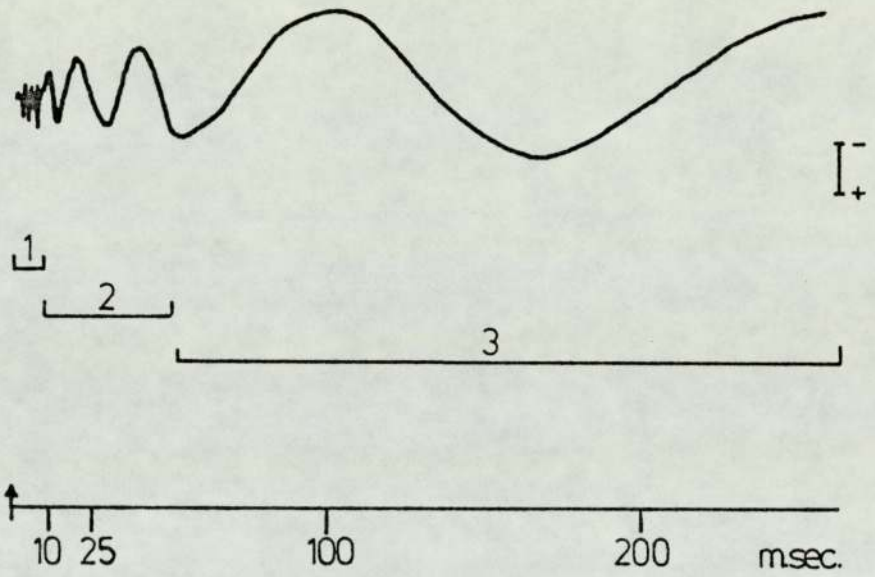
The topographic distribution of the photomyoclonic response can be varied by changing facial expression during photic stimulation as well as enhancing other microflex responses to auditory and somesthetic stimuli (Bickford, 1967) and this is further evidence of the myogenic origin of such responses.

Brainstem Auditory Evoked Potentials

The Brainstem auditory evoked potential (BAEP) is a surface recorded composite potential of extremely low amplitude reflecting activity at several different levels of the subcortical auditory pathway, following an appropriate auditory stimulus. The constituent waves of the BAEP are true 'early components' and the whole EP is complete within 10 m.secs post-stimulus (Stockard, Stockard and Sharbrough, 1980). To put the BAEP into context in relation to the other auditory evoked potentials, a diagrammatic representatio of a composite auditory response is shown in Figure 2.1.1.

FIGURE 2.1.1.

Diagrammatic representation of composite auditory EP illustrating the three major components of the response, categorised by latency. The BAEP comprises the short latency response occurring within the first 10 m.sec. after auditory stimulation.



1 - Brainstem response
2 - Middle latency response
3 - Long latency response

The concept of the BAEP is a recent one relative to all other EPs, Sohmer and Feinmesser (1967) generally being acknowledged as the originators of surface recordings. Using a variety of sites for the active electrode which included a) a subdermal needle electrode in the ear lobe b) a clip electrode on the ear lobe c) a ball-tipped silver wire electrode on the tympanic membrane or on the round window niche, all were referred to the bridge of the nose which was considered to be the site of least muscle noise. The recorded responses were of very low amplitude, of the order of 0.5 μV or less and usually made up of four negative peaks. The first two peaks with latencies of around 1.3 m.secs and 2.23 m.secs respectively and were interpreted as components of the cochlear action potential. The following peaks, whose latency appeared more variable, were regarded as reflecting repetitive firing of auditory nerve fibres or due to the discharges of neurones in brainstem auditory nuclei, which reached the recording site (like the first two components) by volume conduction. The low amplitude of the components made averaging techniques mandatory.

Similar non-surgical recordings were made by Yoshie, Ohashi and Suzuki (1967), but their clinical utility seemed unlikely and the reports met with a degree of scepticism.

However, Jewett (1970) in the first of a number of publications reported a series of experiments which firmly

established the BAEP as a consistent and useful clinical measure. In anaesthetised cats, recordings were made from the scalp and from several brain locations using the tongue as a reference site. By averaging, the response to an auditory click stimulus showed four positive peaks with latencies of less than 10 m.secs, which could be recorded at some distance from the generators of the components, thought to originate from several of the classical auditory pathway structures.

In human subjects the montage used was vertex to "lateral posterior neck". The earlobe, chin and wrist were also used as alternative comparator reference sites. Two thousand click stimuli were presented and the averaged auditory responses consisted of a series of waves with peak latencies between 2 and 7 m.secs. Their short latency again strongly suggested a brainstem origin, each component being related to a specific structure. A myogenic origin for the EP was discounted on the basis of its short latency and that recordings between neck and wrist did not show the waves, which would have been present if originating from the neck musculature. In addition, the sensation levels at which the EP could be recorded were much lower than the levels for the muscular response. Labelling of the waves was deferred, but because of their considerable detail and consistency between the three subjects used, it was suggested that they might be "clinically useful in evaluating sub-cortical function" (Jewett, Romano and Williston, 1970).

In a further study on humans (Jewett and Williston, 1971) recordings were made in twelve subjects using an active electrode at the vertex referred to the right ear lobe. In all cases, the responses to 2048 click stimulus, presented at various rates, were averaged. A distinct series of waves was again recorded, occurring in the first 9 m.secs after stimulation and components were given sequential Roman designations. The first wave (Wave I) had a peak latency as short as 1.4 m.secs (varying between 1.4 and 1.8 m.sec) and the first six waves were detected in all subjects although wave shapes did vary. Wave $\underline{\overline{V}}$ with a latency of between 4.6 and 5.1 m.sec was the most consistent between all subjects and because its amplitude was the highest (between 0.6 and 1.4 μV) it was the most easily identified. The optimal rate of stimulus presentation was between 2 and 5 clicks per second. The use of a wick electrode in the ear canal produced similar, though lower amplitude results and the use of the mastoid instead of the vertex as active electrode site also revealed several similar components.

Similar waveforms could be recorded simultaneously from three active electrode sites - the vertex, 7 cm. anterior to the vertex, and 7 cm. lateral and to the right of the vertex. Control recordings made with the ears blocked but with the remainder of the stimulating and recording system unaltered revealed total absence of any components of the EP. Sites of origin for some of the components were proposed, beginning with the auditory nerve as generator of Wave I and Waves II to IV probably being generated by the brainstem auditory system.

In general, Jewett and Williston (1971) stressed the difficulties in recording such low amplitude EPs at a distance from their generator sites and the need to adopt appropriate stimulus and analysis parameters in order to maximise the signals under consideration.

This short latency auditory EP complex was at this stage in its development simply called an 'auditory evoked far field potential' (Jewett and Williston, 1971; Plantz, Williston and Jewett, 1974) since although proposals had been made for the origins of the components, no totally conclusive evidence was available.

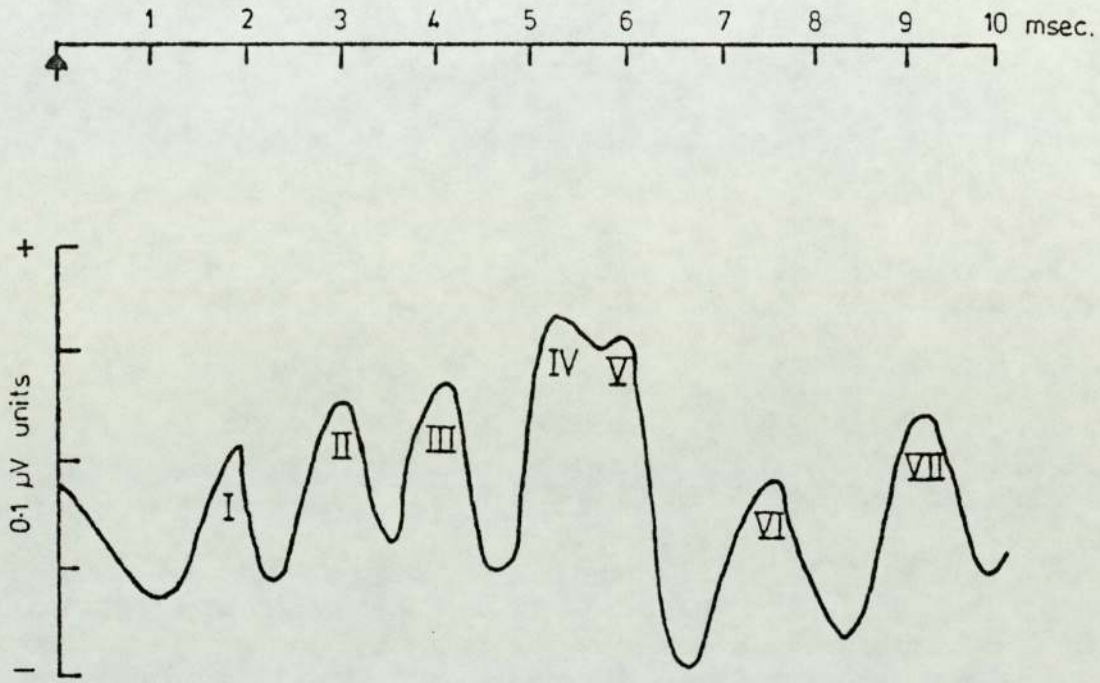
In a study of the spatio-temporal distribution of such auditory EPs in rats and cats (Plantz, Williston and Jewett, 1974) a reference electrode was placed at the base of the tail in rats and either at the base of the tail or back of the neck in cats. A 'roving' active electrode was then used to complete the circuit and 400 responses to monaural click stimuli were averaged. Responses were recorded from a large number of sites around the head and given Roman numeral designations, as described by Jewett and Williston, (1971), thus avoiding any assumptions as to the polarity of the components, since this could be altered depending on recording procedure. Different components were found to have different spatial distributions suggesting again that they were derived from different generators.

An evaluation of components and their origins was made by Picton, Hillyard, Krausz and Galambos (1974) who concluded that Wave I was the summated auditory nerve action potential. Waves II to VI were more complicated to ascribe to particular generators but were simply related to successive activations of the various brainstem auditory nuclei.

The title "Brainstem Auditory Evoked Response" was first used by Hecox and Galambos (1974). Variations in the labelling of the various peaks may lead to confusion but the clearest system appears to be that originated by Jewett and Williston (1971). A simplified diagrammatic representation of the BAEP using this nomenclature is given in Figure 2.1.2. Precise depth correlates of the BAEP are still unknown and it has been suggested that the individual components may be generated largely in the tracts linking the auditory nuclei rather than the nuclei per se (Stockard, Stockard and Sharbrough, 1980). Clues as to the specific sites of origin have been gained by studying the BAEP in a variety of pathological conditions of the auditory system (e.g. Starr and Hamilton, 1976; Stockard, Stockard and Sharbrough, 1977) and simple criteria for normality are specified interpeak latencies and amplitudes of the various components established in the individual laboratory. Components may be totally absent in more specific pathologies of the auditory system (Gibson, 1978) and there are several non-pathologic factors

FIGURE 2.1.2.

Diagrammatic representation of human BAEP with proposed sources of origin of the various components (modified after Stockard, Stockard and Sharbrough, 1977).



I Acoustic nerve
II Cochlear nuclei (medulla)
III Superior olivary complex (pons)
IV Lateral lemniscus (pons)
V Inferior colliculus (midbrain)
VI Medial geniculate (thalamus)
VII ? Auditory radiations (thalamo-cortical)

such as age, sex and body temperature which may have an effect on the BAEP (Stockard, Stockard and Sharbrough, 1978). Reduction of the stimulus (click) intensity has been shown to result in a prolongation of the latency and a decrease in amplitude of all BAEP components (Jones, Harding and Smith, 1980).

The BAEP has now become established as a useful objective measure of the functional integrity of the sub-cortical auditory pathway (McCandless, 1978; Kjaer, 1980a; Kjaer 1980b; Stockard, Stockard and Sharbrough, 1980).

Short Latency EPs Specific to Photic Stimulation

The visual pathway may be considered as a number of sites of synaptic neural activity namely the retina, lateral geniculate body and occipital cortex which are connected by 'tracts', namely the optic nerve and optic tract linking the retina to lateral geniculate body and the optic radiation linking the lateral geniculate body to the occipital cortex.

A number of authors have reported short latency EPs in response to photic stimulation at different sites along the visual pathway and the present author considers the simplest approach to review such literature is to consider the visual pathway (and the respective EPs) in sections, beginning anteriorly with the retina.

This thesis is concerned primarily with EPs in the human visual system, but since many relevant reports are based on animal studies, some of these will be considered. However, direct comparison of animal and human studies can only be made in assessing the general morphology of EPs and relative latencies of responses from different parts of the visual systems. Absolute latency and amplitude measurements cannot be directly compared since the dimensions and physical characteristics of the visual pathways and intervening structures between generator site and recording electrodes will be different.

The Retina

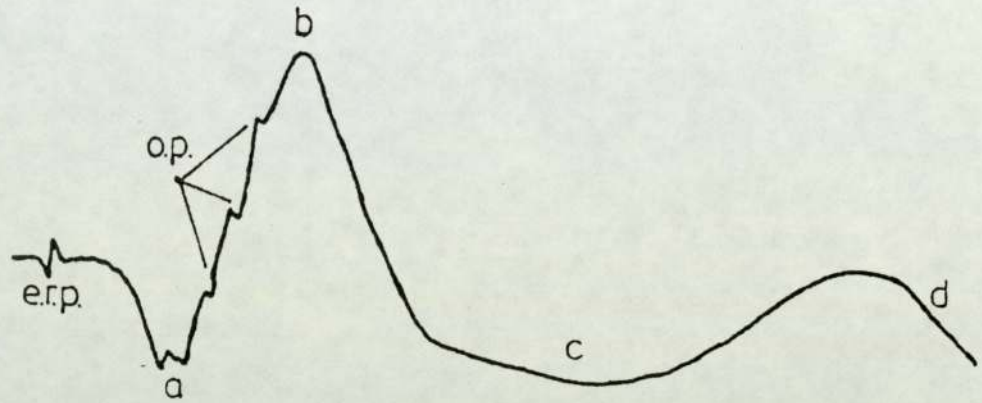
The ERG (being the oldest known photically evoked potential) is a graphical representation of the retinal action potential in response to a photic stimulus (Babel, Stangos, Korol and Spiritus, 1977). Although it reflects retinal activity it is recorded at a distance from the retina via the cornea using a contact lens (Karpe, 1968) or other type of corneal electrode (Arden, Carter, Hogg, Siegel and Margolis, 1979). Alternatively a skin electrode placed on the facial skin in the immediate vicinity of the anterior pole of the eye may be used (Harden, 1974). The ERG is a polyphasic EP consisting of several components and clearly is a summation of potentials generated at different sites in the retina (Granit, 1947; Babel et al. 1977). The characteristics

of the various components are influenced by stimulus variables and use of this is made when separating and assessing scoptic and photopic retinal function.

A diagrammatic representation of the ERG is shown in Figure 2.1.3. The major components of the ERG are the electronegative 'a' wave and the electropositive 'b' wave which follows. The 'a' wave is considered to be generated by the photoreceptors in the outer retina (Armington, Johnson and Riggs, 1952; Babel et al, 1977; Kooi, 1979; Norden, 1979). The peak latency of the 'a' wave varies between 10 - 20 m.secs. (Barlow, 1973; Armington, 1974; Babel et al 1977). Measurements of the peak amplitude of the 'a' wave are dependant on stimulus parameters and states of adaptation and amplitudes between 90 and 200 μV. have been reported. (Barlow, 1973; Babel et al 1977). The 'b' wave thought by some authors to be the most important component of the clinical ERG (Barlow, 1973) is considered to be generated by Müller cells in the inner retina (Miller and Dowling, 1970). It is a more prominent component than the 'a' wave and the peak latency varies between 30 and 50 m.secs (Babel et al 1977; Kooi, 1979). Amplitude measurements are again influenced by stimulus parameters and states of retinal adaptation, varying between 100 and 300 μV. (Ermers and Van Lith, 1973; Galloway, 1981; Babel et al. 1977).

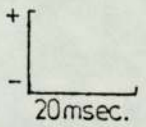
FIGURE 2.1.3.

Diagrammatic representation of the human ERG illustrating the major and minor components. Scales for latency and amplitude are arbitrary since the waveform is dependent on stimulus parameters and state of retinal adaptation.



a : peak of 'a' wave
b : peak of 'b' wave
c : 'c' wave
d : 'd' wave

e.r.p : early receptor potential
o.p : oscillatory potentials



The 'c' wave which follows is derived from the retinal pigment epithelium (Steinberg, Schmidt and Brown, 1970; Barlow, 1973) and is a slow component of low amplitude in humans and rarely used clinically. The subsequent 'd' wave is an off-effect at the end of a light stimulus and again is of very low amplitude and without present clinical use.

A number of 'minor' components of the ERG are now also recognisable. The early receptor potential (ERP) is a high frequency potential occurring before the 'a' wave. Discovered by Brown and Murakami (1964) the ERP comprises an initial negative peak of latency less than 25 μ.secs. followed by a larger positive peak of latency approximately 1 m.secs. Intracellular recordings showed the ERP to be of highest amplitude in the cone-rich foveal area (Brown, Watanbe and Murakami, 1965) and it appears to originate in the outer segments of the photo-receptors, suggesting that it is related to the photochemical processes occurring within (Davson, 1972). The ERP may be recorded clinically using a contact lens electrode and a bright flash stimulus is required to generate it (Yonemura and Kawasaki, 1967; Galloway, 1967) (see Figure 2.1.3.).

A number of ripples or oscillations in the ERG have also been described. Early workers (Einthoven and Jolly, 1908) reported superimposition of ripples on the basic ERG during recording from frog eyes when using high intensity

stimuli. Since the origin of these ripples was uncertain and they were considered to possibly originate from variations in the arc light used or the stimulus, they were excluded from their analysis of the ERG. Frohlich (1914) working on cephalopod eye also noted similar rhythmic activity, demonstrating that its frequency increased with increased flash stimulus intensity. Further evidence was presented by Chaffee, Bovie and Hampson (1923).

Little attention was paid to these fluctuations until Cobb and Morton (1954) demonstrated the phenomenon in man. Using a small platinum plate as the active electrode in contact with the unanaesthetised conjunctiva, an ERG was recorded in response to single bright flash stimuli. Superimposed on the ascending branch of the 'b' wave were four to six smaller waves of about 30 μV amplitude and at about 7 m.secs intervals. The first wave was only seen with the brightest flashes, but the number of waves did not vary with increase in stimulus intensity above that used initially. Local pressure on the eye resulting in temporary blindness (presumably due to transient hypoxia) caused little effect on the 'a' wave but abolished both the 'b' wave and the other superimposed components. Heck and Rendahl (1957) superimposed the successive responses which were produced by recurrent bright stimuli and described four peaks occurring in t he ERG which could be varied in amplitude by variation in the frequency of stimulation.

A number of terms for the waves has been used for example "humps" (Bornschein and Goodman, 1957), "multiple components" (Heck and Rendahl, 1957), 'e' waves (Cobb and Morton, 1961), "y-waves" (Aoki, 1960), "wavelets" (Galloway, 1981). "Oscillatory potential" was another description used (Yonemura, 1962a; Yonemura, Tsuzuki and Aoki, 1962b; Yonemura, Masuda and Hatta, 1963) and this has become the accepted term for these high frequency phenomena superimposed on the ascending branch of the ERG 'b' wave (see Figure 2.1.3.).

The oscillatory potential (OP), most easily recorded in response to high stimulus intensities, was considered to be a distinct, independent component of the ERG and was thought initially to originate in the bipolar cell layer (Yonemura, Aoki and Tsuzuki, 1962c) rather than being artifactual. In monkeys, Brown (1968) reported that the critical factor determining the presence of OPs was the state of the retinal vascular circulation. Clamping the circulation abolished the OPs, this also occurring in humans after central retinal artery occlusion (Thaler, Snyder, Kolder and Hayreh,1978). Reduction or disappearance of the OPs has been advocated as a monitoring index in the early detection of diabetic retinopathy (Galloway, Wells and Barber, 1972 and Galloway, 1981), in which the retinal microcirculation is disturbed. This observation implied that the OPs might originate in the inner portions of the retina. They are clearly demonstrated in vertebrates with well developed nuclear

layers and it has also been suggested that they are produced by the tangentially orientated components of this layer, that is, the amacrine cells. They may also reflect a feed-back circuit in the inner nuclear layer (Algvere, 1968; Brown, 1968; Algvere and Westbeck, 1972 and Ikeda, 1976).

Although the OP proper is a high frequency component superimposed on the ascending branch of the 'b' wave, rhythmic wavelets have also been reported following intense photic stimulation on the descending branch of the 'b' wave. Up to four such wavelets have been demonstrated having similar characteristics to the OPs on the ascending branch of the 'b' wave and this suggested similar origins for the components (Tsuchida, Kawasaki and Jacobson, 1971). These components do not appear to have been explored clinically.

The Optic Nerve

High frequency short latency discharges in the optic nerve following photic stimulation were demonstrated in the frog and conger eel before the advent of the VEP (Adrian and Matthews, 1927). The action currents with frequencies of up to 300/second were related to the intensity of stimulation. With increased intensity the latency of the response was reduced, the maximum frequency of oscillations was reached and the maximum frequency oscillations were produced more quickly than when using lower intensities. When the ERG (i.e. retinal response)

and optic nerve discharges were compared, the ERG 'a' wave occurred at a fixed interval before the beginning of the optic nerve discharge. This 'retina-nerve' interval was thought to be constant because of time lost in conduction through synapses of the retina. The effects of increased intensity were explained by assuming that when the illumination level was increased there was a spread of the excitatory process over more of the retina, thus stimulating more receptors.

These rhythmic oscillations were remarkably regular in appearance and early recordings from mammals were made by Granit (1933) who, working on decerebrate cats, found the usual frequency range of between 100 - 150/second and these oscillations increased in amplitude (but not in frequency) with increasedintensity of stimulation.

According to Granit (1947) the optic nerve discharge is determined by the excitation of ganglionic cells and the 'b' wave of the ERG.

Doty and Kimura (1963) showed in monkeys a series of rhythmic waves in the optic nerve and tract frequencies between 50/second when the animal was deeply anaesthetised and 160/second in a chronically prepared, unanaesthetised monkey. Although intensities of up to 12,700 candelas square metre were used, the high frequency oscillations appeared independent of intensity. An important observation in this study was that surface recordings were less than half the

amplitude of intra-cranial recordings because of the high-resistance connective tissue sheath surrounding the optic paths. Responses in the two optic tracts were very similar for stimulation of one eye and components of the ERG did not seem to be recorded from the optic tract. In addition, there was no attenuation of the response with distance from the retina, as shown by recording from electrodes at different points several millimetres apart along the tract, usually producing identical patterns of oscillation.

Doty, Kimura and Mogenson (1964) again working on monkeys showed an optic tract response beginning 10 - 12 m.secs after photic stimulation. Bright flashes from a stroboscope produced responses of shorter latency than those in response to less bright tungsten lamp stimuli. After the consistent initial positive component, oscillations with a frequency of 150 - 160/second were seen, usually reducing rapidly in amplitude and frequency. Deepening anaesthesia slowed and gradually diminished the response.

Ponte and Monaco (1964) carried out a comparative analysis of the corneal ERG and the potential recorded from the retrobulbar portion of the optic nerve in rabbits. It was suggested that owing to its stability, the optic nerve potential could be regarded like the ERG, as a good index of retinal activity. At high levels of stimulus intensity the optic nerve response consisted of several short latency spikes, while at lower intensities only the first spike was seen. An interesting finding in this study was that in

terms of latency the 'a' wave of the ERG always preceded the optic nerve discharge but the 'b' wave never preceded the optic nerve discharge. At low stimulus intensities the 'b' wave latency was much greater than the optic nerve discharge latency, but at higher intensities the latencies of the responses became much closer, on occasions occurring simultaneously. It was considered unlikely that the 'b' wave was directly related to the transmission of the optic nerve. The exact position of the electrode in the optic nerve is not clear and this may have an influence on the latency of the response from the optic nerve.

Steinberg (1966) used steel electrodes placed in the optic tract to record responses to flash stimuli. The ERG was recorded using a 1 mm. platinum disc electrode in contact with the cornea. During repetitive stimulation, OPs developed on the ascending branch of the ERG 'b' wave and there was a close relationship between this ERG event and the optic tract response which was oscillatory in nature, with a frequency of between 80-120/second. The optic tract response was unchanged by change in flash intensity or rate and could be recorded ipsilateral or contralateral to the stimulated eye. All recordings were from cats.

The OP of the ERG has become an established component in clinical use of the ERG. Several studies have been carried out to evaluate possible relationships between the OPs and similar oscillatory activity in the optic nerve

and tract. Yokoyama, Kaneko and Nakai (1964) made simultaneous recordings of corneal and intraretinal ERG and optic nerve response in rabbits. A relatively short time constant was used (between 0.1 - 0.003 sec.) to facilitate observation of oscillatory activity and bright flash stimuli were presented. Oscillatory activity in the optic nerve consisted of up to four waves and these were found to occur at almost identical latencies to the OPs of the ERG. On occasions, the optic nerve oscillations were found to be of slightly shorter latency than the OPs of the ERG. In some cases the responses in the optic nerve were ill-defined, but could usually be enhanced by changing the stimulus interval. Reduction of stimulus intensity using neutral density filters produced reduction in amplitude of oscillations and prolongation of latencies. The OPs recorded intraretinally at the posterior pole were found to precede those recorded via the cornea and the oscillatory activity of the optic nerve; when recorded intraretinally from the peripheral retina, the OPs were often preceded by the optic nerve response. Since a ganzfeld illumination system was not used, this difference was attributed to variation of illumination between central and peripheral retina. It was concluded that the OPs of the rabbit ERG have an initiator role for the rhythmic activity in the optic nerve.

Similar results were obtained by Yonemura, Tsuchida, Fujimura and Yamada (1967) who, working on rabbits, demonstrated a close time relationship between OPs of the ERG recorded in

the cornea and rhythmic activity of the optic nerve recorded via a platinum needle electrode inserted into the optic nerve. An initial on-wave and a terminal off-wave recorded at the beginning and end of the optic nerve response. Intra-vitreal injection of nembutal caused deterioration of OPs with associated reduction of the optic nerve response and the OPs were again considered as a possible 'pace-maker' for the optic nerve response.

Yonemura, Fujimura and Yamada (1968) studied the albino rabbit ERG and optic nerve response using intense xenon flash stimuli, well above the threshold of the OPs. Under these conditions the first component of the ERP was enhanced and exceeded the wave of the ERG. when the ERP was so large, a rapid potential was found to emerge preceding the early on-wave of the optic nerve response and when the intensity was increased even further this on-wave decreased in latency. This very short latency component was termed the 'short latency optic nerve potential' and differed from the on-wave in that its threshold was 10^6 - 10^7 times higher than that of the on-wave. Similar close time relations between the OPs of the ERG and the optic nerve response were demonstrated in the rabbit by Yokoyama and Taniguchi (1968).

Fujimura (1969) carried out a study of the ERG and optic nerve potential in rabbits using high intensity photic stimuli. The ERG was recorded corneally using a cotton

wick electrode on the limbus and the compound optic nerve responses was recorded intracranially using a coarse tungsten needle electrode. A common reference electrode was not used for both active electrodes, the corneal electrode being referred to the frontal bone and the optic nerve electrode referred to the occipital bone. The OPs demonstrated similarities to the optic nerve response and at the maximum stimulus intensity used (1.6 log units higher than the ERP threshold) the second component of the ERP exceeded the 'a' wave of the ERG in amplitude, but the periods of the OPs remained constant over the whole range of intensities used. The 'short latency optic nerve potential' (Yonemura et al., 1968) was demonstrated preceding the on-wave of the optic nerve response and on occasions fine wavelets were superimposed on this short latency potential. Possible inter-relations were suggested between the 'short latency optic nerve potential' and the ERP.

Yanagida (1978) studied the OPs and optic nerve potential in rabbits, showing that the wavelets of the on and off responses of the optic nerve potential had the same inter-peak intervals and threshold as those of the OPs, reinforcing the theory of interaction between two types of oscillatory activity.

Evidence of oscillatory activity in the optic nerve is clear in animals and its relationship to the OPs of the ERG is consistent. In humans, such literature is sparse.

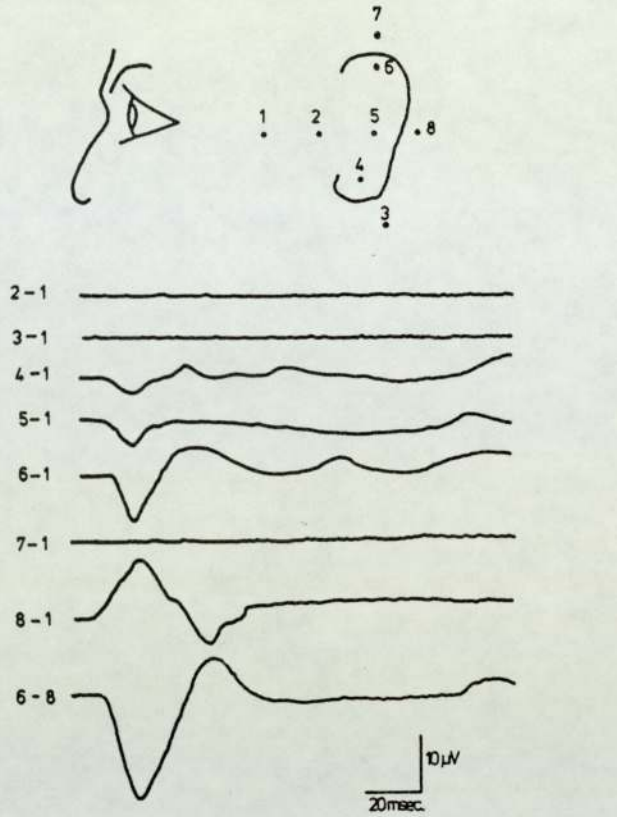
Van Hasselt (1972) made bipolar recordings of EPs from the lower lid, various sites on and around the external ear and from the occipital scalp. Stimuli consisted of 1 to 4 flashes/second, flash energy being 1 joule/flash. The responses to 64 flashes were averaged and are illustrated in Figure 2.1.4. They showed a positive potential of 10 m.secs. latency and of highest amplitude when recorded between the upper part of the external ear and the zygoma. When recordings made between the mastoid and zygoma were compared with those made between this site on the upper portion of the external ear and the mastoid, a clear phase-reversal (Harding, 1969) of components was demonstrated, indicating that the potential originated from the mastoid process. When this 'ear-mastoid' potential was recorded simultaneously with ERG and occipital VEP, the 'ear-mastoid' potential had a latency of 10 m.secs., 3 m.secs. longer than that of the ERG 'a' wave and considerably shorter than that of the occipital potential which showed a negative deflection with a latency of approximately 75 m.sec. (see Figure 2.1.4.). This potential was however, only recorded consistently in 3 out of 10 subjects; 6 subjects showed inconsistent or absent responses and the remaining 1 subject only gave a response on the left side of the head. A control study with the stimulator occluded but with the lamp flashing and with the gas discharge 'click' audible to the subjects showed absence of any response and was proof of a non-auditory origin of the component. Variation of muscular tension in the neck did not affect the response.

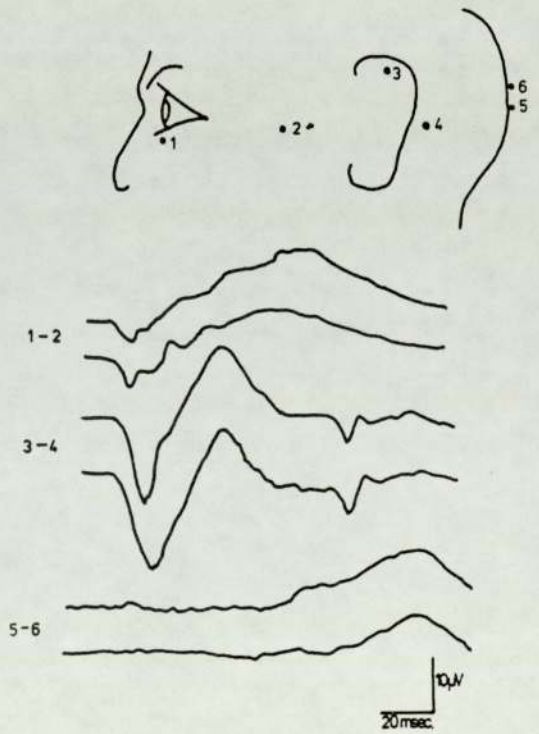
FIGURE 2.1.4.

Short latency visual evoked potentials

(redrawn after Van Hasselt, 1972)

The upper illustration shows potentials recorded using a number of derivations. The lower illustration shows a comparison of ERG (1-2), 'ear-mastoid' potential (3-4) and occipital potential (5-6) (see text for details)


7
6
1
2
5
8
4
3
2-1
3-1
4-1
5-1
6-1
7-1
8-1
6-8
10μV
20msec.


3
6
5
1
2
4
1-2
3-4
5-6
10μV
20msec.

On monocular stimulation, the 'ear-mastoid' potential could only be recorded on the ipsilateral side of the head to the eye stimulated and this, in addition to the preceding findings was concluded to be evidence of an optic nerve origin for the potential. The present author considers that the site from which the potential was maximally recorded would appear anatomically to be posterior to the optic nerve although it is possible that such a potential might be volume-conducted to this site. Although optimal stimuli were not used for production of OPs, several ripples may be seen in the illustration on the ascending branch of the ERG 'b' wave but there does not appear to be any relationship between these and the 'ear-mastoid' potential.

Honda and Okada (1976) recorded ERGs using skin electrodes placed at the medial and lateral canthi, using high gain and short time constants. When the eye was rotated nasally by 40° a normal ERG was recorded from the nasal electrode with approximate latencies of 18 and 45 m.sec. for the 'a' and 'b' waves respectively. On the record from the electrode at the lateral canthus was a series of fast potentials without any underlying slow components. These were up to 7 in number with latencies between approximately 15 and 80 m.secs. The major oscillations appear from the illustrations to occur between approximately 30 and 55 m.secs. The authors concluded that the wavelets in the

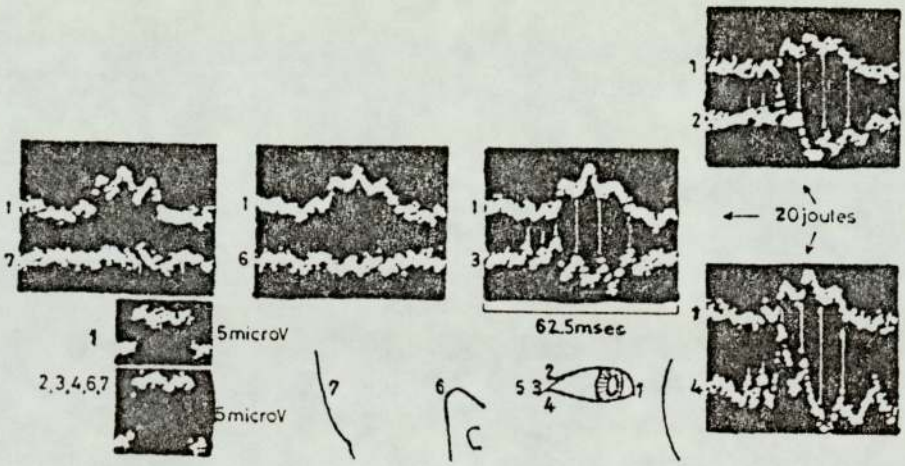
latter phases of the recording (and a time window of 135 m.secs. was used) had very similar latency values to those OPs on the descending branch of the ERG 'b' wave and that they were therefore remnants of these retinal OPs. The wavelets in the early phase were further investigated and it was suggested that the action potential of the optic nerve was a highly possible origin of the wavelets under this experimental condition of nasalward derivation of the eye, which they called 'ERG-neutralisation'. Other possibilities as to their origins included action potentials from extrinsic muscles or orbicularis oculi muscle, or retinal components spreading in a horizontal direction.

Honda (1977) described fast wavelets around the lateral canthus recorded during 'ERG-neutralisation'. Using an electrode at the nasal canthus to record a control ERG, responses at various other cephalic sites were recorded and compared with the control response (see Figure 2.1.5.). All electrodes were referred to linked earlobes. Thirty responses were averaged to 20 joule flashes at a rate of 1/second and a band pass of 100Hz. was used. Under these conditions the control ERG consisted of 'a' and 'b' wave with OPs on both ascending and descending branches of the 'b'wave. In the recording from electrodes around the lateral canthus several wavelets were seen. The latencies of these wavelets (measured to their positive peaks) were 13-15, 18-20, 24-26, 30-31, 37-38 and 44-46 m.secs. respectively. Comparison of the last three sets of wavelets

FIGURE 2.1.5.

Fast wavelets recorded through orbital skin-electrodes near the lateral canthus (Honda, 1977)

Record 1 acts as a control ERG - with which all other records are compared. A number of wavelets are seen, predominantly in records from the lateral canthus (see text for details)


1
2
20joules
1
7
1
6
1
3
62.5msec
1
4
1
5microV
2,3,4,6,7
5microV
7
6
C
5 3 2 4 1

with the control ERG showed a close latency relationship with the OPs superimposed on the descending branch of the b wave. However, the first two or three wavelets did not show consistent correlation with OPs of the ERG and were therefore not regarded as being of ERG origin. The optic nerve was considered as a highly possible source of these early wavelets especially since due to the nasalward deviation of the globe the optic nerve would be simultaneously displaced laterally bringing it closer to the lateral canthus. The possibility that the extraocular or peri-ocular musculature might contribute such components was discounted on the basis that the frequency of the wavelets recorded was very different from the accepted frequencies for muscle action potentials.

Similar conclusions were reached by Siegfried (1980). An active electrode was placed on the temple, approximately 2 cm. from the lateral canthus and on a level with the eye. This was referred to an electrode on the ipsilateral earlobe. A band pass of 1Hz. to 2500Hz. was used and in all recordings from the temple the responses to 1000 flashes presented monocularly at a rate of 2/second were averaged. Serving as controls, recordings were made between temple and earlobe on the side of the head contralateral to the stimulated eye; the ERG was monitored using a platinum corneal electrode referred to the ipsilateral cheek and responses to 100 stimuli averaged; the cortical VEP was monitored using an active midline electrode 1 cm. anterior to the inion and referred to the earlobe. Recordings from the temple consisted of a negative component

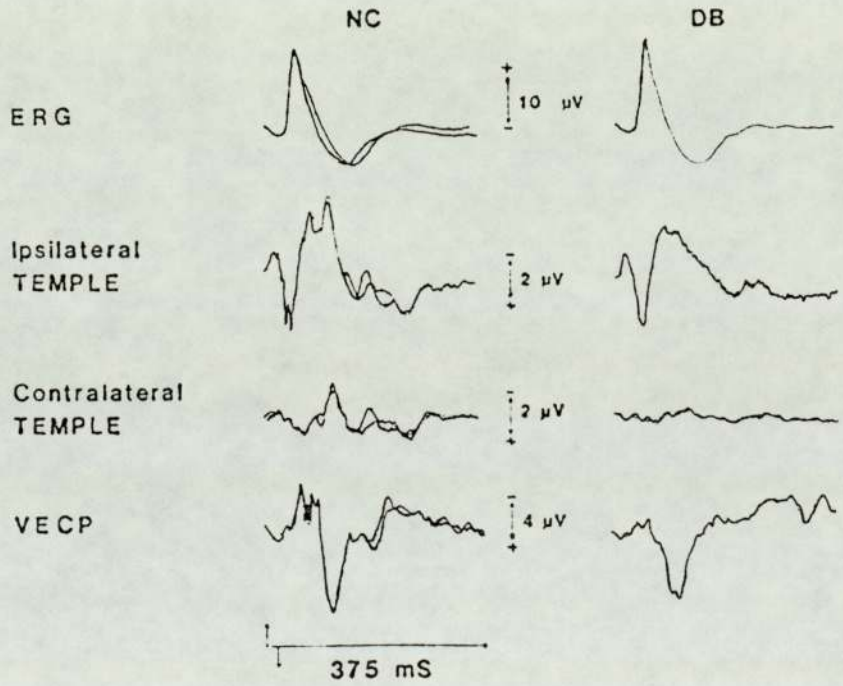
with a latency of approximately 20-23 m.secs., a positive component between 40 and 47 m.secs. and a later negative at 90-95 m.secs. The amplitude of the positive component was between 3 and 4μV.. The response was repeatable and could be recorded consistently from the temple ipsilateral to the stimulated eye but little or no response could be recorded from the contralateral temple (see Figure 2.1.6.).

Latencies of the ERG, cortical VEP and 'temple-potential' were compared and did not appear to bear any relationship to one another and it was concluded that the 'temple potential' was a phenomenon unrelated to ERG or cortical VEP. In a case of unilateral optic neuritis the cortical VEP showed characteristic amplitude reduction and latency delay on stimulation of the affected eye. The 'temple potential' from the affected eye showed a reduction in amplitude and doubling of the waveform with several oscillations being demonstrated. In a patient with confirmed retinitis pigmentosa, simultaneous recording of ERG, 'temple potential' and cortical VEP showed almost total extinction of the ERG but preservation of the 'temple potential' and cortical VEP, although the recording from the temple in this particular case was not well defined. The conclusion reached from these results was that the 'temple potential' was a reflection of optic nerve activity. The present author makes the observation that different stimulus parameters were used for the recording of the ERG and 'temple potential' (only 100 sweeps were averaged in the case of the ERG) and that a

FIGURE 2.1.6.

Early potentials recorded at the temple region of the scalp (Siegfried, 1980)

ERG, 'temple potential' and VECP recordings during monocular stimulation show different components, appearing unrelated. Absence of potentials at the temple contralateral to eye stimulated indicates prechiasmal origin of the potentials (see text for details)


NC
DB
ERG
10 µV
Ipsilateral
TEMPLE
2 µV
Contralateral
TEMPLE
2 µV
VECP
4 µV
375 mS

common reference site was not used for the recording of the ERG and 'temple potential'. These factors might lead to variations and differences in the recorded waveforms.

It is noteworthy that the potentials described by Siegfried (1980) and those described by Van Hasselt (1972) although both being attributed to optic nerve activity are of considerably different latency.

Lateral Geniculate Body and Optic Radiation

Although Goff et al. (1978) in a review of human EPs stated that short latency VEP components reflecting subcortical activity had not up till that time been described, there are several reports in the literature of animal studies.

Doty et al. (1964) described depth recorded photically elicited oscillations in the lateral geniculate body of monkeys. The records shared many of the characteristics of the optic tract oscillations and the onset of the response was between 3-6 m.secs. later than the response of the optic tract. Responses were also noted from the superior colliculus when using intense photic stimulation. These had a typical latency of 22 m.secs. (being 3-6 m.sec. longer than the lateral geniculate body response) and were generally monophasic and of positive polarity. Responses in the optic radiation were also detected, again of oscillatory nature.

Yokoyama, Nakai and Taniguchi (1966) commented that since oscillatory activity had been demonstrated in the optic nerve of rabbits (Tsuchida et al. 1967; Yonemura et al. 1968; Fujimura, 1969 and Yanagida, 1978) and was similar to the OPs of the ERG, such activity might be recorded at more distant structures from the retina. In their study, recordings were made of corneal and intra-retinal ERG and from the lateral geniculate body and flashes of energy 1.4 joules/flash were delivered. Depending on the position of the recording electrode in the lateral geniculate body, oscillatory activity very similar to that of the optic nerve could be seen in the presynaptic areas; a similar oscillatory pattern was seen in the post-synaptic areas of the lateral geniculate body, being described as 'mainly negative deflections' and different from the presynaptic responses which were 'mainly positive deflections'. The rhythm in the presynaptic volley was faithfully followed by post-synaptic neurones. Under certain stimulus conditions comparison of simultaneously recorded ERG and lateral geniculate body potentials revealed parallel behaviours. The intervals between peaks of OPs and peaks of lateral geniculate body oscillations corresponded closely and with decreasing stimulus intensity both oscillatory activities gradually became attenuated. This led to a conclusion that some part of the retinal OP was conductile in nature and it is rather surprising that the frequency of the rhythm is hardly altered despite processes occurring along the visual pathway. The authors postulated that in the lateral

geniculate body some of the synaptic mechanisms might serve in part to 'rebuild' the response pattern, re-establishing the rhythm.

The ERG, optic nerve and subcortical responses were recorded in albino rabbits by Yonemura, Tsuchida, Fujimura and Yamada (1967) in order to investigate possible relationships between the respective oscillatory activities that had been demonstrated. The ERG was recorded with a saline-soaked cotton electrode on the cornea, the optic nerve potential was recorded using an intracranial platinum needle electrode and the subcortical potential was recorded using a similar platinum needle electrode whose tip was located "3mm. deep from the cortical surface at a point of the visual area 1". The exact location of this electrode is not clear to the present author, and the paper contained no illustrations. The optic nerve electrode was referred to the frontal bone, the subcortical electrode referred to the occipital portion of the cranium. Optic nerve wavelets had similar morphology and behaviour to the retina OPs. The subcortical response was similarly rhythmic with close time relations to the ERG and optic nerve response.

In a further study (Yonemura, Yamada, Tsuchida, Fujimura and Morita, 1968) a tungsten needle electrode was inserted into the LGB of rabbits and referred to the frontal bone. A response could be elicited when a strong light flash was used and was generally biphasic (positive-negative).

The authors suggested that it was probably produced post-synaptically and that it was closely related to the short latency optic nerve discharge.

Yamada (1968) recorded responses in the rabbit lateral geniculate body, contralateral to the stimulated eye using tungsten microelectrodes. Two components of the response were demonstrated - a very short latency component (up to 12 m.sec.) followed by a further component of slightly longer latency. The level of illumination at which the short latency lateral geniculate body discharge was abolished approximated that at which the short latency optic nerve response was suppressed and it was concluded that part of the optic nerve response reached the lateral geniculate body.

Simultaneous recordings of ERG, lateral geniculate body response and cortical VEP were made in rabbits by Honda, Okada and Nishida (1974). The technique employed implantation of electrodes into the lateral geniculate body and primary visual cortex and a minimum period of 1 week was allowed for stabilisation before recordings were made. A bipolar electrode was used in the lateral geniculate body whereas a single electrode was placed in the visual cortex and referred to the frontal bone. The ERG was recorded using a contact lens referred to the upper orbital margin of the same eye. Different time constants were used for all three recording channels and ten responses were averaged. Responses recorded from the lateral

geniculate body were shown to be independent of the ERG and cortical VEP as shown after coagulation of the respective portion of the lateral geniculate body where the electrodes were placed producing loss of EP from this area. However, the ERG was unaffected and the authors stated that the cortical VEP was little affected, only the initial negative deflection decreasing in amplitude. Even after complete disappearance of lateral geniculate body responses a cortical VEP could be recorded. During dark adaptation, the amplitude of the lateral geniculate response did not seem to be significantly changed, while the amplitude of the ERG increased. Repeatability of the responses was checked over a period of a month and found to be good, although the pattern of responses was not always identical between each animal. They concluded that analysis of latency and amplitude was of no great value when comparing responses from different animals.

Hughes and Mazurowski (1963) working on monkeys, described fast oscillatory rhythms in response to single flashes, from subcortical regions, but not so prominently from the cortex and commented that the activity might be a general property of the entire visual system, possibly 'driven' by the retinal response. Similar results were obtained by Hughes (1964) who examined the cortical response of monkeys to photic stimulation showing the largest number of wavelets to occur with the most intense stimuli and in the most alert states of awareness.

In humans, Gastaut (1949a) described simultaneous recording of photic EPs at the level of the retina and the optic radiations. Using flash stimuli of up to 8 flashes/second, responses were obtained from the optic radiation by an electrode introduced after trepanation of the skull. Gastaut (1949b) described a procedure by which electrical activity was recorded in a variety of patients at three levels of the visual pathway - the ERG was recorded using a contact lens electrode referred to a supraorbital skin electrode; recordings from the optic radiations or their vicinity made using bipolar needle electrodes inserted via trepanation holes in the skull (the response being called the 'electrosubcorticogram'); the occipital response recorded using occipital scalp electrodes (the response being called simply the 'electroencephalogram'). The ongoing spontaneous EEG was recorded and also that activity evoked by single and repetitive photic stimuli. Typical ERGs were recorded from the eye; in the subcortical regions two types of response were distinguished which were termed the primary and secondary responses. The primary response always began with an initial positive component with a latency of approximately 50 m.sec. followed by a negative component at approximately 70 m.sec. and a further positive component at 90 m.sec., several other slower waves continuing after this. A waveform of a simpler monophasic morphology was sometimes seen with a positive deflection at approximately 30-35 m.sec.. The secondary response always began with an initial negative component at a latency of approximately 20 m.sec. followed by the positive component at approximately 30-35 m.secs..

The author commented that it was not rare to encounter both types of response in the same subject but that the primary response was more common. The hypothesis proposed for the responses was that the primary response was probably related to the actual neural transmission via the optic radiation; the secondary response was probably related to the alpha rhythm.

Jouvet and Courjon (1958) implanted electrodes into the optic radiation of six patients prior to neurosurgical procedures and recorded the EPs to light flashes presented at a rate of 1/second. The effects of attention to the stimulus were also investigated and the amplitude of the recorded response was found to be much higher when the patient concentrated on the stimulus, reducing significantly if concentration was lost and even disappearing altogether on occasions. One record is illustrated in this brief report and the optic radiation response would appear to be of high frequency and polyphasic in morphology, but accurate measurements of absolute latency are not possible.

During recordings between lateral canthus and linked earlobes during ERG-neutralisation (Honda and Okada, 1976 and Honda, 1977) a series of fast oscillatory wavelets was demonstrated. Those occurring between 24 and 38 m.sec. were identified as being related to the OPs of the ERG, but two or three sets of wavelets occurring earlier than this did not appear to be related to the OPs and although

the strongest possibility as to their origin appeared to be the optic nerve, it was also considered that they might be action potentials from the lateral geniculate body, although this would seem unlikely since the lateral canthus is anatomically far from the lateral geniculate body (the reader is referred back to Figure 2.1.5.).

Spire and Hosobuchi (1980) reported depth recordings of an EP from the geniculate region in man. The recording electrode was actually placed in the left optic radiation 4mm. anterior to the lateral geniculate body. Recording of a flash EP from this site demonstrated a potential with a latency of 20-23 m.sec.. Unfortunately, the polarity of this response was not reported, but the authors commented that this was the same latency as the onset of the ERG 'b' wave. This was further evidence of the long latency of the pre-geniculate visual pathway and the authors regarded that intra-retinal processing accounted in part for the delay of the early components of the scalp recorded human VEP.

Visual Cortex

Early components of the VEP have occasionally been mentioned in reports of VEP recordings from the occipital region of the scalp. Monnier (1949a) recorded the ERG and cortical response, stating that the main component of the ERG was the 'b' wave occurring between 30-40 m.sec. after a flash. The most consistent

component of the cortical response was generally a slow, surface positive monophasic potential occurring at 90-120 m.sec.. Earlier components of the cortical response were much more difficult to detect but consisted of a diphasic potential, initially positive with a latency of approximately 40 m.sec.

Employing Dawson's superimposition technique, Cobb (1950) used an active electrode at the inion referred to an electrode up to 18cms. away (the site of the reference electrode not being stated). Brief high intensity full field flashes were delivered and the responses to 50 flashes were superimposed. Considerable individual variations in both form and latency were found but most responses tended to be oscillatory with a frequency of approximately 10/second. Typically, the first phase tended to be the most variable between subjects - in some subjects the latency was at least 60 m.sec., while in others it was not more than 35 m.sec.. In an extension of this work (Cobb and Morton, 1952) the ERG was compared with the cortical response to high intensity flashes. A small positive deflection with a latency of 22-28 m.sec. was noted, followed by a negative at 45 m.sec. and a larger, more constant positive deflection at 70-88 m.sec.. The possibility that the earliest, positive deflection might be an artifact generated by the ERG could not be excluded; however the cortical response at the same latency as the 'b' wave of the ERG was of opposite polarity (negative) and this excluded direct spread of the ERG

over the convexity of the scalp, but transmission along a shorter route - the base of the brain - was considered possible. The illustrations of this paper demonstrate the relative crudity of the technique used and indeed the authors commented that the equipment used was worked at about its limit of resolution, hindering clear separation of the possible retinal and cerebral potentials at the occiput.

These results are similar to those of Monnier (1952) who recorded the cortical response using a variety of bipolar derivations around the occiput. The ERG was recorded via the cornea using a variety of contact and skin electrodes. The earliest VEP component was recorded with a bipolar derivation above the inion and consisted of a small, positive deflection with a latency of 35 $\pm$ 4 m.sec.. Fifty-three records were taken from 3 subjects and this early component was only seen in 26 out of 53, the chief later component (latency 95-115 m.sec.) being seen in 40 out of the 53 records. The early component was given the designation 'potential b', since it corresponded in time with the 'b' wave of the ERG. The author proposed that its positivity suggested it consisted of afferent impulses of the optic pathways to the cortex. The difference in latency between the component of Monnier (1952) and Cobb and Morton (1952) is probably due to differences in stimulus intensity and recording montage.

The concept of 'retino-cortical time' was introduced by

Monnier (1952) - the chief component of the ERG was regarded as the 'b' wave and the latency to onset of the 'b' wave was termed the 'retinal time'; the latency to onset of the first component of the cortical response was termed 'cortical time' and the 'retino-cortical time' was calculated by subtracting retinal time from cortical time. (See Figure 2.1.7.). More recently, Spekreijse, Eztevez and Reits (1977) on the assumption that a myelinated optic nerve fibre with a diameter of 1 μm. could conduct nerve impulses at a velocity of about 6m/second, calculated in man that if the total length of the visual pathway from eye to visual cortex was approximately 20 cm., the time between the onset of the photoreceptor response (ERG) and the arrival of the afferent volley in area 17 would be approximately 35 m.sec., an average value corresponding to the latency of the primary VEP component (when demonstrable).

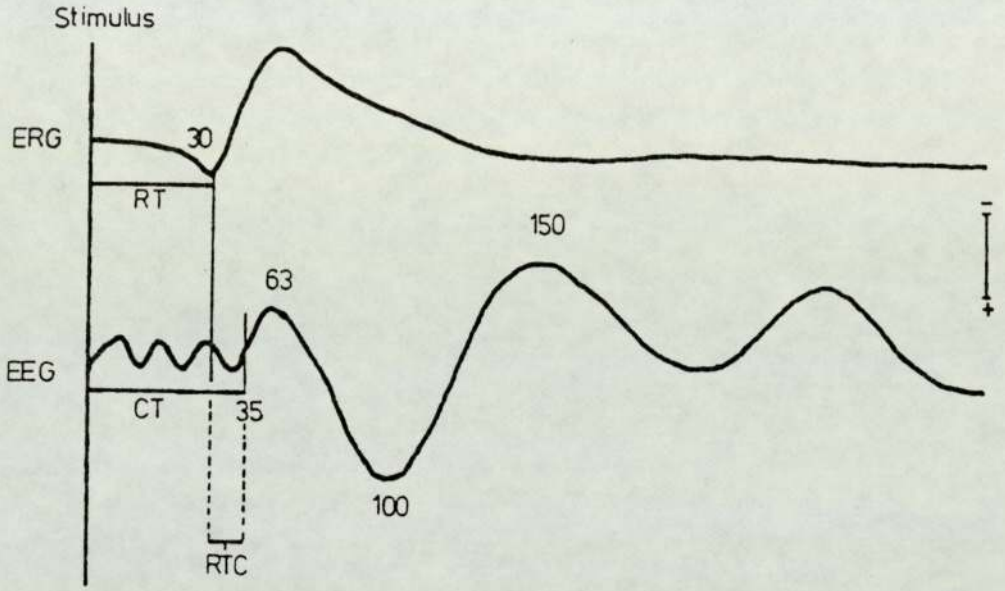
Calvet et al. (1956) used a photographic integration technique to record the cortical response from a midline occipital electrode 1 cm. above the inion. An initial positive component was seen at 30-40 m.sec.. Further evidence of this early positive component was produced by Monnier (1957) who reported a positive deflection at 37.5 m.sec..

Cobb and Dawson (1960) studied occipital potentials evoked by bright flashes in 11 adult subjects. Between 55 and 220 flashes were presented and potentials were recorded from a variety of electrodes around the occiput. The

FIGURE 2.1.7.

Simultaneous recording of ERG and cortical EEG response (modified after Monnier, 1952)

Retino-cortical time was calculated by subtracting the latency of the earliest deflection in the ERG (retinal time) from the latency of the earliest deflection in the cortical EEG response (cortical time) (see text for details)



RT Retinal time
CT Cortical time
RTC Retino - cortical time

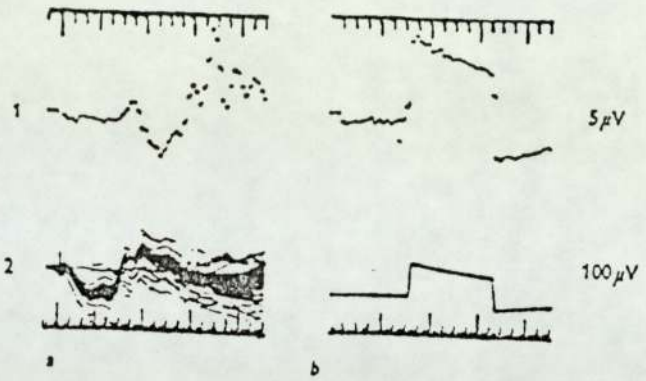
initial deflection in the VEP, detected in 9 out of 11 subjects, had a latency of 20-25 m.sec. and an average amplitude of 1-1.5uV. (see Figure 2.1.8). The following deflection was negative at 40-50 m.sec.. Since none of the deflections of the VEP had the same time course as the ERG it seemed unlikely that the spread of current from the ERG played any significant part in producing the occipital potential. Auditory, electrical and photo-electric origins for the occipital potential were all excluded. When the strength of the flash was reduced, the latency of the early components increased and their amplitudes became reduced (see Figure 2.1.8). The second, negative component of the VEP was found to be enhanced when attention was paid to the stimulus, but the first, positive deflection was found unaffected by state of attention. Similar results were observed by Werre, Smith and Beck (1962). Cobb and Dawson (1960) suggested that although the initial wave had rarely been reported, differences between reports were probably due to the minute amplitude of such early components. With the technique of averaging however, the initial wave was a constant feature of the responses and its clarity was improved.

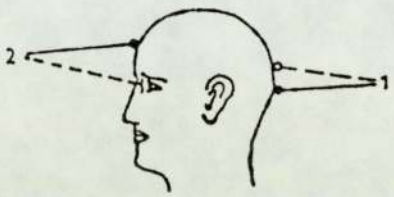
This viewpoint was substantiated by Contamin and Cathala (1961) who reported the irregular occurence of early components, but considered that the more consistent incidence reported by Cobb and Dawson (1960) was due to the higher intensity of stimulation used and the greater

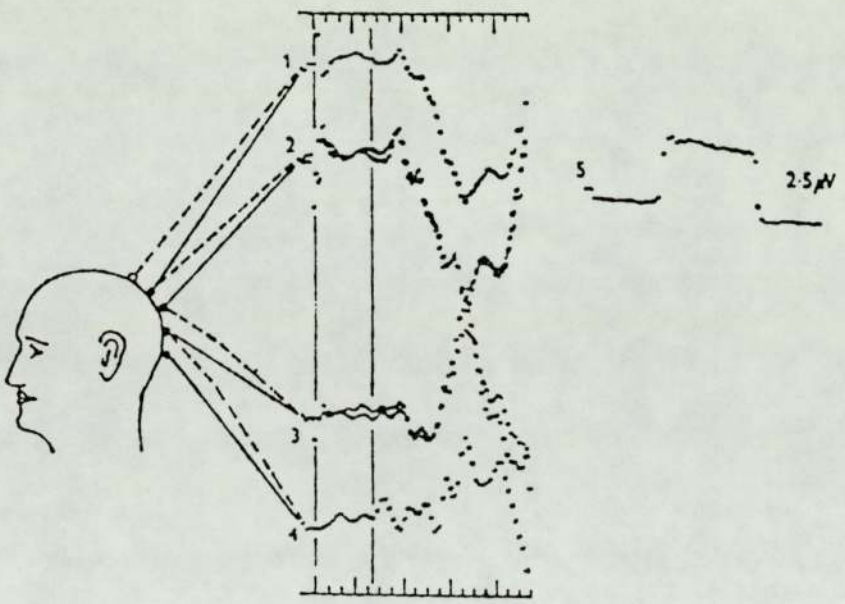
FIGURE 2.1.8.

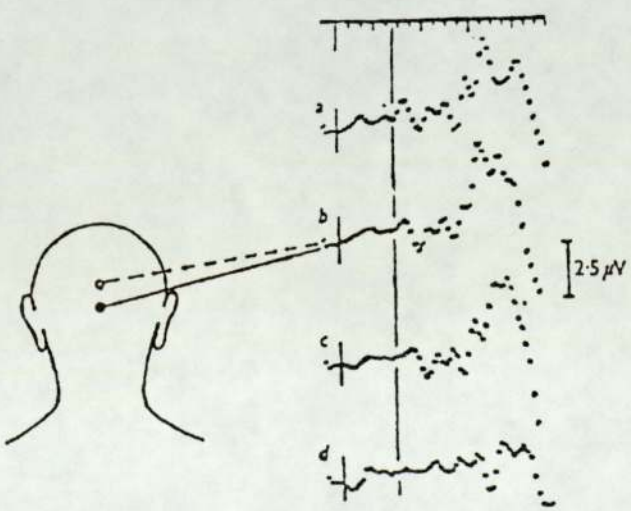
Occipital potentials evoked by bright flashes (Cobb and Dawson, 1960)

The top illustration shows simultaneous recording of ERG and occipital potential. The occipital response begins with early deflections at 20-25 m.sec. The middle illustration shows records from different midline electrode pairs. The bottom illustration shows the effects of different intensities, reducing from a to d, early components being better defined at higher intensities. The time scale shows 5 and 20 m.sec. intervals in all cases (see text for details)


1
5μV
2
100μV
a
b


2
1


1
2
3
4
5
2·5μV


a
b
c
d
2·5μV

sensitivity of their equipment.

Ciganek (1961) who produced one of the first morphological descriptions of the human VEP reported results on 75 subjects. The montage used was O_Z referred to P_Z and flash stimuli delivered at various rates. A positive component was seen at 28.62 $\pm$ 4.76 m.sec., followed by a negative component (component I) at 39.12 $\pm$ 4.18 m.sec.. The amplitude of this negative component was 2.93 $\pm$ 1.6uV.. The component that followed (component II) was positive and had a mean latency of 53.4 $\pm$ 4.42 m.sec.. The primary response (waves I-III) was considered to be that specifically evoked in area 17 due to its short latency and its resistance to variation in stimulus frequency. In a later report (Ciganek, 1965) a comparison was made between visual and auditory EPs in 30 subjects. Examination of the photically evoked waveforms (recorded using the same montage as Ciganek (1961)) reveals a negative component at 18 m.sec., a positive at approximately 23 m.sec., a negative at approximately 33 m.sec. and a positive at approximately 45 m.sec.. The time base used in this report is significantly longer than that used in the earlier report (Ciganek, 1961)., and the present author considers that this factor might influence the observation of early components, the use of a short time base providing better resolution of the components. Ciganek (1969) assessed the variability of the human VEP, concluding that amplitude variability of most components was high and latency values were less variable; latency variability was found to be

greater with the long latency components than the short latency components.

In an early report of the use of the VEP in patients with lesions of the visual pathway (Vaughan and Katzman, 1963) the VEP and ERG were recorded simultaneously in response to a stroboscopic flash. In patients with presumed subcortical lesions the early negative wave alone was depressed or absent, whereas in patients with cortical involvement disortion and increased latency of the later phases was shown. Unfortunately, the authors do not state the latency of the early negative wave. However, a fuller report (Vaughan and Katzman, 1964) described the normal VEP in 45 control subjects and the effects on the VEP in a series of patients with lesions at various sites along the visual pathway. In the normal subjects the VER (derived from active electrodes 1 cm. above and 3 cm. lateral to the inion referred to the vertex) was recorded in response to approximately 200 flashes and showed a negative component at approximately 35 m.sec. followed by a positive at 48 m.sec.. The first wave was present in 67% of subjects, the second wave was present in 97% of subjects. In pathologies of the visual pathway, geniculocalcarine lesions produced loss of the early response while later components often persisted and non-specific projections were considered to contribute to the production of the later components.

A paper providing normative data of the human VEP was

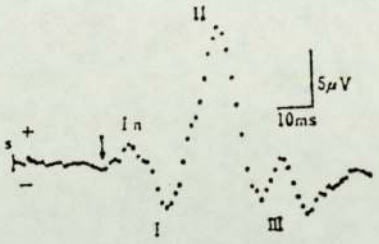
published by Kooi and Bagchi (1964) based on the results of 100 adult subjects. A number of derivations was used, to include a variety of different reference sites, and moderately high flash stimuli were delivered. A small surface positive deflection of latency between 20 and 30 m.sec. was seen in about half the subjects, followed by a more consistent negative component of latency between 30-42.5 m.sec.. In some subjects rapid deflections were seen in the early phases similar to those of Cobb and Dawson (1960); the authors considered that they might be, in part, neurogenic in origin, although they did not discount the possibility of a myoclonic origin.

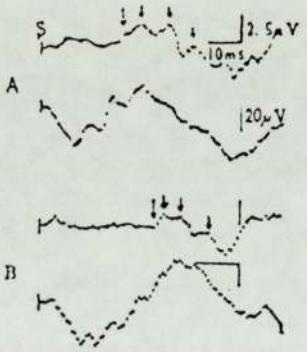
Simultaneous recordings of ERG and VEP were performed by Yokoyama, Taniguti and Yonekura (1966) in order to assess the relationship between the OPs of the ERG 'b' wave and the 'on' rhythms arising in the early phase of the occipital VEP. Sixty to eighty responses were averaged and an initial positive component was illustrated at approximately 24 m.sec., followed by a negative component at approximately 30 m.sec. and a further positive component at 40 m.sec.. OPs of the ERG were often seen to be synchronised with oscillations in the VEP (see Figure 2.1.9). This 'on' rhythm was particularly attenuated in a patient suffering from central retinal pathology ('central retinitis') although to a lesser extent in a smaller central lesion (a macular hole). The rhythm was also generally reduced in lesions of the papillo-macular bundle (a case of unilateral retrobulbar neuritis being

FIGURE 2.1.9.

Oscillations in the VER and ERG (Yokoyama, Taniguti and Yonekura, 1966)

The upper illustration shows the primary response of the human VER, consisting of a number of early deflections. The lower illustration shows two pairs of simultaneously recorded VER (upper trace of each pair) and ERG (lower trace of each pair). A number of oscillations (demarcated by arrows) are shown in the VER with corresponding oscillations in the ERG (see text for details)


II
5μV
10ms
+
In
−
I
III


S
2.5μV
10ms
A
20μV
B

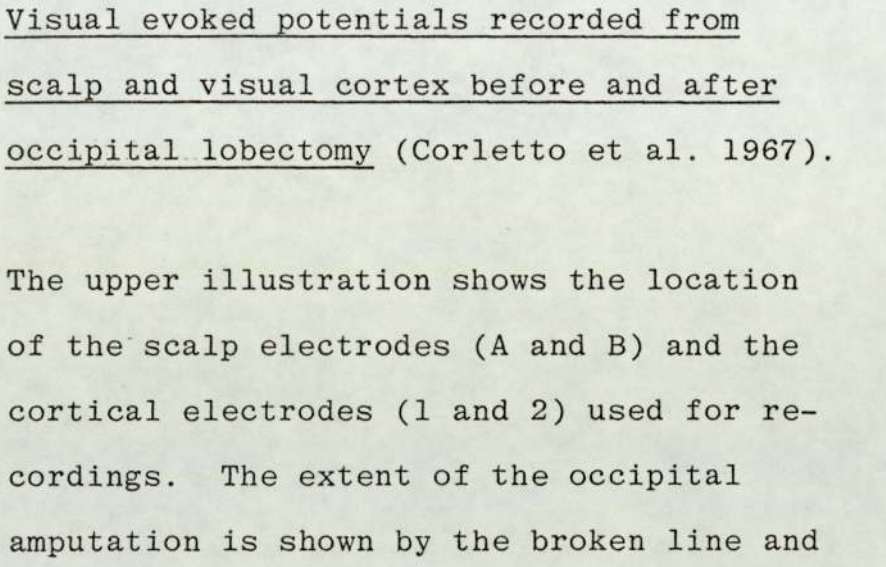
illustrated). These findings were substantiated by Abdullaev, Gadzhieva, Geretienko and Dimitrenko (1975) who found a definite temporal correlation between the formation of the first two OPs of the ERG and the first two components of the cortical EP. The interrelations between the later OPs and the late components of the cortical EP were described as being 'more complicated'.

The records of Suga, Yokoyama and Taniguchi (1966) show a extremely low amplitude negative deflection at 22 m.sec., followed by a positive component at 26 m.secs. and a further negative component at 38 m.sec. when recorded between occiput and earlobe reference. The initial positive component was shown to be recorded more distinctly with a monopolar lead than with a bipolar one.

An ideal clinical case to assess the origins of the early components of the VEP was described by Corletto et al. (1967) who recorded the VEP from the scalp and the visual cortex before and after surgical removal of the occipital pole. The patient was a 26 year old male epileptic who failed to respond to drug therapy. Scalp electrodes were placed 3 cm. above and 3 cm. lateral to the inion and referred to parietal electrodes 7 cm. lateral to the mid-line. The cortical electrodes consisting of chlorided 2 mm. silver balls were placed at several points on the external and medial surfaces of the occipital pole and on the posterior part of the parietal lobe. Fifty to one hundred flash EPs were averaged. The scalp recorded VEP

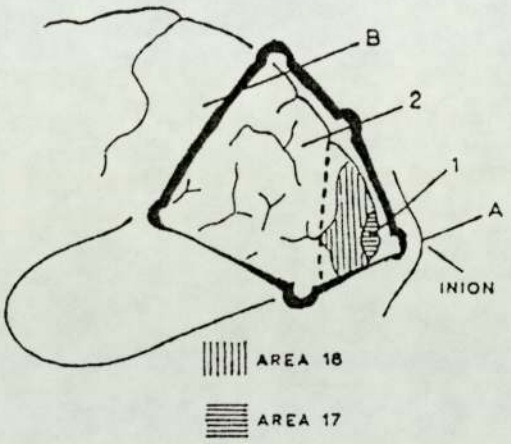
consisted of a low amplitude positive component of peak latency 28 m.sec. followed by a negative component at 40 m.sec. and several later components of alternating polarity. The response recorded directly from the occipital cortex varied in appearance depending on the site of the recording electrode, but when one electrode was placed approximately at Brodmann's area 17 and the other at the border of the occipital and parietal lobes, the response was similar to that recorded from the scalp. However, an additional negative component was seen at approximately 23 m.sec, preceding the positive component at 28 m.sec., which was of higher amplitude, as was the following negative component. Generally, the whole response was of larger amplitude when recorded directly from the occipital cortex. The VEP was then recorded 18 days after surgical removal of the occipital pole and showed preservation of the initial positive component around 28 m.secs. and the following negative component at approximately 40 m.sec., However, the later component were significantly difference from the pre-surgery recordings, as shown in Figure 2.1,10,. The persistence of the early components with latencies less than 45 m.sec. after ablation of the occipital pole was highly suggestive of a non-cortical origin of the components, particularly since later components were affected. In a similar study (Saletu, Itil and Saletu, 1971) EPs were studied in a patient after a left hemispherectomy. Fifty flash stimuli were delivered and typical VEP recordings were derived from the right hemisphere using an occipital

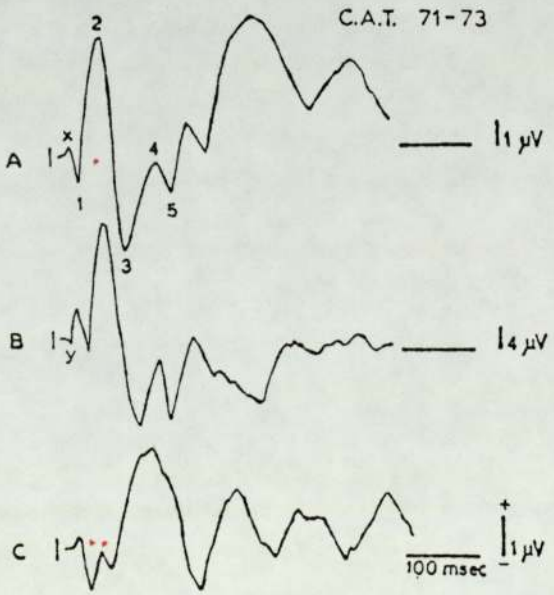
FIGURE 2.1.10.



Visual evoked potentials recorded from scalp and visual cortex before and after occipital lobectomy (Corletto et al. 1967).

The upper illustration shows the location of the scalp electrodes (A and B) and the cortical electrodes (1 and 2) used for recordings. The extent of the occipital amputation is shown by the broken line and the approximate location of Brodmann's areas 17 and 18 is illustrated. The lower illustration shows the scalp recorded VEP (A: before, C: after, surgical removal of occipital pole) and the depth recordings from the cerebral cortex (B). Early components remain after surgical removal of the occipital pole, although later components are significantly different. An additional early component (y) is seen when depth recording was performed and all early components are of higher amplitude when recorded directly from the cortex (see text for details)


B
2
1
A
INION
AREA 18
AREA 17


C.A.T. 71-73
A
B
C
1
2
3
4
5
x
y
11 μV
14 μV
100 msec
1 μV

electrode placed 3 cm. laterally to the right side of the inion and referred to an electrode 7 cm. anterior in the same parasaggital plane. They could not be recorded on the operated side, although low voltage long latency waves (60-100 m.sec.) were sometimes seen, thought to originate in the thalamus. In contrast, auditory tones did evoke consistent responses on both sides, recorded from electrodes 5 cm. lateral to either side of the vertex and referred to the ears.

Vaughan and Cross (1969) studied the VEP recorded in various cephalic regions of unanaesthetised monkeys before and after surgically induced lesions at various sites along the visual pathway in order to assess relative contributions of ipsilateral and contralateral, cortical and subcortical structures to the VEP recorded at the occipital (striate) cortex. Superimposed on the main occipital VEP (which consisted of a negative deflection at 57 $\pm$ 3 m.sec. followed by a positive deflection at 136 $\pm$ 14 m.sec.) were a number of small wavelets each having a duration of 6-13 m.secs.. The maximum number of wavelets seen was nine, the first peaking at 36 m.sec. and the last at 120 m.sec.. When intensity was reduced the wavelets could no longer be identified. Responses from the parietal cortex were similar in overall configuration to the striate responses. Wavelets were again demonstrated. The responses from inferotemporal cortex and frontal cortex differed substantially from those of the parietal and striate cortex. Ipsilateral optic tract section eliminated the wavelets in the striate responses also reducing the

amplitude of the background VEP. Contralaterally, all components of the striate VEP were reduced in amplitude except the wavelets, which were unaffected. Ipsilateral geniculocalcarine input therefore seemed responsible for the wavelets. The responses from the posterior parietal cortex were less affected, but the amplitudes were decreased and ipsilaterally to the optic tract section the wavelets of the parietal response were abolished. After unilateral striate cortex ablation the basic striate VEP from the unaffected cortex was attenuated but the wavelets appeared unchanged. The parietal responses again showed bilateral reduction of the VEP and ipsilateral elimination of the wavelets. Since the wavelets in the striate responses were eliminated by ipsilateral section of the optic tract but unaffected by contralateral tract section or contralateral striate lesions, it suggests that the wavelets reflect the geniculocalcarine input to the striate cortex. This conclusion was endorsed by Riggs (1969) who considered that the early wavelets of the cortical VEP might originate in the optic tract but that the major portions originated in the cortical cells that the tract innervates and by Picton and Hink (1974) who considered that the early components of the VEP perhaps represent activity in the lateral geniculate body or geniculocalcarine tract.

Wilson and Nashold (1969) recorded the VEP of the human subcortex using implanted stainless steel electrodes in a variety of the subcortical nuclei. Responses to flash

stimuli were of short latency. A further report (Wilson and Nashold, 1973) of 13 patients who were investigated during stereoencephalotomy showed that short latency responses could be recorded in response to strong photic stimuli in the region of the thalamus and midbrain. The waveforms (recorded bipolarly) were either 'W' shaped or biphasic. Absolute latencies of the components were not reported.

Borda (1977) advocated the use of flash stimulation particularly in cases of poor subject co-operation and the shortest latency component that could be recorded in a high proportion of normals was a negative component at 40 m.sec., followed by a positive component around 70 m.sec. (recorded using occipital electrodes 2 cm. above the inion and 3 cm. from the midline referred to linked earlobes). In addition, an electrode was placed at the vertex and a response recorded from this site (again referred to linked earlobes) was suggested to represent optic impulses reaching the brainstem centres. The response at the vertex was of identical latency to the occipital VEP and no early components were seen in the case illustrated.

Some components of the VEP occurring between 20 and 80 m.sec. have been considered to reflect different portions of the ERG (Allison, Matsumiya, Goff and Goff, 1977; Goff et al. 1978)and Allison et al.(1977) in a study of the scalp topography of the human flash VEP in 12 subjects used an increased intensity stimulus to accentuate the

early components. Under these conditions the early components were indeed increased but it was also noted that a number of oscillatory wavelets was also induced, particularly in the latency range 80-100 m.sec..

The early components reported by these authors were more commonly seen in anterior derivations and this would support their theory of an ERG origin. The illustrations of occipital recordings show fewer early components.

Nakamura (1978) using linked earlobes as a common reference site recorded photic EPs from lower lid, Fp_z, C_z, P_z and inion sites. The records from lower lid and Fp_z show clear ERG components and that from the inion was typical of an occipital VEP with several early components. Although the records from C_z and P_z were not of typical occipital VEP morphology, early components similar to those seen in the inion recording were clearly demonstrated (see Figure 2.1.11). This would imply that these early components might originate at the reference site.

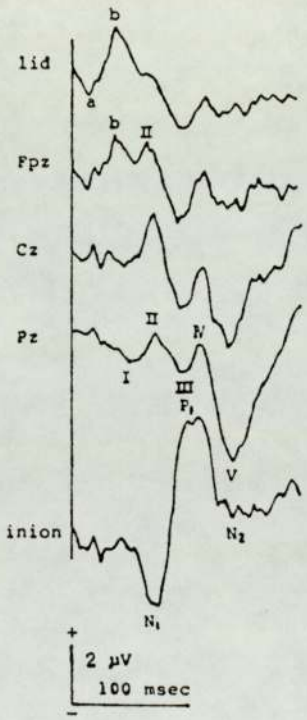
Cracco and Cracco (1978) investigated early oscillatory potentials in the human VEP. Between 1024 and 2048 high intensity flash responses were averaged and a bandwidth between 1 - 2500Hz. was used. Four channels of VEP were recorded at any one time. A series of midline electrodes was generally used (electrodes sited at Fp_z, F_z, C_z P_z and O_z) and in some subjects electrodes were attached to all the standard 10/20 system sites except

FIGURE 2.1.11.

Scalp distribution of ERG and VECP

(Nakamura, 1978)

Using linked earlobes as a common reference, VEPs were recorded from a number of sites. The records from lid and F_{pz} are dominated by the ERG. The inion response shows the characteristic VECP. The response recorded between C_z and linked earlobes shows a clear configuration of short latency components. (see text for details)

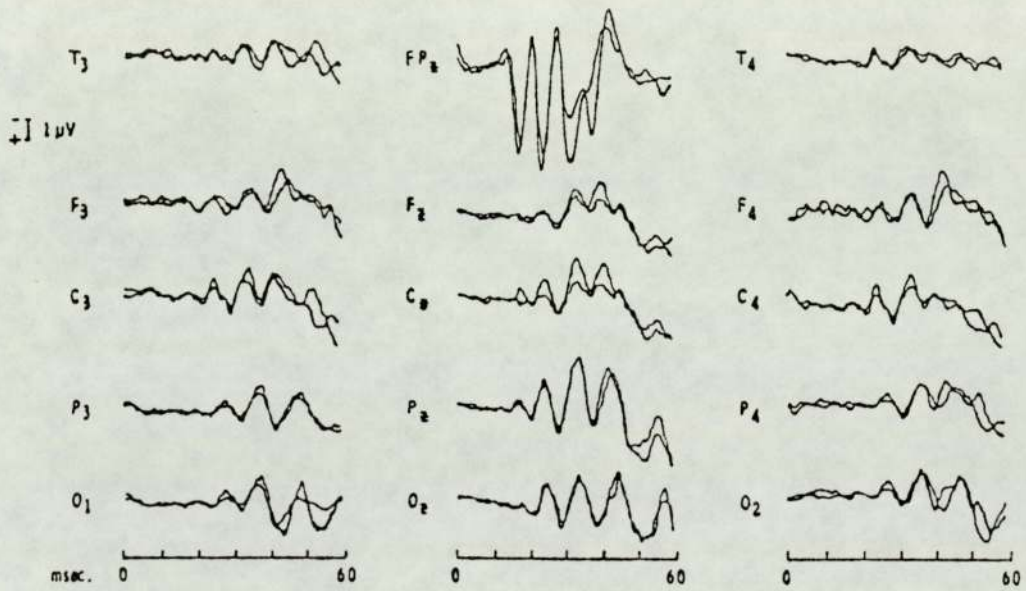

lid
Fpz
Cz
Pz
inion
a
b
II
I
III
IV
V
N1
P1
N2
+
2 μV
100 msec
–

T_5 and T_6. Left or right ear reference recordings were obtained. A series of oscillatory type potentials was recorded at a wide distribution of scalp sites (see Figure 2.112) although more prominently in the midline and para-sagittal derivations, and of higher amplitude in the frontal and occipital derivations than the vertex. The latency of the first potential was approximately 9 m.sec. and the oscillations could even persist up to 90 m.sec. after the stimulus. Monocular stimulation elicited potentials of lower amplitude than the binocular response (usually about half the amplitude) and some of the earliest potentials disappeared completely. Similar amplitude reductions were seen when lower stimulus intensities were used. The potentials recorded at anterior sites were compared with a potential recorded between lower lid and outer canthus and shown to be similar. This was undoubtedly a record of ERG potentials. The authors suggested that in addition to ERG potentials, the oscillations recorded around the anterior-frontal regions might also reflect activity in the optic nerve and tracts. The authors also commented that consistent responses could be recorded from each subject in 1 session but there was considerable variability in amplitude and configuration between subjects. Extended period repeatability trials were not performed. Auditory and myogenic origins for these oscillations were eliminated and the authors suggest that they are similar to the oscillatory potentials recorded from the lateral geniculate body, optic radiation and cortex of animals (as discussed earlier in this section

FIGURE 2.1.12.

Scalp distribution of early visually evoked oscillatory potentials (Cracco and Cracco, 1978)

Using a left ear reference, oscillatory potentials are seen at each scalp electrode location, more prominently in the midline and parasagittal derivations (see text for details)


T3
FPz
T4
1 µV
F3
Fz
F4
C3
Cz
C4
P3
Pz
P4
O1
Oz
O2
msec.
0
60
0
60
0
60

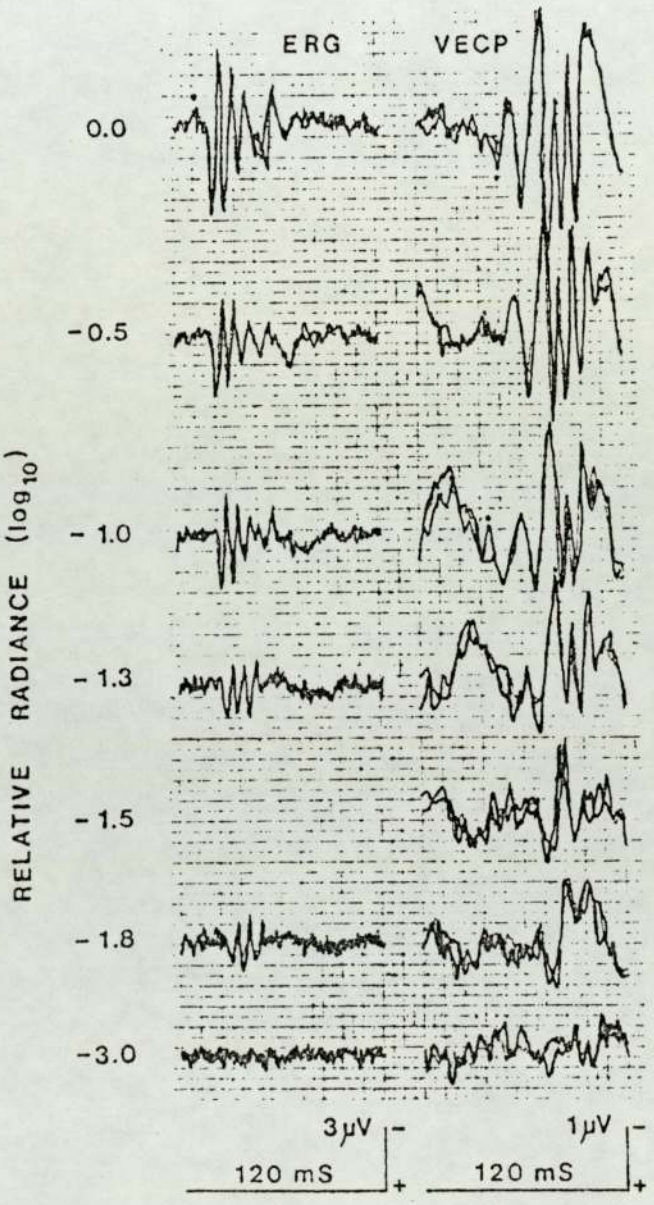
by the present author) and possibly originating in these structures.

More recently, Siegfried and Lukas (1981a,b) have examined early oscillatory potentials in the VEP. An ERG was recorded using a platinum corneal electrode referred to the centre of the forehead and a VEP was recorded using a midline electrode 2 cm. above the O_z site, referred to the left earlobe. A bandpass of 100 - 1000Hz. was used and the responses were averaged to 500 stimuli for the VEP and to 200 stimuli for the ERG. Oscillations were seen in both recordings, particularly at high stimulus intensities and attenuating at lower intensities. Five oscillations were seen in the VEP with latencies between 50 and 101 m.secs.; three oscillations were seen in the ERG with latencies between 23 and 38 m.sec.(see Figure 2.1.13.). Although oscillations were seen in the VEP in only 2 out of 12 subjects examined, the authors concluded that there was a linear relationship between amplitude and latency of the oscillations and the stimulus intensity used; although the oscillations were similar in amplitude to the ERG oscillations, because of the different latencies, volume conduction of the ERG oscillations to the occiput could be ruled out. These authors considered that no discriminable latency difference should exist between a generator and recording electrode due to volume conduction. But, a neurally conducted EP would be expected to be delayed due to the distance between generator and electrode and due to the properties of the neurones involved. The oscillations recorded from

FIGURE 2.1.13.

Wavelets in the ERG and VECP (Siegfried and Lukas, 1981a)

Oscillatory wavelets are seen in both the ERG and VECP reducing in amplitude with reducing intensity of stimulation (see text for details)


ERG
VECP
0.0
-0.5
-1.0
-1.3
-1.5
-1.8
-3.0
RELATIVE RADIANCE (log_{10})
3μV
120 mS
1μV
120 mS

the occiput probably represented initial arrival of the afferent volley at the cortex, or subcortical activity. The present author notes that different reference sites were used for recording ERG and VEP in these studies. Siegfried and Lukas (1981a) explained that this was done so that the VEP recordings would be relatively free of ERG activity and that the ERG activity would be relatively free of VEP activity. The present author considers that common reference recordings would add further information to the argument of these authors.

A selective summary of early components of the human VEP is given in Table 2.1.1..

Author & Year	Recording Montage	Polarity and Latency of Components	Hypothesised Origins
Gastaut (1949b)	Depth recording.	Three types: 1) P50, N70, P90. 2) P30 - 35. 3) N20, P30 - 35.	Optic radiations or their vicinity.
Cobb and Morton (1952)	Inion - anterior midline electrode	P22 - 28, N25.	Earliest component possibly of ERG origin. Later component of cerebral origin.
Monnier (1952)	Bipolar derivations around inion.	P33 - 42, N48 - 63.	Afferent impulses of optic pathways to cortex.
Calvet et al. (1956)	Midline occipital electrode active.	P30 - 40.	-
Cobb and Dawson (1960)	Electrode on and around inion.	P20 - 25, N40 - 50, P55 - 65.	P20 - 25 indicates arrival impulses at cortex.
Ciganek (1961)	Oz - Pz	P28.62, N39.12, P53.4.	Specifically evoked in area 17.
Kooi and Bagchi (1964)	3 cms. above inion - linked ears.	P20 - 30, N30 - 42.5	-
Vaughan and Katzman (1964)	Para - inion - vertex.	N35, P48.	Geniculo-calcarine tract.
Yokoyama et al. (1966)	Inion - Earlobe.	P24, N30, P40.	Arrival of impulses at visual cortex.
Corletto et al. (1967)	Depth and scalp recording (occipital lobe and inion).	Scalp: P28, N40. Depth: N23, P28, N40.	"non-cortical" origin.
Van Hasselt (1972)	Auricle - Mastoid.	P10.	Optic nerve.
Honda, (1977)	Lateral canthus - linked earlobes	Oscillations: P13 - 15; P18 - 20, P24 - 26; P30 - 31; P37 - 38, P44 - 46.	Optic nerve.
Cracco and Cracco (1978)	Full 10/20 system referred to earlobe	P21, N25, P30, N34, P39, N45, P52, N58.	Subcortical and cortical visual structures.
Siegfried (1980)	Temple - ipsilateral earlobe	N20 - 23, P40 - 47.	Optic nerve.
Spire and Hosoouchi (1980)	Depth recording.	20 - 23 m.secs, polarity not reported.	4 mm. ant. to lateral geniculate body.
Siegfried and Lukas (1981 a, b).	Midline electrode 2 cms. above inion - left earlobe.	Wavelets of latencies: 50, 72, 82, 90, 101, m.secs.	a) initial arrival of afferent volley at visual cortex, OR b) Subcortical structures.

TABLE 2.1.1. A selective summary of early components of the human VEP

2.2. REVIEW OF METHODOLOGIES

In addition to physiological variabilities, inter-laboratory differences between recordings of the VEP may be attributed in part to differences in individual methods used for generating and recording the VEP. Since this thesis is concerned with the identification of EPs from various regions of the visual pathway, the topographical distributions of such EPs and their interactions over the scalp, the present section provides a brief review of concepts and methodologies that may be used namely montages and derivations, reference sites, topographical assessment techniques, volume conduction and signal attenuation and stimulus and analysis parameters.

Derivations, Reference Sites and Topographical Studies

The VEP is a graphical record of potential changes with respect to time recorded via scalp electrodes around the occipital area in response to a visual stimulus. The EEG is a record of the electrical activity of the brain occurring and re-occurring semi-randomly over time. The averaged VEP has a fixed temporal relationship to the visual stimulus and using averaging techniques may be "extracted" from the activities of the EEG, which are not temporally related to the stimulus. When potential changes are plotted as a function of time after the stimulus an average VEP is produced.

The potential changes are essentially a measure of electrical potential difference between two points on the scalp and therefore the electrical potential at the scalp overlying the visual cortex can only be measured with respect to a second point (the reference site). The placement of electrodes at both sites is of critical importance in the interpretation of the final record. As a potential difference, the format of the VEP depends on where both electrodes are placed, not simply where one is placed (Fender and Santoro, 1977).

Interlaboratory comparison of VEP recordings is often hampered by lack of standardisation of electrode placement. After several years of assessment, the '10-20' electrode system of the International Federation of Societies for Electroencephalography and Clinical Neurophysiology was established (Jasper, 1958) and this system now has widespread use in EEG laboratories. Although some VEP laboratories do use this system (or at least specifying their electrode locations with reference to adjacent 10-20 system location) many laboratories still use electrode locations specifically decided by the individual investigator. Arguments in favour of the 10-20 system are that electrode position are determined as percentage of head size measured from bony landmarks, a particular electrode therefore lying over the same area of the brain in all subjects, irrespective of age or sex. This permits complete interlaboratory and intersubject comparability.

However, arguments against the 10-20 system appear to be based on the idea that the electrode sites of the system may not locate the electrodes where they yield optimal or maximal information for any particular investigation (Goff, 1974).

Throughout the work reported in this thesis the 10-20 system has been used, sometimes in a modified form, modifications consisting only of additional electrodes positioned at sites closely related to the standard electrode sites.

The electrode placed on the scalp over the area of the brain in which the investigator is interested is often regarded as the 'active' electrode. The reference electrode against which the active electrodes are compared, although often considered to be inactive, must never be considered as totally inactive. Electrical activity (albeit not always related to the visual stimulus) can be recorded at most cephalic electrode sites. The problems which this situation creates can be partially overcome by the use of the differential amplifier. The amplifiers are connected together at their common or earth point and the potential difference between their active leads is compared. In such a set-up when two 'active' leads have the same potential with respect to the common earth, the output is zero and no deflection is noted; when there is a difference in potential between them an output will

be recorded and a deflection noted.

The manner in which scalp electrodes are connected to the physiological amplifier is termed 'derivation', of which there are several methods. It must be remembered however, that all derivations reflect a difference in potential between two points. In bipolar derivation both electrodes used in the recording are regarded as active so that only local potential differences are recorded. In order to localise signals to a particular electrode serial bipolar linkages must be made and simultaneous recordings between each electrode pair compared. In monopolar derivation, the potential at each 'active' point is referred to a single reference point. The term 'monopolar' is often regarded as a misnomer since it implies recording from one electrode; the terms referential or common reference are often used to describe the same technique. Using this type of derivation all 'active' electrodes are compared with one 'common' reference and the activity at each electrode can be easily assessed and compared. However, it must be borne in mind that interelectrode distance may be a confounding factor when using this technique. The smaller the active-reference electrode distance the less will be the difference in potential and vice-versa. Thus, the ideal recording situation all electrodes should be at approximately equal distance from the common reference and in the context of the VEP this is quite feasible. If

electrodes are placed around the occiput and referred to a common, more anterior electrode since the temporal occipital line is a great circle around the rear of the head, inter-electrode distance will be approximately equal. Another technique - 'average-reference' recording - produces an 'average' reference point. All electrodes are linked through a resistance to the reference lead of the amplifier and the theoretical reference point then has a potential which is the arithmetic mean or average of all the scalp electrode potentials. Any active electrode may be chosen and the difference in potential measured between this and the average of all other electrodes (Goldman, 1950; Offner, 1950). Wide diversity of opinion exists on the choice of bipolar or monopolar recording in EP studies (Regan, 1972). Bipolar recording gives an indication of the distribution of an EP field in one particular scalp area but consideration of the absolute values of the potential is lost when the difference in potential between the pairs of electrodes is measured. However, using common reference recording, a number of so called 'active' electrodes can be compared with one reference and absolute potential values at each active site may then be assessed and changes in EP waveform or distribution may be discriminated. In practice a perfectly indifferent (zero potential) electrode site cannot be found and Regan (1972) considered the best working compromise for an indifferent reference site for EP recording was one which showed no consistent time-locked activity with respect to other 'active'

recording sites.

In clinical VEP procedures common reference recording may be used, for example lateral occipital electrodes referred to Fpz (Halliday and Mushin, 1980), or lateral occipital electrodes referred to linked ears (Borda, 1977); bipolar recordings may be used for example bilateral occipital electrodes referred to bilateral Rolandic electrodes (Harding, 1974) or bilateral occipital electrodes referred to bilateral Sylvian and parietal electrodes (the Modified Maudsley system; Holder, 1979), or temporo-occipital chains to locate point of maximal potential, (Harding, et al. 1970).

Differences between the scalp recorded topographical distributions of various EPs generated in the visual pathway are important in differentiation of the sites of origin of the various components. Recording from a single pair of electrodes cannot give sufficient information regarding field distribution of an EP and the most direct method of assessing topographical distributions in the use of simultaneous multi-channel recording from as many scalp electrodes as possible at any one time and a number of techniques has been described.

Scalp distribution and amplitude variation of well identified components around the occiput may be observed using a common reference (Halliday and Michael, 1970); 'contour

maps' of isopotential lines may be constructed in the form of a scalp distribution diagram over a model or drawing of the head (Kooi, 1979; Nakamura and Biersdorf, 1971 and Vaughan, 1968); isopotential lines may be drawn in the form of a chronographical map consisting of scalp potential gradients plotted against time, recorded using closely spaced bipolar electrode pairs (Mezan, Lesevre and Remond, 1968 and Lesevre and Remond, 1972); multi-dimensional lattice models of the VEP round the posterior of the head have been produced by computation using common reference recording (Barrett, Halliday, Halliday and Michael, 1974 and Halliday, Barrett, Halliday and Michael, 1977); contour mapping algorithms have been used to display the time behaviour of equipotential surfaces on the scalp during photic stimulation (Fender and Santoro, 1977).

Lehmann and Brown (1980) advocate that for topographical assessment of EPs, recordings should be made from different electrodes using a common reference site and that in the quantification of EP waveforms, measurements should be made - a) relative to a pre-determined baseline level (considered to be of zero potential) and b) latency values from stimulus onset should be measured. Lehmann and Skrandies (1980) commented that recording of an evoked potential difference between a single pair of electrodes with respect to time, reflected a very restricted and often biased sample of the available electrical field data. They suggested that the number

of electrodes used should exceed a 5 x 5 matrix and in their study of checkerboard EPs they used forty seven channels and a number of common reference sites and an average reference.

The choice of a common reference site in human EP studies depends on the area of the scalp that is being examined. Inter-electrode distances must be maintained more or less equal to avoid alteration of relative amplitude of the EP and enable direct comparison of EP waveforms derived from different sites. It is essential that the reference site should also be chosen to be outside the field of activity that the examiner is investigating and this will enable optimal assessment of potential distributions within the scalp electrical field. The use of a non-cephalic reference site has been suggested (Stephenson and Gibbs, 1951 and Lehtonen and Koivikko, 1971), but this can lead to distortion of the EP due to extraneous artifacts. Certain cephalic sites commonly used as reference during EP recording have been shown to be moderately active (Michael and Halliday, 1971 and Halliday et al. 1977) and VEP waveforms may be significantly altered when the reference site is changed. A further problem in the choice of a reference site is that fields of activity of different EPs or 'contaminants' may overlap. At sites where EP fields do overlap, a component recorded might constitute an 'interaction component' due to interaction, summation or cancellation influences of

the fields involved.(Mackay and Jeffreys, 1973). A forehead or frontal electrode may be affected by the scalp field of the ERG (Nakamura, 1978) or eye movement potentials (Peters, 1967); the chin may easily be affected by myogenic potential artifact (Tepas and Armington, 1962); the earlobe or mastoid is certainly not indifferent with respect to the VEP (Michael and Halliday, 1971 and Halliday et al. 1980), the vertex is also active with respect to the middle and later components of the VEP (Halliday, et al. 1980).

Attenuation of EPs, Volume Conduction and Far Field Concepts

An important consideration during the recording of an EP concerns the localisation of its possible generator(s). This is especially pertinent in the clinical application of EPs were the final diagnosis may be influenced by the apparent findings during EP recording. Localisation of the generators of electrical brain activity has been an enigma for many years and Brazier (1949) summed up the difficulties in the following quotation:

"Most of our work in human electroencephalography is a study of the voltage distribution on the surface of a volume conductor ..... the brain. We would like to know what kind of generators inside this volume conductor would give us the voltage distribution which we find experimentally".

Localisation is usually governed by the anatomical arrangements of the sensory system under observation and it is desirable that electrode sites are determined from which the largest potentials and clearest records will be produced. In addition to the generator of the EP, activities may also arise from scalp musculature and blood vessels; neck, jaw and tongue movements; eye movements; the EP signal being recorded may also be influenced or confounded by activity from other nearby intra-cranial sources and attenuation of the EP recorded at the scalp

will occur due to the impedance of other intra-cranial tissues, the skull and the scalp itself. Of course, the major confounding electrical activity is the background EEG which occurs spontaneously, but will not be time-locked to the particular stimulus used. Potentials or interference from these additional sources are undesirable in the EP record and are regarded as noise, from which the EP signal has to be distinguished. Hence, the aim during recording is to achieve an adequate signal-to-noise ratio and this is performed using the averaging procedure.

The interpretation of scalp recorded waveforms in terms of the underlying neural processes necessitates consideration of an intermediate process - electrical - transmission-between the sources of voltage change and the scalp region from which a sampling recording is made.

Human tissues conduct electrical currents like metals or electrolyte solutions. The region of space in which currents may spread is called a 'volume conductor' and 'volume conduction' describes the purely physical spread of currents in this space (Simpson, 1973). The conductive ions in biological tissues are considerably heavier than the free electrons of metals and the electrical resistivity of biological tissues is therefore many times higher

than that of metals (Geddes and Baker, 1967). Fluids of the body have low resistances compared to solid tissues and similarly the resistance of tissues varies inversely with their fluid content. The outer layer of the skin has a high resistance and bone similarly has a high resistance which may be modified by the presence of vascular channels. In general, resistance of brain tissue is complex and varies as a function of many factors including fluid and electrolyte content, myelin content and regional vascularisation. (Kooi, Tucker and Marshall, 1978).

Volume conduction between generator and scalp electrode is considerably complicated by the inhomogeneity of the intervening tissues which have differing electrical resistivity. The resistance of inactive nerve and muscle cell membranes and that of the myelin sheath of myelinated nerves is extremely high; additionally, structures containing densely packed fibres are anisotropic in nature, possessing considerably higher resistivity in the transverse direction than in the fibre direction (Simpson, 1973). This concept is directly appropriate to the human visual pathway.

Probably the most exact approach of analysis of field potentials is to consider the head as a three-sphere model rather than a single-sphere: that is an inner sphere (the brain) enclosed by inner (the skull) and

outer (the scalp) shells, all of differing resistivity. However, it has been shown that one-sphere and three-sphere models yield increasingly similar results for wide fields or deeply sited generators, (Goff et al., 1978).

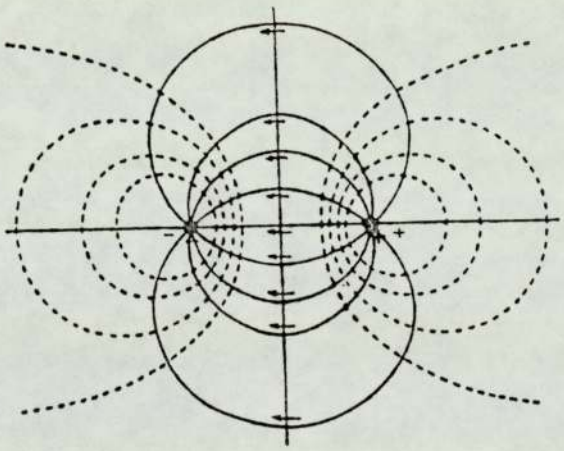
To account for a specific potential difference between two scalp electrodes consideration must be given to the characteristics of primary voltages which may be of differing strength or polarities and which may combine before being scalp recorded; such voltages may be generated in different cephalic structures, having different initial polarities or strengths and generators surrounded by different mediums.

Primary voltage sources are usually viewed as simple dipoles, that is electrical units composed of opposite charges separated in space. The simplest concept of a biological dipole is where the charges are concentrated at two points within an unlimited space of homogenous conductivity, as illustrated in Figure 2.2.1. and conventionally current flows from positive to negative poles. The strength (i.e. current density) of the dipole is greatest along a line (the axis) connecting the points of maximum positive and negative charge. If the surrounding tridimensional conduction medium is infinite the potential along the axis decreases as a function of the square of the distance from the centre of

FIGURE 2.2.1.

Diagrammatic representation of a biological dipole

Charges are theoretically concentrated at two points within an unlimited space of homogeneous conductivity. Current conventionally flows from positive to negative. Current density of the dipole is greatest along the axis connecting the points of maximum positive and negative charge and decreases away from this axis.



the dipole (Kooi, et al. 1978). The current density is largest on the axis and decreases away from it.

This representation of a theoretical electrical field created by the existence of a dipole (as shown in Figure 2.2.1.) is in reality considerably more complex. More than one dipole exists within the brain, charges are rarely concentrated at two points and orientation of the dipoles varies considerably. The volume of the brain is not infinite and this will distort current patterns and fields. Active tissue nearest the recording electrode will generally produce a response of greatest amplitude with a well-defined spatial voltage maximum and steep slopes; a deep source gives a widespread field having only a slight difference between its centre and periphery; a dipole that is most favourably orientated will have the most favourable scalp representation. Therefore, a sample of the electrical activity of the brain recorded at a point on the scalp must be considered as an aggregate or complex response and a field around a recording electrode is appreciated.

In considering the conduction of impulses from generator site to scalp recording electrode the head is usually considered as approximating a sphere of different concentric shells of varying resistivity and thicknesses. This theoretical model is to an extent inaccurate in that the shape is not purely spherical and irregularities in shape

and thickness of the tissue occurs within and between individuals. Such irregularities are considered insignificant for the upper half of the brain but much more significant for inferior portions of the brain where there are wider variations and the shape departs from the form at of a sphere (Vaughan, 1974). Plonsey (cited by Plantz et al., 1974) stated that volume conductor properties of living tissue were in essence purely resistive. Latency differences of EPs seen at various scalp locations may not therefore be directly related to properties of the surrounding media but may be due to spatial properties of the generator or its equivalent dipole model changing its orientation in relation to a specific stimulus.

An interesting clinically recorded anomaly of the theoretical distribution of the major component of the VEP was reported by Barrett, Blumhardt, Halliday, Halliday and Kriss (1976) who using half-field pattern reversal stimulation and a common frontal reference, recorded signals maximally over the mid-line and from electrodes over the hemisphere ipsilateral to the stimulated half-field whereas the response over the contralateral hemisphere was comparatively flat. On a purely neuro-anatomical basis it would be predicted that the response would be maximal over the hemisphere contralateral to the half-field stimulated. A possible explanation of this paradoxical lateralisation of the VEP in normals was that the generators of the cortical pattern-evoked VEP are situated on the medial and postero-medial surfaces

of the visual cortex where the neurones are transversely orientated - electrodes placed over the ipsilateral hemisphere would then be optimally sited to record responses from these generators, whilst electrodes over the contralateral hemisphere would not be optimally sited. Similarly discrepant results have been recorded using the same montage in patients with hemianopias (Halliday, Halliday, Kriss, McDonald and Mushin, 1976). However, Holder (1978) using a different montage and smaller field of stimulation recorded VEPs from patients with hemianopias and showed that the major component was affected over the contralateral hemisphere to the stimulated eye. In several papers examining this phenomenon, attention has been drawn to the influence of stimulus parameters and electrode montage (Holder, 1978; Harding, Smith and Smith, 1980; Halliday, Harding and Holder, 1980 and Van Lith, Henkes and Vijfvinkel-Bruinenga, 1980). It is therefore extremely important to be aware of the influence of such parameters on the ultimate signal recorded and it is vital that the individual laboratory involved in diagnostic procedures on patients is aware of such a paradox and does not misinterpret the recordings or mislocalise a possible lesion.

Scalp recorded potentials are generally attenuated between 60% and 75% of the amplitude of the signal at the cortex (Kooi et al. 1978). However, during simultaneous cortical and scalp recording, attenuations between 50% and

more than 90% have been reported (Abraham and Ajmone Marsam, 1958; Cooper, Winter, Crow and Walter, 1965). In respect of EPs a number of reports concerning attenuation of signals have been presented. Scalp recordings of EPs to flash stimulation were made by Cooper et al. (1965) from occipital and frontal regions. Ten responses were averaged. Depth recordings were made from sites immediately below the scalp electrode sites and it was noted that greater attenuation of signals occurred in the occipital region. The authors commented that the occipital cortex response was specific to the stimuli but frontal cortex response was non-specific. Two patients were studied by Heath and Galbraith (1966) into whom cortical electrodes had been implanted for therapeutic purposes. One hundred flash responses were simultaneously recorded from three pairs of scalp leads and from the arachnoid membrane. Although the authors did not specify the intensity of the flash used, a positive peak of latency 65 m.secs was recorded from all sites. Later components between 100-300 m.secs showed marked differences between depth and scalp recordings. Corletto et al. (1967) made scalp and cortical surface recordings of VEPs (See Figure 2.1.10 in preceding section). A typical array of scalp recorded components was seen with the first component being a low amplitude positive with a latency of 28 m.secs. When recorded directly from the cortex an additional negative component of latency 23 m.secs was seen and the slightly later positive component was of higher amplitude. In

general, the complete response was of slightly higher amplitude compared with the scalp recording. These findings would indicate that low amplitude VEP components may be so attenuated by skull, scalp etc. during scalp recordings as to be non-recordable in the conventional manner. The authors used one hundred averages to record their responses and it is uncertain whether or not if more averages had been performed, the low amplitude component would have been more easily recorded at the scalp.

The elucidation and theories of the BAEP (see section 2.1.) and the methodologies used in its generation have introduced a completely different approach to the recording of EPs when compared with the relatively simple convention used to record the occipital VEP. The short latency components of the BAEP could be recorded, by averaging, from a large number of cephalic sites and were shown to be volume conducted from a number of generators in the brainstem auditory pathway. The responses could only be recorded clearly if a sufficient number of averages was performed to improve the signal to noise ratio (Jewett, 1970; Jewett, et al, 1970b) and this enabled the very low amplitude components to be extracted via the scalp from a generator far from the electrodes.

Jewett and Williston (1971), introduced terms 'near field' and 'far field' to the context of EPs. The near field was defined as being characterised by signifcant differences

in waveshape at electrode positions a short distance apart. The far field was characterised by absence of significant differences in waveshape at closely spaced electrodes; the authors made an additional comment that this latter definition could be made assuming that there was no boundary, extreme inhomogeneity or anisotropism. Considering the evidence presented earlier in this section on variability of homogeneity of tissues, this statement of Jewett and Williston (1972) should be interpreted with reservations. The term far field implies that the generator of the EP is at a distance from the recording electrode and consequently the electrode location is not critical for adequate recordings since due to the depth of the generators the signal will diffuse by volume conduction to cover a wider area of the scalp. Jewett and Williston (1971) also commented that due to the far field concept, potentials from widely spaced generators could be detected at a single electrode. Based on these theories the authors were able to improve the signal to noise ratio (estimated at around 1:500) using a large number of averages (2048 responses were averaged) and consistently record the BAEP from the human scalp using a vertex electrode referred to the right earlobe. The authors criteria for far field recording were met since no significant differences in waveshape were shown during simultaneous recordings from scalp electrodes 7 cm. apart. Plantz et al. (1974) in considering far field potentials in animals suggested that the location of the deep generator

could not be proved by surface recordings alone and depth recordings were also needed.

In the context of the VEP, near field techniques are used conventionally and morphology of the waveforms is altered due to variations in electrode placement. This is due in part to the relatively localised area of active tissue in the region of the occipital (visual) cortex; in addition, the outerlayers of the active tissue are in proximity to the skull, scalp and recording electrodes and hence attenuation of signals is minimised and signal-to-noise ratios are usually good; the VEP is also of sufficiently high amplitude to obviate performance of a large number of averages. The ERG is of such high amplitude (indeed, many times that of the VEP) that a response may be recorded at a distance from the cornea via the skin (Harden, 1974) due to transdermal spread of the signal. Intermediate structures of the visual pathway are in most cases considerably deeper within the brain than the eye or the visual cortex, indeed, the chiasma is usually situated on the midline and the lateral geniculate bodies slightly lateral to the midline. If potentials were to be surface recorded from such deeper structures it is anticipated likely that far field techniques would become necessary. Information from previous literature (see Section 2.1.) indicates that even from depth recordings responses from most intermediate visual pathway structures are of low amplitude.

Stimulus and Analysis Parameters

During the early development of VEP techniques, diffuse flash stimulation of relatively high intensity was used (Cobb and Dawson, 1960; Ciganek, 1961) producing waveforms usually consisting of many components. Gradually it was appreciated that a more sensitive type of stimulation could be achieved by the presentation of lower intensity patterned stimuli (Spekreijse, 1966; Cobb et al., 1967) producing a response to contrast modulation alone, mean luminance being kept constant. Two types of pattern stimulation are now used - pattern appearance/disappearance and pattern-reversal. Different type of response are produce by these stimuli (Spekreijse, 1980) the pattern-reversal response being of similar morphology to the flash response and attracting wider clinical use.

The present author has observed generally in the literature and from experience in the Aston Clinical Neurophysiology Unit that the pattern-reversal response, although presenting the widely acknowledged major component at a latency of approximately 100 m.secs post-stimulus, is of simpler morphology than the flash response in which the major component is again seen, but additional components before and after this are more frequently demonstrated than with the pattern-reversal technique.

It has become apparent that the technique used to stimulate the eye is as important as the collection and analysis of the data. Unfortunately difficulties arise in comparing reports from different laboratories due to lack of standardisation of technique and parameters.

The following discussion on stimulus parameters will be biased towards assessment of the flash technique as this is the one used mainly in the present thesis.

Most authors have found that the components of the VEP increase in amplitude with increasing intensity (energy or brightness) of the stimulus; in addition the waveforms are rather more complex and latencies may be rather shorter (e.g. Cobb and Dawson, 1960; Rietveld, 1963; Shipley, Jones and Fry, 1966; Perry and Childers, 1969). At very high intensities a saturation effect occurs. A reduction in amplitude may even develop at high intensity stimulation levels and in conjunction with this some authors have reported higher amplitude responses when the subjects eyes are closed and high intensity flashes are used (Van Hof, 1960; Vanzulli et al., 1960). An interesting investigation into the effects of attention on the VEP (Koppell, Wither and Warrick, 1969) showed that significant amplitude changes with change in intensity of stimulation only occurred when the subject did not attend to the stimulus. With good attention and fixation, VEP amplitudes were usually maximal and unaltered by variation of stimulus intensity.

The main change in VEP morphology with change in stimulus intensity is reported as an increase in number of components at higher intensities and an accentuation of early components (Cobb and Dawson, 1960; Vaughan and Hull, 1965). Although significant amplitude changes may occur with variation of stimulus intensity, latency variation is considerably less. Several authors report a shortening in latency of most of the VEP components with increasing stimulus intensity (Cobb and Dawson, 1960; Vaughan and Hull, 1965; Shipley et al., 1966; Perry and Childers, 1969).

The duration of the stimulus and frequency of stimulation may also have an effect on the VEP. Modern stroboscopes present very brief, pulse-like stimuli generally of the order of 10-20 μ.secs. duration but duration of stimulation per se has not been widely investigated. The effects of variation of frequency have been more thoroughly explored. Rates of stimulation have ranged widely for example one flash every several seconds up to rates at which the stimulus is presented as a purely flickering source or is even above the critical fusion frequency. The occipital VER remains intact and of an interpretable morphology only at slower rates of stimulation which ensure that the primary reponse to one flash is complete before the next flash occurs. At high rates of stimulation the successive VEPs may overlap such that the tail of one response will present at the beginning of

the succeeding response. This complicates the examination and quantification of the VEP (Rietveld, 1963; Perry and Childers, 1969 and Kinney, McKay, Mensche and Luria, 1973).

The more recent implementation of pattern stimulation has undoubtedly increased in accuracy of clinical (and indeed non-clinical) use of the VEP, but the widely differing working set-ups between laboratories are perplexing. Differing types of response occur to pattern-reversal and pattern appearance/disappearance and these responses themselves are affected by electrode placement; stimulus contrast; reversal rate etc., and the author considers that for the purposes of this thesis a discussion of these factors is unnecessary since most of the techniques employed in the work described utilise unstructured flash stimulation. The reader is referred to the texts of Desmedt (1977) and Barber (1980) for contemporary theory of pattern stimulation for VEP generation.

Analysis parameters play a significant role in the final format of the VEP. Filtering of the scalp recorded signal can alter the morphology of the tracing as can variation of the time-base or sampling period used to record the VEP.

The time-window usually used in VEP laboratories may extend to between 200 and 500 m.secs. after stimulation

and thus any response occurring within this time period after the stimulus will be seen on the recording. This has the advantage in covering a wide latency zone and many components can be simultaneously recorded. For practical purposes the display or write-out of the VEP waveform must be kept within the limitations of compactness and the graphical display of the waveform per centimetre has to be controlled. For example, in the Aston Clinical Neurophysiology Unit, 50 m.sec. of trace is routinely represented graphically as 10 mm. (the complete time-window of 500 m.secs. being represented by 10 cm. on the graph). This system, however, has the disadvantage that a high frequency potential change occurring for example over a period of 15 m.sec. will appear compressed almost as a spike discharge and its analysis becomes difficult. When recorded on a shorter or faster time-base, such a high frequency potential will appear more widely spaced over the graph and easier to analyse (Ikeda, 1976 and Bowsher, 1970), although for practical purposes the time-window used then must be made rather narrower than 300-500 m.sec. Ciganek (1965) when comparing the use of different time-bases demonstrated that earlier components of EPs were more clearly recorded using a faster time-base.

The bandwidth of the recording system is of importance in EP recording since there may be a wide range of frequencies in the EP, and is determined by the use of

low and high frequency filters in the amplifier which may be adjusted independently for different recording situations. The low-frequency filter determines the way in which sensitivity decreases as frequency is reduced. The setting of the low-frequency filter regulates the frequency at which slow, low-frequency signals will pass through the amplifier without distortion. The filter is usually called the 'time-constant'; the time constant is defined as the time taken for the output of DC voltage to reduce the 37% of the applied and original voltage. The time constant is therefore specified in seconds. The use of a very short time constant is suggested to optimise the delineation of the OPs of the ERG (Yonemura, 1962a and Tsuchida, Kawasaki, Kazumasa and Jacobson, 1973) and this is relevant to the work described in the present thesis. Tsuchida et al. (1973) assessed the use of different filters in the isolation of fast components (that is, OPs) of the ERG and suggested that to isolate the OPs, the slow components of the basic ERG should be eliminated using very short time constants. A problem associated with varying the time constant is that different time constants will produce different percentage loss in sensitivity and the shorter the time constant the more phase-shift or time displacement is induced in the waveform. Similarly, the shorter the time constant, the more attenuated the signal becomes. The use of a very short time constant may produce shortening of the latency of EPs (Kiloh, McComas and

Osselton, 1972 and Cooper, Osselton and Shaw, 1980).

The high-frequency filter regulates the responsiveness of that amplifier to relatively high frequencies, determining the frequency at which fast, high-frequency signals will pass through the amplifier without distortion. The filter ideally is labelled with the frequencies at which the sensitivity is 70.7% of its maximum value; it may be labelled with the frequencies at which a 30% fall in sensitivity occurs; occasionally no specific value is given. The more open the high-frequency filter setting the more high-frequency activity will pass through. Opening of this filter beyond what is needed permits excessive high-frequency myogenic potentials and other extraneous noise to be recorded and this acts in reducing the signal-to-noise ratio. The latency of an EP may be prolonged if excessive high-frequency filtering is used to reduce myogenic contamination (Thompson, 1978 and Cooper et al. 1980).

The bandwidth of the recording system is governed by the settings of the high and low-frequency filters and the best filter settings are those which eliminate the maximum spurious potentials without altering the waveform of the EP (Goff, 1974). The use of filters to 'clean-up' records is deprecated by some authors who suggest ensuring maximum patient comfort and satisfactory application of electrodes to remove artifacts (Harding, 1968).

2.3. INITIAL PILOT STUDIES

In the following sections the experimental work carried out in the Aston Clinical Neurophysiology Unit between December 1978 and January 1981 is reported. The experiments are inter-related, but will be considered in the order in which they were performed and will be presented in the format of laboratory reports.

2.3.1. Preliminary Assessment of Electrode Sites and EPs.

Initial experimental work consisted of observation of waveforms recorded from many of the 10/20 electrode sites, in response to flash stimulation in a small group of subjects. A time-window of 125 m.sec. was generally used and 1000 flashes delivered. The technique was considered semi-random in design and early components were only observed in a few derivations, mainly those involving the earlobe as one of the electrodes. However, these studies led to a more organised system of investigation.

The first organised experimental study was performed on a small sample of subjects in order to assess in gross terms the extent of the ERG and occipital VEP fields of activity over the scalp surface and to make observations of any early EP components.

Materials and Method

Observations were made on 5 normal volunteer subjects (3 male, 2 female) aged between 17 and 25 years (mean 20.2 years).

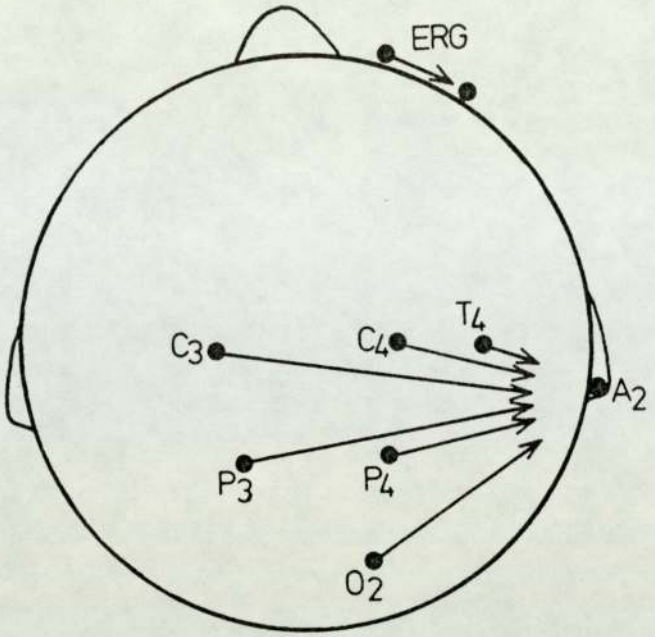
All had visual acuities of 6/6 or better and full visual fields. A number of derivations were used as shown in Figure 2.3.1.. Common reference sites at frontal pole (F_Z) and right earlobe (A_2) were chosen and all 'active' electrodes referred to these sites. A control ERG was recorded using a right lower lid electrode referred to the outer canthus and a control occipital VEP was recorded between O_Z and either A_2 or F_Z.

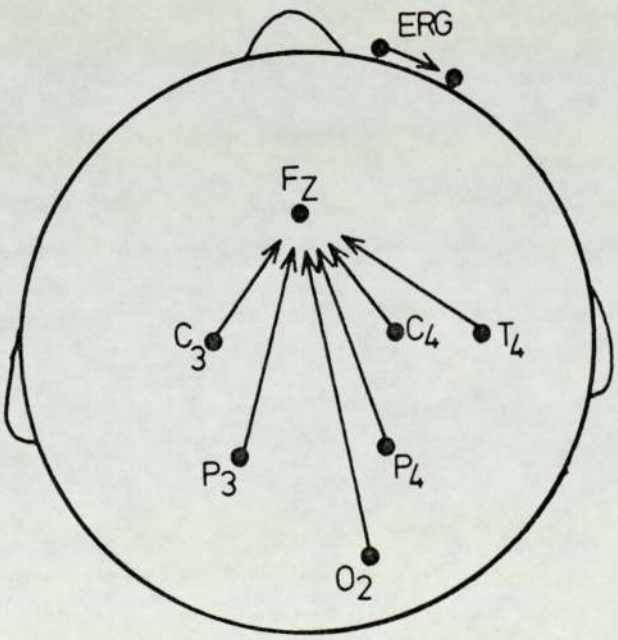
7mm. silver/silver chloride EEG electrodes were affixed to the scalp with collodion and the resistance maintained below 5K ohms. The responses from seven channels of EEG recorded using an Elema Schonander machine were averaged simultaneously using a PDP8E computer and the resulting waveforms plotted using a Bryans 26000 X-Y plotter. In all recordings the bandpass of the EEG machine was opened maximally using a high frequency cut out at 700Hz. and a time constant of 0.015 sec. (producing a bandpass of 66-700Hz.). Such a bandpass was considered necessary in order to permit transmission of a wide variety of frequencies and despite the inevitable increased content of myogenic artifact and other contaminants transmitted using such a wide bandpass, narrower bandpasses were not

FIGURE 2.3.1.

Montages used in preliminary pilot study

Comprising a number of 'active' sites with common reference sites at F_Z and A_2 (right earlobe). An ERG was recorded between right lower lid and outer canthus.


ERG
T4
C3
C4
A2
P3
P4
O2


ERG
FZ
C3
C4
T4
P3
P4
O2

considered to be useful. Evidence presented in Section 2.1. suggests that photically evoked activity from intermediate sites between retina and visual cortex is generally of a frequency of at least 100Hz.. A time window of 100 m.secs. was used throughout the experimental work and attention was directed towards the first 50 m.sec. post-stimulus, although other components within this time window were also monitored.

Photic stimulation (consisting of flashes of 10μsec. duration) was delivered from a Grass PS22 photostimulator placed 25 cms. from the subjects eyes (subtending a visual angle of 29^{o} at the eyes). Intensities used varied between 1925 nits and 9661 nits (for details of settings and intensity ratings of the Grass PS22 photostimulator, see Appendix 1). Between one and two thousand flashes were presented to the subjects in an attempt to simulate a far-field technique (see Sections 2.1. and 2.2.) and in order to avoid subject fatigue and restlessness the flashes were delivered at a rate of 6/second. Binocular stimulation was performed throughout this early study.

Results

Samples of the resulting waveforms are illustrated in Figures 2.3.2. and 2.3.3.. The waveforms were analysed manually, latency and peak-to-peak amplitude measurements being made of all components within the time window used.

The mean latency values for the ERG 'a' and 'b' waves were 12.3 $\pm$ 1.52 m.sec. and 31.0 $\pm$ 3.46 m.sec. respectively and their mean amplitudes were 7.25 $\pm$ 2.18uV. and 20.95 $\pm$ 3.74uV. respectively. Mean latency values for the recorded components of the occipital VEP when recorded between O_2 and A_2 were 59.2 $\pm$ 5.38 m.sec. and 73.3 $\pm$ 7.63 m.sec. and these components had mean amplitudes of 11.6 $\pm$ 5.25 and 11.35 $\pm$ 0.92uV. respectively. Waveforms recorded from sites P_3 and P_4 were dominated by occipital VEP components irrespective of reference site. However, when A_2 was used as a reference site additional early components were occasionally seen in the records from P_3 and P_4, but these were never seen when F_z was used as reference. Such early components were not seen in the recordings from O_2.

The maximum number of components occurring before 50 m.sec. was six, occurring only in one subject with the following polarities and latencies: N17; P22; N27; P34; P47, these components being recorded between electrodes C_3 and C_4 referred to the earlobe, A_2. From these results, A_2 was regarded as the probable origin of the early components and therefore the active electrode. Therefore, the polarity notation of the components given above is reversed accordingly when compared with Figures 2.3.2. and 2.3.3., in which A_2 was used as reference site. In other subjects fewer early components were demonstrated and the following incidence rates for these six components was noted, with

FIGURE 2.3.2.

Resultant waveforms using preliminary pilot study montages

Using A_2 as reference site a number of early components (consisting of P17, N22, P27, N34, P40, N47) are seen mainly in recordings from C_3 and C_4. These components were not seen in recordings from C_3 and C_4 when F_z was used as reference site. Recordings from P_3, P_4 and O_2 are dominated by components of the cortical VEP (consisting of a P63-65 component). The ERG is recorded with reversed polarity to all other channels.

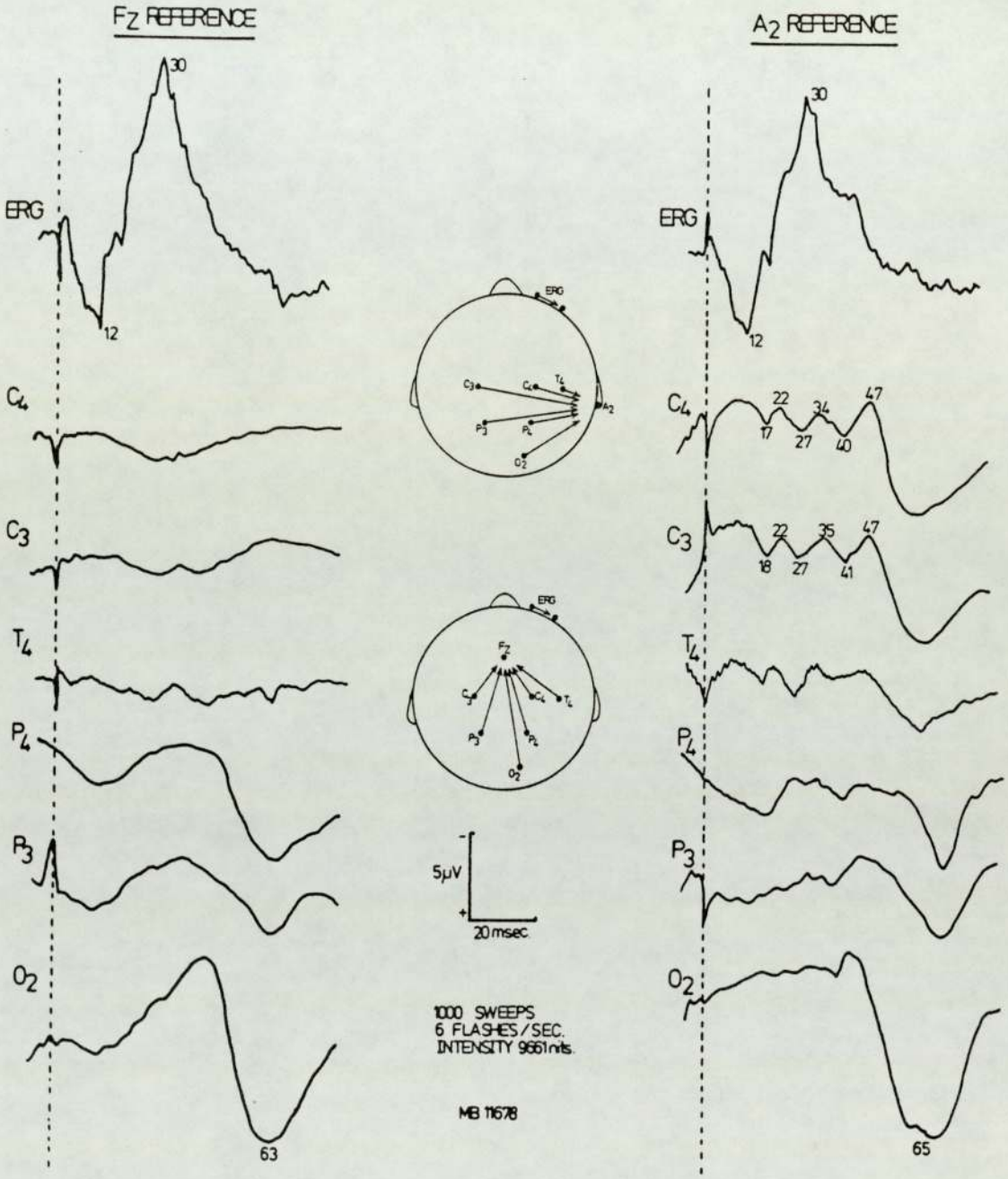
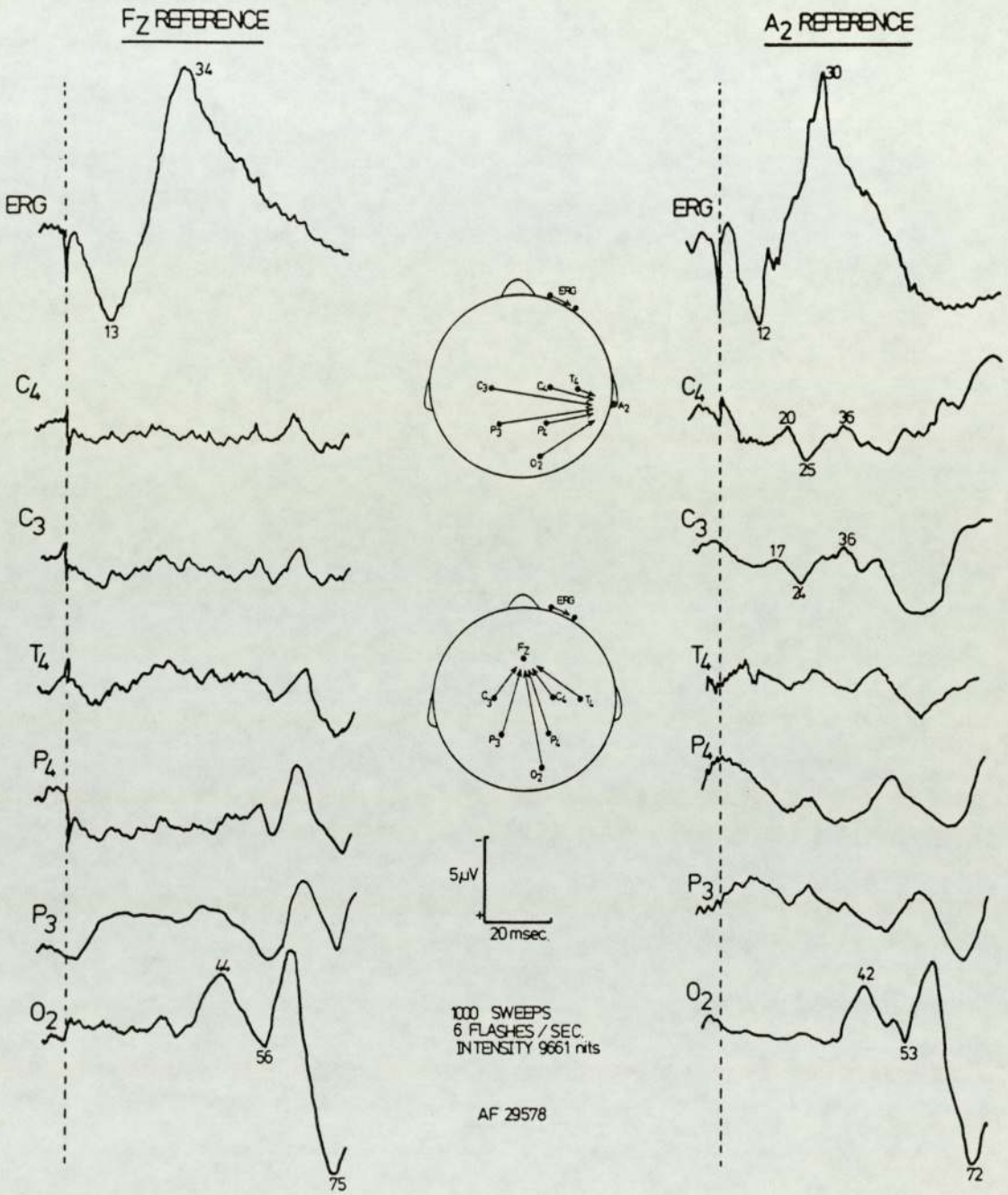

FZ REFERENCE
A2 REFERENCE
ERG
C4
C3
T4
P4
P3
O2
30
12
63
65
22
17
27
34
40
47
18
41
35
5μV
20 msec.
1000 SWEEPS
6 FLASHES / SEC.
INTENSITY 9661nits.
MB 11678

FIGURE 2.3.3.

Resultant waveforms using preliminary pilot study montages

Using A_2 as reference site early components (consisting of N20, P25, N36) are seen in records from C_3 and C_4. These components were not seen in recordings from C_3 and C_4 when F_z was used as reference site. Recordings from P_3, P_4 and O_2 are dominated by a number of components of the cortical VEP. The ERG is recorded with reversad polarity to all other channels.


FZ REFERENCE
A2 REFERENCE
ERG
C4
C3
T4
P4
P3
O2
34
13
30
12
20
25
36
17
24
36
44
56
42
53
75
72
5μV
20 msec.
1000 SWEEPS
6 FLASHES / SEC.
INTENSITY 9661 nits
AF 29578

mean latency and peak-to-peak amplitude measurements:

Component	Incidence	Mean Latency(m.sec.)	Preceding Peak-to-Peak Mean Amplitude(μV)
N17	2/5	16.33 ± 1.15	
P22	3/5	25.00 ± 2.45	2.00 ± 1.70
N27	3/5	27.66 ± 0.58	2.00 ± 0.54
P34	3/5	35.50 ± 1.80	2.60 ± 1.63
N40	4/5	40.25 ± 0.50	3.93 ± 1.85
P47	3/5	48.00 ± 3.60	4.00 ± 1.74

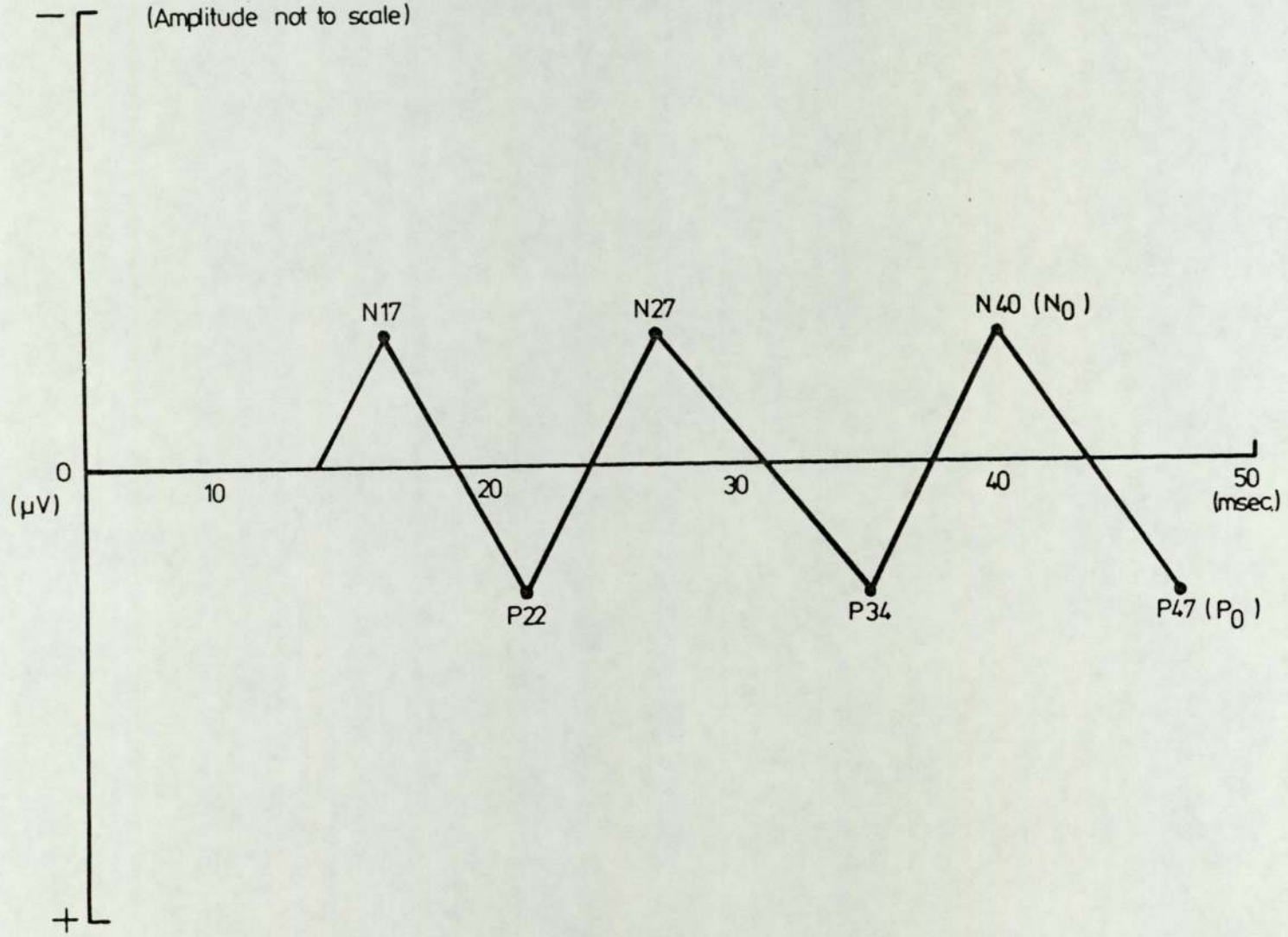
In general, the maximum number of early components was seen in this small sample of subjects in recordings between para-vertex electrodes (C_3 and C_4) and the ear-lobe (A_2) although some of the components were seen in the recordings between parietal electrodes (P_3 and P_4) and A_2. The early components reported here were most clearly demonstrated using intensity levels of 3939 nits and 9661 nits (intensity settings 8 and 16). At the upper level however, due to the brightness of the stimulus, subjects usually became more tense and myogenic artifact was accentuated in the records making identification of the low amplitude EP components more difficult. At lower intensity levels than these, early components were not repeatably recorded in any of the derivations.

These observations on a small sample of subjects led to the drawing of a schematic waveform of early VEP components recorded under the specified conditions (see Figure 2.3.4)

FIGURE 2.3.4.

Schematic waveform of early VEP components based on preliminary pilot study

Four components were seen - N17, P22, N27, P32 - although the initial N17 component was extremely variable in its presentation. The later components (N40, P47) were considered to be the N_o and P_o components of the cortical response. The polarity configuration is such that a positive change at the earlobe (A_2) gave a downward pen deflection.


(Amplitude not to scale)
−
+
0
(μV)
N17
N27
N40 (N0)
P22
P34
P47 (P0)
10
20
30
40
50
(msec.)

Conclusion

From these preliminary experiments and observations it is clear that a number of early EP components may be generated in response to high intensity photic stimulation. By comparing two reference sites and a number of 'active' electrode sites the early components were far more clearly defined using an earlobe reference site. Since the early components were seen in the records from several 'active' electrode sites using a common reference on the earlobe, the implication that these originated from the reference site seemed a most likely explanation. The general absence of these components when recording between the same active electrodes and a common frontal electrode (F_Z) would also reinforce this argument.

In order to clarify the scalp topographies of the ERG and occipital VEP and to assess the scalp distribution of the early components demonstrated in this section further experiments were carried out.

2.3.2. Investigation of the Scalp Topography of Early Components of the VEP

In this second series of experiments the scalp topography of the early components of the VEP was investigated. From the preceding section, up to six components had been observed to occur in the first 50 m.sec. post-stimulus, but the author considered that the last two components (N40, P47) probably constituted the No and Po components of the conventionally recorded VEP and therefore, although they could not be excluded from reflecting pre-cortical activity, were regarded as part of the cortical VEP.

The earliest component (N17) was found to be extremely variable and was not consistently recorded, even in repeated recordings in the same session. When recorded, its amplitude was unstable and the author anticipated that this particular component would not be consistent enough to be considered in later analysis, although was monitored throughout all the work.

In the first study, the anterior-posterior topography was examined using a chain of seven electrodes in the anterior-posterior direction; in the second study a transverse series of electrodes was used to assess the transverse topography. This combination of electrodes was used to localise the scalp distribution of the early components described in the preceding section.

As described in Section 2.2., difficulties may arise in the choice of monopolar or bipolar recordings and in the choice of a common reference site if the monopolar technique is chosen.

Anterior-Posterior Topography

Materials and Method

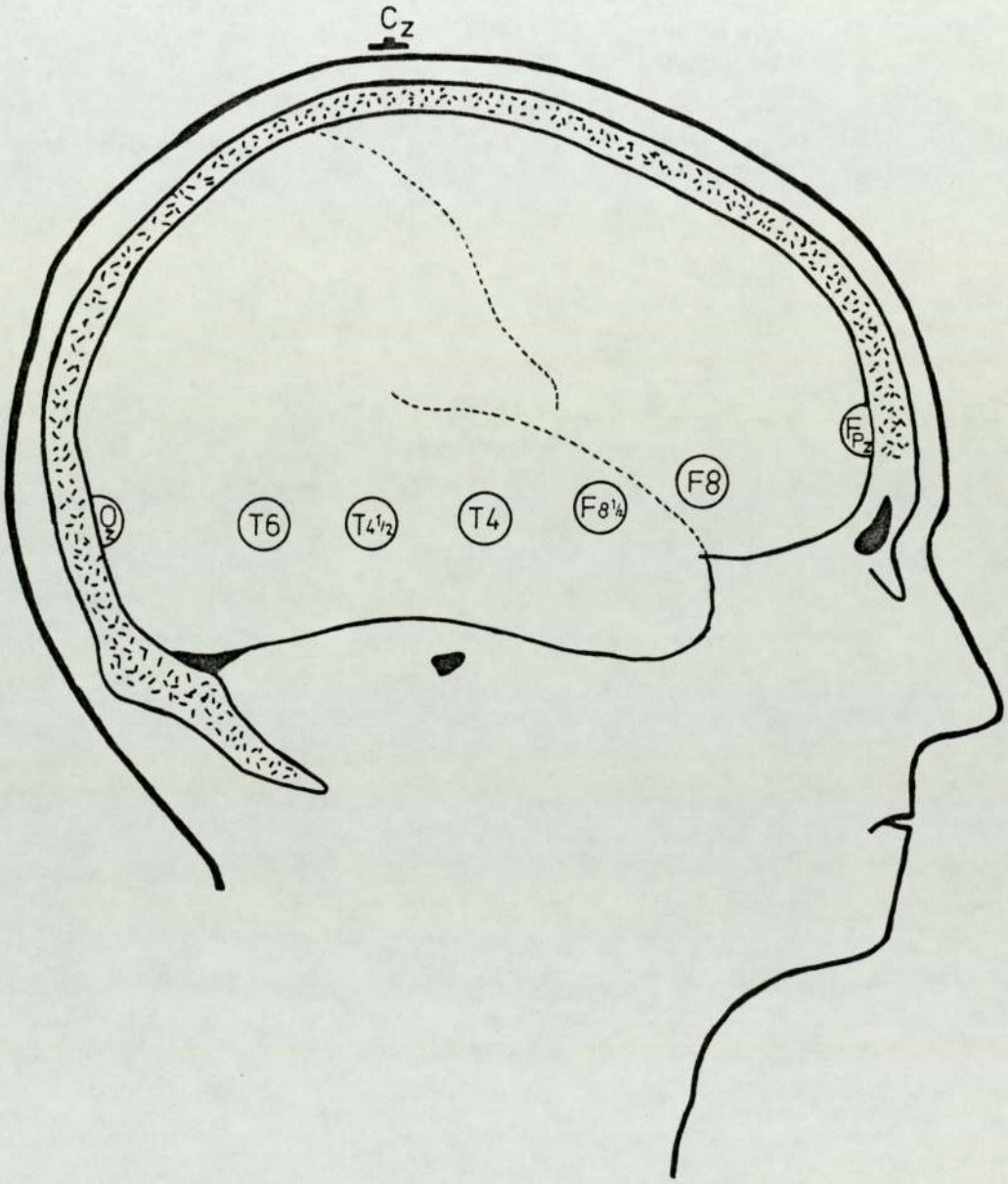
Observations were made on 14 normal volunteer subjects (8 male, 6 female) aged between 19 and 38 years (mean age 26 years). All had visual acuities of 6/6 or better and full visual fields. Silver/Silver chloride electrodes were affixed with collodion and the resistance maintained below 5K ohms. The electrodes were sited at F_{pz}, F_8, T_4, T_6 and O_z. Additional half-distance electrodes were sited at $F_{8\frac{1}{2}}$ (being mid-way between T_4 and T_8) and at $T_{4\frac{1}{2}}$ (being mid-way between T_4 and T_6). All electrodes were referred to a common reference sited at the vertex, C_z, as illustrated in Figure 2.3.5.. This reference site was considered the best compromise site for this anterior-posterior electrode chain since a more anterior site would be contaminated by ERG artifact and a more posterior site would be contaminated by occipital VEP artifact (as found by observation by the author); additionally, the vertex site enabled inter-electrode distance to be kept approximately constant for all 'active' electrodes in the chain.

From the preceding experiment (Section 2.3.1.) a general observation was that a large number of averages had to

FIGURE 2.3.5.

Scalp distribution of electrodes used in anterior-posterior topographical study of early components of the VEP

Standard 10/20 system sites were F_{pz}, F_8, T_4, T_6 and O_z. Additional half-distance electrodes were sited at $F_{8\frac{1}{2}}$ (mid-way between T_4 and F_8) and $T_{4\frac{1}{2}}$ (mid-way between T_4 and T_6). All electrodes were referred to a common reference at the vertex, C_z.


Cz
O2
T6
T4½
T4
F8¼
F8
FP2

be performed in order to clearly detect and define any early components. The optimum number of flashes used was between 500 and 1000. More flashes than 1000 simply increased subject tension and restlessness with no improvement in signal-to-noise ratio (indeed, prolonged periods of stimulation were occasionally noted to reduce the signal-to-noise ratio). Therefore, throughout the following section 500 sweeps were used routinely, being increased to 1000 in cases of very low signal-to-noise ratio in an attempt to produce clearer delineation of components. Flashes were presented binocularly at a rate of 6/second from a Grass PS22 photostimulator placed 25 cms. from the eyes. Simultaneous multichannel recordings were made using Elema Schonander machine and a PDP8E computer averaged the responses. A time window of 100 m.sec. was used and a bandpass of 66-700Hz.

Results

Illustrations of the scalp distributions of the various EPs are shown in Figures 2.3.6. and 2.3.7.. At the frontal site (Fp_z) the high amplitude ERG is predominant. Throughout this and all the subsequent work the ERG is illustrated in an inverted form in accordance with EEG convention, such that a positive potential change at the 'active' electrode results in a downward deflection. This permitted direct comparison of the ERG waveforms with all other recorded waveforms and was considered very important in these topographical studies. Oscillatory potentials (usually two in number) were seen

FIGURE 2.3.6.

Distribution of potentials in anterior-posterior topographical study of early components of the VEP

The activity of the frontal pole (F_{pz}) shows the inverted ERG and its OPs and a number of more posterior sites show this activity with decreased amplitude. At $T_{4\frac{1}{2}}$ a complex of early components (P24, N30, P34) appears, reducing in amplitude at more posterior sites. At O_z some components of the cortical response are seen.

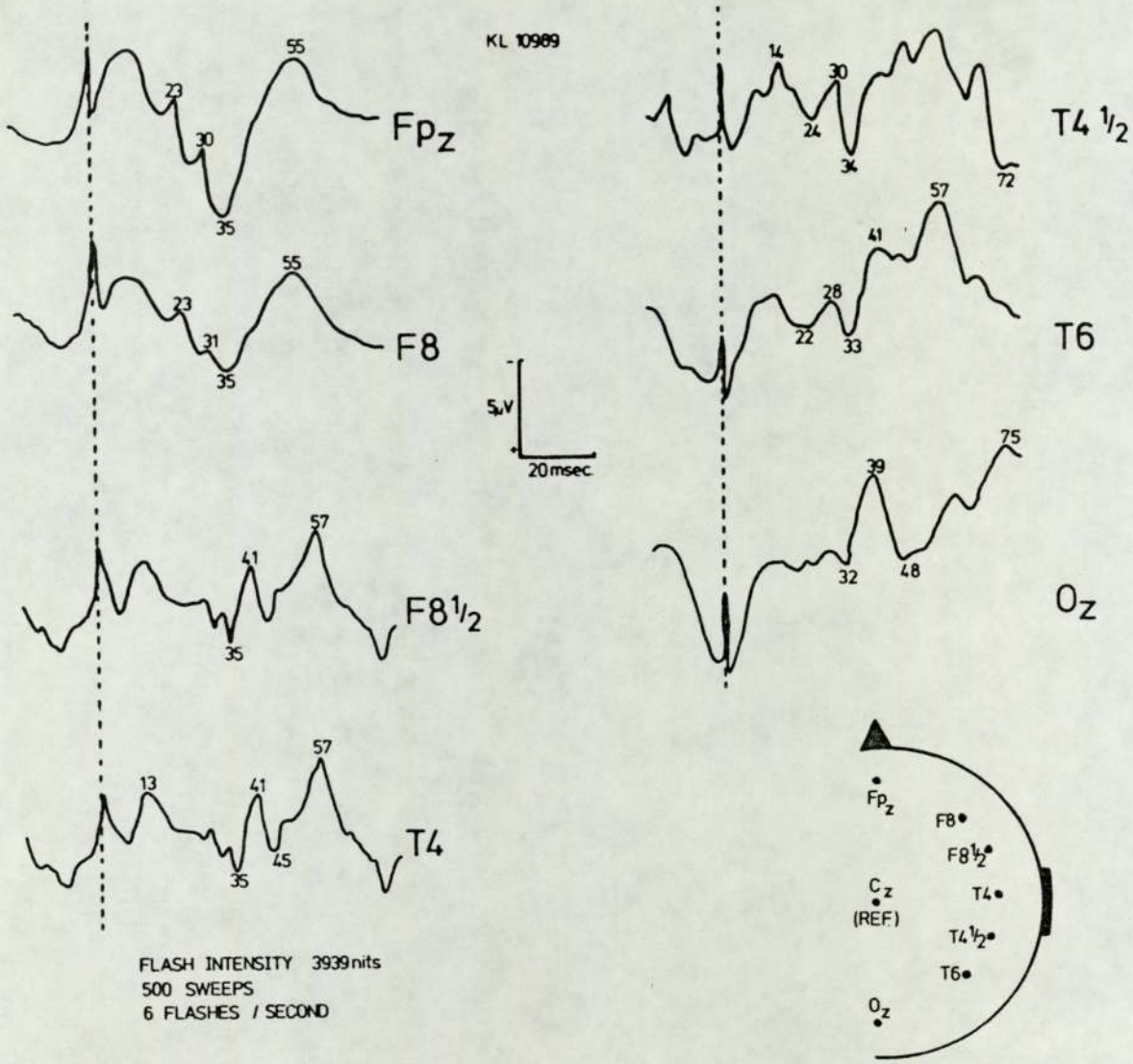
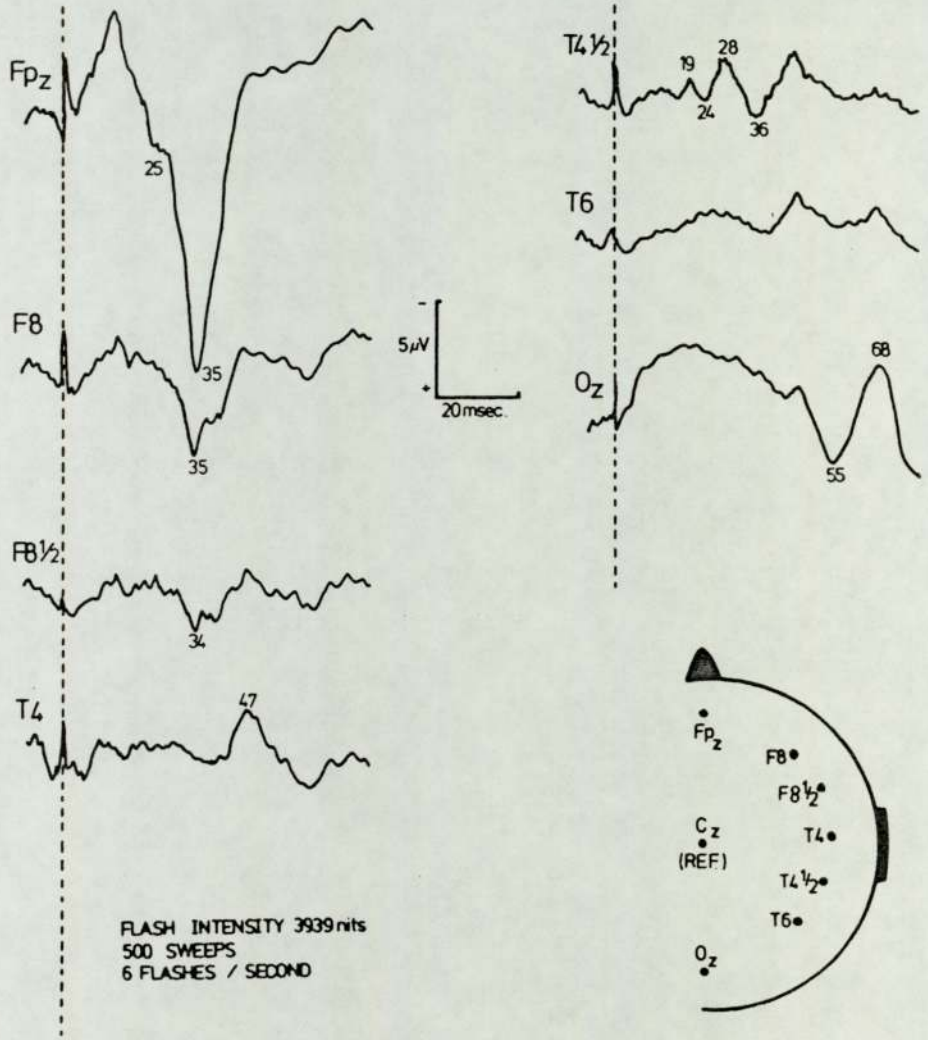

KL 10989
Fpz
F8
F8 1/2
T4
T4 1/2
T6
Oz
55
23
30
35
55
23
31
35
57
41
35
57
13
41
35
45
14
30
24
34
72
57
41
28
22
33
75
39
32
48
5µV
20msec
Fpz
F8
F8 1/2
Cz
(REF)
T4
T4 1/2
T6
Oz
FLASH INTENSITY 3939nits
500 SWEEPS
6 FLASHES / SECOND

FIGURE 2.3.7.

Distribution of potentials in anterior-posterior topographical study of early components of the VEP

The activity of the frontal pole (F_{pz}) shows the inverted ERG which is conducted to a number of more posterior sites. At $T_{4\frac{1}{2}}$ a localised complex of components (N19, P24, N28, P36) is seen. The cortical response dominates the record from O_z.


Fpz
25
F8
35
35
5μV
20msec.
F8½
34
T4
47
T4½
19
28
24
36
T6
O2
68
55
Fpz
F8
F8½
Cz
(REF.)
T4
T4½
T6
O2
FLASH INTENSITY 3939 nits
500 SWEEPS
6 FLASHES / SECOND

superimposed on the 'b' wave of the ERG. The ERG was widely distributed and recorded at more posterior electrode sites, namely F_8 and $F_{8\frac{1}{2}}$. At these fronto-temporal electrode sites the signal recorded differs from that at the frontal pole (Fp_Z) only in that the amplitude of the signal at the fronto-temporal sites was smaller than that at Fp_Z and that the amplitude gradually reduced more posteriorly. The most accessible index was the 'b' wave amplitude. The OPs became indistinct even at a short distance from the frontal pole at electrode $F_{8\frac{1}{2}}$.

As the ERG remnants rapidly reduced in amplitude and clarity a 'trough' of relative inactivity for early components was recorded around electrode T_4. At the next more posterior electrode in the chain ($T_{4\frac{1}{2}}$), although the later components which had been noted in all recordings remained essentially similar to those recorded at more anterior sites, a number of early components were also noted.

Considering the occipital VEP (recorded at electrode O_Z) some components (generally the No and Po components) were seen clearly, also recorded with a reduced amplitude from electrode T_6.

The most consistent early components recorded at electrode $T_{4\frac{1}{2}}$ comprised a triphasic complex (of P-N-P polarity) with an occasional preceding negative wave. These three

components were similar to several of those constituting the schematic waveform shown in Figure 2.3.4. following the initial pilot study. This triphasic complex was observed in twelve out of the fourteen subjects (85.7% incidence). The earlier (N17) component was observed in six out of the fourteen subjects (43% incidence). The mean latencies (in milliseconds) of these components were P21.30 ($\pm$ 1.63), N28.1 ($\pm$ 2.07), P35.90 ($\pm$ 1.10); the mean amplitudes were P-N 1.09uV. ($\pm$ 0.71), N-P 2.05uV. ($\pm$ 0.80), only two values being calculated for amplitude since peak-to-peak measurements were made.

Conclusion

Considering the results of this study it was shown that elements of the ERG (being such a high amplitude EP) were recordable (with reduced amplitude) at several cephalic sites far from the cornea without significant alteration in latency. Similar spread forward of potentials was seen from the posterior pole of the head, namely the components of the occipital VEP. Those early components recorded at electrode site $T_{4\frac{1}{2}}$ appeared to be unrelated directly to any other components either of ERG or occipital VEP origin.

Transverse Topography

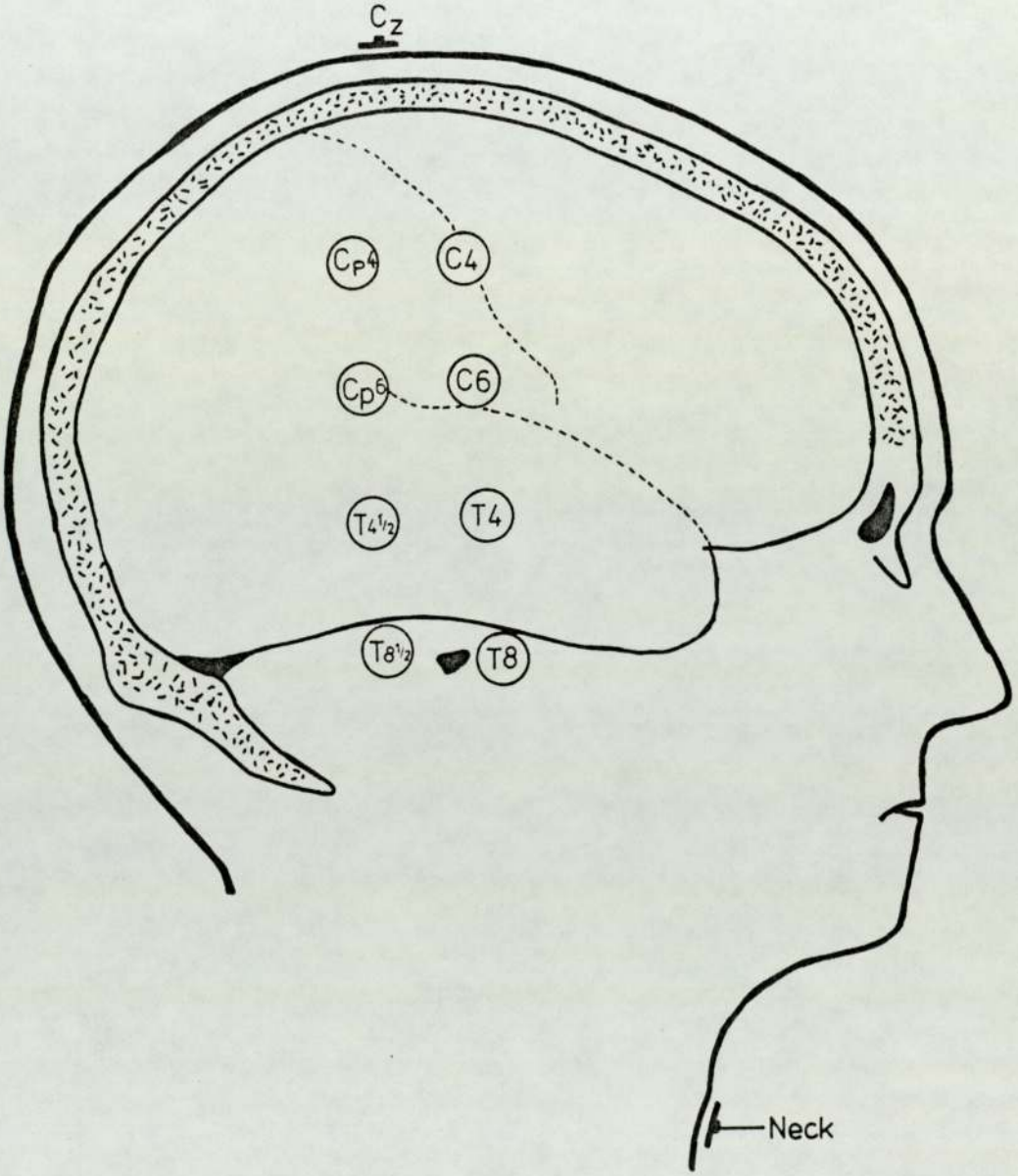
Materials and Method

Observations were made on the same fourteen normal subjects as in the preceding topographic study. Silver/silver chloride electrodes were affixed at the following sites: C_4, C_6, T_4, T_8. Additional half-distance electrodes were sited at Cp_4, Cp_6, $T_{4\frac{1}{2}}$ and $T_{8\frac{1}{2}}$, as illustrated in Figure 2.3.8.. The choice of a reference site in this study was more difficult than in the previous study. The vertex site which was previously chosen, despite being relatively inactive compared with more anterior or more posterior electrodes was not equidistant from all the electrodes in the present topographical study, being nearest to the centro-rolandic electrodes and furthest from the lower electrodes. However, in order to permit direct comparability with the anterior-posterior topographical study the vertex, C_z, was again chosen as one reference site. As a supplementary comparator a reference electrode was also placed on the anterior neck. This site was a closer approximation to being equidistant from most of the 'active' electrodes than C_z. This site was probably slightly closer to the lower electrodes than the upper, centro-rolandic electrodes. Stimulus and analysis parameters were maintained as in the preceding topographical study.

FIGURE 2.3.8.

Scalp distribution of electrodes used in transverse topographical study of early components of the VEP.

Standard 10/20 system sites were C_4 and T_4. Additional electrodes were placed at C_6, T_8, C_{p4}, C_{p6}, $T_{4\frac{1}{2}}$ and $T_{8\frac{1}{2}}$. Two common reference sites were used as comparators sited at the vertex (C_z) and on the anterior neck.


Cz
Cp4
C4
Cp6
C6
T4½
T4
T8½
T8
Neck

Results

Illustrations of the transverse topography of the early component complex are given in Figures 2.3.9. and 2.3.10.. Recordings from electrodes relatively close to the vertex reference site were almost 'flat' indicating equipotentiality due to short inter-electrode distance, but the triphasic early component complex was seen to develop at several electrode sites namely $T_{4\frac{1}{2}}$, $T_{8\frac{1}{2}}$ and T_8, being of maximal amplitude at $T_{4\frac{1}{2}}$ and $T_{8\frac{1}{2}}$. These two sites are in anatomical terms situated on the mastoid process behind the pinna of the ear slightly above and below the level of the external auditory meatus respectively. When the anterior neck reference was used, an increased amount of electromyogenic artifact was inevitably present in the records; however, with repeated recordings and superimposition of averaged waveforms it was observed that the activity recorded at the central and paracentral electrode sites (C_4, Cp_4, C_6, Cp_6) was only slightly different from that recorded using the vertex as reference and early components were not recorded from these electrode sites; however, the triphasic early component complex was clearly seen in the same sites as when referred to the vertex namely from electrodes $T_{4\frac{1}{2}}$, $T_{8\frac{1}{2}}$ and T_8, although poorly formed in the records from T_8. The two subjects reported in the anterior-posterior topographical study from whom no consistent early component could be recorded similarly showed no response at any of the electrode sites used in the transverse study.

FIGURE 2.3.9.

Distribution of potentials in transverse topographical study of early components of the VEP

Using C_z as reference site (Ref.1) a well demarcated triphasic early component complex is seen (P19-21, N25, P34-35) and is localised to electrodes $T_{4\frac{1}{2}}$ and $T_{8\frac{1}{2}}$. When using an anterior neck reference (Ref.2) as a comparator, despite increased myogenic artifact, the early component complex is still seen at the same sites, but not at any other electrodes.

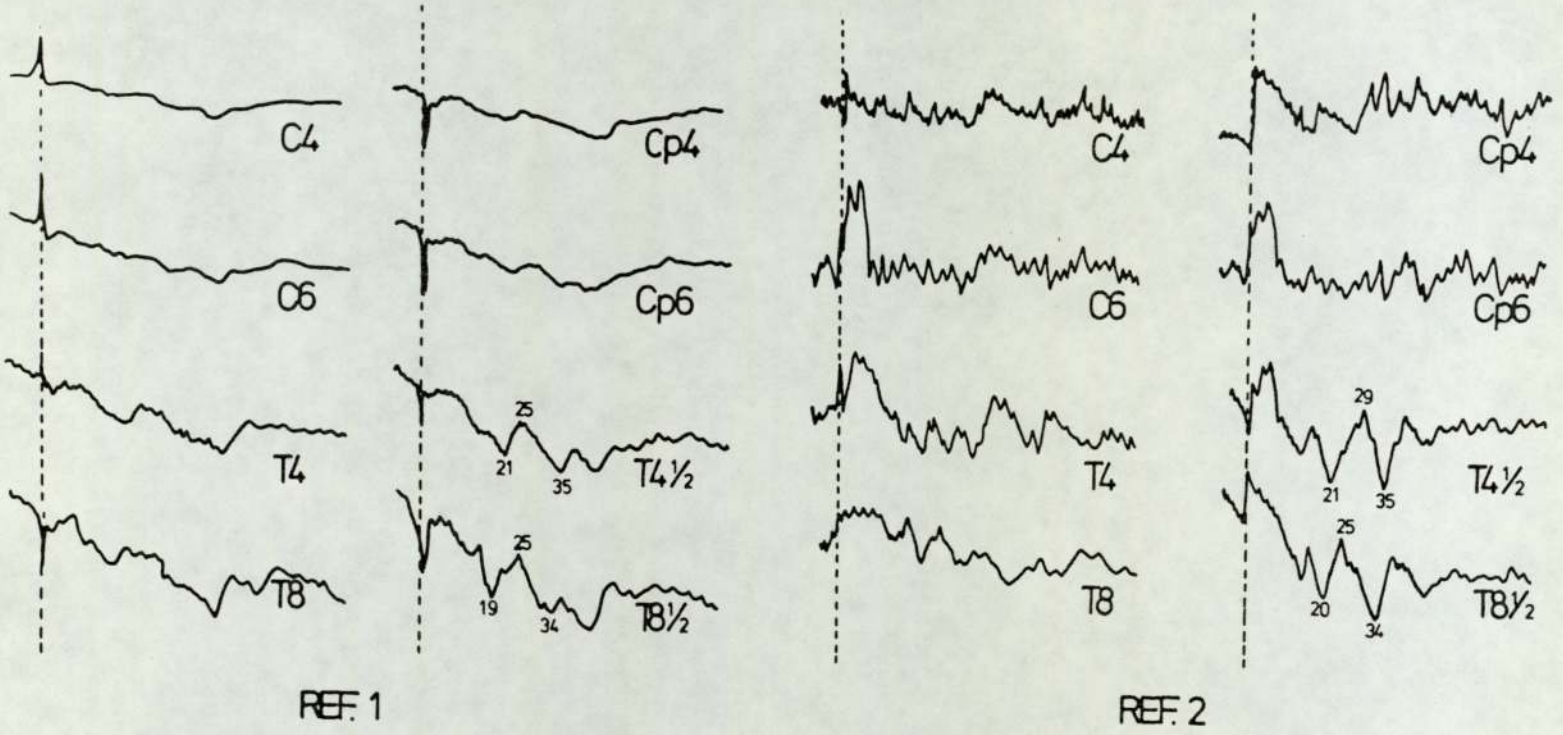
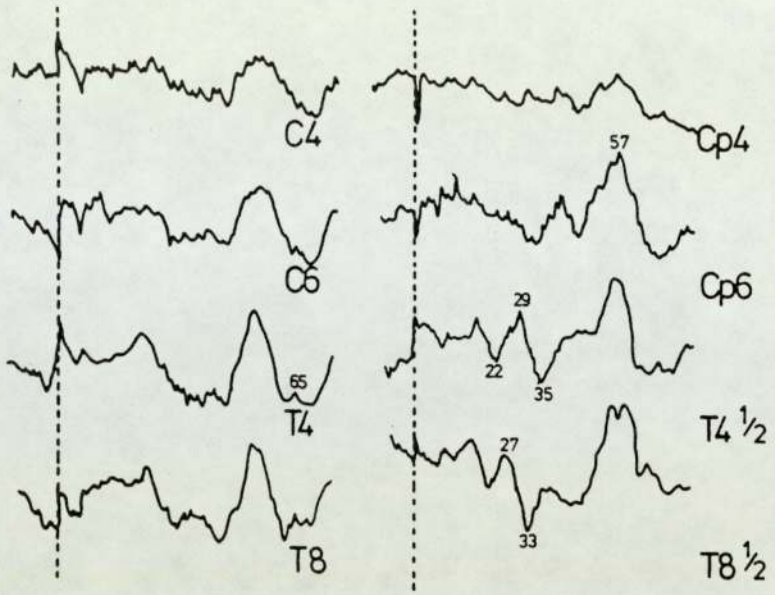

C4
Cp4
C6
Cp6
T4
25
21
35
T4½
25
19
34
T8½
T8
REF. 1
C4
Cp4
C6
Cp6
T4
29
21
35
T4½
25
20
34
T8½
T8
REF. 2
FLASH INTENSITY 3939nits
500 SWEEPS
6 FLASHES / SECOND
T8
T8½
T4
T4½
C6
Cp6
C4
Cp4
Cz
Ref. 1
Neck
Ref. 2
5 µV
20msec.

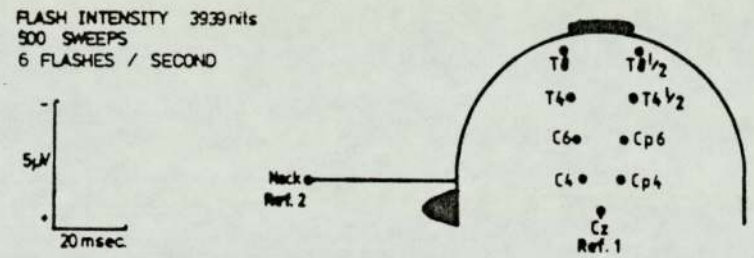
FIGURE 2.3.10.

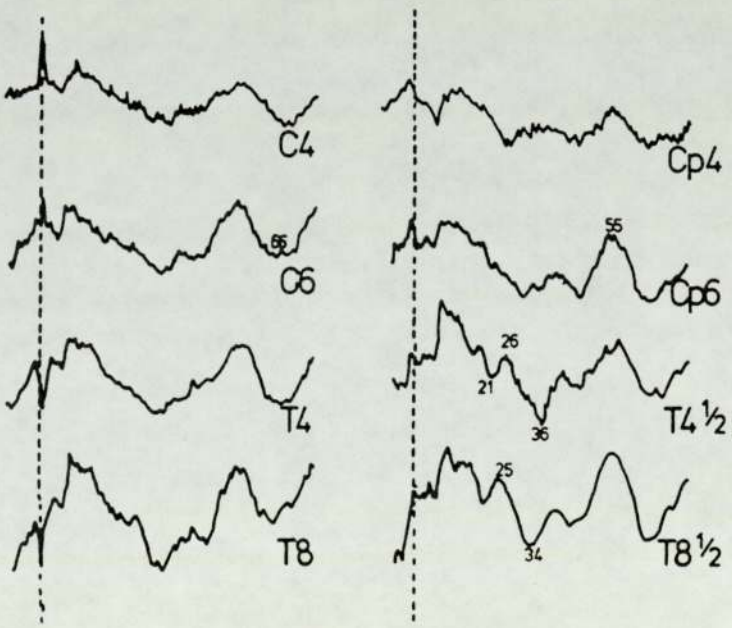
Distribution of potentials in transverse topographical study of early components of the VEP

Using C_z as reference site (Ref.1) a triphasic early component complex (P20-22, N27-29, P33-35) is seen (preceded by a small N17 deflection) of maximal amplitude at electrodes $T_{4\frac{1}{2}}$ and $T_{8\frac{1}{2}}$. When using an anterior neck reference (Ref.2) as a comparator, the early component complex is still seen at the same sites, but not at any other electrodes.


C4
Cp4
57
C6
Cp6
29
22
35
65
T4
T4 ½
27
33
T8
T8 ½

REF. 1


FLASH INTENSITY 3939 nits
500 SWEEPS
6 FLASHES / SECOND
5µV
20 msec.
T8
T8 ½
T4
T4 ½
C6
Cp6
C4
Cp4
Neck
Ref. 2
Cz
Ref. 1


C4
Cp4
65
55
C6
Cp6
26
21
36
T4
T4 ½
25
34
T8
T8 ½

REF. 2

Conclusion

The results of this transverse topographical study indicated that the previously isolated triphasic early component complex was clearly localised anatomically to the mid-mastoid process, behind the pinna. This was shown to be irrespective of which reference-site was used.

The earlobe site used in the initial pilot study may be considered for the purposes of electrophysiological recording procedures, to be anatomically analogous to the mastoid since it is simply a cartilaginous extension covered by the same dermal sheath as the nearby mastoid bone. Comparison of the records of the initial pilot study and those of the two topographical studies indicated that the early negative deflection noted in the initial pilot study (i.e. the N17 component of the schematic diagram depicted in Figure 2.3.4.) was extremely variable and often completely absent at all sites in either of the topographical studies.

2.3.3. Clarification of site of origin of early components

The triphasic complex of early VEP components isolated in the preceding sections in 12 out of 14 subjects (incidence 85.7%) had mean latencies (in milliseconds) of P21.3 ($\pm$ 1.63), N28.1 ($\pm$ 2.07), P35.9 ($\pm$ 1.10). Since these latency values corresponded on occasions to

certain components of the simultaneously recorded ERG (recorded from the Fp_z site) it was important to further delineate more exactly the site(s) of origin of this early triphasic complex.

Accordingly, in several subjects demonstrating well defined early component complexes, the effects of monocular and binocular stimulation were compared.

Having established the scalp topography of these most consistent early components of the VEP, a simplified montage of electrodes was selected for use in further experiments. This consisted of a pair of frontal electrodes (Fp_1 and Fp_2); a pair of temporal electrodes ($F_{7\frac{1}{2}}$ and $F_{8\frac{1}{2}}$); a pair of mastoid electrodes ($T_{3\frac{1}{2}}$ and $T_{4\frac{1}{2}}$) from which the strongest early component complex signal had previously been shown to be recorded; a pair of occipital electrodes (O_1 and O_2). All were referred to the vertex, C_z. On some occasions the temporal electrodes ($F_{7\frac{1}{2}}$ and $F_{8\frac{1}{2}}$) were omitted.

Results

The comparative effects of monocular and binocular stimulation are shown in the records of two subjects in Figures 2.3.11. and 2.3.12. On binocular stimulation ERG responses were recorded at electrodes Fp_1 and Fp_2, triphasic early component complexes recorded at $T_{3\frac{1}{2}}$ and $T_{4\frac{1}{2}}$, occipital responses recorded at electrodes O_1 and O_2; all

FIGURE 2.3.11.

Effects of monocular stimulation on the early component complex of the VEP

The upper section shows on binocular stimulation, symmetrical ERG responses (F_{p1} and F_{p2}), early component complexes ($T_{3\frac{1}{2}}$ and $T_{4\frac{1}{2}}$) and cortical responses (O_1 and O_2). In the lower section, on monocular stimulation, the ERG from the stimulated eye is intact, but that from the occluded eye is considerably reduced in amplitude; the early component complexes are however reduced bilaterally to approximately half the amplitude of that on binocular stimulation.

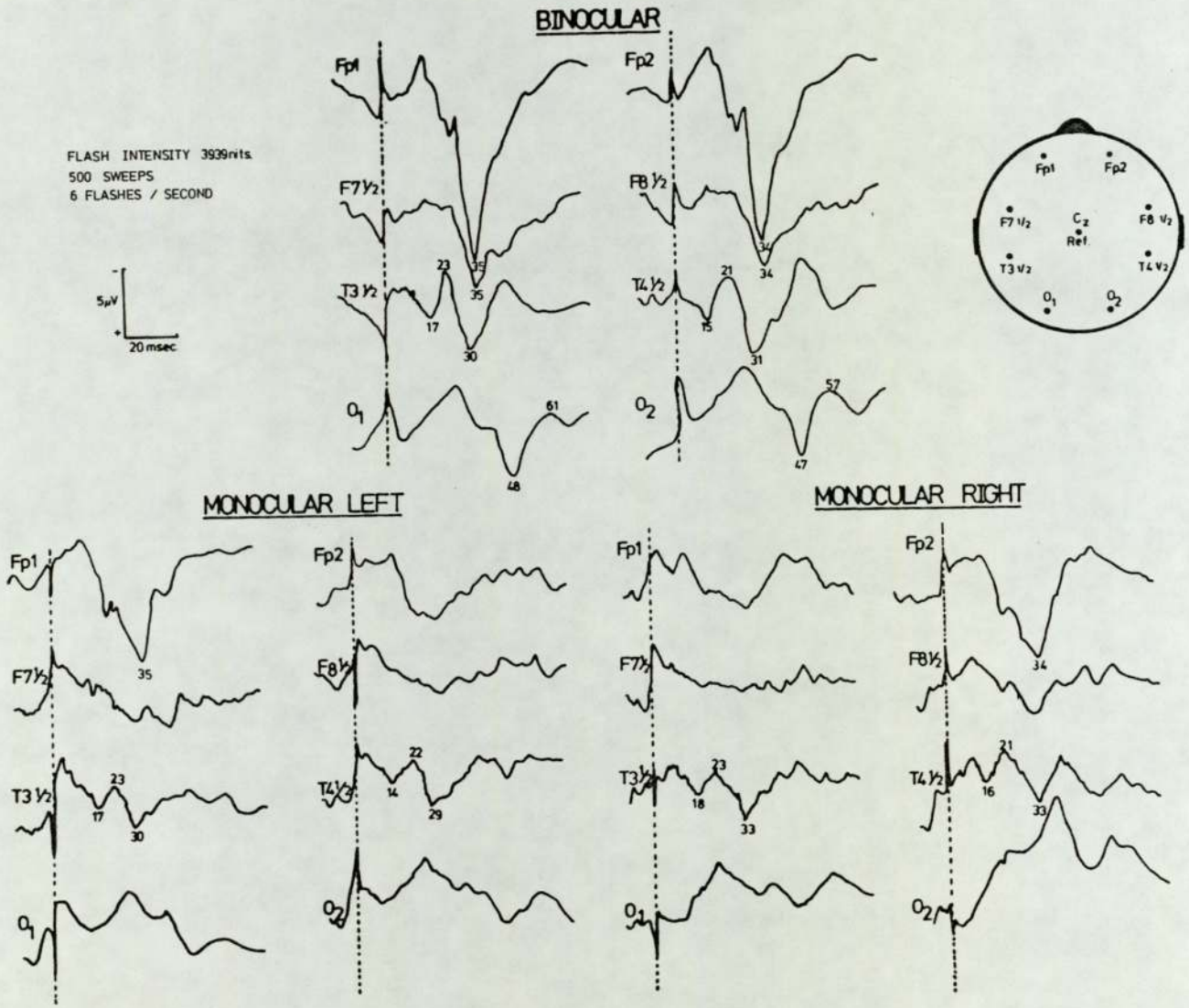
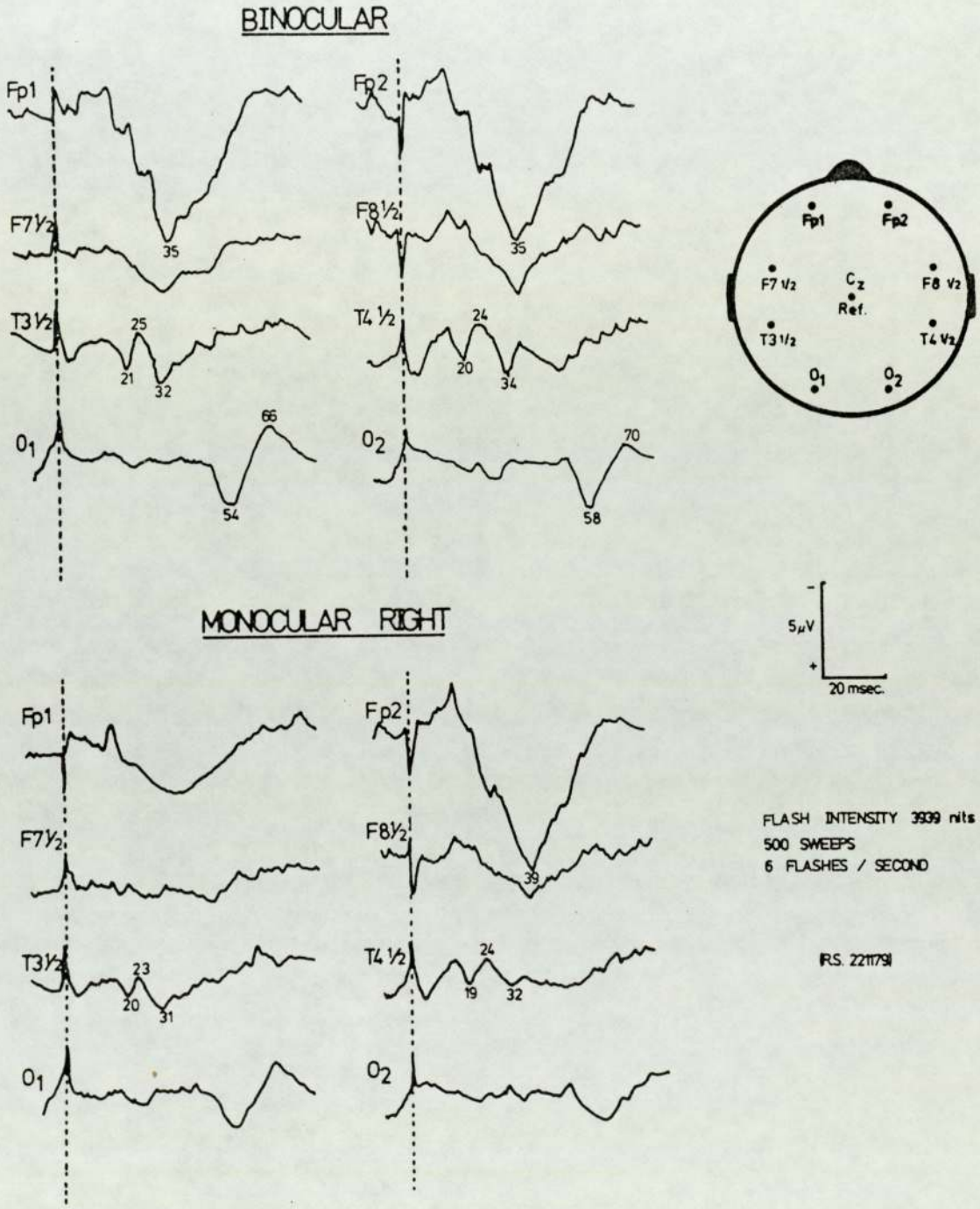

BINOCULAR
FLASH INTENSITY 3939nits.
500 SWEEPS
6 FLASHES / SECOND
5μV
20 msec
Fp1
Fp2
F7½
F8½
T3½
T4½
O1
O2
MONOCULAR LEFT
MONOCULAR RIGHT
Ref.

FIGURE 2.3.12.

Effects of monocular stimulation on the early component complex of the VEP

The upper section shows, on binocular stimulation, symmetrical ERG responses (F_{p1} and F_{p2}), early component complexes ($T_{3\frac{1}{2}}$ and $T_{4\frac{1}{2}}$) and cortical responses (O_1 and O_2). In the lower section, on monocular stimulation of the right eye, the ERG response is considerably reduced from the occluded left eye but the early component complexes are reduced bilaterally to approximately half the amplitude of that on binocular stimulation. Similar results were found on monocular stimulation of the left eye.


BINOCULAR
Fp1
Fp2
F7½
F8½
T3½
T4½
O1
O2
35
35
25
21
32
24
20
34
66
54
70
58
Fp1
Fp2
F7½
Cz
Ref.
F8½
T3½
T4½
O1
O2
MONOCULAR RIGHT
Fp1
Fp2
F7½
F8½
T3½
T4½
O1
O2
23
20
31
39
24
19
32
5μV
20 msec.
FLASH INTENSITY 3939 nits
500 SWEEPS
6 FLASHES / SECOND
IRS. 2211791

were recorded bilaterally and were symmetric in latency and amplitude. On monocular stimulation, the ERG signal from the site nearer to the occluded eye was, as expected, almost totally extinguished, the response from the other frontal electrode, near the stimulated eye, being unaffected. The responses from electrodes $T_{3\frac{1}{2}}$ and $T_{4\frac{1}{2}}$ were unaffected with respect to latency but were reduced in amplitude bilaterally to approximately half the binocular amplitude. The occipital components recorded at O_1 and O_2 were also reduced in amplitude bilaterally. This consistent and repeatable effect on the triphasic early component complex was found in all twelve subjects examined and indicated that the complex was unlikely to be of retinal or optic nerve origin and undoubtedly of post-chiasmal origin; if the complex was of pre-chiasmal origin (that is, of retinal or optic nerve origin) monocular stimulation should have resulted in abolition or gross reduction of the complex ipsilateral to the occluded eye, but unaffected ipsilateral to stimulated eye. If of post-chiasmal origin, bilateral reduction in amplitude should (and did) occur on monocular stimulation of either eye. In none of the subjects examined was the complex abolished ipsilateral to the occluded eye.

The findings thus far did not however permit further differentiation of the possible generator(s).

During simultaneous recording from F_{p1}, F_{p2}, $T_{3\frac{1}{2}}$, $T_{4\frac{1}{2}}$, O_1 and O_2, the early component complex was seen in records from $T_{3\frac{1}{2}}$ and $T_{4\frac{1}{2}}$, but almost never seen in the records from O_1 and O_2, as shown in Figure 2.3.13.. Since a common reference (C_z) was used for all recordings it was most likely that the occipital VEP components and those derived from the areas underlying electrodes $T_{3\frac{1}{2}}$ and $T_{4\frac{1}{2}}$ were of different origins and reflected different stages in transmission of the afferent volley along the visual pathway.

Since the particular photostimulator used in these experiments produced an audible 'click' with each discharge and a large number of stimuli were delivered, control experiments were run on a number of subjects to eliminate the possibility of an auditory origin for the early component complex.

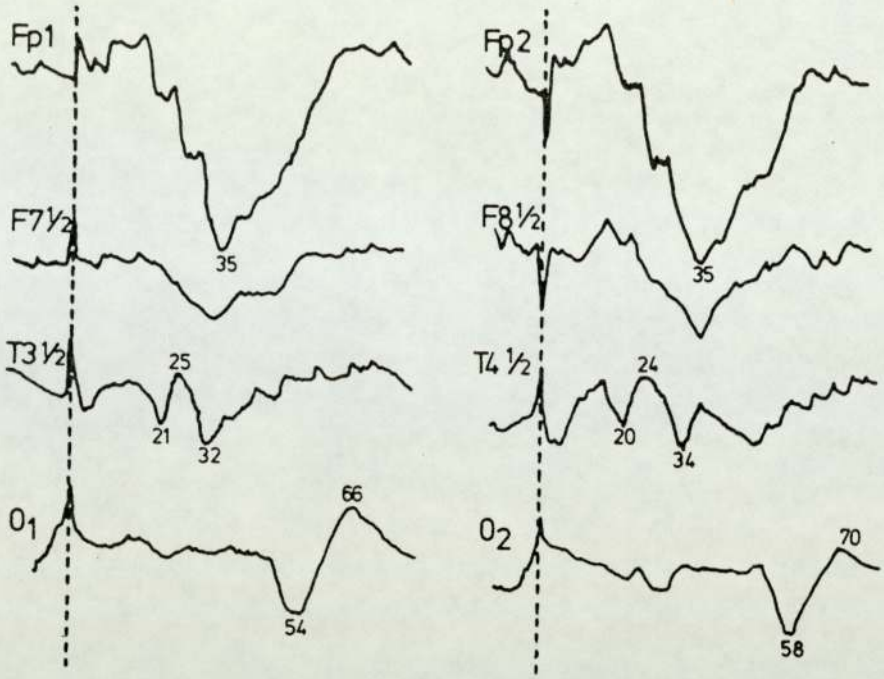
In some cases, the photostimulator was completely occluded and the subject observed the stroboscope which was set running producing an audible click without associated photic stimulation. The results of multichannel recordings are shown in Figures 2.3.14 and 2.3.15 with and without photic stimulation. Simultaneous recordings of ERG, early component complex and occipital VEP were made, which on occlusion of the stroboscope were all abolished.

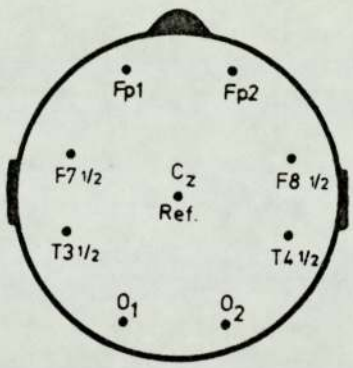
In other cases, the sound of the click of the photostimulator was masked by white noise delivered to the subjects via

FIGURE 2.3.13.

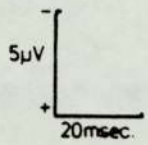
Simultaneous recording of ERG, early component complex and occipital response

In two subjects the ERG (at F_{p1} and F_{p2}), early component complex (at $T_{3\frac{1}{2}}$ and $T_{4\frac{1}{2}}$) and occipital response (O_1 and O_2) were simultaneously recorded. Early components (in the upper subject consisting of P20-21, N24-25, P32-34 and in the lower subject consisting of P24-27, N29-30, P35) were clearly recorded at $T_{3\frac{1}{2}}$ and $T_{4\frac{1}{2}}$ but are not seen in the records from O_1 and O_2. In both subjects the peaks of the ERG 'b' waves have similar latencies to the second positive peak of the early component complexes (see text for details)





FLASH INTENSITY 3939 nits
500 SWEEPS
6 FLASHES / SECOND



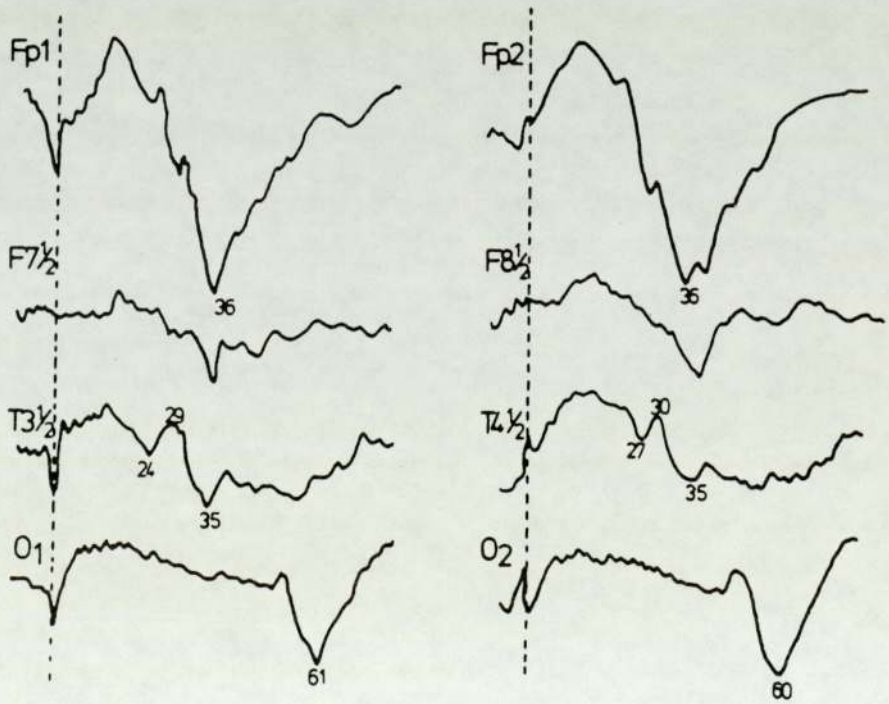


FIGURE 2.3.14.

Effects of occlusion of photo-stimulator on early component complex of the VEP

On binocular stimulation clear ERG responses (F_{p1} and F_{p2}), early component complexes ($T_{3\frac{1}{2}}$, $T_{4\frac{1}{2}}$) and cortical responses (O_1, O_2) are demonstrated. On occlusion of the activated photo-stimulator, which produced an audible click with each flash, all responses were abolished, indicating a non-auditory origin of the early component complex.

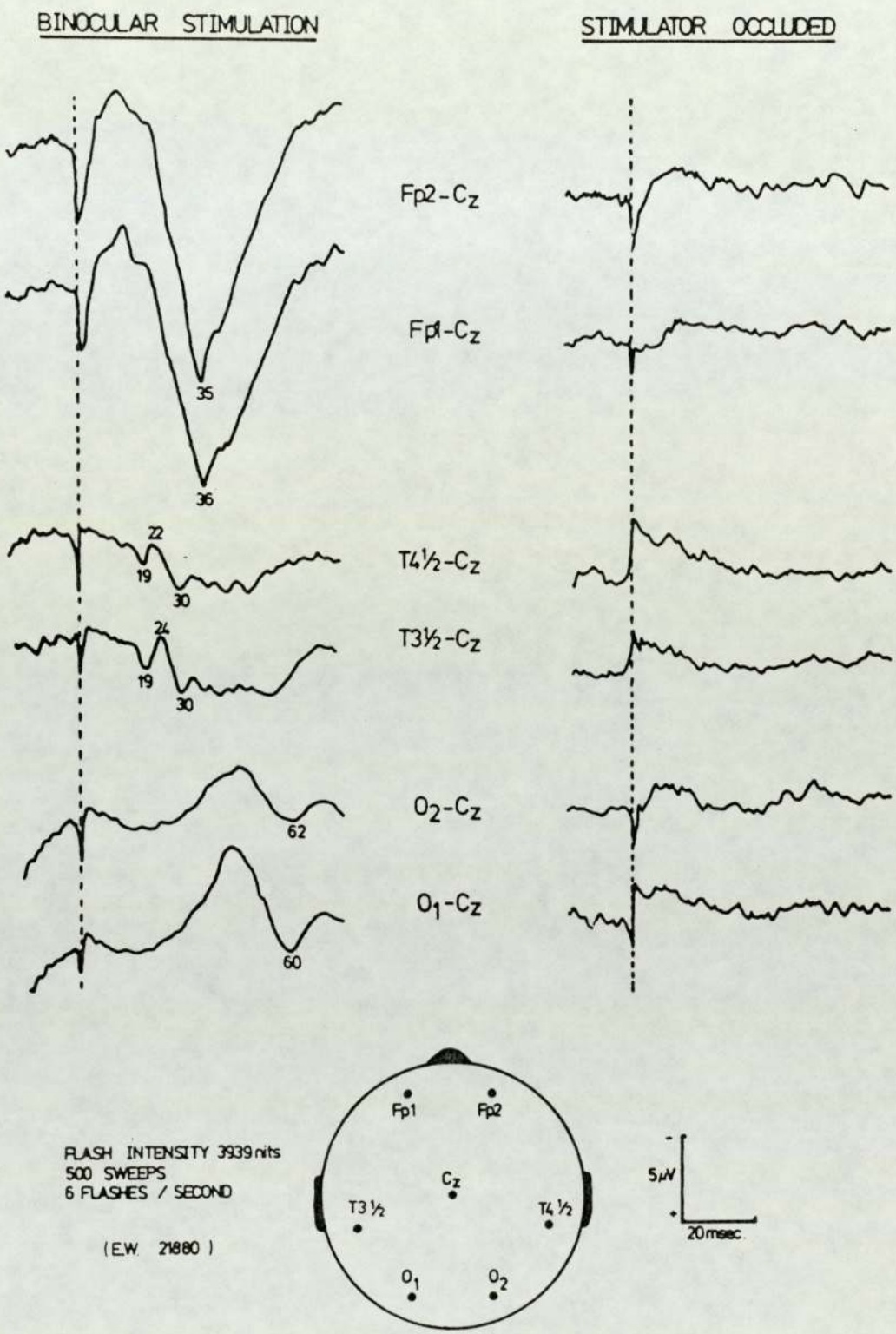
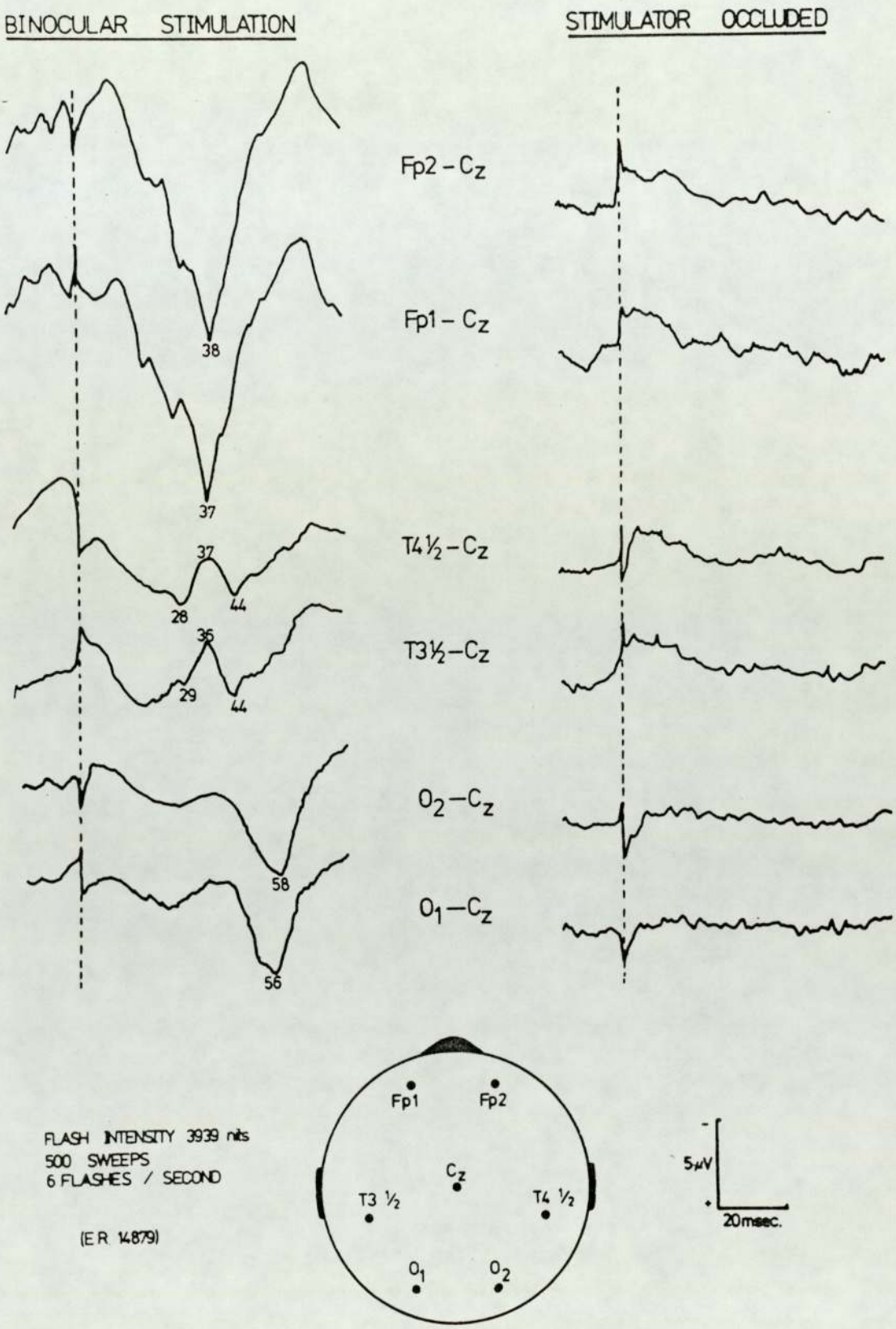

BINOCULAR STIMULATION
STIMULATOR OCCLUDED
Fp2-Cz
Fp1-Cz
T4½-Cz
T3½-Cz
O2-Cz
O1-Cz
35
36
22
19
30
24
19
30
62
60
FLASH INTENSITY 3939 nits
500 SWEEPS
6 FLASHES / SECOND
(E.W. 21880)
Fp1
Fp2
Cz
T3½
T4½
O1
O2
5μV
20 msec.

FIGURE 2.3.15.

Effects of occlusion of photo-stimulator on early component complex of the VEP

On binocular stimulation clear ERG responses (F_{p1}, F_{p2}) early component comlexes ($T_{3\frac{1}{2}}$, $T_{4\frac{1}{2}}$) and cortical responses (O_1, O_2) are demonstrated. On occlusion of the activated photo-stimulator, which produced an audible click with each flash, all responses were abolished, indicating a non-auditory origin of the early component complex


BINOCULAR STIMULATION
STIMULATOR OCCLUDED
Fp2 – Cz
Fp1 – Cz
T4½ – Cz
T3½ – Cz
O2 – Cz
O1 – Cz
38
37
37
28
44
36
29
44
58
56
FLASH INTENSITY 3939 nits
500 SWEEPS
6 FLASHES / SECOND
(E.R. 14879)
Fp1
Fp2
Cz
T3 ½
T4 ½
O1
O2
5μV
20msec.

headphones whilst observing the flashing stroboscope. Resulting waveforms during simultaneous multichannel recording are illustrated in Figure 2.3.16.. In this case, no effects were noted on the recordings from any of the electrodes.

Conclusion

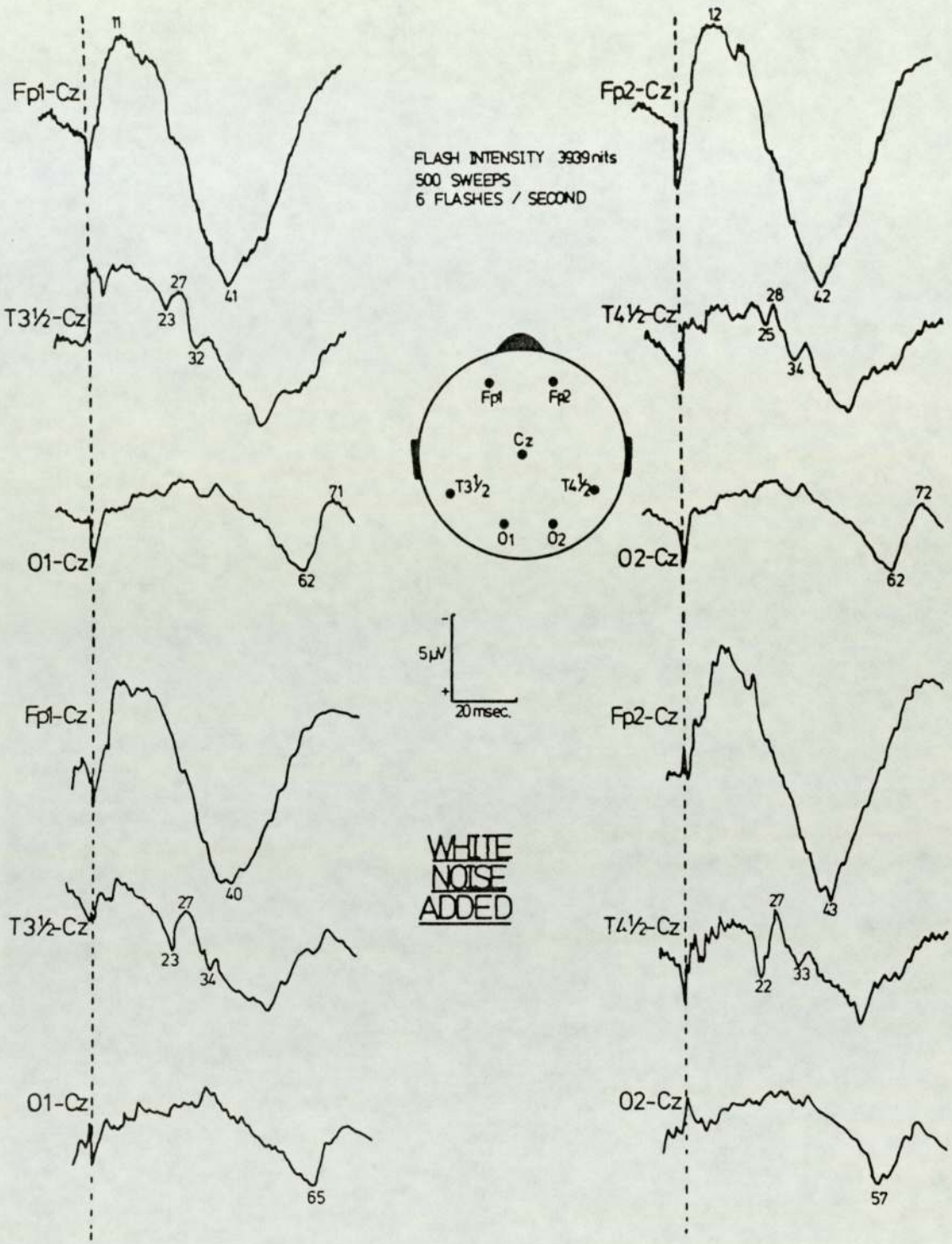
The results of monocular and binocular stimulation clearly indicated a post-chiasmal origin of the early component complex. The auditory control experiments indicated that the complex was unrelated to auditory stimulation.

These observations in conjunction with the anatomical location of the site from which the signal was derived led to the opinion that the triphasic early component complex must be a reflection of subcortical activity and it was therefore termed the 'Visually Evoked Subcortical Potential ' (VESP) (Harding and Rubinstein, 1980a,b,c, and Harding and Rubinstein, 1981a,b).

FIGURE 2.3.16.

Effects of white noise masking on the early component complex of the VEP

The effects of masking of the audible photo-stimulator click with white noise are shown in one subject. ERG responses (F_{p1}, F_{p2}), early component complexes ($T_{3\frac{1}{2}}$, $T_{4\frac{1}{2}}$) and cortical responses (O_1, O_2) are illustrated in the upper sets of recordings. In the lower sets of recordings, when white noise is added via headphones, no significant difference is seen in any of the recordings, confirming a non-auditory origin for the early component complex


Fp1-Cz
11
T3½-Cz
27
23
41
32
O1-Cz
71
62
Fp2-Cz
12
T4½-Cz
28
25
42
34
O2-Cz
72
62
FLASH INTENSITY 3939nits
500 SWEEPS
6 FLASHES / SECOND
Fp1
Fp2
Cz
T3½
T4½
O1
O2
5μV
20msec.
WHITE NOISE ADDED
Fp1-Cz
40
T3½-Cz
27
23
34
O1-Cz
65
Fp2-Cz
43
T4½-Cz
27
22
33
O2-Cz
57

CHAPTER 3

STUDIES ON THE VISUALLY EVOKED SUBCORTICAL POTENTIAL

3. STUDIES ON THE VISUALLY EVOKED SUBCORTICAL POTENTIAL

Although in Section 2.3.3. the effects of monocular and binocular stimulation on the VESP were indicative of a post-chiasmal origin, in some subjects during simultaneous recording of ERG, VESP and occipital response, the latencies of the VESP peaks often coincided with those of the ERG, particularly the second positive peak of the VESP which on occasions had the same or similar latency to the peak of the ERG 'b' wave as shown in Figure 2.3.13. This observation necessitated the clarification of the relationship (if any) between the VESP and the ERG.

3.1. SCALP AND FACIAL TOPOGRAPHY OF THE ERG.

During the early development of ERG techniques in man it was realised that contact had to be made with the anterior surface of the eye in order to derive the signal and complete the recording circuit (Dewar, 1877). Early procedures involved the enclosing of a conducting fluid (saline) around the eye (Dewar, 1877 and Hartline, 1925), but this was superceded by the 'wick' electrode placed in contact with the anterior surface of the eye (Sachs, 1929). The development of haptic contact lenses incorporating an embedded corneal electrode enabled accurate clinical recording of the ERG (Riggs, 1941 and Karpe, 1945) and this technique has persisted in most laboratories.

The recording of the ERG in the early days of contact

lenses was often found by the patient to be very unpleasant and prolonged investigations were avoided. Motokawa and Mita (1942) therefore suggested the use of a recording electrode placed on the bridge of the nose. Satisfactory, though rather attenuated signals were recorded, avoiding any contact with the cornea.

This important report demonstrated that the ERG, being of such a high amplitude, could be recorded at a significant distance from its site of origin. Non-corneal electroretinography has now become an established technique in clinical ophthalmology and plays a significant role in a number of clinical situations in which the use of a corneal electrode is contraindicated. For example, a compromised anterior segment following trauma (Jayle and Tassy, 1970); in paediatric practice when general anaesthesia is inadvisable and the use of a corneal contact lens is impractical (Harden, 1974; Jones and France, 1977 and Uchida, Mitsuyu-Tsuboi and Honda, 1979); when prolonged periods of recording are necessitated (Jacobson, Uchida and Masuda, 1966). Since the amplitude of the ERG is attenuated and myogenic artifact is increased when using skin electrodes, averaging techniques must be employed to improve the signal-to-noise ratio (Berry, 1976; Skalka, 1979 and Mustonen and Sulg, 1980). The highest amplitude non-corneal ERG is generally recorded from an electrode placed on the lower lid surface (Adachi and Chiba, 1971; Noonan, Wilkus, Chatrian and Lettich, 1973; Nakamura, 1975 and Nakamura, 1978) and

estimates of the amplitude of the ERG 'b' wave at this site have varied considerably between 1/30 to 1/2 of that recorded directly from the cornea (Nakamura, 1978). Latencies of ERG components at corneal and non-corneal sites remain almost identical (Gur and Gath, 1979).

Since the eye is surrounded by a volume conductor it should be possible to record an ERG signal at any point in the field of activity around the eye (Krakau, Enokson and Hedbys, 1958). ERG signals are recognised contaminants of EEG recordings (when performing photic stimulation) from frontal electrodes, i.e. sites Fp_1 and Fp_2 of the International 10/20 system (Samson, Samson-Dollfus and Pinchon, 1959 and Jordan, Worchel, Bajandas and Grice, 1979) and indeed, in cases of irreversible coma where an isoelectric EEG has been shown, photic stimulation has elicited ERG type signals in anterior-frontal regions, persisting for many hours after the extinction of spontaneous activity (Arfel, 1967). This spread of electrical activity presumably is volume conducted from the cornea via the upper lid, brow etc.. Horsten, Wildboer-Venema and Winkelman (1961) showed in cats and in one patient that when one eye was enucleated and replaced with a saline soaked gauze pad an ERG type signal could be recorded from the socket when the intact eye was dark adapted and then strongly illuminated. Similar findings were also reported in cats after transection of the optic nerve or coagulation of the chiasma and it was concluded that this transmission of signals

did not take place via a nervous pathway, but by direct transmission of currents via the intervening tissues. These findings were endorsed by Yonemura, Strzyzewski and Jacobson (1965) who worked on cats and who made an additional comment that the field of ERG activity in the cat did not extend from the stimulated eye to the contralateral cheek. Topographical studies of the human ERG were carried out by Nakamura (1975) and Nakamura (1978). In both these communications a control corneal ERG was recorded using a contact lens electrode; skin electrodes around the orbit and face were used to detect any ERG-type signals. It was shown that the field of activity spread up to the forehead and down the cheek ipsilateral to the eye stimulated; very little conduction occurred across the median line of the face and was also minimal along the temple.

In order to verify that the VESP was unrelated to the ERG, a study of the scalp and facial topography of the ERG was carried out using the same stimulus and analysis parameters as in the preceding experiment reports. In addition, using these experimental parameters, a brief evaluation was made of a new type of corneal electrode for recording of the ERG and to assess its utility in the Aston Clinical Neurophysiology Unit. It is stressed that the evaluation of this electrode was not regarded by the author as being fully comprehensive, but as a pilot study secondary to the main theme of the thesis.

This electrode - the Gold Foil Electrode (GFE) - has been developed in recent years in an attempt to enable good ERG recordings with the minimum of contact with the cornea and the avoidance of patient discomfort. It is simply hooked over the lower lid margin making minimal contact with the lower limbus and cornea and is advocated for use in circumstances which require prolonged testing of retinal function or in eyes with corneal pathology. The electrode was originally described by Chase, Fradkin and Tsuda (1976) and consisted of a thin sheet of Mylar (a flexible plastic) coated with aluminium which could be shaped to form a 'hook' which was placed over the lower lid, and a connecting wire was led off to the recording apparatus. Borda, Gilliam and Coats (1978) and Arden et al. (1979) found that the aluminium coating rapidly detached from the Mylar and variations in resistance confounded the recordings obtained. Consequently, the electrode was modified by coating the Mylar with Gold Foil (Borda et al. 1978 and Arden et al. 1979) and this has been found to make the electrode more stable. Close correlation in performance between the GFE and standard contact lens electrodes has been reported (Borda et al. 1978 and Arden et al. 1979). The GFE electrodes used in the present study were of the same type as those used by Arden et al. (1979).

Materials and Method

Evaluation of the GFE was made by comparing ERGs recorded using the GFE with those recorded with a conventional Henkes contact lens electrode (HCL). Recordings were made on 10 normal volunteer subjects (5 male and 5 female) aged between 20 and 35 years (mean 24.3 years); monocular stimulation of both eyes was performed, permitting recordings from 20 eyes. Topical corneal anaesthesia was induced using 0.4% Benoxinate Hydrochloride (oxybuprocaine hydrochloride) drops; the vertex was used as reference site for both corneal electrodes. Recordings were made using the GFE first and the HCL second; this order was chosen (a) in an attempt to maintain patient relaxation, since it was considered that the HCL would be a more unpleasant electrode for the subjects to tolerate and therefore best used after the GFE, (b) since the use of the HCL very often causes a mild degree of corneal oedema, it was preferable to avoid this until the end of the experiment. A period of 15 minutes was allowed between recordings using the GFE and HCL in order to regain a degree of retinal adaptation. No period of dark adaptation was used prior to recordings and since such a large number of bright flashes was used, the records may be regarded as reflecting a purely photic response. Stimulus and analysis parameters were the same as in Sections 2.3.2. and 2.3.3.. Three responses were recorded using each electrode, latency and peak-to-peak

amplitude measurements of the 'a' and 'b' waves being made manually and the mean values of the measurements calculated.

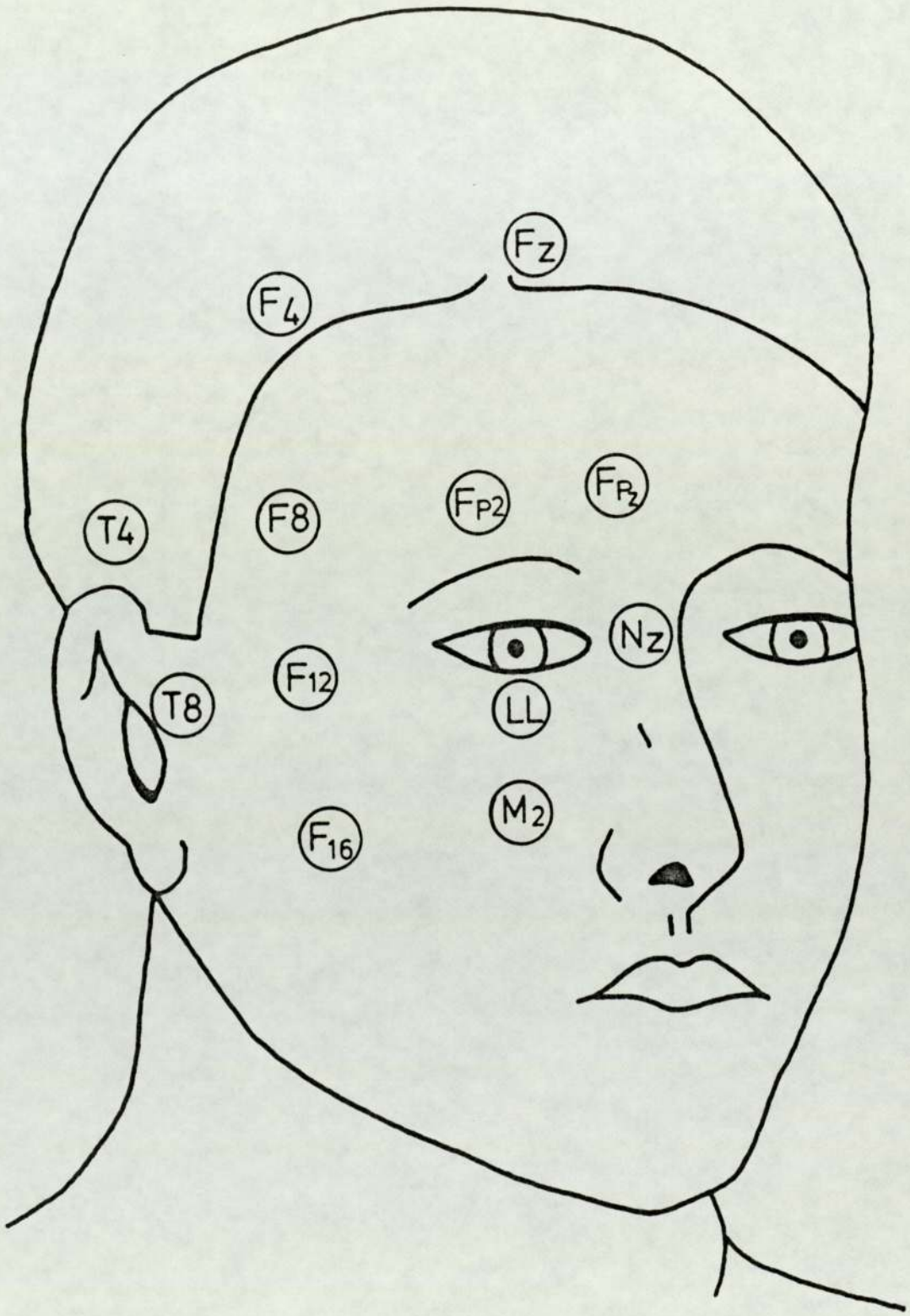
At the end of the procedures a drop of fluorescein was instilled into the lower fornix of each eye and slit-lamp examination performed to check anterior segment integrity.

For the topographical study, observations were made on twelve normal volunteer subjects, 6 male and 6 female, aged between 20 and 28 years (mean 23 years). All had visual acuities of 6/6 or better and full visual fields. None of these subjects had been included in the previous topographical studies. Electrodes were again placed according to the International 10/20 system in a modified form as shown in Figure 3.1.1.. Standard sites used were F_{pz}, F_z, F_{p2}, F_8, F_4, T_4. Additional electrodes were placed at N_z, F_{12} and T_8 (being 20% lower than F_{pz}, F_8 and T_4 respectively) and at M_2 and F_{16} (being 20% lower than F_{p2} and F_8 respectively). One electrode was placed in the centre of the right lower lid as close as possible to the lid margin, at LL. In order to ensure an accurate topographical assessment, common reference recordings were made using the vertex (C_z), the contralateral occiput (O_1) and the anterior neck as comparator reference sites. The VESP was monitored using electrodes placed at $T_{3\frac{1}{2}}$ and $T_{4\frac{1}{2}}$, the pre-determined optimal sites for recording the VESP (see Sections 2.3.2. and 2.3.3.) and referred

FIGURE 3.1.1.

Scalp and facial distribution of electrodes used in topographical study of the ERG

Standard 10/20 system sites were F_{pz}, F_z, F_{p2}, F_8, F_4 and T_4. Additional electrodes were placed at N_z, F_{12}, T_8 (10% lower than F_{pz}, F_8 and T_4, respectively) and at M_2 and F_{16} (20% lower than F_{p2} and F_8, respectively.


Fz
F4
T4
F8
FP2
FP1
Nz
F12
T8
LL
M2
F16

to the vertex, C_z. 7mm. silver/silver chloride EEG electrodes were affixed with collodion to the scalp and with adhesive discs to the face and the resistance maintained below 5K ohms. The base-line corneal ERG was recorded as a control, using the GFE. As determined in Section 2.3.2. and 2.3.3., 500 flashes at intensity 3939 nits were presented to the subjects at a rate of 6/second from a Grass PS22 photostimulator placed 25 cms. from the eyes. Direct viewing of the photostimulator was maintained during all the recordings and the stimuli presented binocularly and then monocularly to each eye, the unstimulated eye being carefully occluded.

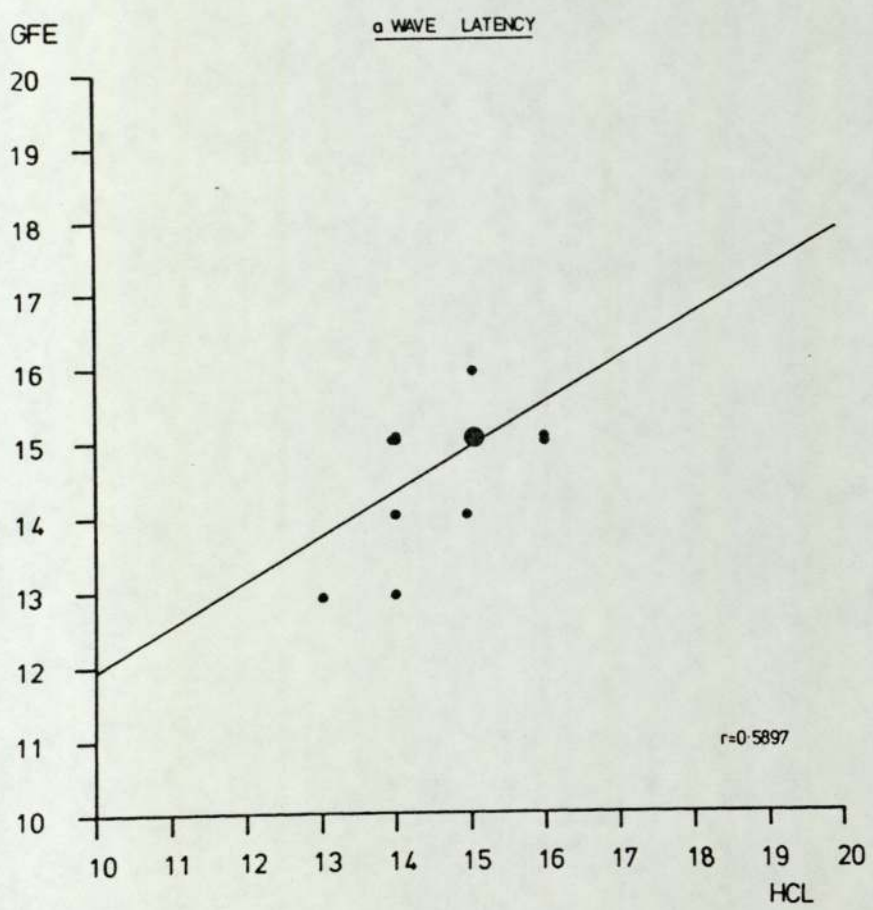
Results

Latency and peak-to-peak amplitude measurements of 'a' and 'b' waves of the ERG recorded using GFE and HCL are displayed in the correlation graphs shown in Figures 3.1.2. and 3.1.3. (raw data being given in Appendix 2). The results obtained using the GFE were considered to be the dependent variable, those obtained using the HCL were considered to be the independent variable and the 'control' measurement. High correlation of both latency and amplitude measurements was found for both 'a' and 'b' waves as shown below:

'a' wave latency	r = 0.5897
'a' wave amplitude	r = 0.9161
'b' wave latency	r = 0.9473
'b' wave amplitude	r = 0.9591

FIGURE 3.1.2.

Correlation graphs of ERG 'a' wave latency and amplitude using GFE and HCL (see text for details)


a WAVE LATENCY
GFE
20
19
18
17
16
15
14
13
12
11
10
10 11 12 13 14 15 16 17 18 19 20
HCL
r=0·5897

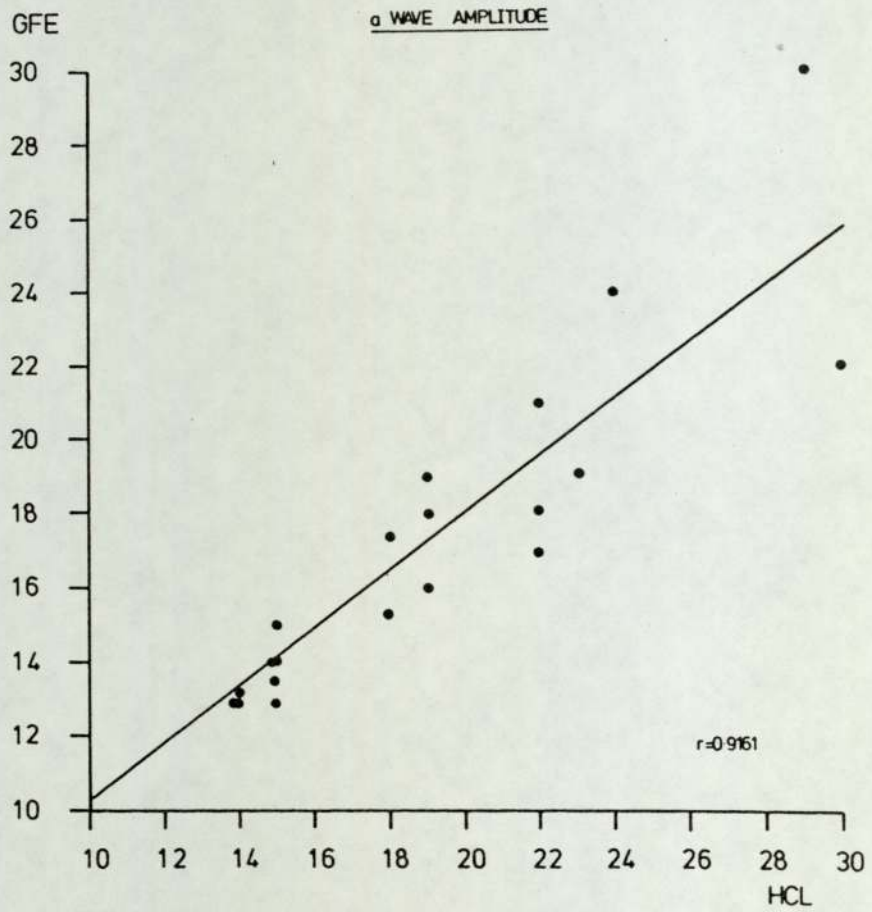
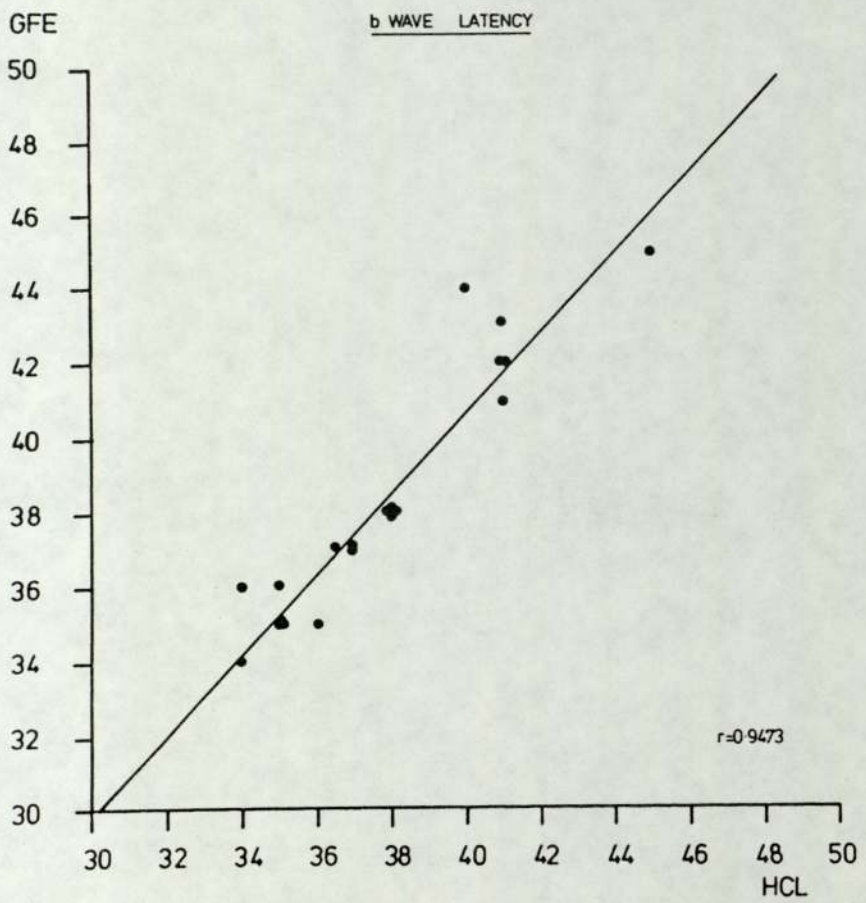
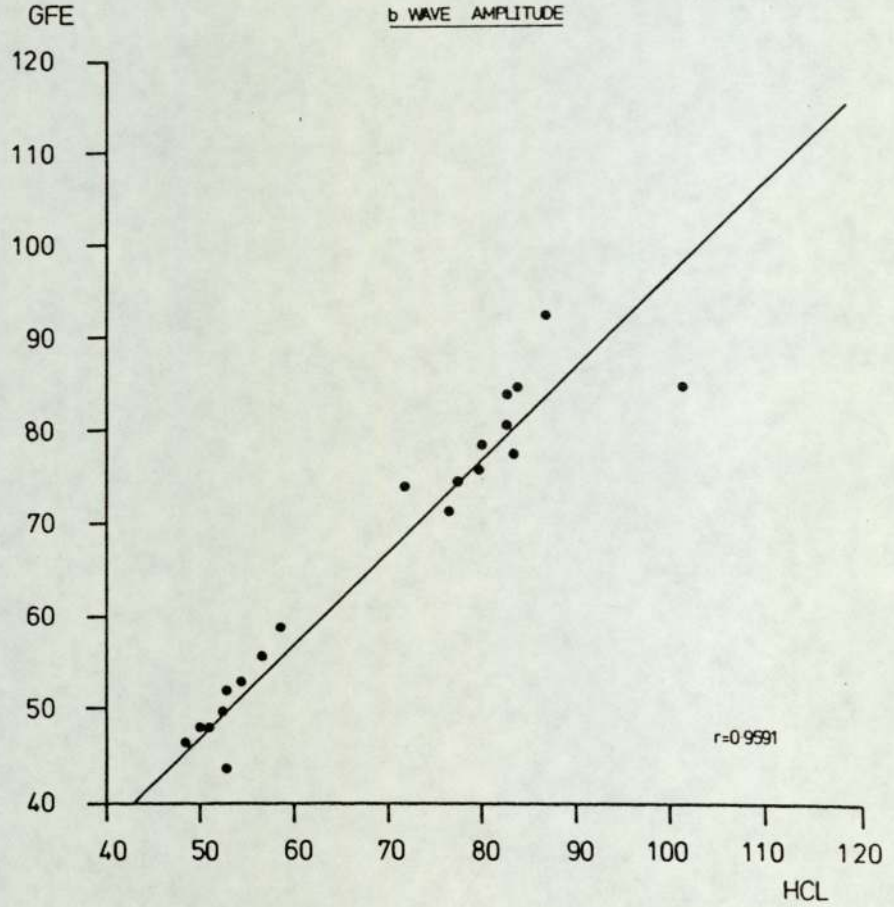

a WAVE AMPLITUDE
GFE
30
28
26
24
22
20
18
16
14
12
10
10 12 14 16 18 20 22 24 26 28 30
HCL
r=0·9161

FIGURE 3.1.3.

Correlation graphs of ERG 'b' wave latency and amplitude using GFE and HCL (see text for details)


GFE
b WAVE LATENCY
50
48
46
44
42
40
38
36
34
32
30
r=0.9473
30 32 34 36 38 40 42 44 46 48 50
HCL


GFE
b WAVE AMPLITUDE
120
110
100
90
80
70
60
50
40
r=0.9591
40 50 60 70 80 90 100 110 120
HCL

With reference to the data points for 'a' wave latency, a large number of points formed a cluster at the 15 m.sec. intersection as shown in Figure 3.1.2.. The result of this was the finding of a much lower correlation efficient than initially would be expected on examination of the data points. Significance of the differences in latency and amplitude measurements using both electrodes was estimated using the Students' t-test. Both 'a' and 'b' wave latency values were found to be not significantly different. However, 'a' and 'b' wave amplitude measurements were found to be significantly different ('a' wave $p < 0.0005$; 'b' wave $p < 0.005$), amplitude when using the HCL being significantly higher than when using the GFE. The GFE was found by the novice operator to be rather a difficult electrode to manipulate and was frequently 'sprung-out' of the lower fornix by subject blinking or eye movements. With practice a technique was developed of tapeing the connecting lead to the cheek and improving stability of placement of the GFE. Generally, subjects reported the GFE to be a far more comfortable electrode than the HCL.

Considering the topographical study, control ERG signals recorded with the GFE referred to the vertex revealed a mean 'a' wave latency of 14.82 m.secs. ($\pm$ 1.16 m.secs.) and a mean amplitude of 15.40 uV. ($\pm$ 4.71 uV.); a mean 'b' wave latency of 37.36 m.sec. ($\pm$ 1.85 m.secs.) was found with a mean amplitude of 57.58 uV. ($\pm$ 16.67 uV.). Two OPs were seen on the 'b' wave of the ERG in most

subjects with mean latencies of 17.22 m.secs. ($\pm$ 1.09 m.secs.) and 25.22 m.secs. ($\pm$ 1.48 m.secs.). The use of either an anterior neck or contralateral occipital reference site produced negligible effect on amplitude or latency of the ERG, indeed, the anterior neck site produced increased myogenic artifact in the response, making the identification of OPs more difficult. Amplitude and latency measurements of the waveforms derived from the various electrode sites were made manually and the mean values of the amplitude of any detectable ERG-type signal expressed as a percentage of the control corneal ERG amplitude as shown in Table 3.1.1.

The amplitude of the ERG response from skin electrodes was found to diminish acutely as distance from the eye increased and artifact became accentuated, but latencies however remained almost identical to those of the GFE (see Table 3.1.1). The amplitude of the response from the lower lid was found to be the highest of the non-corneal sites, that of the 'a' wave being 26.8% and that of the 'b' wave being 31.16% of the control ERG signal. Figure 3.1.4. illustrates the scalp and facial distribution of ERG-type signals in five subjects with various amplitudes of corneal ERG. As distance between the cornea and the recording electrode increased, the 'a' wave was abolished earlier than the 'b' wave, as would be expected from their relative amplitudes. A remnant of the 'b' wave was however detectable in most subjects at almost all electrode sites, although often

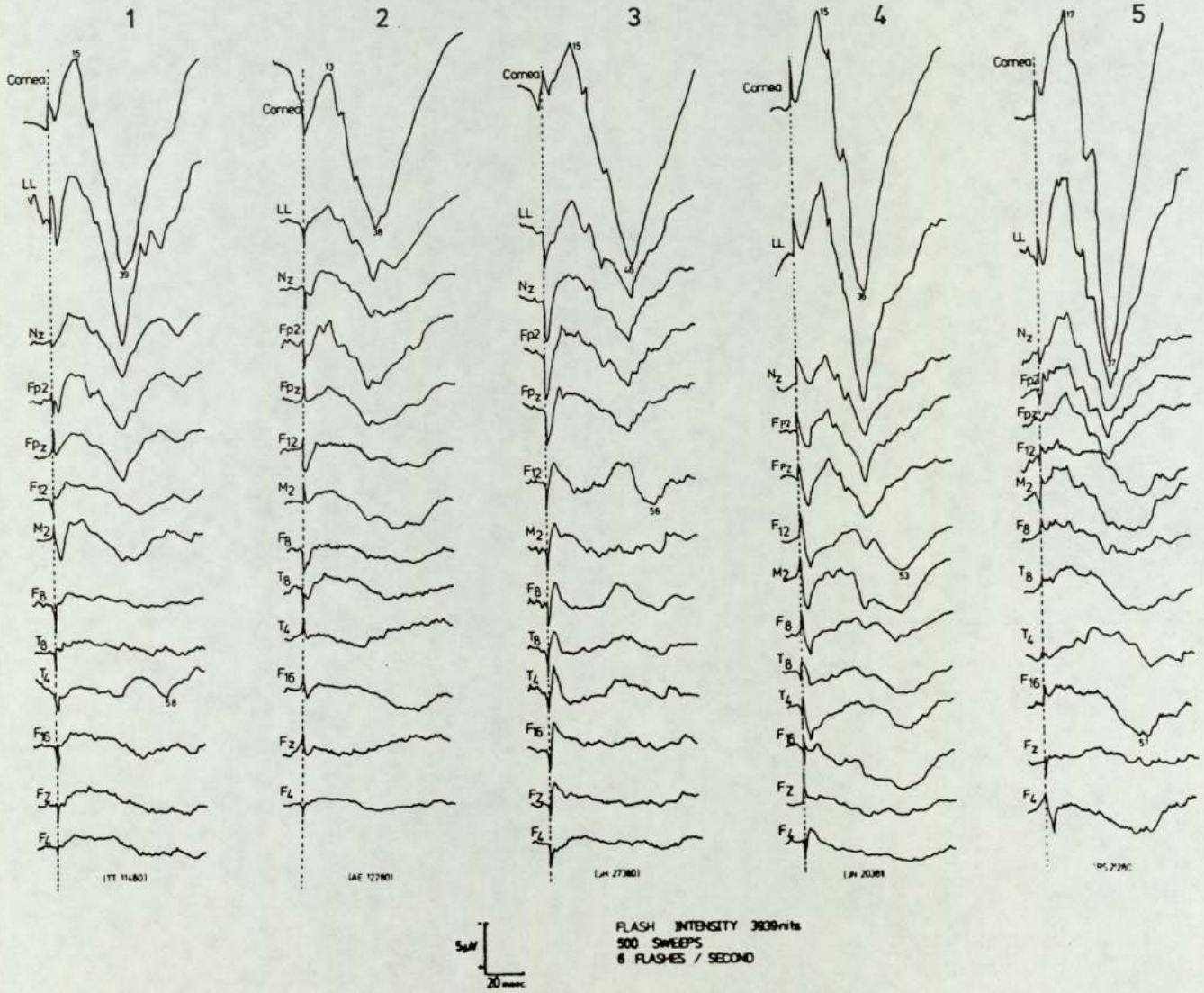
ELECTRODE SITE	'a' WAVE			'b' WAVE		
	LATENCY (m.sec)	AMPLITUDE (uV)	% CONTROL AMPLITUDE	LATENCY (m.sec)	AMPLITUDE (uV)	% CONTROL AMPLITUDE
CORNEA	14 ± 1.16	15.40 ± 4.71	100	37.36 ± 1.85	57.58 ± 16.67	100
LL	18.83 ± 1.46	4.13 ± 3.20	26.8	37 ± 3.45	17.94 ± 12.8	31.16
N_z	12.75 ± 2.38	1.75 ± 0.55	11.38	33.75 ± 2.82	9.69 ± 5.36	16.82
Fp_2	12.75 ± 4.41	1.11 ± 0.63	7.21	35.83 ± 2.3	6.88 ± 2.66	11.96
Fp_z	11.5 ± 5.37	1.12 ± 0.71	7.27	35.66 ± 2.74	5.85 ± 1.78	10.16
F_{12}	-	-	-	36.62 ± 3.61	1.27 ± 1.31	2.20
M_2	14.5 ± 1.25	0.36 ± 0.44	2.32	35.9 ± 2.54	4.91 ± 3.80	8.53
F8	12.1 ± 2.4	0.05 ± 0.19	0.37	36.67 ± 1.79	1.54 ± 1.85	2.67
T8	-	-	-	36.8 ± 2.13	0.58 ± 0.86	1.01
T4	-	-	-	35.25 ± 2.38	0.35 ± 0.54	0.60
F16	-	-	-	34.2 ± 0.74	1.07 ± 1.27	1.87
F_z	-	-	-	-	-	-
F4	-	-	-	36.4 ± 3.25	0.4 ± 0.95	0.69

TABLE 3.1.1. Mean amplitude and latency measurements of ERG-type waveforms at non-corneal sites. Amplitude is expressed as a percentage of the corneal (control) response. - : no measurable response

FIGURE 3.1.4.

Scalp and facial distribution of ERG-type signals in five subjects

All electrodes are referred to the vertex (C_z) and the corneal signal is recorded with a GFE at half the gain of all other channels. All subjects show similar distributions of signals, the extent of the field being in direct proportion to the amplitude of the corneal signal. At temporal sites T_4 and T_8 a very low amplitude 'b' wave remnant is seen in some cases (see text for details)


1
2
3
4
5
Cornea
LL
Nz
Fp2
Fpz
F12
M2
F8
T8
T4
F16
Fz
F4
FLASH INTENSITY 3939mits
500 SWEEPS
6 FLASHES / SECOND
5μV
20 msec

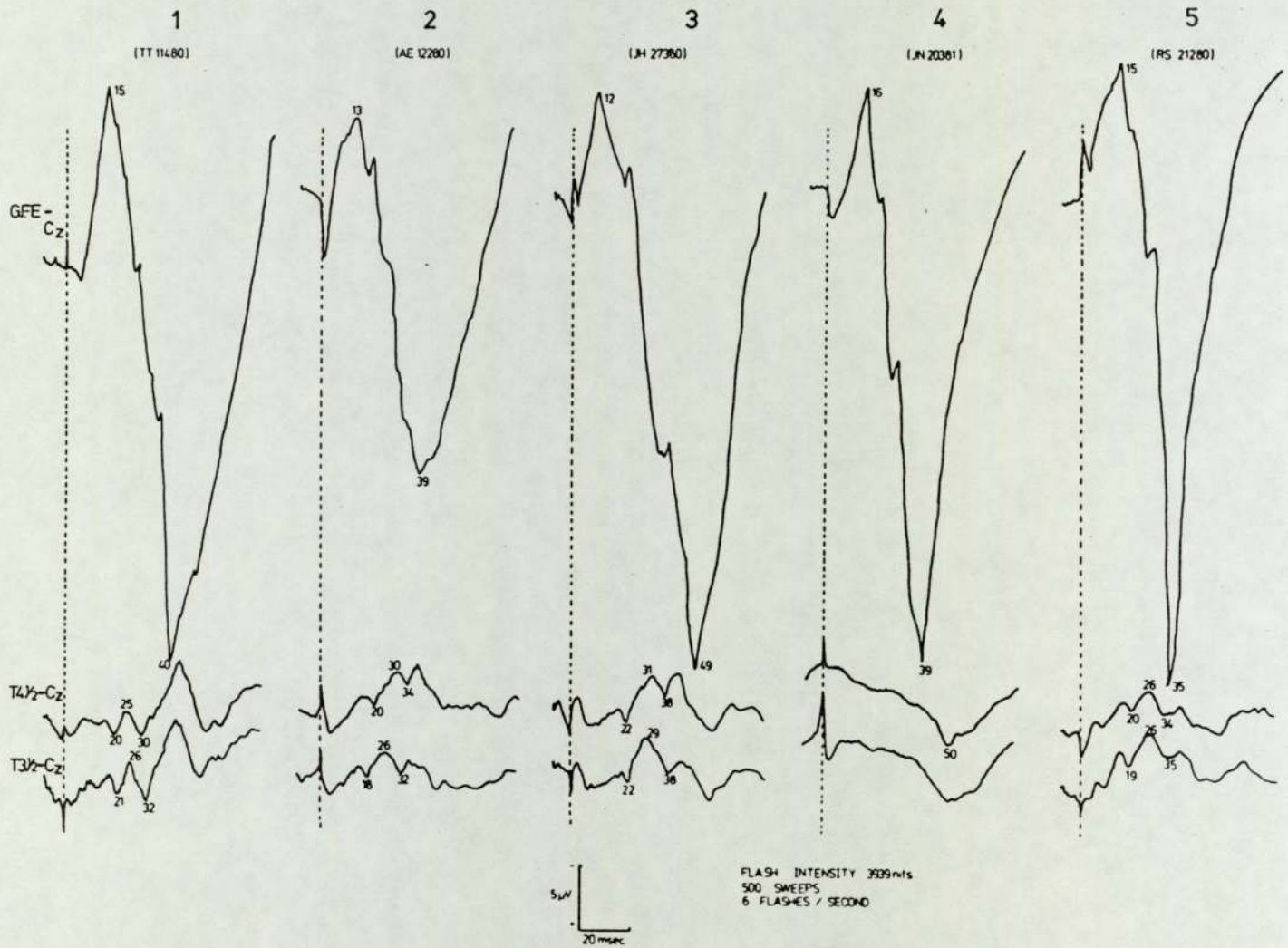
appearing as an extremely low amplitude deflection difficult to discern from myogenic artifact except by the superimposition of consecutive recordings. Similarly, the amplitude of the OPs reduced rapidly as the distance from the cornea increased. Myogenic and lid-blink artifact varied between subjects and in some cases confounded the ERG signal at skin electrodes relatively close to the cornea. The extent of the field of activity produced was directly proportional to the amplitude of the corneal ERG as shown in Figure 3.1.4. , subject 5 demonstrating a wider distribution of ERG-type signals than subject 2. On binocular stimulation the response at sites N_z and Fp_z was found to be twice that produced on monocular stimulation of either eye and the response at Fp_2 was around one and a half times the monocular response from the right eye, indicating interaction of the two monocular ERG fields. The response at LL was not enhanced on binocular stimulation nor was that at any other electrode site.

The results of simultaneous recording of corneal ERG and VESPs in the same five subjects are shown in Figure 3.1.5. Subjects 1,2,3 and 5 demonstrate well formed bilateral VESP components all with clear triphasic configurations. The latencies of the VESPs recorded in subjects 1, 2 and 3 are clearly unrelated to those of the ERG, but in subject 5 there is a closer relationship between the peak of the ERG 'b' wave and the final, positive peak of the VESP. The results from subject 4 are atypical. This is a subject from whom no VESP has ever been recorded

FIGURE 3.1.5.

Simultaneous recording of corneal ERG and VESP

Subjects 1, 2, 3 and 5 demonstrate well-formed VESP components bilaterally (at electrodes $T_{3\frac{1}{2}}$ and $T_{4\frac{1}{2}}$). Subject 4 is atypical - repeated attempts to record VESPs have been usuccessful, although no neurological or ophthalmological abnormalities were detected and a normal ERG signal could be recorded in this subject (see text for details)


1
(TT 11480)
2
(AE 12280)
3
(JH 27380)
4
(JN 20381)
5
(RS 21280)
GFE - Cz
T4½-Cz
T3½-Cz
FLASH INTENSITY 3939 mls
500 SWEEPS
6 FLASHES / SECOND
5 µV
20 msec

despite repeated attempts on a number of occasions over a period of 14 months and the use of variations in electrode montage and stimulus parameters. A normal corneal ERG, however, was recorded in this subject as was the occipital VEP to both flash and pattern-reversal stimulation. No neurological or ophthalmological abnormality could be detected. Later components were seen at certain electrode sites, consisting in 10 subjects of a positive peak around 45-55 m.sec. latency. In 3 subjects a negative peak of latency around 60-70 m.sec. was also seen. The origin of these components was determined by comparison of responses using the three reference sites. The positive component around 45-55 m.secs. was present in recordings from electrodes F_{12}, T_8, T_4 and M_2 when using the vertex (C_z) as reference (see Figure 3.1.4.), but was absent when an anterior neck reference was used, although the ERG topography remained the same. The use of O_1 as reference revealed similar responses to those obtained using the vertex site. This would suggest that the component may be surface negative around C_z and therefore probably of cortical origin, probably spreading from the occiput. Indeed, this component was probably the N_1 component of the occipital VEP (trials in the Aston Clinical Neurophysiology Unit using flash stimulation show that the N_1 component has a mean latency of 56.1 m.secs. ($\pm$ 6.8 m.secs.).

Conclusions

The GFE provides an accurate method of recording the ERG and is potentially useful in a number of specific anterior segment pathologies. It was, however, found to be rather unsuitable for use in un-cooperative subjects who performed excessive blinking or eye movements and a period of operator experience or 'training' was considered necessary. Amplitudes of ERG components were generally found to be lower when recorded with the GFE rather than the HCL (this difference being statistically significant) although latencies were not significantly different, and this is considered to be related to the field of ERG activity around the anterior segment per se. This finding is in agreement with previous authors (Borda et al. 1978; Arden et al. 1979 and Cummins and Kaluzne, 1979). The amplitude of ERG components has been found to be maximal when using the maximal size of contact lens in effect when covering the maximum area of the cornea (Sundmark, 1955). Moreover, the amplitude of the ERG components has been found to be maximal at the centre of the cornea, reducing towards the limbus and sclera (Krakau, 1958; Sundmark, 1958 a, b, c; Sundmark, 1959 a,b; and Holland and Herr, 1964). In general, when the use of a contact lens electrode is contraindicated, the GFE permits reading of a satisfactory ERG of considerably higher amplitude than a skin electrode placed at the lower lid margin, although the choice of skin electrode or GFE depends on the individual case under consideration.

Considering the topographical study of the ERG, it was clear that the ERG signal produced under the same conditions used to elicit the VESP was distributed over a wide field around the orbit and this is in agreement with other authors (Nakamura, 1978). The measurable extent of the field of activity of the ERG was dependent partly on the amplitude of the corneal signal and partly on the degree of myogenic artifact present. The reduction in amplitude of the ERG components by over 60% across the lower lid, which constitues 2-3 mm. of insulating tissue is remarkable. The fields from either eye clearly overlapped medially, but were separated by the nasal insulator. Since the interaction of the fields did not extend to the lower lid site, the recording of monocular responses without occlusion of the opposite eye would be possible and this may be of value in the clinical situation, particularly in paediatric electrophysiological assessment.

At the more posterior sites used in the study (namely, T_4 and T_8) any measurable remnant of the ERG 'b' wave took the form of a small monophasic deflection generally less than 1 μV. in amplitude, dependent on corneal ERG amplitude. The VESP however assumes a triphasic P-N-P configuration and its peak-to-peak amplitudes are of the order of 1.5 μV. and 2.5 μV. respectively.

The subject from whom no VESP signals could be recorded (Figure 3.1.5.) was unusual, although being neurologically and ophthalmologically normal. The ERG from

the cornea was of equally high amplitude when compared with other subjects, with similar scalp and facial distribution of ERG-type responses to the other subjects considered.

The distinct difference in morphology between the VESP and the ERG 'b' wave remnant recordable at the temporal sites described and the relative disparity in amplitudes therefore strongly suggested that the VESP was not attributable to a volume-conducted ERG response.

3.2. FURTHER EVIDENCE OF THE INDEPENDENCE OF ERG AND VESP

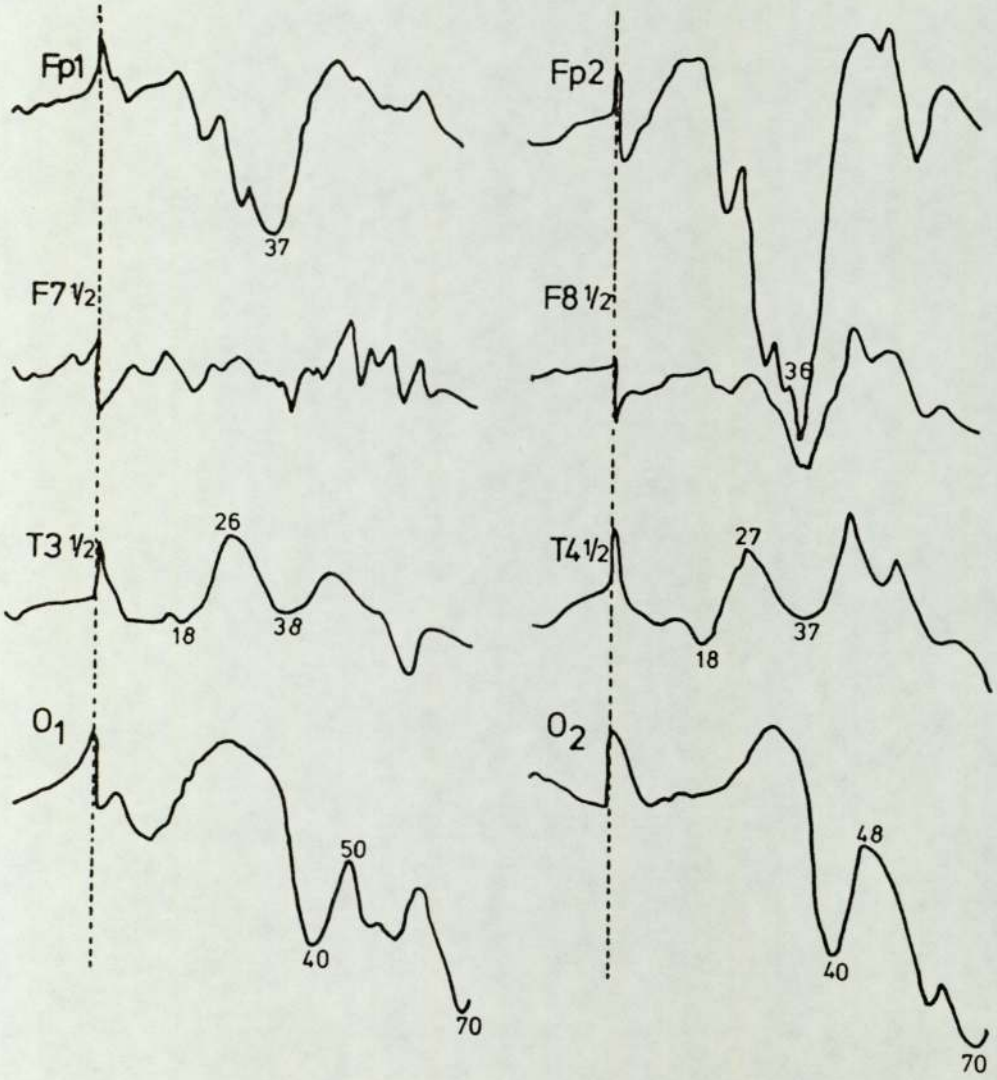
A number of selected cases studied during the period of the author's research are also presented in order to strengthen the argument that the VESP is not related to the ERG. The ERG, VESP and occipital VEP (VECP) have been simultaneously recorded. In principle, if the VESP and ERG were identical they would be expected to correlate under certain conditions. A reduced amplitude or absent ERG from one eye (e.g. due to retinal detachment) would be associated with similarly reduced or absent VESP ipsilateral to the reduced ERG if they were of similar origins, but the VESP should be unaffected if of a different origin; the VECP would also be intact and symmetrical. In the case of unilateral optic nerve trauma or lesions, the VECP would be anticipated to be reduced or absent at both occiputs on stimulation of the affected eye, the ERG remaining bilaterally and the VESP affected in a similar manner to the VECP if unrelated to the ERG.

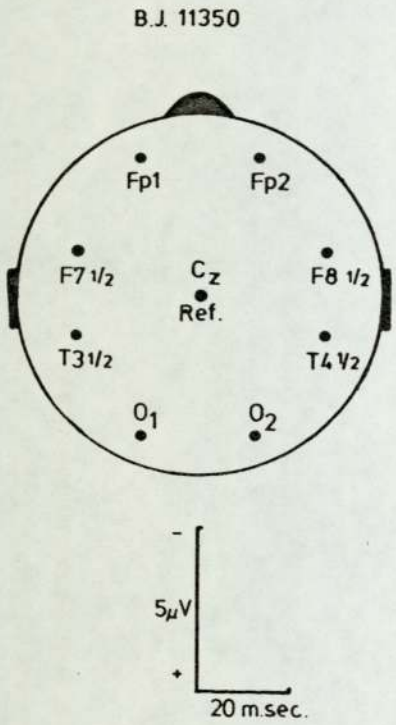
In two normal volunteer subjects, simultaneous recordings were made of ERG (at Fp_1 and Fp_2), VESP (at $T_{3\frac{1}{2}}$ and $T_{4\frac{1}{2}}$) and VECP (at O_1 and O_2). In both subjects the amplitudes of the ERG signals were markedly asymmetric, although latencies were approximately equal in both eyes, as illustrated in Figures 3.2.1. and 3.2.2.. . However, the VESPs were fully formed bilaterally and of symmetrical

FIGURE 3.2.1.

Simultaneous recording of asymmetric ERGs and symmetric VESPs

In a normal subject, the ERG from the left eye (F_{p1}) is of lower amplitude than that from the right eye (F_{p2}) although VESPs ($T_{3\frac{1}{2}}$ and $T_{4\frac{1}{2}}$) are of almost identical amplitudes. The early components of the cortical response (O_1, O_2) are also symmetrical (see text for details)



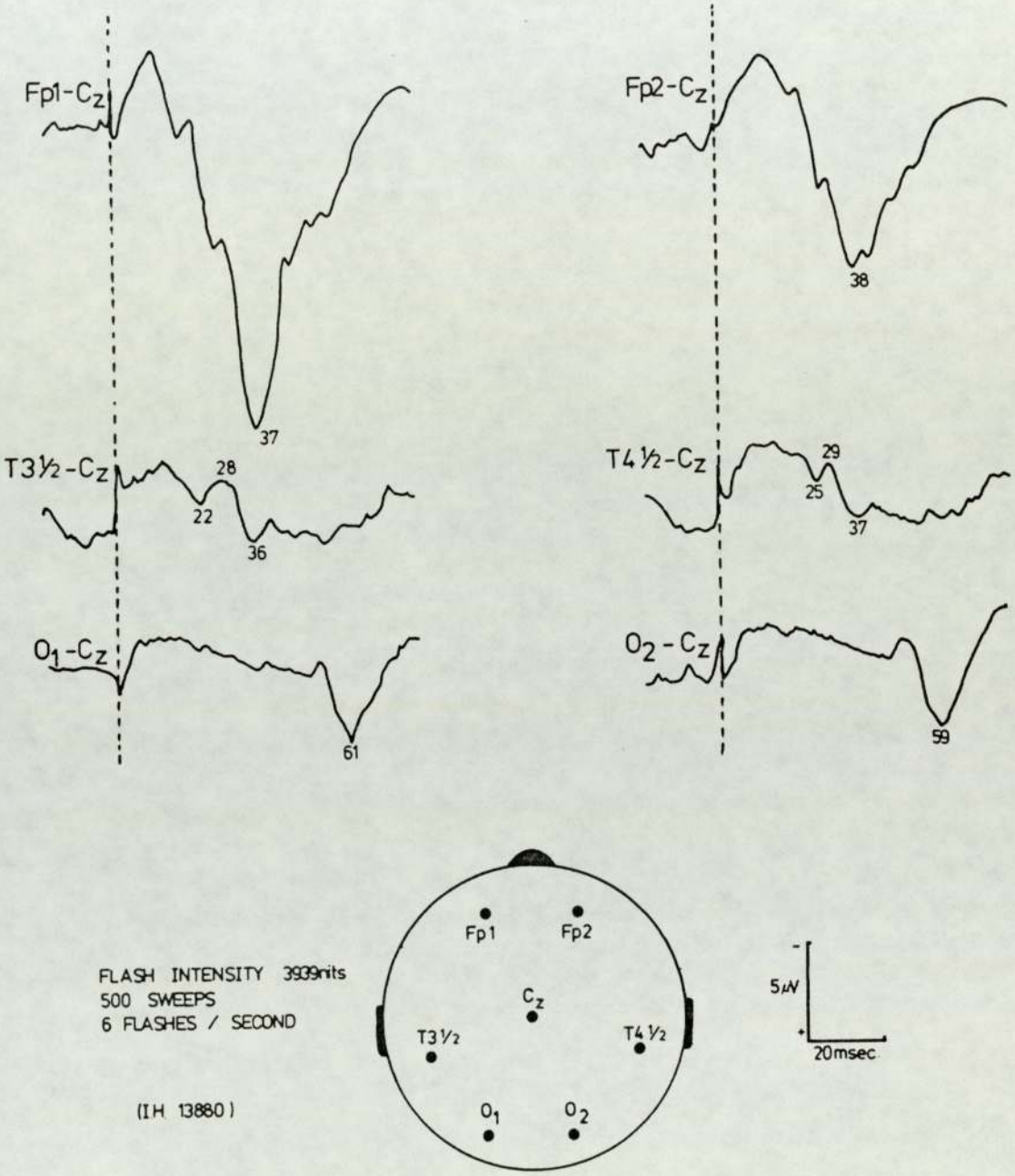


FLASH INTENSITY 3939 nits
500 SWEEPS
6 FLASHES / SECOND

FIGURE 3.2.2.

Simultaneous recording of asymmetric ERGs and symmetric VESPs

In a normal subject, the ERG from the right eye (F_{p2}) is of lower amplitude than that from the left eye (F_{p1}) although VESPs ($T_{3\frac{1}{2}}$, $T_{4\frac{1}{2}}$) are of almost identical amplitudes. The early components of the cortical response (O_1, O_2) are also symmetrical (see text for details)


Fp1-Cz
37
Fp2-Cz
38
T3½-Cz
28
22
36
T4½-Cz
29
25
37
O1-Cz
61
O2-Cz
59
FLASH INTENSITY 3939nits
500 SWEEPS
6 FLASHES / SECOND
(I.H. 13880)
Fp1
Fp2
Cz
T3½
T4½
O1
O2
5μV
20msec.

amplitudes in both subjects. The response recorded from the occiput was also recorded symmetrically from either hemisphere in both subjects. These findings were consistent and repeatable on different occasions using a variety of recording electrodes at the specified sites. Both subjects (one male (BJ) aged 36 years; one male (EH) aged 20 years) had, on further investigation, corrected visual acuities of $^{6}/_{5}$ in both eyes, full visual fields (plotted using a Goldmann perimeter) and ophthalmoscopic examination was unremarkable. Although the existence of ERG and VEP asymmetries is well documented (Armington, 1974; Kooi, 1979 and Harmony, Ricardo, Otero, Fernandez, Llorente and Valdes, 1973), the co-existence of almost 50% asymmetries in ERG with symmetrical VESP and occipital VEP (as seen in the two subjects reported by the author) wasindicative of independence of the respective EPs.

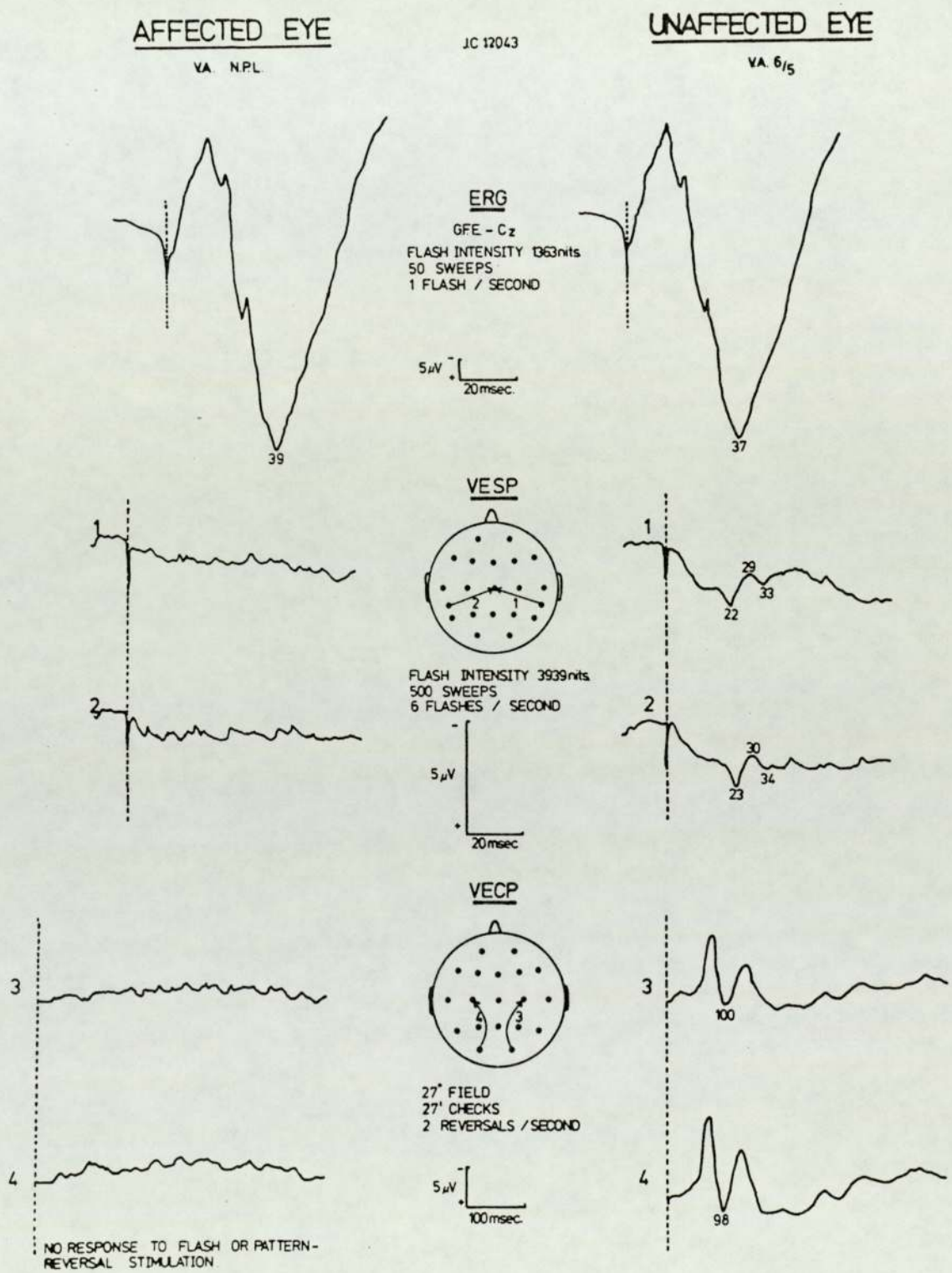
Three patients with distinct and discrete pathologies were also examined and provided further information:

Case 1 (JC: male age 39 years) during a fall, sustained a fracture of the left zygoma and orbit, with an associated left optic nerve injury. Vision in the left eye was reduced to no light perception and the optic disc was pale and atrophic. Electrophysiological examination (illustrated in Figure 3.2.3.) revealed normal photopic ERGs from both eyes, recorded using the GFE. Stimulation of the affected eye failed to elicit any consistent

FIGURE 3.2.3.

Electrophysiological examination of patient with left optic nerve injury

Normal ERGs are recorded from both eyes and stimulation of the unaffected eye shows a normal VESP and VECP (to pattern-reversal stimulation). Stimulation of the affected eye fails to reveal any consistent VESP or VECP (see text for details)


AFFECTED EYE
V.A. N.P.L.
JC 12043
UNAFFECTED EYE
V.A. 6/5
ERG
GFE - Cz
FLASH INTENSITY 1363nits.
50 SWEEPS
1 FLASH / SECOND
5μV
20msec.
39
37
VESP
FLASH INTENSITY 3939nits.
500 SWEEPS
6 FLASHES / SECOND
5μV
20msec
1
2
29
33
22
30
34
23
VECP
27° FIELD
27' CHECKS
2 REVERSALS / SECOND
5μV
100msec.
3
4
100
98
NO RESPONSE TO FLASH OR PATTERN-REVERSAL STIMULATION

VESPs, and VECPs were also absent when high intensity flash stimulation was used. VESP and VECP recordings from the unaffected eye were of normal latency and amplitude. Despite the observation that the VECP was of higher amplitude over the left occiput, there was no significant asymmetry in the monitoring EEG.

Case 2 (RR: male age 22 years) suffered a penetrating wound of the left eye with a retained metallic intra-ocular foreign body. Subsequent to the removal of the foreign body the retina detached, involving the macular area, and the vision was reduced to accurate projection of light. Electrophysiological examination (illustrated in Figure 3.2.4.) revealed extinction of the ERG of the affected eye. VESPs were recorded bilaterally, at normal latency and of normal amplitude for monocular stimulation and a VECP could be consistently recorded bilaterally using flash stimulation, although no response could be recorded using pattern-reversal stimulation using any check size. The VECPs from the affected eye were slightly delayed compared with those from the unaffected eye, although the VESPs were of compatible amplitude and latency.

Case 3 (NS: male age 22 years) presented with a gradual reduction in vision of the right eye over a period of three weeks. No other symptoms or past history were reported and ocular examination was normal; visual acuities were $^{6}/_{12}$ right, $^{6}/_{5}$ left. Two months later

FIGURE 3.2.4.

Electrophysiological examination of patient with retinal detachment of left eye

The ERG from the affected is is totally extinguished; VESP and VECP (to flash stimulation) are present bilaterally although no VECP could be elicited from the affected eye with pattern-reversal stimulation. Recordings of ERG, VESP and VECP from the unaffected eye are normal (see text for details)

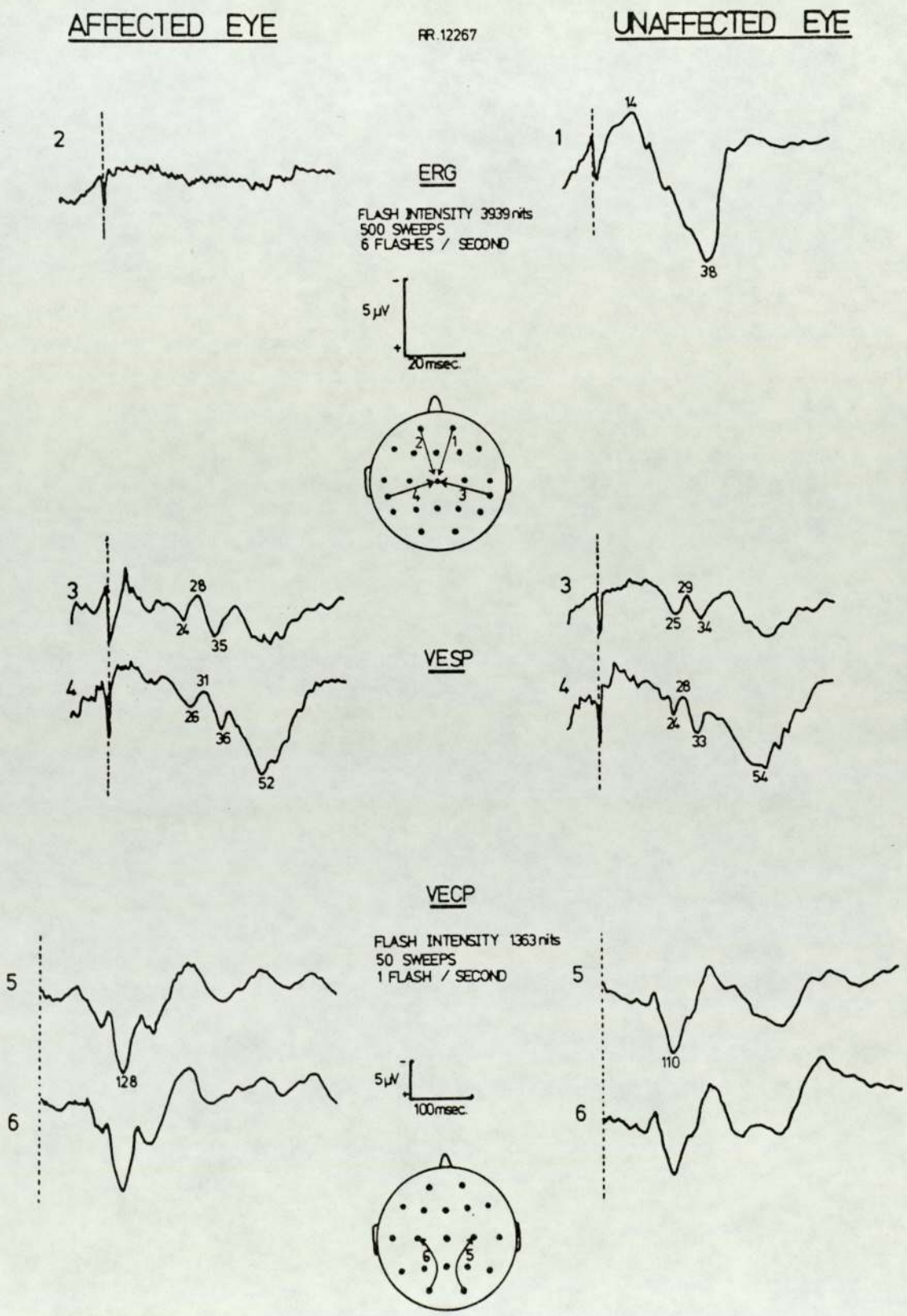
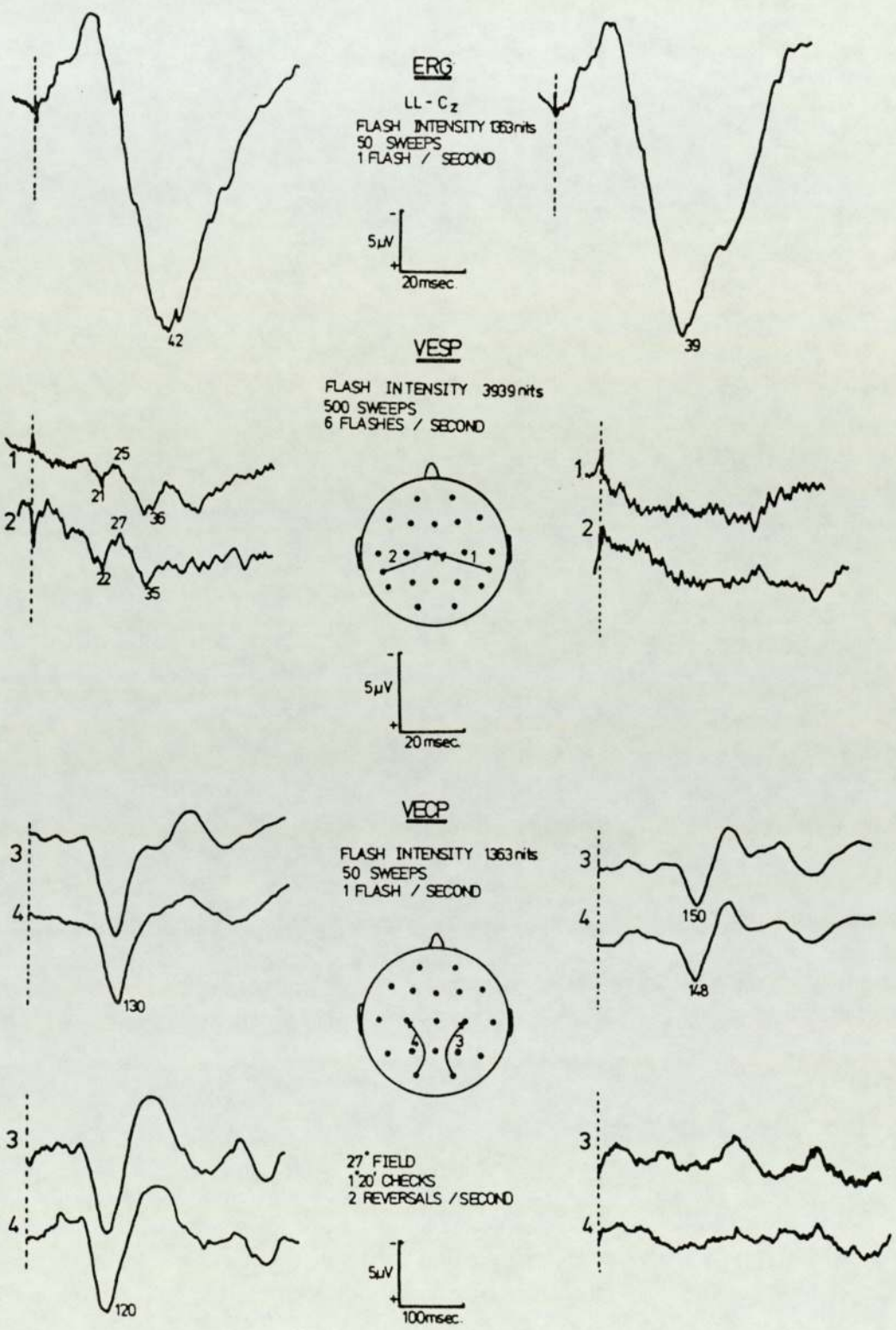

AFFECTED EYE
RR.12267
UNAFFECTED EYE
2
1
14
38
ERG
FLASH INTENSITY 3939 nits
500 SWEEPS
6 FLASHES / SECOND
5 µV
20 msec.
2
1
4
3
3
28
24
35
4
31
26
36
52
VESP
3
29
25
34
4
28
24
33
54
VECP
FLASH INTENSITY 1363 nits
50 SWEEPS
1 FLASH / SECOND
5
6
128
5 µV
100 msec.
6
5
5
110
6

FIGURE 3.2.5.

Electrophysiological examination of patient with right optic nerve lesion

Normal ERGs were recorded from both eyes. No consistent VESP could be recorded from the affected eye although a low amplitude delayed VECP to flash stimulation could be recorded but no pattern-reversal VECP could be elicited. The VESP (P21-22, N25-27, P35-36) and VECP (to both flash and pattern-reversal stimulation) were recorded normally over both hemispheres when the unaffected eye was stimulated (see text for details)


UNAFFECTED EYE
VA 6/5
NS 12318
AFFECTED EYE
VA 6/36
ERG
LL - Cz
FLASH INTENSITY 1363 nits
50 SWEEPS
1 FLASH / SECOND
5µV
20msec
42
39
VESP
FLASH INTENSITY 3939 nits
500 SWEEPS
6 FLASHES / SECOND
1
2
25
21
27
36
22
35
5µV
20msec
VECP
FLASH INTENSITY 1363 nits
50 SWEEPS
1 FLASH / SECOND
3
4
130
150
148
27° FIELD
1°20' CHECKS
2 REVERSALS / SECOND
120
5µV
100msec

the vision in the right eye had deteriorated to $^{6}/_{36}$. Fundal examination revealed a normal optic disc and no obvious lesion of the macula. No visual field defect could be elicited, but Friedmann macular function test was 2.6 in the left eye, but reduced to 1.8 in the right eye and a lesion of the right optic nerve was suspected. The results of electrophysiological examination are shown in Figure 3.2.5. . ERG recordings, were made using lower lid electrodes referred to the vertex and were of normal latency and approximately equal amplitude from either eye. VESPs of normal latency and amplitude were recorded bilaterally on stimulation of the left eye, but no consistent response could be obtained from the affected right eye. The VECP to flash stimulation of the affected eye was delayed and of approximately half the amplitude of the response from the left eye. No consistent response could be obtained from the right eye with pattern-reversal stimulation, all available check sizes being tried.

The results obtained from these three patients demonstrated that in Case 1, due to unilateral optic nerve trauma, despite the survival of an ERG of normal amplitude and latency from the affected eye, the VESP and VECP were absent. Case 2 demonstrated that the extinction of the ERG in one eye due to retinal detachment could co-exist with bilateral survival of both the VESP and VECP from the same eye. Case 3 demonstrated that due to a probable optic nerve lesion

the VESP may be abolished bilaterally on stimulation of the affected eye with a normal ERG response remaining intact.

Conclusion

On the basis of the evidence of the topographical study of the ERG; the co-existence of intact ERG and extinct VESP and vice-versa in pathological states; the results presented of a subject with normal ERG topography, but 'physiologically' absent VESPs, and the effects of monocular versus binocular stimulation on the VESP, the author concluded that the ERG and VESP were distinct and unrelated electrophysiological phenomena (Rubinstein and Harding, 1981).

3.3. FURTHER EVIDENCE OF A SUBCORTICAL ORIGIN OF THE VESP

A number of patients with pathologies at distinct levels of the visual pathway have been studied in some of whom a clearly defined clinical diagnosis has been made on the grounds of history and symptoms, visual fields, skull X-ray, CAT scan etc. and on whom electrophysiological examinations were performed to observe the differential effects on the VESP and VECP and in order to corroborate the inference that the VESP is indeed of subcortical origin.

Case 1 (FG: male, aged 46 years) suffered a brainstem vascular disturbance (cerebellar syndrome) secondary to a congenital cardiac atrial septal defect. He presented with a right homonymous hemianopia, horizontal nystagmus on lateral gaze to either side and mild right sided facial weakness. There was bilateral ataxia of all four limbs more evident on the right than left, tendon reflexes were brisk and plantars were flexor. CAT scan revealed global atrophy involving particularly the left cerebral hemisphere but also the cerebellum. On attending for electrophysiological assessment a dense right homonymous hemianopia with macular sparing was still present, visual acuities being right and left $^{6}/_{6}$. The visual fields and VECP records are shown in Figure 3.3.1. The VECP to flash is partly reduced contralateral to the field defect (using occipital electrodes referred to C_3 and C_4 respectively) and phase-reversals were clearer to the right

FIGURE 3.3.1.

Electrophysiological examination of patient with brainstem vascular disturbance (VECP and visual fields)

The VECP is partly reduced in amplitude contralateral to the visual field defect (channels 1 and 2) and phase-reversals (channels 3,4,5 and 6) were clearer to the right occiput than the left occiput (see text for details)

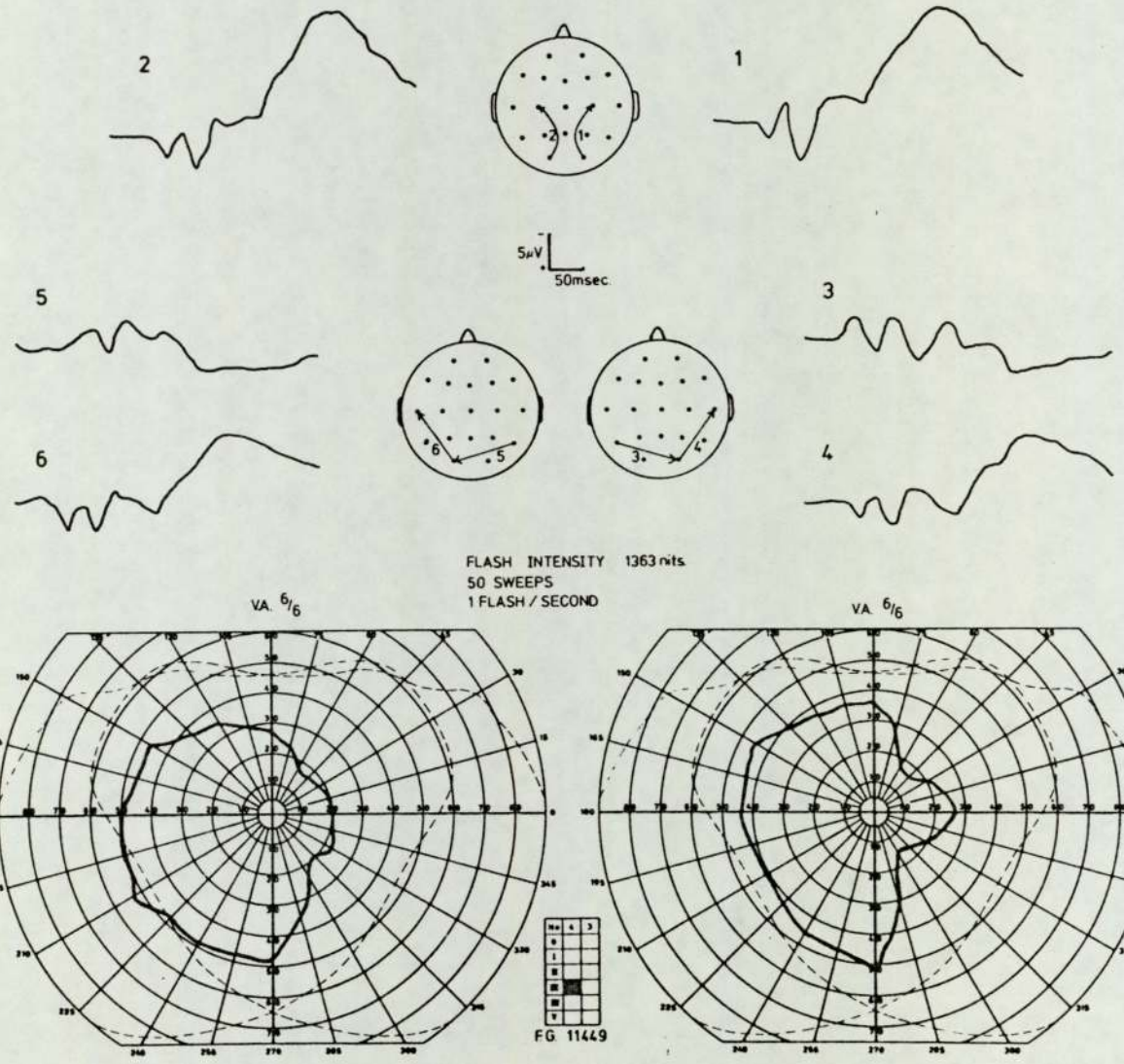
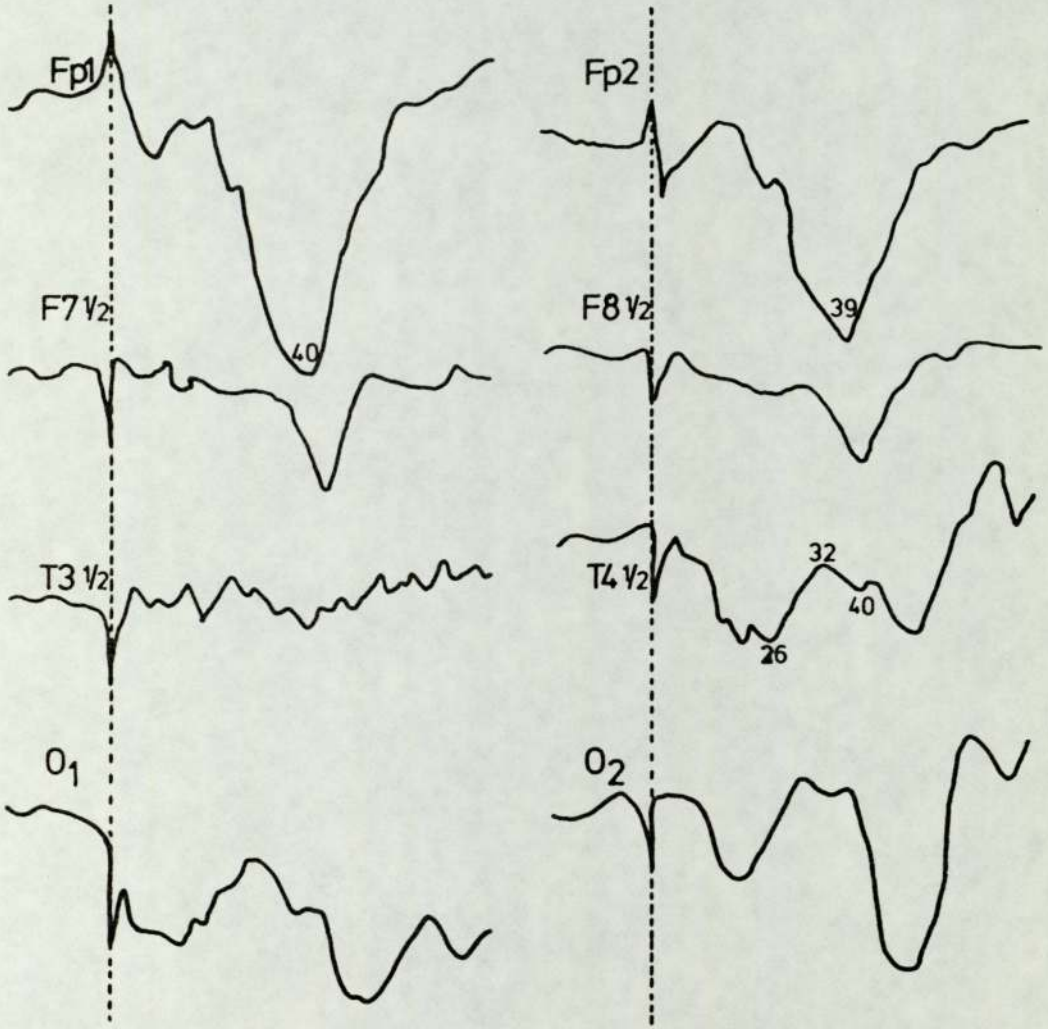

2
1
5μV
50msec.
5
3
6
4
FLASH INTENSITY 1363 nits.
50 SWEEPS
1 FLASH / SECOND
V.A. 6/6
V.A. 6/6
FG. 11449

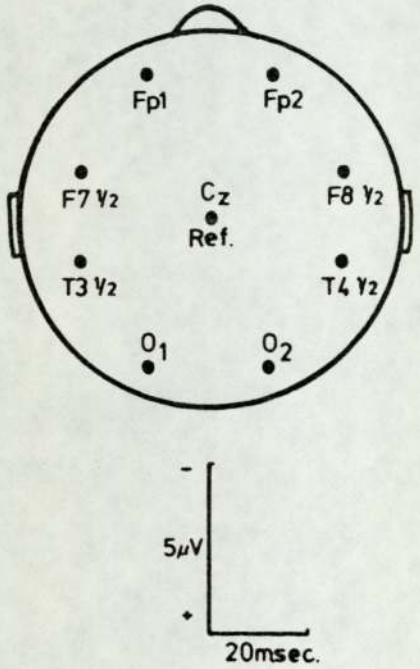
FIGURE 3.3.2.

Electrophysiological examination of patient with brainstem vascular disturbance (ERG and VESP)

The ERGs from both eyes (F_{p1},F_{p2}) are normal although of higher amplitude from the left eye. A clear VESP complex is seen on the right at $T_{4\frac{1}{2}}$ (P26, N32, P40) but no VESP is seen on the left ($T_{3\frac{1}{2}}$). The VECP is of lower amplitude on the left (O_1) than the right (O_2) (see text for details)



F.G. 11449



FLASH INTENSITY 3939 nits.
500 SWEEPS
6 FLASHES / SECOND

occiput. These findings were consistent with the visual field defect. In Figure 3.3.2. the VESP results are shown. A clear VESP formation was repeatably recorded on the right side of the head but no consistent recording could be obtained on the left. The reduction of the VESP was more marked than that of the VECP. ERG recordings were obtained bilaterally and indeed the response from the left eye was of higher amplitude than that from the right eye. These findings were entirely consistent with the clinical history and demonstrated the behaviour of the VESP in a case of brainstem disturbance, indicating a post-chiasmal but pre-cortical origin of the VESP.

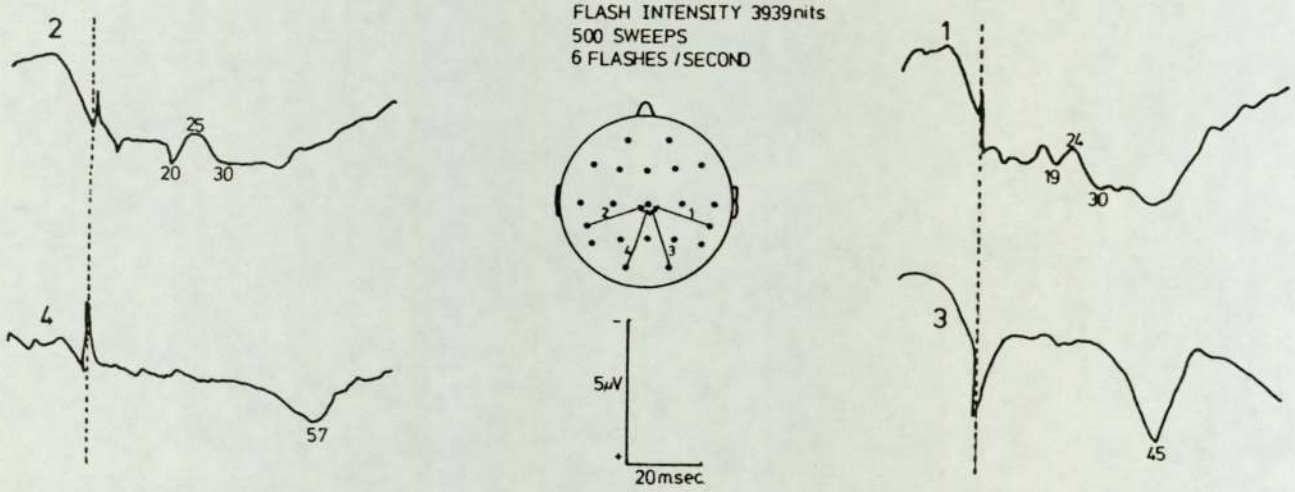
Case 2 (HB: male, aged 8 years) was a child who presented with sudden loss of coordination of the right limbs and of head movements. The only relevant past history being a fall down stairs 5 years previously. The background EEG showed a slight reduction in amplitude over the left hemisphere. Although visual acuities of $^{6}/_{5}$ were recorded for both eyes, accurate visual field plotting could not be performed due to lack of patient cooperation. The results of electrophysiological assessment are shown in Figure 3.3.3.. The VECP showed a clear reduction in amplitude of both the P_1 and P_2 components from the left visual cortex when compared with the response from the right visual cortex. The VESP however was intact bilaterally and of normal amplitude and latency. These findings were highly suggestive of a marked visual field loss in the right visual field; the EP findings would

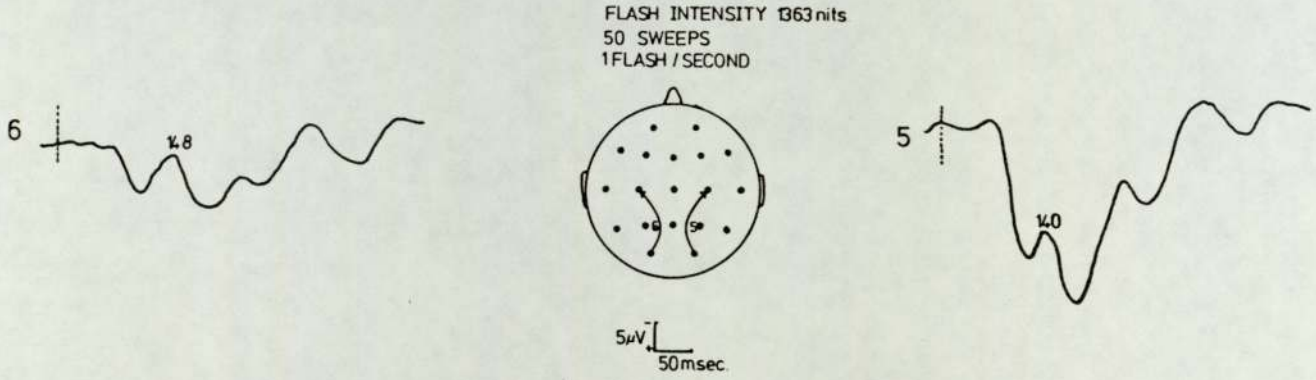
FIGURE 3.3.3.

Electrophysiological examination of patient with cortical disturbance

On binocular stimulation the VECP to flash stimulation is markedly reduced in amplitude and slightly delayed from the left occiput (channel 6) when compared with the response from the right occiput (channel 5). The VESP is clearly formed bilaterally (channels 1 and 2), but the P_1 component of the occipital response is reduced and delayed from the left occiput (channel 4) when compared with the right occiput (channel 3) (see text for details)

HB 1679


FLASH INTENSITY 3939 nits
500 SWEEPS
6 FLASHES / SECOND
2
25
20
30
4
57
1
24
19
30
3
45
5μV
20 msec.


FLASH INTENSITY 1363 nits
50 SWEEPS
1 FLASH / SECOND
6
14.8
5
14.0
5μV
50 msec.

indicate that any tissue damage was cortical and did not involve the subcortical visual pathways.

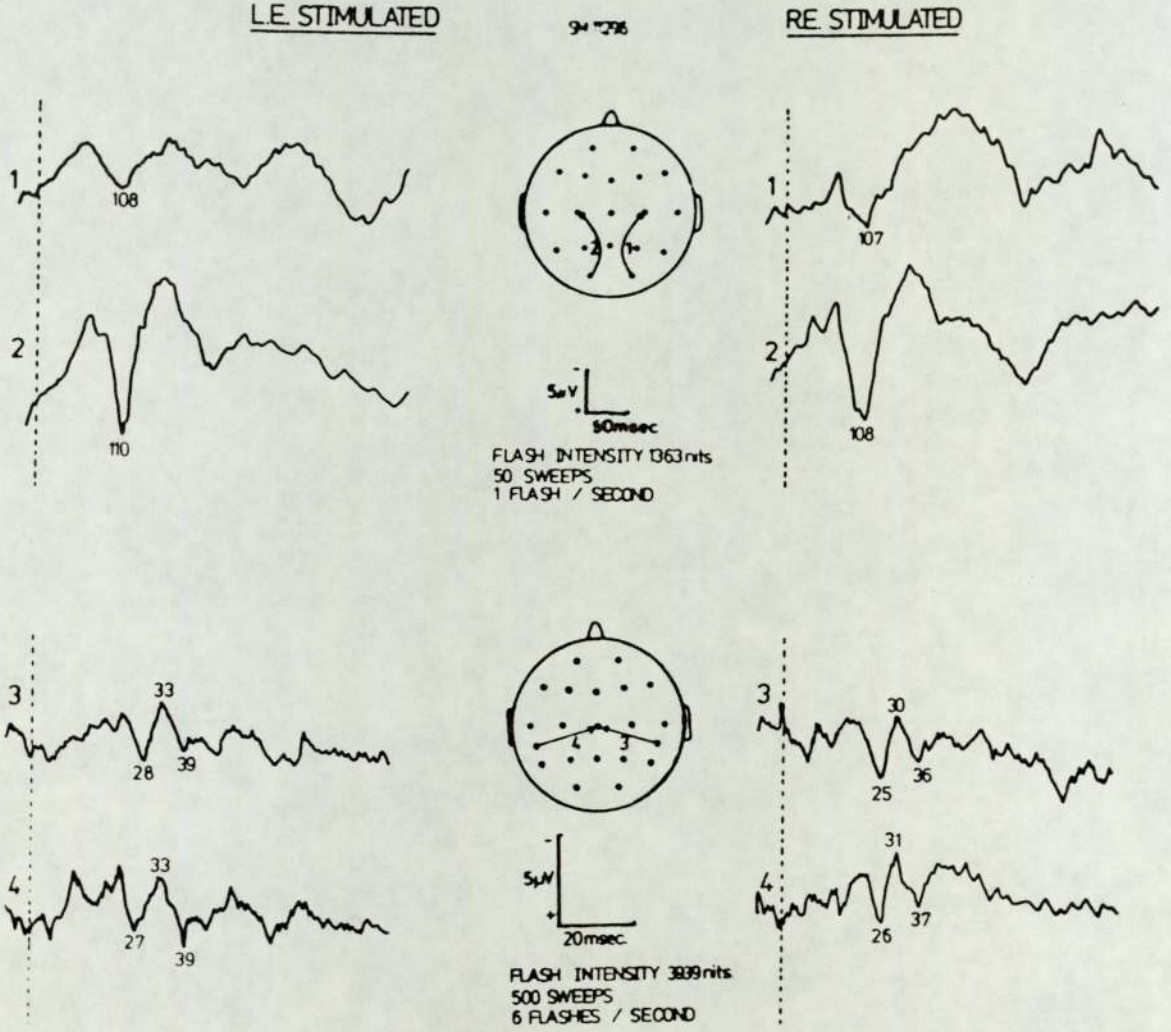
Case 3 (SM: male, aged 3 years) was a child who had fallen 25 feet from a window, sustaining an occipital bone fracture. Having regained consciousness after 24 hours, recovery was fairly good but impaired vision was suspected since the child appeared not to recognise familiar objects. The EEG was found to be symmetrical and within normal limits although there was a reduction in photic driving on the right. Formal visual field plotting was not possible but the results of electrophysiological assessment are shown in Figure 3.3.4.. The VECP was recorded to flash stimulation and revealed clear major positive components formed over the left occiput but poorly formed and of low amplitude over the right occiput. Poor phase reversals were demonstrated to the right occiput although good to the left occiput. Pattern-reversal stimulation was not possible due to patient age. VESPs were clearly formed bilaterally of normal amplitude and latency for monocular stimulation. These findings were considered to be consistent with a left homonymous hemianopia and since the VESPs appeared intact the damage was thought to be cortical and this correlated with the clinical findings.

Case 4 (RS: male, aged 28 years) was referred for EP assessment following a left occipital lobe infarction two months previously. This had been confirmed by CAT

FIGURE 3.3.4.

Electrophysiological examination of patient with occipital trauma

The major positive component of the flash VECP is of low amplitude and poor outline over the right hemisphere (channel 1) but clearly defined and of normal amplitude over the left hemisphere (channel 2). VESP responses, although contaminated by myogenic artifact, are seen bilaterally (channels 3 and 4) on stimulation of either eye (see text for details)


L.E. STIMULATED
RE. STIMULATED
1
108
2
110
5μV
50msec
FLASH INTENSITY 1363 nits
50 SWEEPS
1 FLASH / SECOND
107
108
3
33
28
39
4
33
27
39
5μV
20msec
FLASH INTENSITY 3939 nits
500 SWEEPS
6 FLASHES / SECOND
30
25
36
31
26
37

scan and the patient had a residual dense right homonymous hemianopia with a degree of macular sparing, visual acuities being right $^{6}/_{6}{}^{-2}$, left $^{6}/_{9}$. The history was complicated by a past left frontal lobe abcess twelve years previously, secondary to heroin abuse. This had been treated but the patient had become affected by late onset epilepsy (signs being clearly evident in EEG recording) and controlled with sodium valproate. Electrophysiological assessment (illustrated in Figure 3.3.5. with visual field plots) revealed that the VECP to both flash and pattern-reversal stimulation was within normal limits for latency but of considerably lower amplitude over the left occiput. VESPs were elicited bilaterally on stimulation of either eye and these findings were entirely consistent with the confirmed clinical diagnosis of a left occipital lobe infarction.

Case 5 (PR: male, aged 42 years) was involved in a road traffic accident and remained unconscious for four weeks. Although no evidence of any skull fracture could be seen a left homonymous hemianopia was demonstrated. Visual acuities were $^{6}/_{9}{}^{-}$ right and left and both optic discs were pale. The results of electrophysiological assessment are shown, with visual field plots, in Figure 3.3.6.. The VECP to both flash and pattern-reversal stimulation was of considerably lower amplitude over the right occiput and on some occasions was completely absent. Phase reversals were seen bilaterally but much less clearly to the right occiput. However, the VESPs were

FIGURE 3.3.5.

Electrophysiological examination of patient with left occipital lobe infarction

Visual field plotting shows a right homonymous hemianopia. The VECP to flash stimulation is shown in the top set of recordings and the major positive component is of lower amplitude over the left hemisphere (channel 2) when compared with that over the right hemisphere (channel 1). The VECP to pattern reversal stimulation, shown in the middle set of recordings, is similarly asymmetric. The VESPs are seen in the lower sets of recordings (channels 3 and 4) to be bilaterally intact and symmetrical (see text for details)

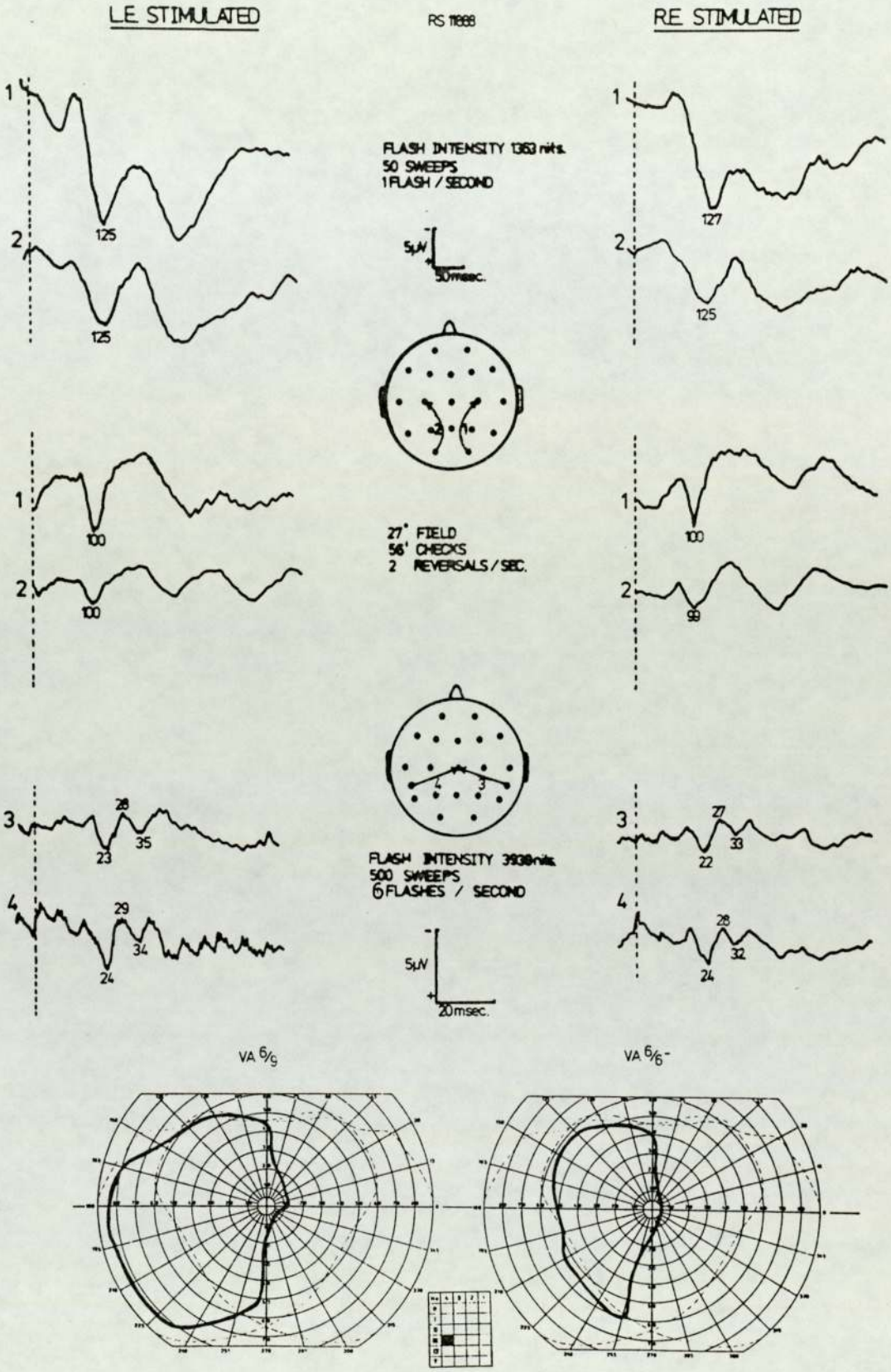
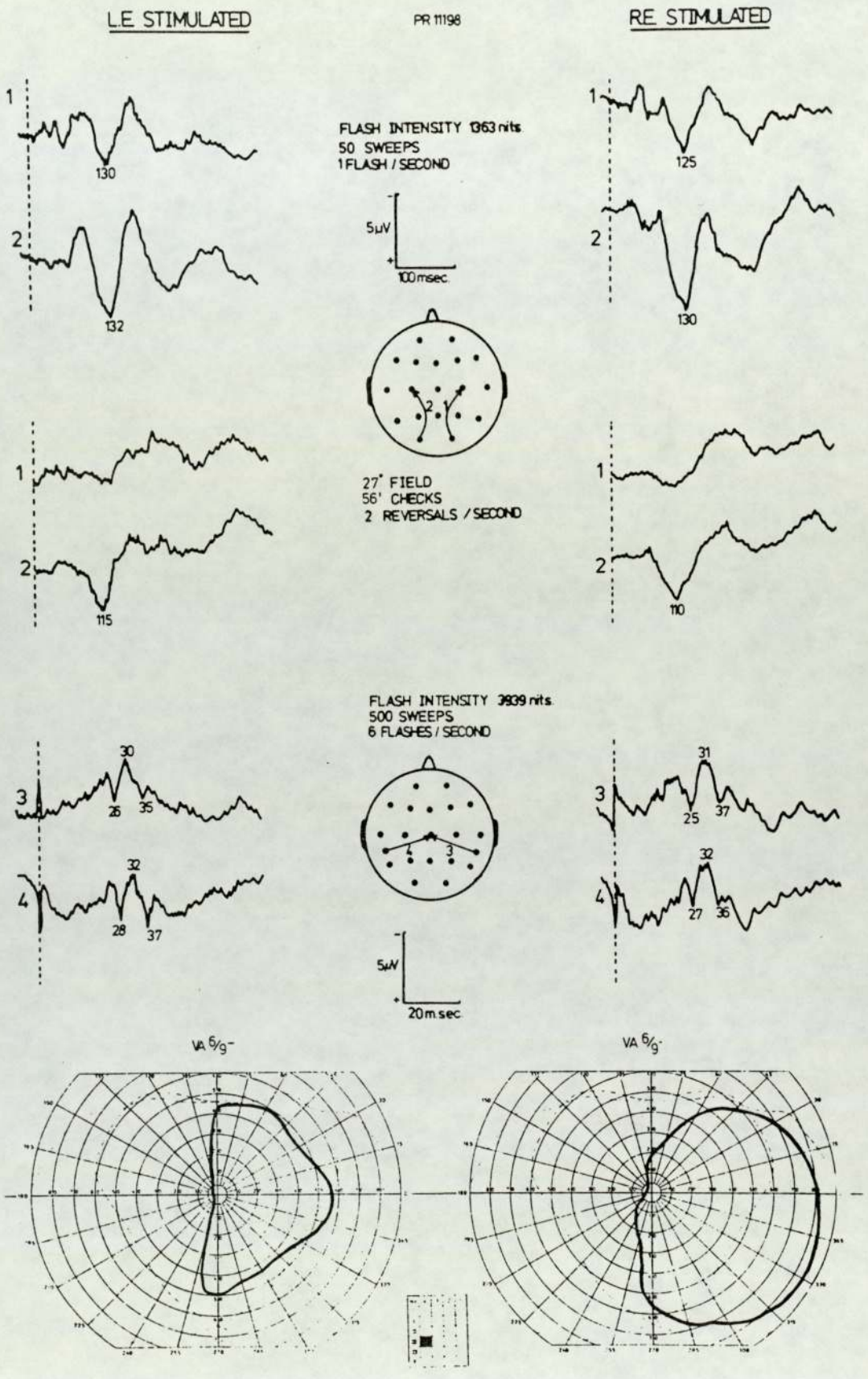

LE STIMULATED
RS 11888
RE STIMULATED
FLASH INTENSITY 1363 mlts.
50 SWEEPS
1 FLASH / SECOND
5μV
50msec.
27° FIELD
56' CHECKS
2 REVERSALS / SEC.
FLASH INTENSITY 3938mlts.
500 SWEEPS
6 FLASHES / SECOND
5μV
20msec.
VA 6/9
VA 6/6-

FIGURE 3.3.6.

Electrophysiological examination of patient with right occipital lobe trauma

Visual field plotting shows a left homonymous hemianopia. The VECP to flash stimulation is shown in the top set of recordings and the major positive component is of lower amplitude over the right hemisphere (channel 1) when compared with that over the left hemisphere (channel 2). The VECP to pattern-reversal stimulation, shown in the middle set of recordings, shows an almost complete absence of the major positive component over the right hemisphere (channel 1) although it is normal over the left hemisphere (channel 2). The VESPs are seen in the lower sets of recordings (channels 3 and 4) to be bilaterally intact and symmetrical, despite myogenic artifact (see text for details)


L.E. STIMULATED
PR 11198
R.E. STIMULATED
1
130
2
132
FLASH INTENSITY 1363 nits
50 SWEEPS
1 FLASH / SECOND
5µV
100 msec.
1
125
2
130
1
2
115
27° FIELD
56' CHECKS
2 REVERSALS / SECOND
1
2
110
FLASH INTENSITY 3939 nits
500 SWEEPS
6 FLASHES / SECOND
3
30
26
35
4
32
28
37
5µV
20 m.sec.
3
31
25
37
4
32
27
36
VA 6/9-
VA 6/9-

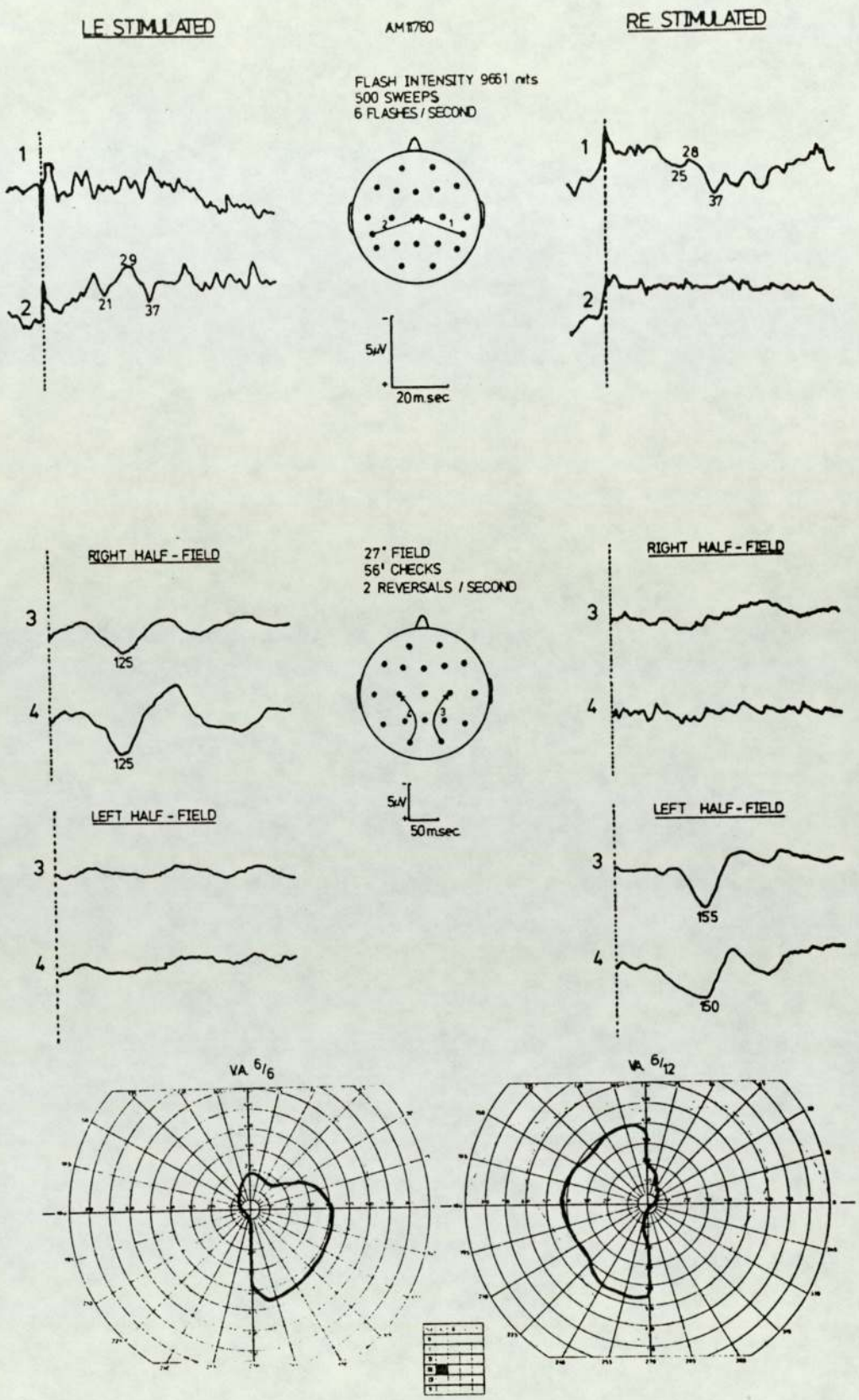
intact bilaterally and were considered normal. It was concluded that damage had occurred in the region of the right occiput and since there was also some slow activity in the right mid-to post-temporal derivations of the EEG, it was probable that the damage was cortical.

Case 6 (AM: female, aged 66 years) was a patient who presented at routine ophthalmic examination with a bitemporal hemianopia, but without any history of headache, vomiting, polyuria or other symptoms. Visual acuities were $^{6}/_{12}$ right, $^{6}/_{6}$ left; optic discs were pale. CAT scan revealed a large supra-sellar cystic space occupying lesion with expanded pituitary fossa and erosion of the floor and posterior clinoids. The pituitary neoplasm was found to have reached a level where it was producing obstructive hydrocephalus. Results of electrophysiological assessment and visual field plots are shown in Figure 3.3.7.. The VESP was unidentifiable over the right cerebral hemisphere when the left eye was stimulated; the VESP was similarly absent over the left cerebral hemisphere when the right eye was stimulated. Pattern-reversal half-field stimulation with 56' checks revealed VECPs as follows: right half-field stimulation of the right eye and left half-field stimulation of the left eye failed to reveal any VECP; left half-field stimulation of the right eye and right half-field stimulation of the left eye produced clearly defined major positive components of the VECP; the latency of the response from the right eye was approximately 20 m.secs.

FIGURE 3.3.7.

Electrophysiological examination of patient with chiasmal compression

Visual field plotting shows a bitemporal hemianopia. When the left eye was stimulated a clear VESP was seen on the left (P21, N29, P37 at channel 2) but not on the right (channel 1). When the right eye was stimulated a clear VESP was seen on the right (P25, N28, P37 at channel 1) but not on the left (channel 2). Using half-field pattern-reversal stimulation the major positive component of the VECP was seen on right half-field stimulation of the left eye and left half-field stimulation of the right eye; left half-field stimulation of the left eye and right half-field stimulation of the right eye failed to reveal any consistent major positive components (see text for details)


LE STIMULATED
A.M.1760
RE STIMULATED
FLASH INTENSITY 9661 nts
500 SWEEPS
6 FLASHES / SECOND
1
2
29
21
37
5μV
20m.sec
28
25
37
RIGHT HALF - FIELD
27° FIELD
56' CHECKS
2 REVERSALS / SECOND
3
4
125
125
5μV
50m.sec
LEFT HALF - FIELD
155
150
VA. 6/6
VA. 6/12

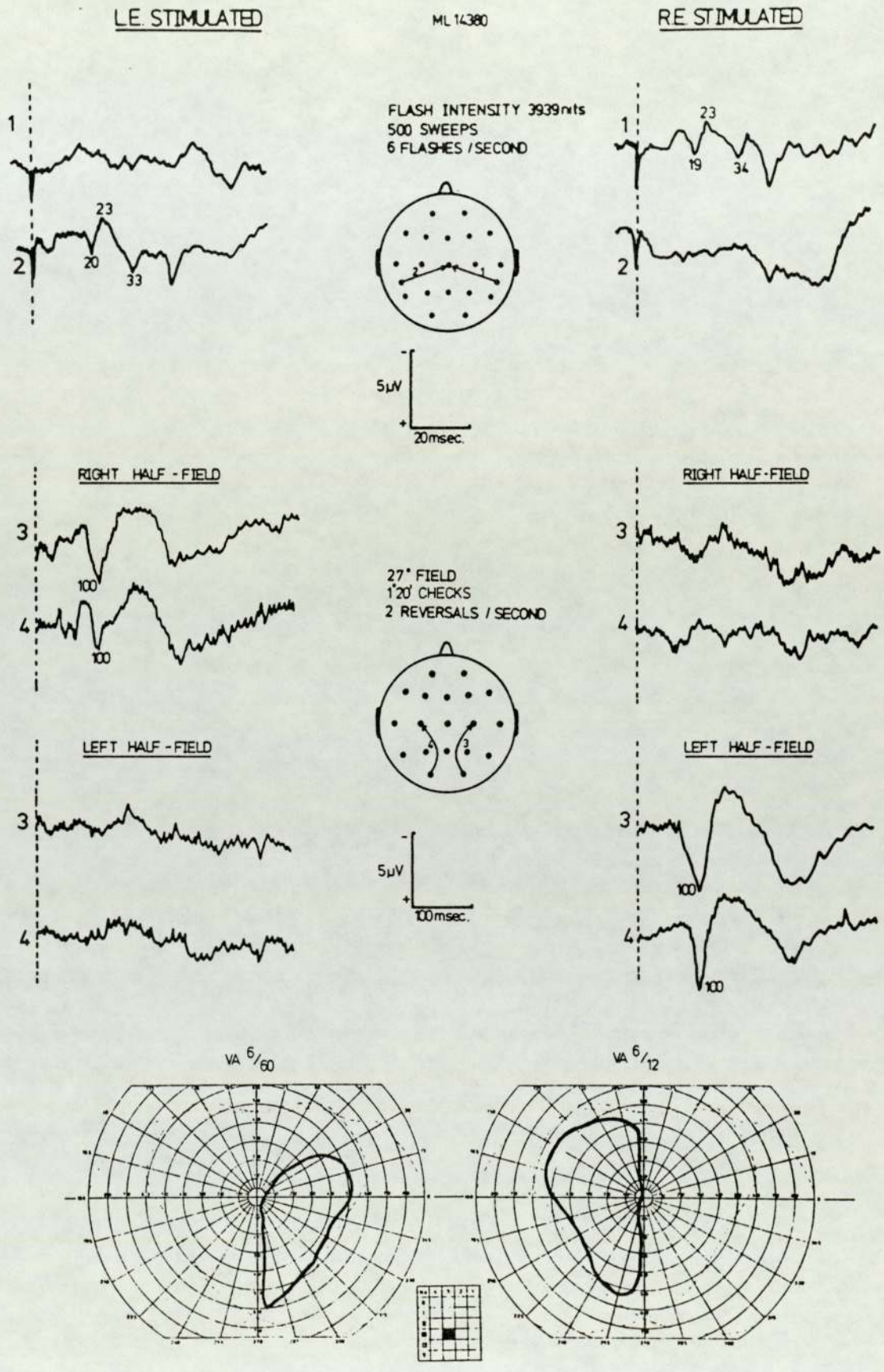
longer than that from the left eye and this was considered to be due to the differences in degree of macular sparing.

Case 7 (ML: female, aged 57 years) was a patient who initially noticed a deterioration in the left temporal field of vision but gradually noticed development of a similar defect in the right temporal field. Physical examination was unremarkable, but ocular examination revealed a bi-temporal hemianopia and visual acuities of right $^{6}/_{12}$, left $^{6}/_{60}$. Skull X-ray showed a large sella, rather 'ballooned' with some thinning and backward displacement of the dorsum. Some erosion of the anterior clinoid process was noted and the overall appearance was considered consistent with an intra-sellar tumour. The visual fields and results of electrophysiological examination are shown in Figure 3.3.8., When the right eye was stimulated a poor VESP response was seen on the left but on the right a clear response was seen; when the left eye was stimulated a poor VESP response was seen on the right but clear components were seen on the left. Pattern-reversal half-field stimulation using $1^{o}20'$ checks revealed VECPs as follows: right half-field stimulation of the right eye and left half-field stimulation of the left eye produced no response; left half-field stimulation of the right eye revealed major positive components bilaterally with a latency of 100 m.secs. and of higher amplitude on the right; right half-field stimulation of the left eye revealed major positive components bilaterally with a latency of 100 m.secs. of lower amplitude than that

FIGURE 3.3.8.

Electrophysiological examination of patient with chiasmal compression

Visual field plotting shows a bitemporal hemianopia. When the left eye was stimulated a clear VESP was seen on the left (P20, N23, P33 at channel 2) but not on the right (channel 1). When the right eye was stimulated a clear VESP was seen on the right (P19, N23, P34 at channel 1) but not on the left (channel 2). Using half-field pattern-reversal stimulation, the major positive component of the VECP was seen on right half-field stimulation of the left eye and left half-field stimulation of the right eye; left half-field stimulation of the left eye and right half-field stimulation of the right eye failed to reveal any consistent major positive components (see text for details).


L.E. STIMULATED
ML 14380
R.E. STIMULATED
FLASH INTENSITY 3939nits
500 SWEEPS
6 FLASHES / SECOND
1
2
23
20
33
19
34
5μV
20msec.
RIGHT HALF - FIELD
RIGHT HALF-FIELD
3
4
100
27° FIELD
1°20' CHECKS
2 REVERSALS / SECOND
LEFT HALF - FIELD
LEFT HALF-FIELD
5μV
100msec.
VA 6/60
VA 6/12

from the right eye, but again of higher amplitude over the right occiput.

Conclusion

The EP findings in these seven selected case studies in whom lesions occurred at a number of sites at different levels along the visual pathway clearly demonstrate differential effects on the VESP and VECP.

In hemianopia of subcortical origin, the VESP was shown to be absent contralateral to the visual field defect, the VECP being affected in accordance with the visual field defect. In hemianopia of cortical origin, bilaterally intact VESPs were seen with VECPs reduced over the affected occiput, contralateral to the visual field defect (using the standard Aston Clinical Neurophysiology Unit montage). In bitemporal hemianopia due to chiasmal compression, the VESP was seen to be absent from the hemisphere contralateral to the stimulated eye and the VECP to half-field stimulation was shown to be consistent with the visual field defect.

Such findings provide further important evidence that the VESP is indeed of a post-chiasmal but pre-cortical origin and the term 'subcortical' is appropriate. Although the precise generator of the VESP cannot be precisely located by scalp recordings alone, it seems likely that it originates in the area of the thalamus,

lateral geniculate body or optic radiation. Indeed it may represent a composite potential from these structures.

3.4. USE OF STRUCTURED STIMULI TO GENERATE THE VESP

The technique of visual stimulation used to generate the VESP in the work reported has consisted of the presentation of a large number of high intensity, unstructured flashes at a fast rate. Using a large number of averages the VESP can be recorded around the upper mastoid sites ($T_{3\frac{1}{2}}$ and $T_{4\frac{1}{2}}$) and can be distinguished from the inherent myogenic responses that are known to be easily recorded in this area (see Section 2.1.) and are easily accentuated by jaw clenching or active movement of the scalp around the ears or the cervical musculature. By the very nature of the stimulus used, subjects often become tense and fatigued and artifact in the recording then becomes extensive, isolation and identification of the VESP being possible only by superimposition of consecutive recordings and the assessment of repeatability of waveforms.

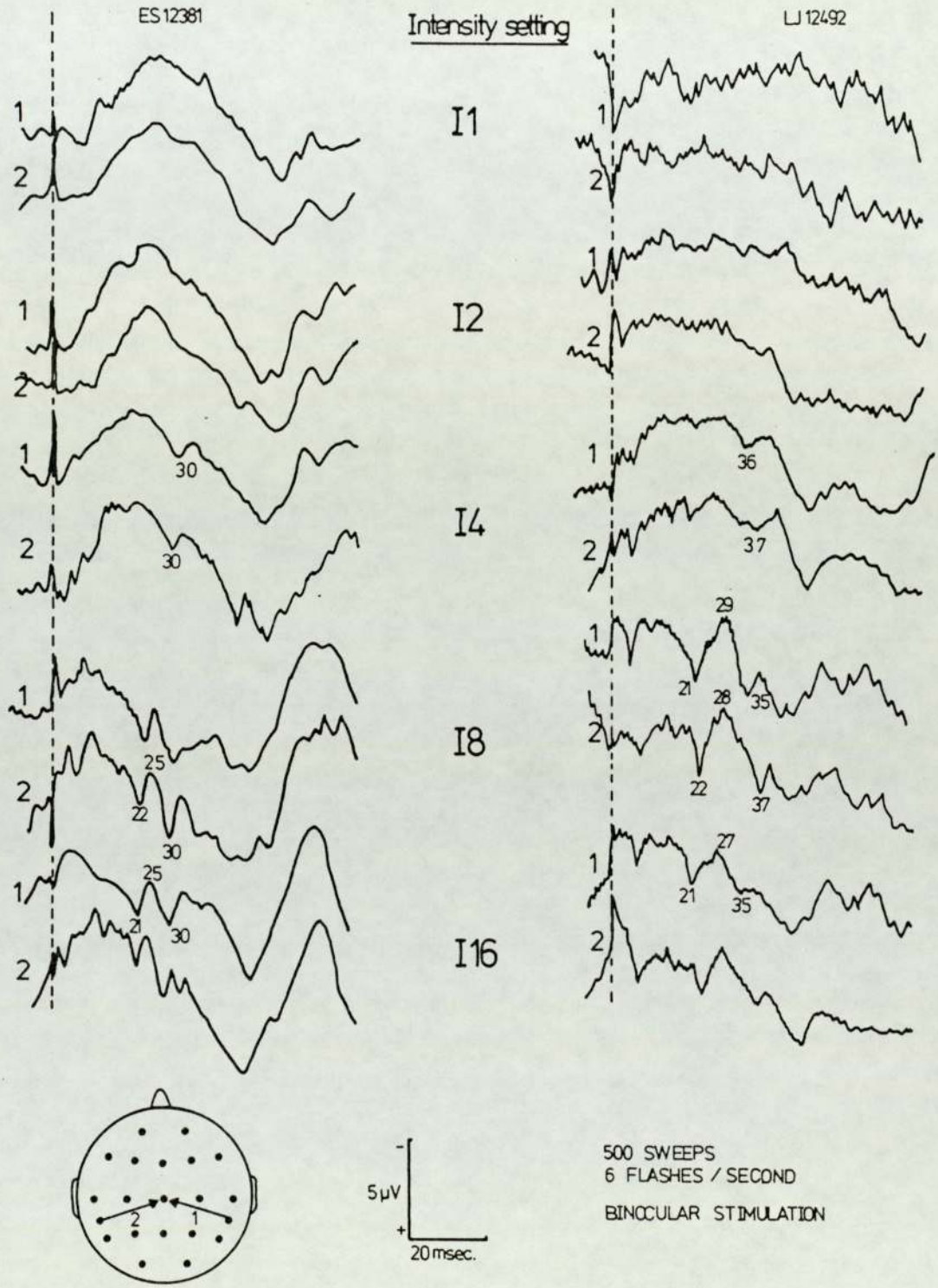
Initial observations (Section 2.3.) showed that the VESP could only be recorded using high intensities of stimulation and this is illustrated in Figure 3.4.1.. At intensities below level 8 (3939 nits) the VESP rapidly reduces in amplitude and at levels 2 (1363 nits) and level 1 (1058 nits) is extinct. Variations in intensity have not been found to have any effect on the latency of the VESP.

Because of the disadvantages of bright flash stimulation, enumerated above, the use of a less intense

FIGURE 3.4.1.

Effects of stimulus intensity on the VESP

VESP records are illustrated in two subjects using the full range of intensity settings of the Grass PS22 Photostimulator. At low levels (I1 and I2) no VESP components are seen. At I4 the first sign of the second positive peak emerges (in one subject at 30 m.sec. in the other subject at 36-37 m.sec.). At intensity 8 the complete VESP complex is seen in both subjects (in one subject P22, N25, P30, in the other subject P21-22, N28-29, P35-37). At maximum intensity (I16) there is no noticeable enhancement of components and in the subject on the right a slight amplitude reduction is seen.


ES 12381
Intensity setting
LJ 12492
I1
I2
I4
I8
I16
1
2
30
25
22
21
29
28
35
36
37
27
5 µV
20 msec.
500 SWEEPS
6 FLASHES / SECOND
BINOCULAR STIMULATION

stimulus technique was attractive, for example, the use of pattern-reversal stimulation. The use of a structured stimulus would be useful if found to produce good VESP responses since subject comfort would be improved with an anticipated concomitant reduction in the amount of myogenic artifact in the recordings.

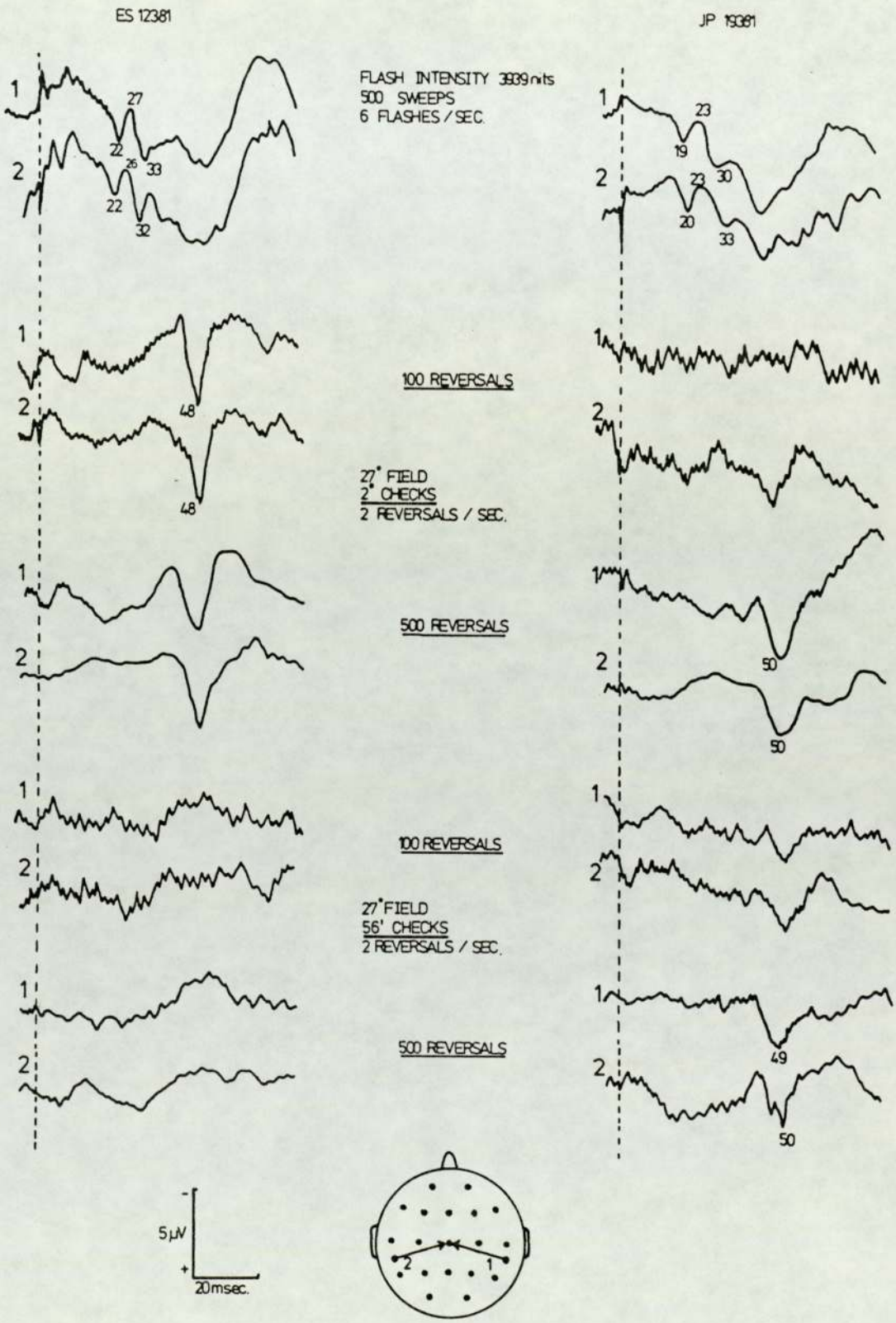
With reference to the reviewed literature of early photically evoked activity in the post-retinal visual pathway (Section 2.1.), it is clear that both in animals and man, relatively high intensities of stimulation are required for the generation of such activity and the observations of the present author confirm this. The use of structured stimuli to generate early photically evoked activity in the post-retinal visual pathway has not previously been assessed, although recent reports (Korth and Rieman, 1979 and Korth, 1980) have described techniques of generating OPs (of the ERG) using pattern-reversal stimulation and averaging a large number of responses.

Trials using the conventional pattern-reversal technique with various check sizes and numbers of averages were not found to produce VESP responses (see Figure 3.4.2.). Even when the response to five hundred reversals was averaged, despite the improvement in signal to noise ratio VESPs could not be identified, although later components within the time window used were present. From the results of the effects of variation in intensity on the VESP and the findings that pattern-

FIGURE 3.4.2.

VESP trials using pattern-reversal stimulation

VESPs generated using bright flash stimulation are shown in two subjects at the top of the figure (in one subject P22, N26-27, P32-33; in the other subject P19-20, N23, P30-33). In the lower recordings pattern-reversal stimulation is performed using 2^{o} and 56' checks and 100 and 500 reversals. In neither subject could VESPs be generated using pattern-reversal stimulation under these conditions. The P_{o} component of the cortical response is seen in both subjects (latency 48-50 m.sec.) to be enhanced when using 2^{o} checks but not when using 56' checks (see text for details)


ES 12381
JP 19381
FLASH INTENSITY 3939 mlts
500 SWEEPS
6 FLASHES / SEC.
100 REVERSALS
27° FIELD
2° CHECKS
2 REVERSALS / SEC.
500 REVERSALS
100 REVERSALS
27° FIELD
56' CHECKS
2 REVERSALS / SEC.
500 REVERSALS
5 µV
20 msec.

reversal did not produce any VESP components, it was considered that either a) the VESP was a luminance-related phenomenon rather than contrast-related and was not dependent on the presence of any structure in the stimulus or b) a high luminance stimulus was needed to produce a signal that was of sufficient amplitude to be recordable using a skin electrode.

The possible use of a structured stimulus to generate the VESP however remained of interest and in an attempt to produce a structured stimulus which would also incorporate luminance changes the concept of 'flashed-on-pattern' stimulation has been considered. One method of constructing such a stimulus was described by Spehlmann (1965) who used cardboards upon which were printed geometric patterns. These cards were illuminated by a strobe lamp placed behind the subject. A similar technique using photographic transparencies projected onto a screen by a flashing projector was described by Pastrnakova and Peregrin (1977).

The present study was regarded purely as a pilot investigation (due to limitations in time) and was not considered as being definitive.

Materials and Method

To facilitate direct comparison with the previous VESP work using unstructured flash stimulation, the existing

Grass PS22 Photostimulator was used as a light source. The photostimulator casing had previously been modified to incorporate a carrier on the front of the lamp so that slides might be superimposed between the lamp and the subject.

3 mm. transparent perspex sheet was cut into slides (14 x 13.5 mm.) to fit into the carrier. Checkerboard patterns (i.e. alternating black and transparent squares) were drawn by hand on flexible acrylic sheet and fixed to the perspex slides with the result that a combined 'checkerboard and flash' stimulus could be used, with variable check size and flash intensity. Slides constructed were of four check sizes - 1cm.; 0.75cm; 0.50cm.; 0.25cm.. The 0.25 cm. checks were not drawn by hand but pre-printed Lettraset sheet was used. The Grass PS22 Photostimulator has a diameter of 13 cms. and when placed at 25 cms. from the eyes subtends a visual angle of 29^{o}. The angles of subtense of the four check sizes considered, at a viewing distance of 25 cms. were as follows:

Grid	Square Size	Visual angle at 25cms.
A	1cm.	2^{o} 18'
B	0.15cm.	1^{o} 42'
C	0.50cm.	1^{o} 12'
D	0.25cm.	36'

Twelve normal volunteer subjects were used in the study, 6 male and 6 female between the ages of 17 and 29 years

(mean 19.5 years). All had visual acuities of $^{6}/_{6}$ or better and full visual fields. None of these subjects had been included in any previous study on the VESP. Electrodes were fixed to the scalp with collodion and impedance maintained below 5Kohms. Electrode sites used were F_{p1} and F_{p2} (to record skin ERGs), $T_{3\frac{1}{2}}$ and $T_{4\frac{1}{2}}$ (standardised sites for VESPs) and O_1 and O_2 (to record the occipital response). All electrodes were referred to the vertex.

Recordings from all 6 channels were made using diffuse flash stimulation. The procedure was then repeated using the 4 grids superimposed on the strobe, in random order. In accordance with previous data on the VESP, recordings in response to the strobe at intensity 8 were made to give baseline data for the diffuse flash response. Since all grids contained an equal number of black and transparent squares, the superimposition of a grid in front of the strobe would reduce the intensity by half. This was confirmed by retroilluminating the grids and checking the transmission with a hand-held photometer. Therefore, recordings in response to the use of superimposed checkerboards were performed with the strobe functioning at intensity 16 to compensate for this change in luminance. Trials using the photo-stimulator at intensity 8 with superimposed grids, produced responses of poor definition. Binocular stimulation was used throughout the procedures and analysis parameters remained as in the preceding studies. Measurements of latency and peak-to-peak amplitude of

waveforms were made manually and the measurements of recordings, using grids were compared with those of the recordings using diffuse flash. Mean differences between diffuse flash and grid results were calculated.

Results

The mean differences in latency and peak-to-peak amplitude measurements of ERG 'a' and 'b' wave, VESP components and the P_1 component of the VECP when generated by diffuse flash and by the flashed-on-pattern technique are given in Table 3.4.1. with levels of significance calculated using the Students t-test. Representative waveforms of the effects of the grids in two subjects are illustrated in Figures 3.4.3. and 3.4.4.. Raw data are given in Appendix 3.

Latency of ERG 'a' and 'b' waves were minimally affected by the grids, 'a' wave latency generally being shortened by a maximum mean value of 1.0 m.sec. (using grids B and C), the 'b' wave latency generally being increased by a maximum of 1.0 m.sec. using grid D. These differences were found to be non-significant. Amplitudes of the 'a' wave were usually reduced, the maximum mean reduction of 1.56 uV. being produced by grid C and these reductions were found to be significant (see Table 3.4.1.); the 'b' wave amplitude was also reduced, but by a greater amount than the 'a' wave, the maximum mean reduction again being produced by grid C, these reductions all being highly significant ($p < 0.001$).

	ERG				VESP					VECP (P1)	
	LATENCY (m.sec).		AMPLITUDE (uV)		LATENCY (m.sec)			AMPLITUDE (uV)		Latency	Amp.
	a	b	a	b	P	N	P	P–N	N–P		
GRID A	- 0.50 ns	+ 0.62 ns	- 0.88 p< 0.05	- 3.2 p< 0.001	+ 0.25 ns	+ 0.91 ns	+ 1.33 ns	+ 0.12 ns	+ 0.34 ns	+ 0.25 ns	+ 0.73 ns
GRID B	- 1.00 ns	+ 0.37 ns	- 0.70 ns	- 3.08 p< 0.001	+ 1.12 p< 0.02	+ 1.08 p< 0.05	+ 1.79 p< 0.02	+ 0.18 ns	+ 0.07 ns	+ 0.16 ns	+ 0.12 ns
GRID C	- 1.00 ns	+ 0.37 ns	- 1.56 p< 0.02	- 4.25 p< 0.001	+ 0.91 ns	+ 1.08 ns	+ 1.37 p< 0.02	+ 0.12 ns	+ 0.22 ns	+ 1.08 ns	+ 0.56 ns
GRID D	- 0.08 ns	+ 1.00 ns	- 1.26 p< 0.02	- 3.73 p< 0.001	+ 0.75 p< 0.05	+ 0.75 ns	+ 1.12 p< 0.02	+ 0.10 ns	+ 0.22 ns	+ 1.08 ns	+ 0.81 ns

- : Reduction in amplitude
  Shortening of latency

+ : Increase in amplitude
  Prolongation of latency

ns : non-significant

TABLE 3.4.1. Mean difference (and their significance levels) in measurements of ERG, VESP and VECP when generated by diffuse flash and 'flashed-on-pattern' technique using superimposed grids (based on data from 12 subjects)

FIGURE 3.4.3.

VESP trials using

'flashed-on-pattern' technique

ERG (channels 1 and 2), VESP (channels 3 and 4) and occipital response (channels 5 and 6) were simultaneously recorded. The uppermost of each group of recordings in response to diffuse flash stimulation and below this the recordings produced using superimposed grids A, B, C and D are shown (see text for details)

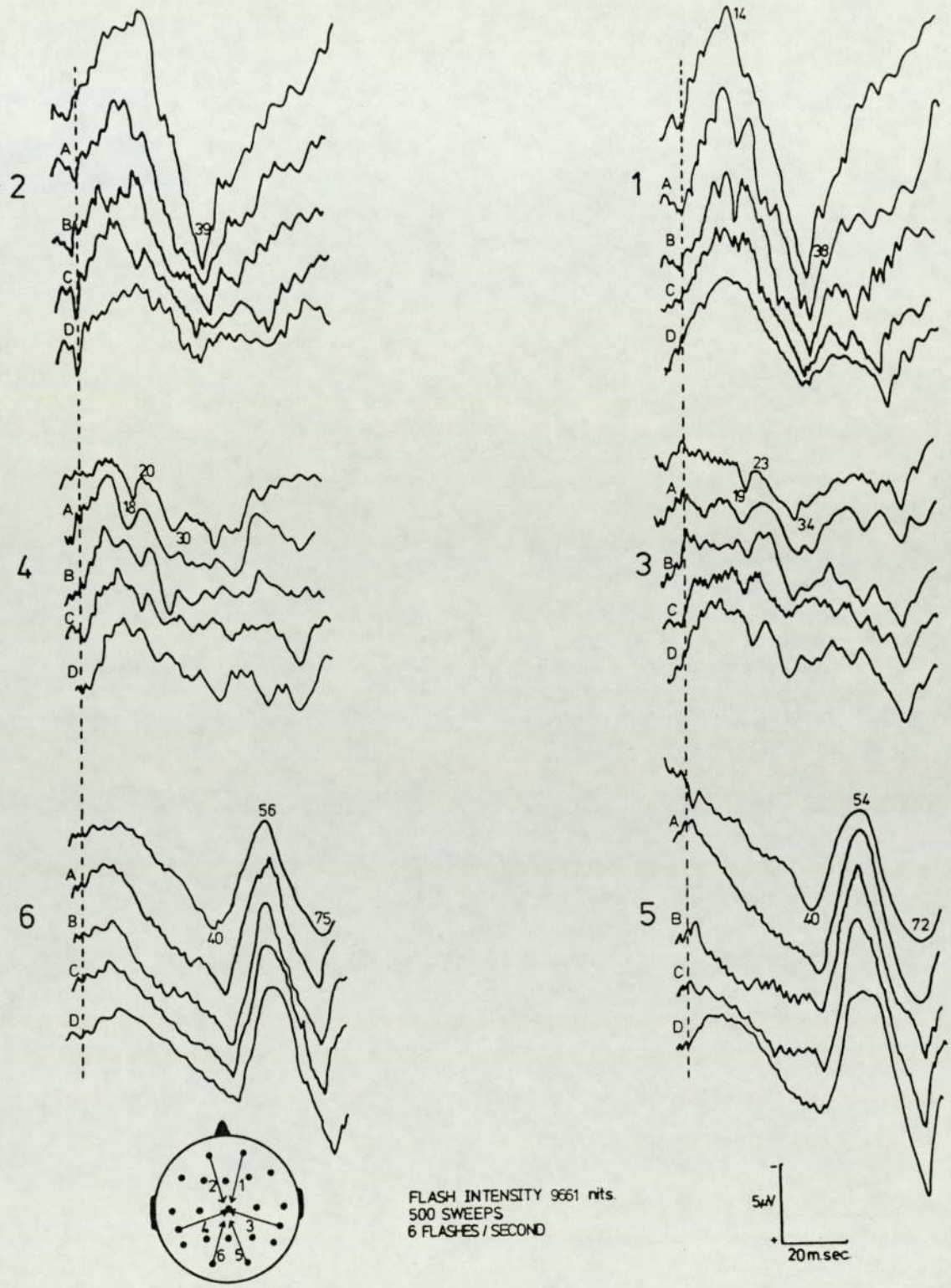
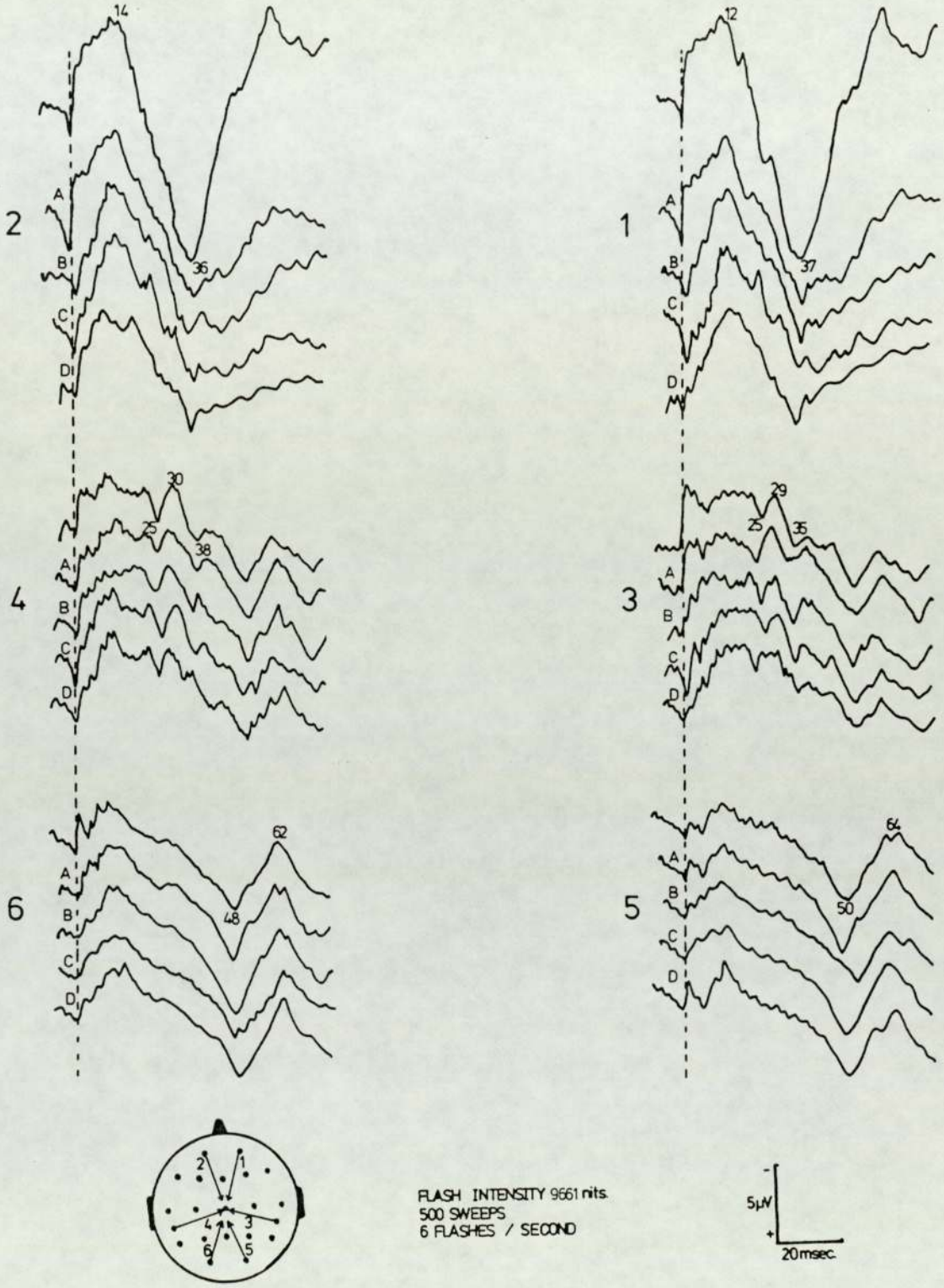

1
2
3
4
5
6
A
B
C
D
14
38
39
23
19
34
20
18
30
54
40
72
56
40
75
1
2
3
4
5
6
FLASH INTENSITY 9661 nits.
500 SWEEPS
6 FLASHES / SECOND
5μV
20m.sec

FIGURE 3.4.4.

VESP trials using

'flashed-on-pattern' technique

ERG (channels 1 and 2), VESP (channels 3 and 4) and occipital response (channels 5 and 6) were simultaneously recorded. The uppermost of each group of recordings in the response to diffuse flash stimulation and below this the recordings produced using superimposed grids A, B, C and D are shown (see text for details)


2
14
A
B
C
D
36
1
12
37
4
30
25
38
3
29
25
35
6
62
48
5
64
50
FLASH INTENSITY 9661 nits.
500 SWEEPS
6 FLASHES / SECOND
5μV
20msec.

Considering the VESP, all components were found to have a mean latency increase when grids were used, this being most marked for the second positive peak. However, the significance of these differences appeared to be random (see Table 3.4.1.). Amplitude of the VESP components was increased very slightly, but the increases were in all cases found to be non-significant. All values fitted within two standard deviations for normal subjects.

The P_1 component of the VECP showed a mean increase in latency, but the maximum mean increase was only 1.08 m.sec. and was not found to be significant; the amplitude of the P_1 component consistently showed a mean increase, with a maximum mean increase of 0.81 μV., these increases similarly being non-significant.

Discussion and Conclusions

These results show under the conditions used for producing a 'flashed-on-pattern' stimulus that ERG components were significantly reduced in amplitude when superimposing grids in the path of the photostimulator. Conversely, the P_1 component of the VECP was usually increased in amplitude, although this increase was not statistically significant. In a similar manner the amplitude of the VESP components was increased when all grids were used but not statistically significantly, and indeed, these amplitude variations fit well within the differences found in repeatability trials (see later section); the

effect of grids on the latency of the VESP components was inconsistent between grids, although grid B (0.75 cm. checks) produced significantly prolonged latencies of all three peaks.

The technique therefore produced differential effects on the three EPs recorded and effectively provided further support to the hypothesis that the origins of the ERG, VESP and VECP are separate.

The use of 'flashed-on-pattern' stimulation in the form described was however not of significant success in improving the amplitude or definition of the VESP. The responses to this type of stimulus must be considered as a combination of response to luminance and contrast changes; since the VESP is not successfully generated by conventional pattern-reversal stimulation and the use of the 'flashed-on-pattern' technique as described in this section did not produce any useful effects on the VESP, particularly in terms of improvement of subject comfort with concomitant improvement in clarify of components, the author concluded that on the basis of the experimental work reported, the VESP must be a response to high intensity flash stimulation and not a contrast related response.

The use of the technique described was therefore not considered on the basis of these results to be a useful adjunct to the generation of the VESP.

3.5. VESP FINDINGS IN UNILATERAL OPTIC NEURITIS

The study of VEP changes in patients with optic neuritis has attracted overwhelming attention since the late 1960's and resulted in a large number of publications. Early clinical studies were restricted to the use of unstructured flash stimulation and markedly diverse reports were presented. Rouher, Plane and Solé (1969) studied a small group of patients and showed a reduction in amplitude of the major component of the flash VEP when compared with a normal control group. Richey, Kooi and Tourlelotte (1971) also reported changes of the flash VEP, in 40% of patients, but the most consistent criterion for abnormality was an increase in latency of the major component. No significant amplitude changes were detected. This finding was endorsed by Feinsod, Abramsky and Auerbach (1973). Namerow and Enns (1972) found a high incidence of abnormally delayed flash VEPs in a group of patients and make an important observation that patients whose visual acuity had apparently returned to normal could still show abnormalities of the VEP.

Following the introduction of the use of structured stimuli into the clinical application of the VEP, a number of reports on the effect of optic neuritis on the pattern VEP were presented. Comparing flash and pattern VEPs, Halliday, McDonald and Mushin (1972) indicated that the pattern-reversal VEP showed less intersubject variability in waveform and latency than did the flash VEP and this was of importance and use when assessing abnormalities

in patients. These authors showed a delayed major positive component in a high percentage (96%) of multiple sclerosis patients. It was also indicated that the flash VEP since it was of greater variability than the pattern VEP was less useful clinically. Halliday et al. (1972) also found that the delay of the pattern VEP major component would persist after resolution of an acute attack of optic neuritis. Other laboratories report different percentage incidence of delay of the major VEP component and this is inevitably partly due to differences in criteria for abnormality and also differences in stimulus parameters (e.g. Asselman, Chadwick and Marsden, 1975 and Hennerici, Wenzel and Freund, 1977).

Halliday and his group have continued their pioneering work (see review of Halliday, McDonald and Mushin, 1977) and it has become clear that both the flash and pattern VEP may be affected in cases of optic neuritis, in different ways. At the acute stage, when the patient reports characteristic symptoms (e.g. fairly sudden deterioration of vision, usually unilateral; pain on eye movement etc.) the amplitude of the major positive component of the pattern VEP is reduced and it may even be abolished completely for a period. A similar reduction in flash VEP amplitude may occur, but abolition of the flash VEP usually only occurs when vision is reduced to the level of perception of light, or less. The reduction in pattern VEP amplitude appears to be related to the level to which the visual acuity is reduced, showing a return to normal as the visual acuity

improves during resolution of the attack. Latency of the pattern VEP however rarely recovers (Halliday and Mushin, 1980).

It is important to remember that a delay in the latency of the major component of the pattern VEP is not specific to optic neuritis and electrophysiological data must, of course, be considered in the context of the case history. For example, similar findings have been reported in glaucomatous patients (Sokol, Domar, Moskowitz and Schwartz, 1981 and Huber, 1981).

The present author considered that it might be interesting to examine the effects of unilateral optic neuritis on the VESP in a small group of patients in whom clearly delayed major positive components of the pattern-reversal VECP were demonstrated. In most of the patients considered, the major positive component of the flash VECP was also delayed.

Materials and Method

Observations were made on 7 patients, all female, aged between 27 and 48 years (mean 33.6 years). All patients had presented with acute deterioration of vision in one eye, the other eye being unaffected. No previous history of ocular disorder was reported by any of the patients and all had good general health and no family history of ocular disorders. In all cases, therefore, the

diagnosis of unilateral acute optic neuritis had been made by the referring ophthalmologist.

The following electrophysiological examinations were performed on all patients - a) flash VECP, b) pattern-reversal VECP, c) VESP. All were performed monocularly, the unstimulated eye being carefully occluded.

The time period between onset of the condition and the electrophysiological assessment was variable between patients, between two to four weeks after onset.

Electrodes were affixed with collodion at O_1 and O_2 and referred to C_3 and C_4 to record the VECP and at $T_{3\frac{1}{2}}$ and $T_{4\frac{1}{2}}$ referred to the vertex, C_z, to record the VESP. Impedance was maintained below 5Kohms. Flash stimulation was delivered from a Grass PS22 Photo-stimulator placed 25 cms. from the eyes, and 50 flashes at intensity 2 (1363 nits) were used. Pattern-reversal checkerboard stimulation was delivered using a back projection mirror system designed by Drasdo (1976); check sizes used were usually, 1^{o} 20', 56' and 27', but all sizes were not used in every case. The reversing checkerboard had a field size of 27^{o} and 50 reversals at a rate of 2 reversals per second were presented to the patient. For the VESP, stimuli were presented as in the preceding sections. Latency and peak-to-peak amplitude measurements of the major positive component of the VECP were made manually, similar measurements

of the triphasic VESP also being made.

The fellow (unaffected) eye was used as a control in this study and no other specific control sample was used, although the results were compared with normative data previously accumulated in the Aston Clinical Neurophysiology Unit. Only one recording session was used in this study and the progression/remission of the condition was not monitored.

Results

For the seven patients considered in this study measurements of latency and 'peak-to-peak' amplitude of the major positive component and the peaks of the VESP were made and are shown in Table 3.5.1., Since on monocular stimulation asynchronies in the VECP between hemispheres never exceeded 3 m.sec. for latency and 2 μV. for amplitude, the mean value of latency and amplitude was considered. Asynchronies for VESP components were less than those for the VECP and therefore the results from both hemispheres were averaged and the mean value has been considered. The mean differences in latency and amplitude of the EP components from affected and unaffected eye were calculated and the significance of the differences tested using the Students t-test, as shown in Table 3.5.2.. Records from two patients are illustrated in Figures 3.5.1. and 3.5.2.. Raw data are given in Appendix 4.

			VECP (Major Positive Component)				VESP				
	Eye Stimulated		Flash		Pattern Reversal		Latency (m.secs)			Amplitude (uV)	
Subject	Affected/ Unaffected	V.A.	Latency (m.sec)	Amplitude (uV)	Latency (m.sec)	Amplitude (uV)	P	N	P	P-N	N-P
GW	U	6/5	125	13.0	105	10	19.5	25	34.5	1.75	2.0
	A	6/24	128	8.0	147	6.5	20	24.5	35	2.0	2.1
VL	A	6/9	123	5.0	155	4.5	20	23	30	2.0	2.5
	U	6/5	118	8.0	125	12	20	23	30	2.0	2.75
SM	U	6/5	127	7.5	90	4.0	24.5	28	32.5	1.12	1.12
	A	6/12	145	7.5	137	4.0	24	28.5	33	1.25	1.5
SF	A	6/18	113	6.0	116	3.75	19.5	22.5	35	2.0	2.8
	U	6/6	118	8.0	95	6.0	20.5	25	30	1.75	2.25
JH	U	6/6	132	10.0	105	6.5	25	31	39	1.12	2.5
	A	6/12	147	6.0	150	2.75	22	31	35	1.0	1.87
AB	U	6/5	110	12.0	100	5.0	20.5	28	32.5	2.1	2.35
	A	6/9	137	5.5	150	5.0	21	27.5	33	2.5	2.4
DW	U	6/4	108	6.5	95	12	19	24.5	36	2.1	3.0
	A	6/5	138	5.0	140	12	19.5	25	37	1.65	2.5

TABLE 3.5.1. Latency and peak-to-peak amplitude measurements of VECP major positive component and VESP components on stimulation of affected and un-eyes in 7 patients with unilateral optic neuritis

VECP (Major Positive Component)				VESP				
FLASH		PATTERN REVERSAL (56')		LATENCY (m.sec)			AMPLITUDE (μV)	
Latency (m.sec)	Amplitude (uV)	Latency (m.sec)	Amplitude (uV)	P	N	P	P-N	N-P
+ 16.14 (±10.10)	- 3.14 (±2.21)	+ 40.0 (±10.52)	- 2.43 (±2.78)	- 0.42 (±1.29)	- 0.35 (±1.02)	+ 0.50 (±2.61)	+ 0.06 (±0.28)	+ 0.043 (±0.43)
p< 0.01	p< 0.01	p< 0.001	p< 0.05	ns	ns	ns	ns	ns

- : Reduction in amplitude
  Shortening of latency

+ : Increase in amplitude
  Prolongation of latency

ns : non-significant.

TABLE 3.5.2. Mean differences (and their significance levels) of VECP and VESP latency and peak-to-peak amplitude measurements on stimulation of affected and unaffected eyes (based on data from 7 subjects)

FIGURE 3.5.1.

Electrophysiological examination of patient with unilateral retrobulbar neuritis

In a patient with left retrobulbar neuritis VESP recordings are seen to be of normal latency and amplitude on the right consisting of P22, N27-30, P33-34; on the left P19-22, N27, P33-35). The VECP major positive component to flash stimulation is delayed from the affected eye (latency 140-142 m.sec.) compared with the unaffected eye (latency 109-110 m.sec.). The VECP to pattern-reversal stimulation is also delayed from the affected eye (latency 140 m.sec.) compared with the unaffected eye (latency 96-97 m.sec.)

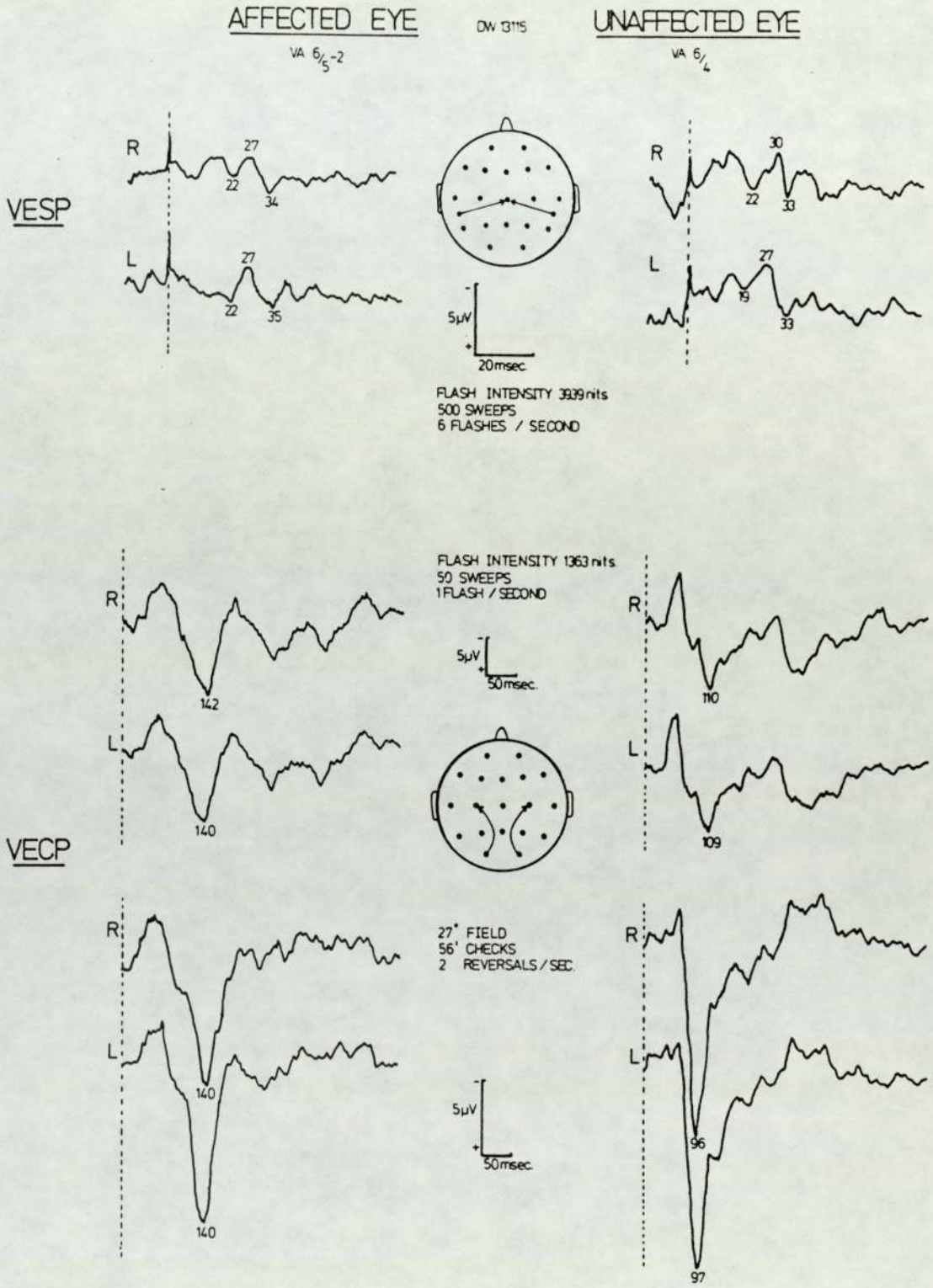
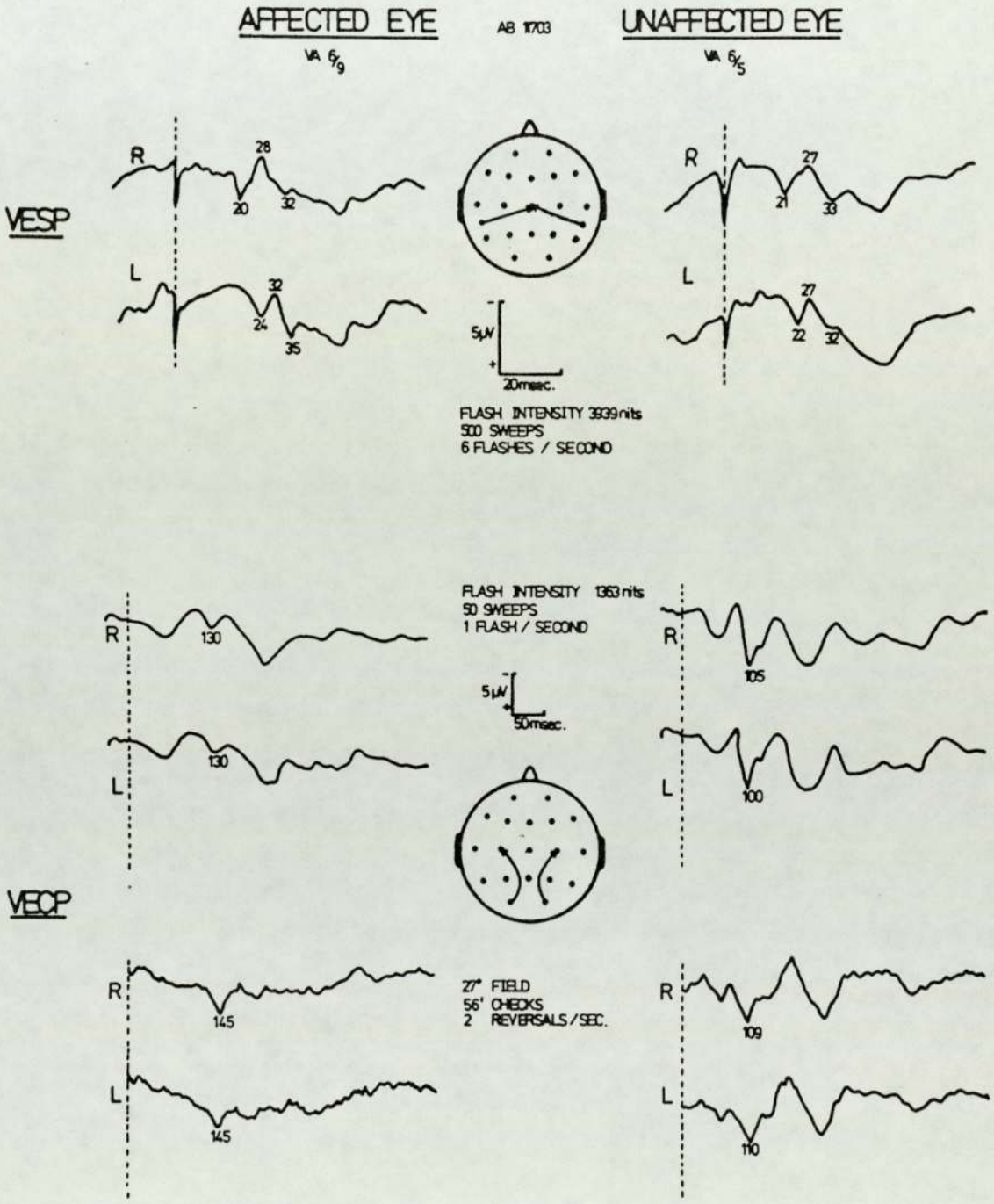

AFFECTED EYE
VA 6/5-2
DW 13115
UNAFFECTED EYE
VA 6/4
VESP
R
L
27
22
34
27
22
35
30
22
33
27
19
33
5μV
20msec.
FLASH INTENSITY 3939 nits
500 SWEEPS
6 FLASHES / SECOND
VECP
FLASH INTENSITY 1363 nits
50 SWEEPS
1 FLASH / SECOND
142
140
110
109
5μV
50msec.
27° FIELD
56' CHECKS
2 REVERSALS / SEC.
140
140
96
97
5μV
50msec.

FIGURE 3.5.2.

Electrophysiological examination of patient with unilateral retrobulbar neuritis

In a patient with left retrobulbar neuritis VESP recordings are seen to be of normal latency and amplitude (consisting of P20-21, N27-28, P32-33 on the left; P22-24, N27-32, P32-35 on the left). The VECP major positive component to flash stimulation is delayed and considerably reduced in amplitude from the affected eye (latency 130 m.sec.) compared with the unaffected eye (latency 100-105 m.sec.). The VECP to pattern-reversal stimulation is also delayed (and considerably reduced in amplitude) from the affected eye (latency 145 m.sec.) compared with the unaffected eye (latency 109-110 m.sec.).


AFFECTED EYE
VA 6/9
AB 1703
UNAFFECTED EYE
VA 6/5
VESP
R
L
28
20
32
32
24
35
27
21
33
27
22
32
5μV
20msec.
FLASH INTENSITY 3939 nits
500 SWEEPS
6 FLASHES / SECOND
VECP
R
L
130
130
FLASH INTENSITY 1363 nits
50 SWEEPS
1 FLASH / SECOND
5μV
50msec.
105
100
27° FIELD
56' CHECKS
2 REVERSALS / SEC.
145
145
109
110

The major positive component to flash stimulation was delayed in all subjects (although in one subject the delay was only of 5 m.sec.) and the peak-to-peak amplitude of the component was lower from the affected eye in all but one subject. These differences were in both cases found to be significant ($p < 0.01$). The major positive component to pattern-reversal stimulation (56' checks) was delayed in all cases from the affected eye and this was statistically highly significant ($p < 0.001$); the amplitude of the component was reduced in four subjects, but remained unaffected in the other three subjects, the amplitude reduction being significant ($p < 0.05$). Considering the VESP, latency of the three peaks was only randomly affected often being of the same value when either eye was stimulated. Differences in response between eyes were found to be non-significant. A similar lack of marked trend was found with the amplitude measurements of the VESP, although surprisingly calculation of the mean differences between eyes indicated a fractionally higher amplitude from the affected eye, but this did not occur in all patients and differences between eyes were found to be non-significant. These findings were in marked contrast to those of the VECP.

Assessment was attempted of the components of the VECP preceding the major positive (P_2) component, that is, the N_1, P_1 and N_2 components, but this was hampered by their poor presentation. When using pattern-reversal

stimulation the P_1 and N_2 components were seen in two patients and in both cases P_1 was unaffected but the N_2 was delayed slightly in both cases. The response to flash stimulation produced slightly more consistent components - in three patients N_2 was delayed compared with the unaffected eye and in one patient P_1 was delayed (although only by 3 m.sec.). In all cases in which these differences were seen the delay of components preceding P_2 was less than the delay of the P_2 component itself.

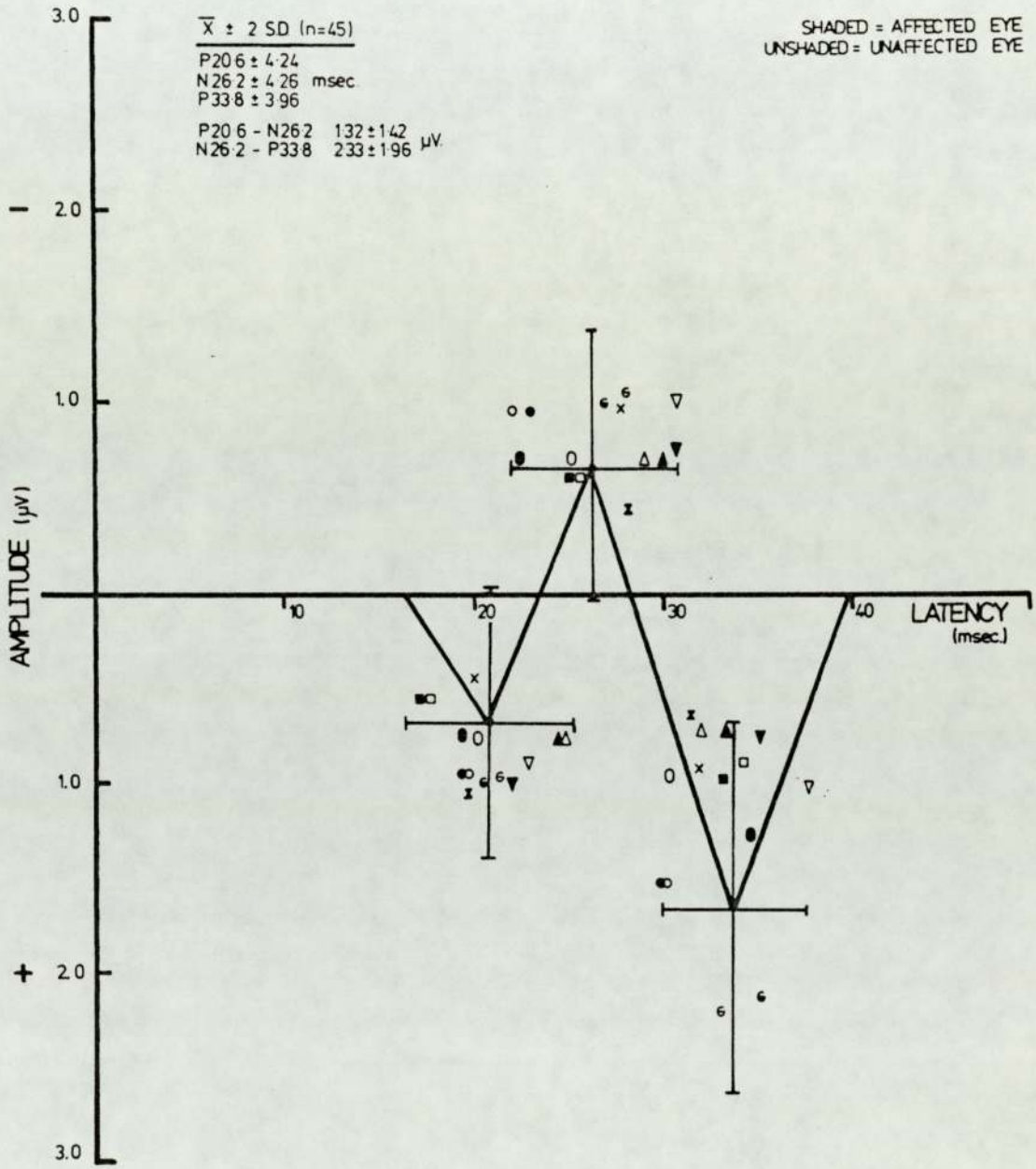
Discussion and Conclusion

In the small sample of patients considered, delayed (and often reduced amplitude) major positive components of the VECP to pattern-reversal and flash stimulation were demonstrated from the eye affected by optic neuritis, the delay and reduction being significant when compared with the fellow (unaffected) eye. However, VESP components from the affected eye were not significantly different from those from the unaffected eye and all values of latency and amplitude fell within two standard deviations from normative data, as shown in Figure 3.5.3. which is a schematic representation of VESP data based on the results from forty-five normal subjects and on which have been superimposed the VESP results from the seven patients with optic neuritis considered in this study. This finding raises some interesting issues relating to the mechanisms of the characteristic VECP changes in optic neuritis and to the processing of different stimuli by the visual system.

FIGURE 3.5.3.

Results of VESP recordings in seven patients with unilateral retrobulbar neuritis superimposed on schematic VESP waveform

The schematic VESP waveform is based on data from forty-five normal subjects and incorporates two standard deviations from the normal. The VESP results from affected and unaffected eyes of seven patients with unilateral optic neuritis are superimposed on the waveform and are seen to fall within the range of normative data (see text for details)


$\bar{X}$ ± 2 SD (n=45)
P20·6 ± 4·24
N26·2 ± 4·26 msec
P33·8 ± 3·96
P20·6 - N26·2 132 ± 142
N26·2 - P33·8 233 ± 196 μV
SHADED = AFFECTED EYE
UNSHADED = UNAFFECTED EYE
AMPLITUDE (μV)
3.0
2.0
1.0
1.0
2.0
3.0
10
20
30
40
LATENCY
(msec.)

Acute optic neuritis is most commonly an early manifestation of multiple sclerosis (MS) and is due to foci of demyelination in the optic nerve. It is frequently the initial sign of MS (Francois, 1979 and Perkin and Rose, 1979). Demyelination may account for the sudden onset of visual loss in acute optic neuritis, but the mechanism involved in the often equally rapid recovery of vision is less certain and the presence of oedema and swelling of the nerve during the acute state with subsequent absorption has been proposed (Halliday and McDonald, 1977), since as visual acuity does usually recover, the block in conduction must be almost reversible. When the vision is reduced to the level of perception of light this must represent blockage of conduction in a very large proportion of fibres (both central and peripheral) in the optic nerve and when the vision is only partially reduced (with or without central or para-central scotomata) this reflects conduction block of a proportion of the macular fibres, the level of visual acuity being an index of the proportion of fibres affected. The macular fibres are of smaller diameter than the peripheral ones and are arranged with higher density than the fibres subserving the more peripheral parts of the visual field and this factor might render these fibres more susceptible to damage than the less dense peripheral fibres. Post-mortem studies of the optic nerve in MS patients has shown that demyelination plaques do tend to extend outside the limits of the macular fibres (Perkin and Rose, 1979), although such extensive areas of demyelination

might be due to recurrent episodes of demyelination.

McDonald (1977) has shown experimentally that demyelination of fibres of the central nervous system may produce complete block of conduction if the lesion is large and impairment of conduction with smaller lesions. Additionally, the velocity of conduction is reduced, experimental results showing a reduction of up to $^{1}/_{25}$ of normal in peripheral demyelination. Partial demyelination also produces an inability of the nerve to transmit faster trains of impulses due to the increased refractoriness in the nerve after transmission of a single impulse (Halliday and McDonald, 1977). McDonald (1977) took post-mortem biopsies of optic nerve demyelination plaques and related the length of the plaques to the delay in impulse conduction across them. With a lesion of mean length 1 cm., assuming an internodal length of 0.2 mm. and a normal conduction velocity of 10 m/sec., if delays of up to 25 times could occur, 25 m.sec. would be required to traverse the 1 cm. plaque. This calculation assumes that peripheral conduction is comparable with central conduction. With respect to the VECP, this was considered as an average delay in the major component of the pattern-reversal VECP and it was proposed that the theoretical calculation of delay across a plaque of demyelination corresponded fairly well with VECP delays. However, the author expressed certain other reservations - a) delays of the order of 25 m.sec. had not been demonstrated across focal experimental de - myelinating lesions and b) with several consecutive

plaques in the visual pathway, conduction could be expected to fail completely. Delays in the pattern-reversal VECP are however often considerably greater than 25 m.sec. and this would imply considerably greater sized plaques or more than one plaque. Other proposals for the delay of the pattern-reversal VECP are a) the selective blocking of faster fibres, leaving slower fibres unaffected to conduct impulses and produce a delayed response. However, macular fibres are considered to be of slower conduction than peripheral fibres (Perkin and Rose, 1979) and this would tend to obviate this argument, b) the question of a retinal contribution to the delay, although this is far from conclusive (McDonald, 1977). The effect of optic neuritis on the flash VECP is less well defined, but it appears to be affected more often in severe cases where visual acuity is dramatically reduced producing a delay and reduction of the VECP (Halliday and Mushin, 1980 and Harding, Crews and Good, 1980). Intrestingly in the present, small study, significant delays and amplitude asymmetries of the flash VECP were found in several of the subjects, although the lowest level of visual acuity, in one patient (GW), was $^{6}/_{24}$ and the latency in this case was only 3 m.sec. delay compared with the unaffected eye, although the amplitude was 5 uV. lower from the affected eye (Table 3.5.1.).

In an attempt to account for the difference in characteristics between the flash and pattern-reversal VECP in optic neuritis, Halliday et al. (1972) suggested

that the two responses might be mediated by different groups of optic nerve fibres; the pattern response reflected central visual processing and this related to the portion of the visual field most frequently affected in optic neuritis; the flash response was possibly mediated by fibres serving the more peripheral field and thus remained unaffected. Presumably, when a flash response is abnormal, a proportion of the fibres serving the peripheral field is also affected. It seems likely that the pattern-reversal response should reflect more central parts of the visual field, but it must be remembered that fixation may be variable in a patient with reduced acuity with or without a central/para-central scotoma during the acute stage. The nature of the conventional pattern-reversal stimulus is such that scattered stray-light is minimal (if existent at all) and hence, with good fixation, the area of retina stimulated can be precisely controlled. However, with diffuse flash stimulation, scattered stray-light is inevitable particularly when fixation is poor. Thus, flash stimulation would seem to be a technique involving stimulation of the overall area of the retina and not precisely controlled.

Considering the VESP, the findings of this experiment indicated that recordings from the affected eye were not significantly different to those from the unaffected eye in latency or amplitude. This at first sight implies that, overall, the fibres producing this EP appear to be

unaffected by the optic neuritis. In relation to the preceding comments on different types of fibres and their transmission properties and the differences in stimulus localisation and precision between pattern-reversal and flash techniques, the nature of the stimulus used to generate the VESP must be considered: a large number of high intensity flashes presented at a fast rate clearly produces an overall, full-field stimulus to the retina and at the intensity level used, must produce a considerable proportion of stray-light. The VESP must therefore be an overall response from the whole retina.

It is evident from work presented in Sections 3.1. and 3.2. that the VESP is not a volume conducted manifestation of the ERG and the results in this study can be assumed not to be a reflection of retinal function, which has been proposed by some authors to be unaffected in optic neuritis (Halliday et al. 1972). A possible explanation of the lack of delay or amplitude reduction of the VESP from the eye affected by optic neuritis is related to the area of retina stimulated and the visual pathway fibres conducting the afferent volley. If it is expected that the bright flash causes stimulation of a wide area of retinal receptors and initiates impulses in a mixture of central and peripheral optic nerve fibres, the response is probably a composite of that from both types of fibre and the overall EP remains unaffected despite demyelination. The amplitude of the flash VECP is usually increased with increasing latency (Section 2.2.) and at the intensity level used to

generate the VESP, the volley may be of such a nature as to cross a plaque of demyelination and remaining unaffected, whilst impulses produced by less robust stimuli are retarded by the plaque. In this context, Cant, Hume and Shaw (1978) examined the effects of luminance on the pattern-reversal VECP and found that the latency of the major positive peak and the earlier (P60) peak was inversely proportional to the log of pattern luminance (latency increasing with lower luminance) and concluded that the pattern luminance could significantly affect the proportion of abnormal major component latency values in a group of patients, influencing the number of correctly diagnosed patients. Interestingly, the latency increase of the major positive component was found to be double that of the earlier positive component and the authors suggested that this finding and the difference in their latencies indicated that the two component must reflect different aspects of function in the visual pathway, possibly mediated by different neuronal sub-systems. Overall, they considered that a delayed pattern VECP in MS was not entirely due to slowed optic nerve conduction.

These comments of Cant et al. (1978) are relevant to the present small study and until further work is performed on the effects of demyelination on the VESP (and possibly the flash VECP) the results presented remain somewhat of an enigma.

CHAPTER 4

DISCUSSION AND CONCLUSIONS

4. DISCUSSION AND CONCLUSIONS

4.1. Resumé of Data

Recordings for normative data on the VESP have been collected from sixty normal volunteer subjects (30 male, 30 female) aged between 16 and 41 years (mean 22.5 years) raw data being given in Appendix 5. VESP components have been successfully recorded in fifty-seven of these subjects (95% incidence). Mean latency values for this sample are P21.0 $\pm$ 2.59 m.secs., N26.24 $\pm$ 2.41 m.secs., P33.67 $\pm$ 2.52 m.secs., mean peak-to-peak amplitude values are P-N 1.28 $\pm$ 0.75μV., N-P 2.36 $\pm$ 0.91μV.. A schematic representation of this data is illustrated in Figure 4.1.1. including two standard deviations from all the mean values. Recordings have also been made on a very small number of older subjects.

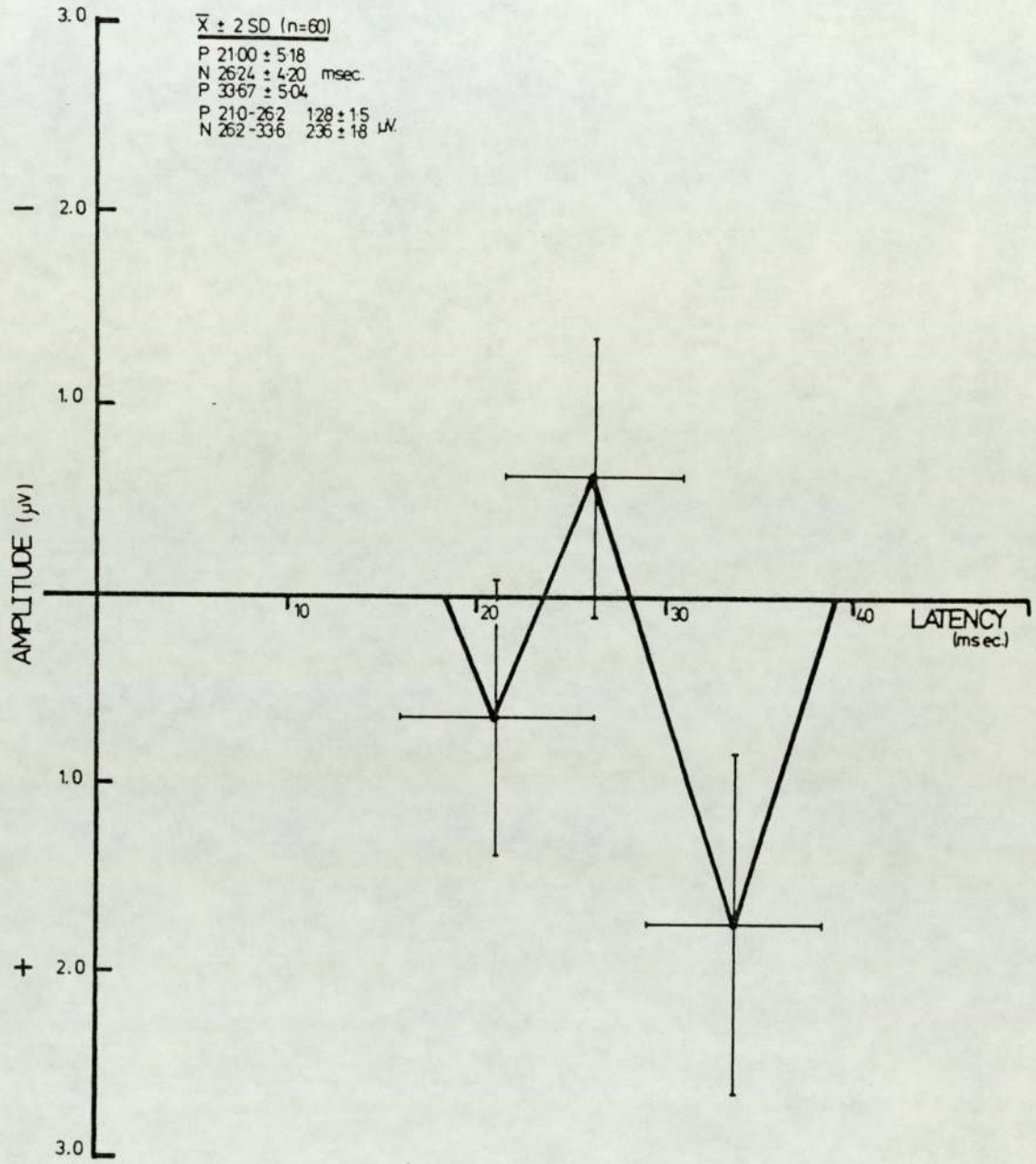
The recordings from male and female subjects were compared using the Students t-test to assess any statistical significance in differences between groups. It was found that differences in latency and peak-to-peak amplitude of all components were non-significant. The recordings from older subjects, although very few in number, did not appear on gross inspection to be significantly different from the data of the major group.

The reliability of the technique was assessed by trial-retrial repeatability of measurements on 30 subjects

FIGURE 4.1.1.

Schematic VESP waveform based on data from sixty normal subjects

The waveform includes two standard deviations from the normal (see text for details)


X̄ ± 2 SD (n=60)
P 21·00 ± 5·18
N 26·24 ± 4·20 msec.
P 33·67 ± 5·04
P 210-262 128 ± 1·5
N 262-336 236 ± 18 μV
3.0
2.0
1.0
1.0
2.0
3.0
AMPLITUDE (μV)
10
20
30
40
LATENCY
(msec.)

(16 female, 14 male), raw data being given in Appendix 6; one set of retrials was performed on each of these subjects, trial-retrial intervals varying between subjects between 1 week and 1 year. Examples of repeated VESP waveforms are illustrated in six subjects in Figure 4.1.2.. Latency and peak-to-peak amplitude measurements were made manually and derived data were plotted in correlation graphs; the initial trial (trial 1) was regarded as the control (i.e. independent variable) and the repeated trial (trial 2) regarded as the dependent variable. The data are illustrated in Figure 4.3. and it can be seen from inspection that the latency values of the three components have high repeatability and a correlation coefficient of 0.9486 was calculated. Repeated peak-to-peak amplitude measurements however were found to be more variable between trials and a correlation coefficient of 0.7248 was calculated. The regression lines drawn in Figure 4.1.3. are regarded as 'best-fit' lines. Mean differences for the repeated measurements are given below:

LATENCY	P	0. 9 ± 1.19 m.sec.
	N	1. 3 ± 1.38 m.sec.
	P	1. 5 ± 1.13 m.sec.
AMPLITUDE	P-N	0.35 ± 0.37μV.
	N-P	0.58 ± 0.36μV.

The differences between trial 1 and trial 2 for latency

FIGURE 4.1.2.

Repeated VESP waveforms in six subjects

Repeated VESP waveforms are illustrated in six subjects with differing trial-retrial intervals (see text for details)

VESP REPEATABILITY

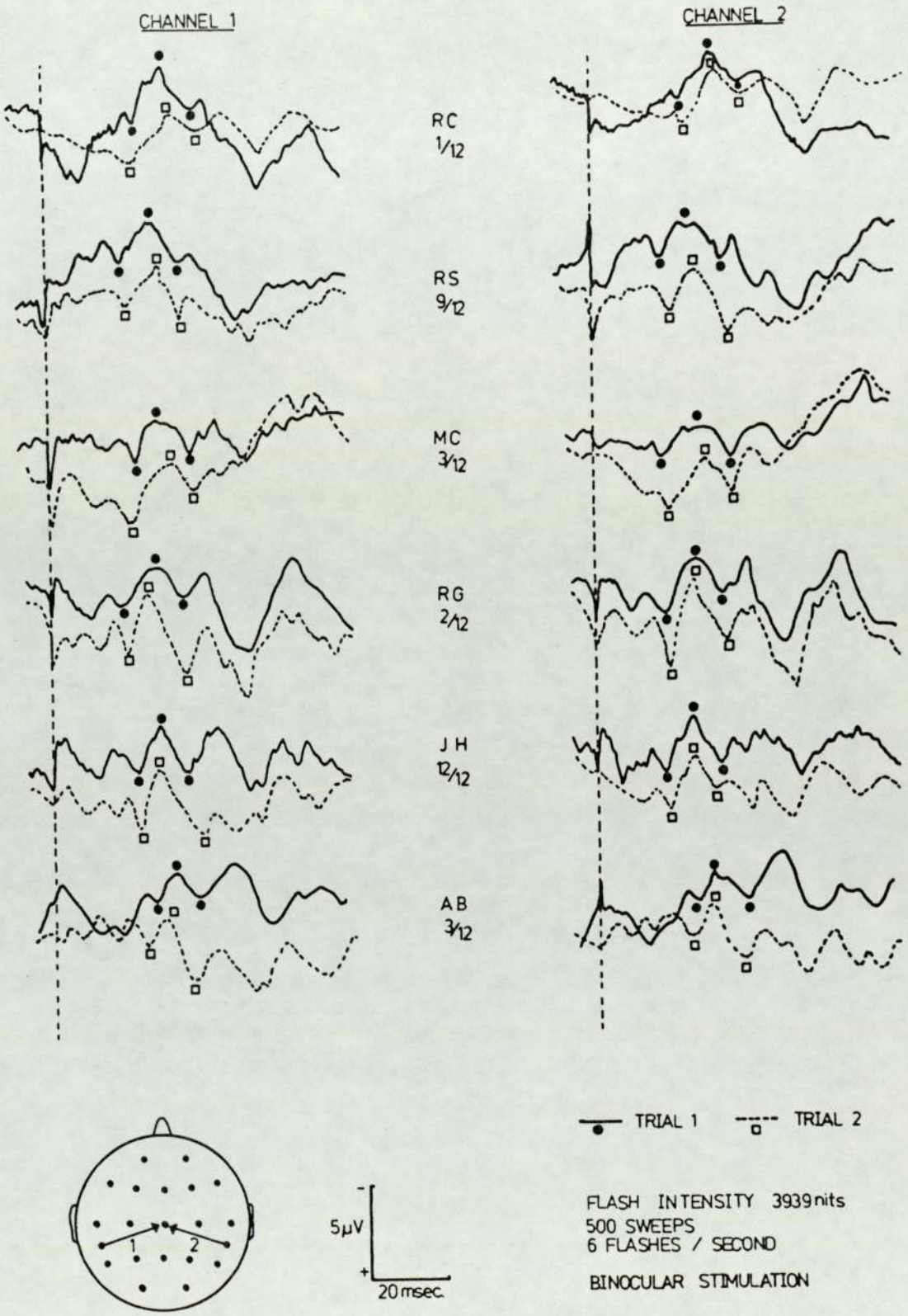
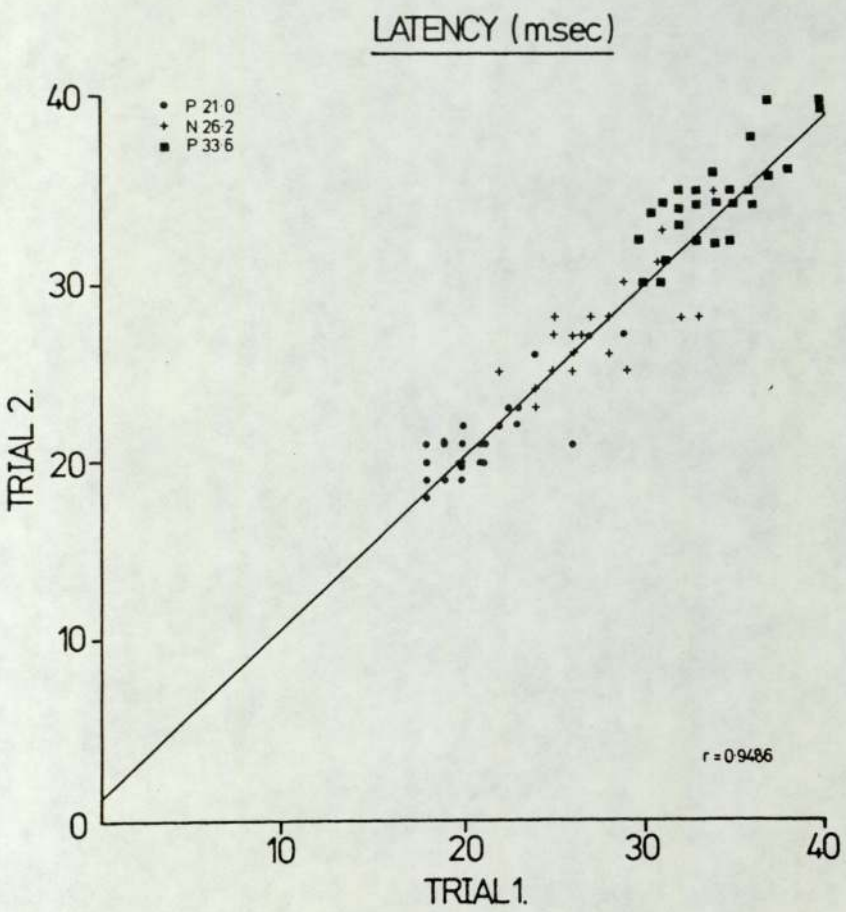
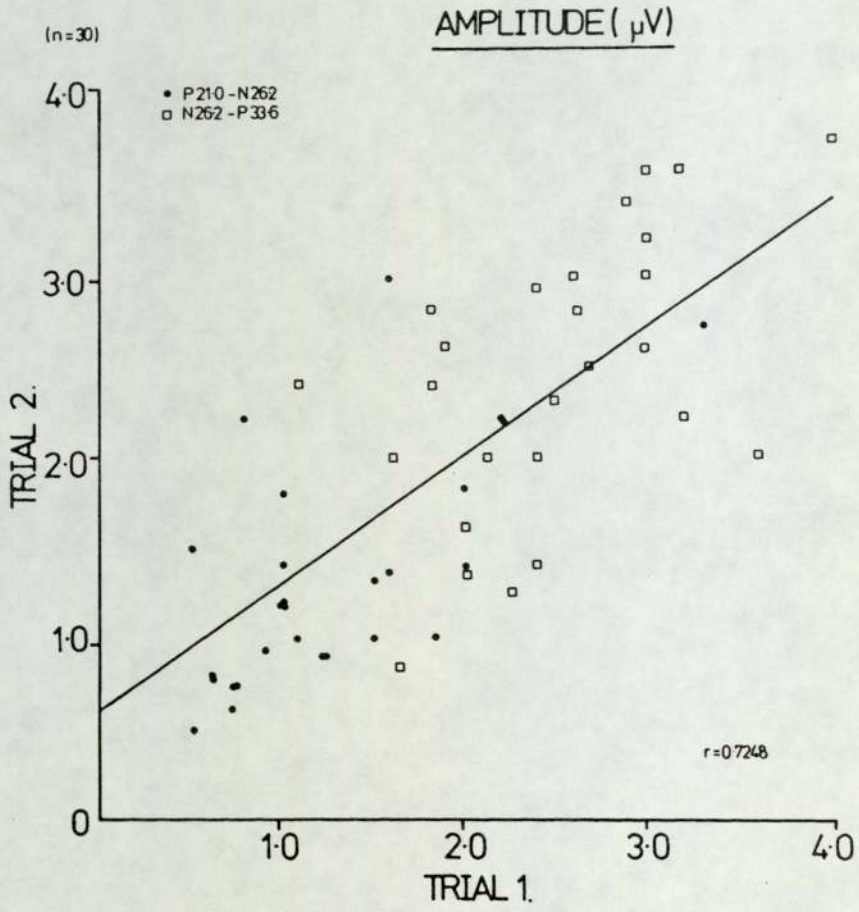


FIGURE 4.1.3.

Scattergrams of VESP latency and amplitude trial-retrial repeatability

Repeated measurements on thirty normal subjects are illustrated. The regression line of y (trial 2) on x (trial 1) is drawn and considered as a "best-fit" line. Latency repeatability is seen to be good, but amplitude is less consistent (see text for details)


LATENCY (m.sec)
P 21·0
N 26·2
P 33·6
r = 0·9486
TRIAL 2.
TRIAL 1.
0
10
20
30
40


(n = 30)
AMPLITUDE (μV)
P 21·0 - N 26·2
N 26·2 - P 33·6
r = 0·7248
TRIAL 2.
TRIAL 1.
0
1·0
2·0
3·0
4·0

and peak-to-peak amplitude measurements were tested for significance using the Students t-test; in all cases differences were found to be non-significant, but t-values were higher for repeated amplitude measurements and of these the P-N measurement t-value was higher than that of the N-P measurement, indicating greater variability for the amplitude of the P-N component.

In the series of sixty subjects examined, there were three subjects (1 female, 2 male) in whom no VESP response could be consistently recorded. One of these subjects has been described in Section 3.1.. The other two subjects were examined on two or more occasions and no consistent early components could be elicited; the only components seen in the time window used were a positive component at around 55 m.sec., followed by a later negative component. The VECP to flash and pattern-reversal in both subjects was normal and both were ophthalmologically and neurologically normal. These three subjects were included in the trial - retrial repeatability data.

4.2. Discussion, conclusions and proposals for further work.

The initial aim of the work described in this thesis was to attempt to delineate any photically evoked activity that occurred in the visual pathway between the retina and the occipital cortex, that is, activity unrelated to the ERG and VECP. A proposal was made that 'early

components' of the VECP were reflections of pre-cortical activity and review of the existing literature corroborated this proposal. In recordings of the VECP under conventional conditions the 'early components' are extremely variable and often not demonstrable. The concept of far-field techniques was borrowed from the now established work on the BAEP, in which large numbers of stimuli are presented (in conjunction with a wide band-pass) in order to enhance the extremely short latency, low amplitude components.

Under these modified conditions an early component complex was established, with latencies of less than 50 m.sec. and its scalp topography was plotted showing the complex to be maximal around the upper mastoid process. A major consideration was whether this complex was in any way related to the high amplitude ERG, known to dominate the anterior portions of the scalp, since latencies of the components were often similar to those of the ERG. In the first instance, the effects of monocular and binocular stimulation were compared and showed on monocular stimulation an almost total extinction of the ERG from the unstimulated eye, but bilateral reduction in amplitude of the early component complex. This was indicative of a post-chiasmal origin of the complex. This finding and the anatomical location of the maximal amplitude of the complex led to the hypothesis that the complex was of subcortical origin, and the VESP was evolved. Confirmation of a non-ERG

origin for the VESP was provided a) by a topographical study of the ERG which showed that any recordable remnants of the ERG at sites proximal to the mastoid were of lower amplitude than the VESP and of different morphology, b) in two cases where ERGs were markedly asymmetric, but co-existed with symmetric VESPs, c) in a number of pathological cases in which due to optic nerve pathology the ERG was seen to be recordable bilaterally, but the VESP and VECP were abolished on the affected side, and in a case of retinal detachment when the ERG from the affected eye was abolished, but the VESP and VECP was recorded bilaterally. In order to prove that the VESP was indeed of subcortical and not cortical origin, a number of selected cases were examined electrophysiologically; these consisted of a) a case of brainstem vascular disturbance in which the VESP was abolished contralateral to the existing dense homonymous hemianopia, although the VECP was only partially affected, b) in several cases of occipital trauma or lesion not involving the subcortical visual pathway in which normal VESPs co-existed with grossly asymmetric VECPs, c) in two cases of bitemporal hemianopia associated with chiasmal compression, VESPs were absent over the hemisphere contralateral to the eye stimulated and the VECP was consistent, on half-field pattern-reversal stimulation, with the visual field defect. Any possible auditory origin for the VESP was eliminated and the question of a myogenic origin was eliminated by

trials of forced muscle tension and maximal relaxation with the subject lying supine, in both cases the VESP was unaffected; the manner in which the VESP has been shown to be differentially affected in pathological states of the visual system also strongly contradicted the possibility of a myogenic origin.

Reports of systematic studies of early components of the VEP in man are sparse but the work and conclusions presented in the present thesis may be compared with these. From the literature reviewed in Section 2.1. it was shown that in animal studies in which depth recordings had been made that oscillatory-type activity could be recorded in the optic nerve, lateral geniculate body and other regions in response to high intensity photic stimulation. A distinct temporal relationship was often shown to exist between this activity in different anatomical regions and proposals were made that the ERG and its OPs might act as a 'pace-maker' for this generalised type of activity.

The morphology of the VESP described in the present thesis differs from other workers' findings of early components of the VEP and there is indeed marked variation between these other workers' findings, despite claims as to similar origins for the components. As the present author stressed in Section 1.3., reports from different laboratories are markedly affected by different apparatus and techniques, confounding inter-laboratory comparisons,

particularly of poorly established phenomena such as those described in this thesis. By comparing monocular and binocular stimulation (Van Hasselt, 1972) and by simultaneous recording from both temples during monocular stimulation (Siegfried, 1980) these two authors proposed that their recordings were of pre-chiasmal origin and both proposed that their findings were not due to volume conduction of the ERG or the VECP. Van Hasselt (1972) showed records with a positive component at a latency of 10 m.sec. of maximal amplitude when recorded between the auricle and mastoid, whilst Siegfried (1980) illustrated a negative component at 20-23 m.sec. followed by a positive component at 40-47 m.sec. and a later negative component at 90-95 m.sec., recorded between temple and ipsilateral earlobe. Although both authors suggested that these components were of optic nerve origin the recording sites and latencies were markedly different and it would be difficult to consider them as reflecting the same activity. The component of Van Hasselt (1972) is probably analogous to one of those recorded by the present author with shorter latency than the VESP. The low incidence of this wave in the study of Van Hasselt (1972) may be due to inappropriate stimulus parameters. The initial component of Siegfried (1980) is of similar latency to the second component of the VESP and may well be the same component. Certainly, the present author considers that the later components reported are of such a relatively long latency as not to be of optic nerve origin. Honda (1977) recorded a number of wavelets near

the lateral canthus with latencies ranging between 13 and 46 m.sec.; since the eye was rotated nasally, this brought the optic nerve (and presumably the retina) nearer to the lateral canthus and the author considered that the last three sets of wavelets corresponded to OPs of the ERG; the earlier sets of wavelets were not coincident with any ERG activity and probably reflected optic nerve activity. The present author has shown (Section 3.1.) that the ERG has a wide field of activity, under the specified stimulus conditions, and clearly the ERG is volume conducted along the sides of the head ipsilateral to the stimulated eye. Early studies of the VECP made mention of early components (Section 2.1.), but these were considered by most authors to be too variable and unreliable to be of any clinical use and this was probably due to the use of inappropriate stimulus and analysis parameters for the recording of such components. The systematic studies of Cracco and Cracco (1978) and Siegfried and Lukas (1981a,b) show different early components of the VECP which are also different from those of the present study. Cracco and Cracco (1978) showed that oscillatory activity could be recorded at a wide distribution of scalp sites, predominantly in the midline derivations. A common reference on the ear was used for all recordings although trials using a hand reference were also claimed to produce the same results, but these were not illustrated. Oscillations in the frontal derivations were undoubtedly of ERG origin,

but the authors did also consider an optic nerve origin. Other components were seen of alternating polarities with latencies between 18 and 58 m.sec.; there is a greater number of components demonstrated within the time window used by these authors than in the VESP including components earlier and later than the VESP. The latency of a number of the components was similar to those of the VESP and amplitudes were of the same order of magnitude. The authors presented postulates as to the origins of the components, possibly being of subcortical origin. The reports of Siegfried and Lukas (1981a,b) revealed a number of wavelets in occipital recordings with latencies of between 50 and 101 m.sec.. These seem to be of completely different latency to either the report of Cracco and Cracco (1978) or the present author's findings. The active electrode was placed 2 cm. above the inion and referred to the left earlobe and hence the response recorded was from the region expected to produce an optimal cortical response. A control ERG was recorded, demonstrating a number of oscillations and the oscillations recorded in the occipital derivation were not regarded as volume conducted ERG remnants. The present author considers that the use of different reference sites for the recording of ERG and VECP was inappropriate when comparing the different wavelets since it prevented a true comparison of recordings. Any components earlier than 50 m.sec. were thought by the authorsto be of ERG origin, but the

later components (with latencies between 50 and 101 m.sec.) were possibly reflections of the initial arrival of optic radiation activity at the cortex or subcortical activity. These findings are certainly markedly different from those of Cracco and Cracco (1978) and of the present author and the relatively long latency of the wavelets and the site from which the recordings were made would suggest that they were not of subcortical origin.

The few reports of depth recording studies relevant to this thesis are of extreme importance in supporting the hypothesis and conclusions of the present author. Gastaut (1949b) showed that a number of waves could be recorded in the vicinity of the optic radiations - a 'primary response' consisted of a positive component at 50 m.sec., negative at 70 m.sec. and further positive at 90 m.sec.; however, a 'secondary response' consisting of a negative at 20 m.sec. followed by a positive at 30-35 m.sec. could also occasionally be recorded. Corletto et al. (1966) provided excellent depth recording evidence of the preservation of several early components (of latency less than 50 m.sec.) but abolition of later components following occipital lobectomy and suggested a non-cortical origin of these components. Wilson and Nashold (1969) recorded short latency responses from the human thalamus and midbrain and Spire and Hosobuchi (1980) reported a short latency response with a latency of 22-23 m.sec., in the region of the optic radiation.

In normal subjects the VESP has been shown to be a consistent and repeatable phenomenon in a high percentage of individuals. It is clearly a similar type of response to the BAEP in terms of latency and amplitude, both being short latency, low amplitude responses occurring before the higher amplitude, more consistent portions of the respective EPs. However, the VESP appears to differ from the BAEP in the following respects: a) the BAEP is a true 'far-field' EP in that due to the depth of the generator, diffusion of the signal (by volume conduction) occurs over an extensive area such that it may be recorded at a wide range of scalp locations significantly far apart without distortion of the waveforms (see Section 2.1.); from the topographical studies described in this thesis the VESP appears to be precisely localised to the upper mastoid process and small excursions away from this site resulted in distortion or total abolition of the response. This difference was remarkable and a possible explanation is that if the VESP response was mainly generated at the level of the lateral geniculate body, the scalp site of maximum definition of the response might be related to the orientation of the generator and the arrangement of the neuronal representation and synapses within the generator, although under the stimulation conditions used it was anticipated that fibres from the whole retina rather than exclusively macular fibres would be activated simultaneously; b) the VESP is of longer latency than

the BAEP probably simply because in the visual system the initial response to a photic stimulus begins at the level of the retina (manifested as the ERG), whereas the first component of the BAEP reflects the initial response in the auditory nerve. The VESP is not therefore considered to be the initial EP to be generated in response to photic stimulation; c) the BAEP consists of seven components each reflecting activity at different anatomical sites of the auditory pathway whereas the VESP per se consists of three components. Components of shorter latency than the VESP were inconsistently recorded throughout the work described consisting of a negative component immediately preceding the VESP and occasional very low amplitude and inconsistent deflections of even shorter latency. Because of the inconsistency of these earlier components they have been excluded from assessment in this thesis, but the author considers that they probably reflect processing in portions of the visual pathway anterior to the lateral geniculate body. On a purely neuro-anatomical basis it is expected that the auditory pathway would produce more EP components due to the number of synaptic nuclei present, and the visual pathway should produce far fewer components since there is only one synapse (the lateral geniculate body) between retina and cortex.

The results of the present work have shown that certain of the early components of the human VEP are of subcortical origin; the triphasic VESP has been shown to

be a consistent and reliable phenomenon in normal subjects and in clearly diagnosed pathological cases with lesions at selected sites of the visual pathway it is differentially affected. At this stage in the development of the VESP, the author considers that more work must be performed in order to further substantiate its clinical utility. Because of its low amplitude and the type of stimulus and analysis parameters used in its generation and recording, difficulties have frequently arisen in identification of the components, serial recording and superimposition of traces being found to be the most satisfactory method of detecting its presence in difficult cases.

Proposals for further work suggested by the author are:

a) Large groups of older and younger normal subjects should be examined to assess any age variation in the VESP.

b) Further trials on clinical cases with established diagnosis should be performed to further categorise the 'behaviour' of the VESP under clearly defined clinical conditions, in order to evaluate its utility as a diagnostic aid in less clearly defined pathological conditions.

c) Because of the results of the VESP trials in

cases of unilateral retrobulbar neuritis, this work should be further developed in an attempt to possibly improve concepts of the processing of visual stimuli in demyelination of the anterior visual pathway.

d) Further trials might be conducted to evaluate the effects of different structured stimuli on the VESP.

e) It would be most interesting if depth recordings could be performed during surgical procedures in the subcortical area and to relate the findings to those of the scalp recorded VESP.

At the present stage, the VESP has been shown to be an electrophysiological phenomenon and it is hoped that its evaluation has added to the existing wealth of knowledge on human photically evoked potentials. In historical terms, immense progress has been made since the early 1960's and the first systematic studies on the VEP and only in recent years have attempts been made to analyse photically evoked potentials from sites between the retina and visual cortex. Provided that further studies are made with favourable outcome, the phenomenon of the VESP may become a useful addition to the established armament of electrodiagnostic tests for the clinical assessment of the human visual system.

APPENDICES

APPENDIX 1

[Grass PS 22 Photostimulator - intensity information]

Setting	Intensity (nits = candelas/m²)
1	1058
2	1363
4	1925
8	3939
16	9661

Flash duration = 10 μsec

APPENDIX 2

[Raw data in evaluation of GFE.]

Latency (msec)		Amplitude (uV)		
HCL	GFE	HCL	GFE	
14.0000	15.0000	30.0000	22.0000	
14.0000	14.0000	22.0000	21.0000	
15.0000	14.0000	19.0000	18.0000	
16.0000	15.0000	22.0000	18.0000	
15.0000	15.0000	22.0000	17.0000	
15.0000	15.0000	23.0000	19.0000	
14.0000	15.0000	18.0000	15.0000	
15.0000	16.0000	19.0000	16.0000	
15.0000	15.0000	24.0000	24.0000	
15.0000	15.0000	30.0000	29.0000	
13.0000	13.0000	18.0000	18.0000	'a' wave
14.0000	13.0000	18.0000	17.0000	
15.0000	15.0000	15.0000	13.0000	
14.0000	15.0000	14.0000	13.0000	
15.0000	15.0000	14.0000	13.0000	
15.0000	15.0000	15.0000	15.0000	
15.0000	15.0000	14.0000	13.0000	
16.0000	15.0000	15.0000	14.0000	
15.0000	15.0000	15.0000	14.0000	
15.0000	15.0000	15.0000	14.0000	

Latency (msec)		Amplitude (uV)		
HCL	GFE	HCL	GFE	
36.5000	37.0000	101.5000	85.0000	
35.0000	36.0000	76.5000	71.0000	
34.0000	36.0000	87.0000	92.0000	
34.0000	34.0000	84.0000	85.0000	
41.0000	43.0000	78.0000	75.0000	
40.0000	44.0000	80.0000	79.0000	
38.0000	38.0000	53.0000	43.0000	
38.0000	38.0000	49.0000	38.0000	
45.0000	45.0000	71.0000	74.0000	
41.0000	42.0000	83.0000	83.0000	'b' wave
35.0000	35.0000	80.0000	76.0000	
36.0000	35.0000	84.0000	79.0000	
38.0000	38.0000	51.0000	48.0000	
38.0000	38.0000	49.0000	46.0000	
41.0000	41.0000	58.0000	55.0000	
41.0000	42.0000	59.0000	57.0000	
35.0000	35.0000	52.0000	52.0000	
35.0000	35.0000	54.0000	52.0000	
37.0000	37.0000	50.0000	47.0000	
37.0000	37.0000	52.0000	50.0000	

APPENDIX 3

[Raw data in evaluation of flashed-on-pattern technique - ERG]

Diffuse	+Grid A	+Grid B	+Grid C	+Grid D	
14.0000	12.0000	14.0000	15.0000	14.0000	
14.0000	14.0000	12.0000	14.0000	13.0000	
16.0000	14.0000	10.0000	10.0000	12.0000	
16.0000	14.0000	15.0000	14.0000	16.0000	
12.0000	14.0000	12.0000	14.0000	12.0000	
14.0000	15.0000	14.0000	14.0000	14.0000	latency (msec)
12.0000	10.0000	10.0000	10.0000	12.0000	
12.0000	12.0000	12.0000	12.0000	12.0000	
11.0000	12.0000	14.0000	14.0000	14.0000	
14.0000	11.0000	10.0000	10.0000	14.0000	
10.0000	12.0000	11.0000	10.0000	11.0000	
15.0000	14.0000	14.0000	10.0000	15.0000	
1.2000	0.6000	0.8000	0.6000	0.8000	'a' wave
4.4000	2.5000	0.8000	1.0000	1.0000	
1.0000	0.6000	1.0000	0.8000	0.6000	
0.5000	0.7500	0.5000	0.2500	0.2500	
0.4000	1.0000	2.8000	0.4000	0.6000	
1.2000	1.2000	1.0000	2.0000	1.2000	amplitude (uV.)
3.6000	4.0000	3.8000	2.8000	3.0000	
4.0000	2.0000	1.6000	1.0000	3.0000	
7.0000	6.6000	2.6000	6.4000	5.0000	
2.4000	1.6000	2.4000	1.2000	2.0000	
5.0000	3.0000	5.0000	1.0000	3.0000	
6.5000	2.8000	6.5000	1.0000	1.6000	
36.0000	36.0000	36.0000	35.0000	36.0000	
35.0000	40.0000	35.0000	36.0000	35.0000	
36.0000	40.0000	40.0000	40.0000	39.0000	
38.0000	38.0000	40.0000	38.0000	38.0000	
35.0000	38.0000	36.0000	40.0000	37.0000	
38.0000	36.0000	37.0000	36.0000	36.0000	latency (msec.)
43.0000	42.0000	42.0000	40.0000	42.0000	
40.0000	36.0000	38.0000	37.0000	40.0000	
34.0000	35.0000	34.0000	38.0000	42.0000	
35.0000	35.0000	35.0000	34.0000	35.0000	
34.0000	35.0000	36.0000	35.0000	34.0000	
35.5000	36.0000	35.0000	35.0000	36.0000	'b' wave
8.7000	5.6000	8.6000	6.4000	8.0000	
16.0000	12.6000	14.0000	11.0000	10.0000	
15.0000	10.4000	8.8000	6.8000	7.5000	
8.2000	5.2000	6.0000	5.5000	3.7500	
15.6000	10.0000	12.4000	9.6000	10.0000	
18.0000	15.0000	14.0000	20.0000	14.0000	amplitude (uV.)
14.6000	13.6000	14.0000	14.0000	14.0000	
18.0000	16.8000	16.0000	12.0000	14.0000	
18.0000	17.0000	15.2000	11.6000	15.0000	
12.8000	8.4000	10.4000	9.4000	10.4000	
16.0000	10.8000	9.8000	8.0000	10.0000	
14.5000	11.6000	9.2000	10.0000	14.0000	

APPENDIX 3

[Raw data in evaluation of flashed-on-pattern technique - VESP latencies in msec.]

Diffuse	+ Grid A	B	C	D	
26.5000	25.0000	26.0000	24.0000	25.0000	
23.0000	24.0000	23.0000	22.0000	23.0000	
16.0000	18.0000	17.0000	19.0000	17.0000	
18.0000	17.0000	20.0000	19.0000	20.0000	
18.0000	22.0000	19.5000	22.0000	19.0000	
19.5000	18.0000	22.0000	22.0000	20.0000	P
22.5000	20.0000	22.0000	19.0000	23.0000	
20.0000	22.0000	22.0000	22.0000	20.0000	
21.0000	22.0000	24.0000	22.0000	23.0000	
22.5000	20.0000	24.0000	24.0000	23.0000	
21.5000	24.0000	24.0000	24.0000	22.0000	
23.5000	23.0000	22.0000	24.0000	26.0000	
29.0000	29.0000	30.0000	27.0000	29.0000	
28.0000	28.0000	26.0000	28.0000	26.0000	
28.0000	28.0000	28.0000	30.0000	28.0000	
21.5000	21.5000	22.0000	21.0000	24.0000	
28.0000	28.0000	27.0000	30.0000	27.0000	
24.5000	24.5000	23.0000	26.0000	26.0000	
26.0000	22.0000	28.0000	23.0000	26.0000	N
24.0000	24.0000	25.0000	25.0000	26.0000	
24.0000	24.0000	24.0000	25.0000	26.0000	
26.0000	26.0000	30.0000	30.0000	28.0000	
24.5000	24.5000	26.0000	28.0000	28.0000	
26.5000	26.5000	28.0000	30.0000	29.0000	
35.0000	37.5000	36.0000	36.0000	35.0000	
32.0000	34.0000	34.0000	34.0000	33.0000	
35.0000	36.0000	35.0000	37.0000	35.0000	
31.0000	30.0000	32.0000	32.0000	34.0000	
32.0000	39.0000	40.0000	35.0000	35.0000	
37.0000	37.0000	36.0000	34.0000	36.0000	
32.0000	30.0000	32.0000	31.0000	33.0000	P
32.0000	33.0000	34.0000	34.0000	33.0000	
33.0000	32.0000	33.0000	34.0000	34.0000	
33.0000	35.0000	35.0000	34.0000	34.0000	
32.5000	34.0000	36.0000	37.0000	35.0000	
35.0000	38.0000	38.0000	38.0000	36.0000	

APPENDIX 3

[Raw data in evaluation of flashed-on-pattern technique - VESP amplitudes in uV.]

	+ Grid				
Diffuse	A	B	C	D	
0.6000	1.2000	1.6000	1.2000	0.9000	
0.4000	0.6000	0.8000	0.6000	0.5000	
1.0000	2.0000	1.0000	2.0000	1.5000	
0.5000	0.6000	0.7000	0.4000	0.6000	
1.0000	0.8000	1.2000	0.8000	1.0000	
1.8000	1.0000	1.8000	1.6000	0.8000	P-N
1.0000	1.0000	1.8000	0.8000	1.2000	
1.2000	0.8000	0.0000	1.3000	1.0000	
0.7000	0.8000	0.4000	0.6000	0.4000	
0.5000	0.4000	0.6000	0.3000	0.6000	
0.8000	0.6000	1.6000	0.6000	1.0000	
0.8000	2.0000	1.0000	1.6000	2.0000	
2.3000	0.0300	3.8000	3.2000	3.0000	
2.0000	0.8000	2.0000	2.2000	2.0000	
2.0000	2.0000	2.1000	3.0000	2.2000	
3.0000	1.7000	2.0000	1.8000	1.4000	
1.8000	4.0000	4.0000	2.8000	1.6000	N-P
3.0000	2.0000	3.4000	2.8000	2.0000	
3.0000	2.6000	2.4000	1.6000	2.8000	
2.6000	2.0000	1.2000	1.3000	2.8000	
2.9000	3.1000	2.8000	2.8000	2.0000	
1.0000	1.2000	2.0000	1.0000	1.0000	
3.1000	2.7000	2.0000	2.2000	3.0000	
3.1000	3.6000	3.0000	2.4000	3.3000	

APPENDIX 3

[Raw data in evaluation of flashed-on-pattern technique - VECP P_1 component]

	+Grid				
Diffuse	A	B	C	D	
50.0000	44.0000	44.0000	42.0000	44.0000	
60.0000	65.0000	65.0000	65.0000	64.0000	
50.0000	48.0000	50.0000	46.0000	42.0000	
56.0000	57.0000	54.0000	58.0000	52.0000	
70.0000	75.0000	75.0000	72.0000	70.0000	
60.0000	58.0000	60.0000	60.0000	55.0000	Latency (msec)
60.0000	60.0000	60.0000	60.0000	60.0000	
63.0000	60.0000	64.0000	62.0000	64.0000	
41.0000	44.0000	44.0000	42.0000	50.0000	
54.0000	50.0000	50.0000	46.0000	54.0000	
54.0000	54.0000	50.0000	52.0000	50.0000	
70.0000	70.0000	70.0000	70.0000	70.0000	
8.8000	5.0000	5.0000	5.0000	4.6000	
5.0000	5.0000	5.0000	4.5000	5.0000	
10.0000	14.0000	10.0000	17.2000	14.0000	
4.4000	5.0000	4.0000	4.2000	4.1000	
4.0000	5.0000	3.0000	4.0000	4.0000	
6.0000	7.0000	5.0000	6.0000	8.0000	Amplitude (uV.)
4.0000	4.0000	5.2000	4.6000	4.4000	
3.2000	3.2000	4.6000	4.0000	6.8000	
13.0000	18.0000	15.0000	15.0000	16.0000	
7.0000	7.0000	6.0000	6.5000	7.0000	
9.2000	9.0000	9.6000	9.4000	10.0000	
8.0000	9.2000	8.8000	9.0000	8.4000	

APPENDIX 4

[Raw data of VECP major positive component in unilateral optic neuritis]

Unaffected	Affected	
125.0000	128.0000	
118.0000	123.0000	
127.0000	145.0000	latency (msec)
118.0000	133.0000	
132.0000	147.0000	
110.0000	137.0000	
108.0000	138.0000	
		FLASH
13.0000	8.0000	
8.0000	5.0000	
7.5000	7.5000	
8.0000	6.0000	amplitude (uV)
10.0000	6.0000	
12.0000	5.5000	
6.5000	5.0000	
105.0000	147.0000	
125.0000	155.0000	
90.0000	137.0000	
95.0000	116.0000	latency (msec)
105.0000	150.0000	
100.0000	150.0000	
95.0000	140.0000	
		PATTERN-REVERSAL
10.0000	6.5000	
12.0000	4.5000	
4.0000	4.0000	
6.0000	3.7500	amplitude (uV)
6.5000	2.7500	
5.0000	5.0000	
12.0000	12.0000	

APPENDIX 4

[Raw data of VESP in unilateral optic neuritis]

Unaffected	Affected		
19.5000	20.0000		
20.0000	20.0000		
24.5000	24.0000		
20.5000	19.5000	P	
25.0000	22.0000		
20.5000	21.0000		
19.0000	19.5000		
25.0000	24.5000		
23.0000	23.0000		
28.0000	28.5000		
25.0000	22.5000	N	(Latency) msec.
31.0000	31.0000		
28.0000	27.5000		
24.5000	25.0000		
34.5000	35.0000		
30.0000	30.0000		
32.5000	33.0000		
30.0000	35.0000	P	
39.0000	35.0000		
32.5000	33.0000		
36.0000	37.0000		
1.7500	2.0000		
2.0000	2.0000		
1.1200	1.2500	P-N	
1.7500	2.0000		
1.1200	1.0000		
2.1000	2.5000		
2.1000	1.6500		
			(Amplitude) uV.
2.0000	2.1000		
2.7500	2.5000		
1.1200	1.5000	N-P	
2.2500	2.8000		
2.5000	1.8700		
2.3500	2.4000		
3.0000	2.5000		

APPENDIX 5

[VESP raw data]

				LATENCY (ms)			AMPLITUDE (uV)	
No	Initials	Age	M/F	P	N	P	P-N	N-P
1	AE	23	M	20	27	33	1.5	1.5
2	CD	24	F	24	28	35	0.8	3.6
3	KL	21	F	23	30	34	1.4	2.6
4	RW	22	M	22	26	36	1.0	1.8
5	MP	38	M	21	28	35	1.0	2.0
6	DG	33	M	23	26	35	1.0	1.7
7	MC	24	M	20	28	35	0.9	1.6
8	JW	26	M	20	27	35	1.2	3.2
9	JP	25	F	21	28	35	1.05	0.9
10	JH	24	F	19	33	37	1.6	1.6
11	JN	21	F	-	-	-	-	-
12	MR	25	M	-	-	-	-	-
13	DT	21	M	19	25	32	3.0	1.37
14	BJ	36	M	18	25	37	2.7	2.7
15	JC	20	F	19	23	32	2.2	4.8
16	SP	27	M	20	24	35	1.0	1.8
17	EB	16	F	22	27	35	1.7	3.0
18	GG	17	M	21	25	33	1.3	2.8
19	JL	18	F	23	27	32	1.2	4.0
20	PM	17	M	17	26	31	3.0	2.5
21	MC	17	F	15	24	30	1.25	1.125
22	MC	23	F	20	25	33	0.8	2.0
23	RS	20	M	20	25	35	1.8	1.6
24	UB	21	F	18	28	36	1.5	2.7
25	AB	28	M	18	28	32	1.0	1.8
26	TP	23	F	21	26	32	0.8	2.5
27	TT	21	M	20	25	32	1.4	1.25
28	RG	21	F	18	26	34	3.3	4.34
29	MM	21	M	20	25	36	2.0	3.2
30	RS	25	M	20	25	34	0.8	2.0

M: Male F: Female -: no response

APPENDIX 5
[VESP raw data (cont'd)]

				LATENCY (ms)			AMPLITUDE (μV)	
No	Initials	Age	M/F	P	N	P	P-N	N-P
31	RC	26	M	22	31	37	2.2	1.6
32	JL	41	M	26	28	38	0.5	2.6
33	SR	23	M	21	26	31	1.5	2.25
34	DW	26	F	20	25	36	1.0	1.1
35	ES	22	F	20	22	31	0.6	4.0
36	LJ	35	F	19	26	34	1.0	2.5
37	JS	18	F	23	27	34	0.5	1.5
38	SD	17	M	20	22	30	0.5	2.7
39	BZ	18	F	21	24	32	1.7	2.4
40	IM	17	M	23	27	35	0.8	1.1
41	KL	17	F	21	24	32	0.8	3.1
42	IH	18	M	23	26	35	1.1	3.3
43	AJ	18	M	22	26	33	0.5	1.0
44	EW	18	F	22	26	32	0.01	3.0
45	LJ	23	F	20	22	30	0.6	3.2
46	DC	25	F	19	25	37	1.9	3.0
47	KS	22	M	18	21	31	0.5	3.0
48	RS	22	F	26	29	35	0.6	2.3
49	RL	16	F	23	28	32	0.4	2.0
50	ES	20	F	20	24	32	1.1	2.6
51	BS	20	F	21	24	33	0.7	2.9
52	WR	24	M	16	28	35	1.0	2.0
53	JT	25	M	-	-	-	-	-
54	CS	20	F	22	30	30	0.8	2.1
55	ST	20	F	27	41	41	0.7	1.8
56	JM	20	F	17	29	29	4.0	3.8
57	SL	19	M	26	40	40	0.8	2.8
58	JP	19	F	21	31	31	0.8	2.6
59	IP	20	M	23	31	31	0.5	0.5
60	CB	23	M	25	35	35	1.1	2.8

M: Male F: Female -:no response

APPENDIX 6

[Raw data of VESP repeatability : latencies in msec.]

P		N		P	
1	2	1	2	1	2
26.0000	21.0000	32.0000	28.0000	35.0000	35.0000
23.0000	23.0000	28.0000	30.0000	34.0000	34.0000
21.0000	20.0000	28.0000	27.0000	35.0000	35.0000
24.0000	23.0000	28.0000	26.0000	35.0000	32.0000
20.0000	20.0000	27.0000	28.0000	33.0000	32.0000
19.0000	21.0000	33.0000	28.0000	37.0000	36.0000
18.0000	18.0000	28.0000	27.0000	36.0000	34.0000
18.0000	19.0000	26.0000	27.0000	34.0000	32.0000
20.0000	20.0000	25.0000	25.0000	35.0000	34.0000
18.0000	21.0000	28.0000	25.0000	32.0000	35.0000
22.0000	22.0000	31.0000	33.0000	37.0000	40.0000
26.0000	25.0000	28.0000	28.0000	38.0000	36.0000
21.0000	21.0000	26.0000	26.0000	31.0000	31.0000
20.0000	19.0000	25.0000	28.0000	33.0000	35.0000
20.0000	20.0000	25.0000	25.0000	36.0000	38.0000
20.0000	19.0000	22.0000	22.0000	31.0000	30.0000
19.0000	19.0000	26.0000	25.0300	34.0000	36.0000
24.0000	26.0000	34.0000	35.0000	40.0000	40.0000
20.0000	22.0000	22.0000	25.0000	30.0000	30.0000
21.0000	21.0000	26.0000	26.0000	33.0000	34.0000
20.0000	20.0000	24.0000	23.0000	32.0000	34.0000
22.5000	23.0000	26.5000	27.0000	30.5000	34.0000
20.0000	21.0000	23.0000	24.0000	30.0000	32.0000
27.0000	27.0000	31.0000	31.0000	42.0000	40.0000
18.0000	20.0000	22.0000	22.0000	31.0000	34.0000
20.0000	20.0000	25.0000	27.0000	36.0000	35.0000
23.0000	22.0000	24.0000	24.0000	32.0000	33.0000

1 : Initial trial
2 : Repeated trial

APPENDIX 6

[Raw data of VESP repeatability : amplitudes in uV.]

P-N		N-P	
1	2	1	2
1.8000	1.0000	2.4000	2.0000
1.6000	1.4000	1.9000	2.6000
1.2000	0.9000	2.0000	1.6000
2.0000	1.8000	3.6000	2.0000
1.6000	2.2000	2.4000	1.4000
1.6000	3.0000	1.6000	2.0000
1.5000	1.3000	2.7000	2.5000
3.3000	2.7000	4.0000	3.7000
1.0000	1.2000	3.0000	2.6000
1.0000	1.2000	1.8000	2.8000
2.2000	2.2000	1.6000	0.8000
0.5000	0.5000	2.6000	2.8000
1.5000	1.0000	2.2500	1.2500
1.0000	1.2000	2.0000	1.4000
2.2000	1.0000	1.1000	2.4000
0.6000	2.2000	4.0000	3.0000
0.8000	2.2000	2.5000	2.3000
0.6000	1.0000	3.0000	3.2000
0.6000	0.8000	3.2000	2.2000
0.7000	0.7000	2.9000	3.4000
1.1000	1.0000	2.6000	3.0000
0.6000	0.8000	2.1000	2.0000
0.8000	0.9000	2.4000	2.9000
0.7000	0.6000	1.8000	2.4000
0.5000	1.5000	3.0000	3.0000
2.0000	1.4000	3.2000	3.6000
1.0000	1.4000	3.0000	3.6000

1: Initial trial
2: Repeated trial

PUBLICATIONS

Reprinted from INVESTIGATIVE OPHTHALMOLOGY & VISUAL SCIENCE, St. Louis
Vol. 19, No. 3, Pages 318-321, March, 1980 (Printed in the U. S. A.)

The scalp topography of the human visually evoked subcortical potential.

G. F. A. HARDING AND M. P. RUBINSTEIN.

Stimulus and analysis parameters have been adjusted to provide optimum conditions for producing and recording the early components of flash visual evoked potentials. A visual evoked subcortical potential (VESP) of mean latency P_{23}-N_{28}-P_{34} has been recorded in 86% of subjects. The triphasic wave was maximal at an electrode position slightly posterior to the Rolandic/Sylvian fissure and topographically separate from the lid electroretinogram and the visual evoked cortical potential. Monocular stimulation shows bilateral reduction of the amplitude of the VESP, indicating that the wave is independent of the retina and optic nerve and must be arising from a postchiasmal site.

The early components, i.e., components before 50 msec latency, of the visually evoked potential in man are poorly documented because of their minute amplitude, intersubject variability, and poor repeatability under the standard experimental conditions used for eliciting the visual evoked cortical potential (VECP).[1]

Van Hasselt[2] reported an "ear-mastoid" potential of 10 msec latency which could only be recorded in a small percentage of subjects and suggested the optic nerve as its origin. Cracco and Cracco[3] described early oscillatory potentials at 100 cy/sec recorded from a wide scalp distribution of electrodes, referred to earlobe electrodes. Early in 1979 we identified a triphasic positive-negative-positive component (msec) in some subjects at latencies of positive 22 (P_{22}), negative 27 (N_{27}), and positive 35 (P_{35}).[4] Since it appeared important to delineate this component from both the scalp-recorded ERG and the VECP, we have carried out a topographic study of the scalp distribution.

Materials and method. Observations were made on 14 normal volunteer subjects (eight male and six female) ages between 19 and 38 years (mean 26 years). All had visual acuities of 6/6 or better. For this topographical study, electrodes were placed according to the International 10/20 system.[5] In the first study, an anterior-posterior series of electrodes at FP_z, F_8, T_4, T_6, and O_z and half-distance electrodes at $F_{8½}$ and $T_{4½}$ were used (Fig. 1). For the study of the transverse distribution, electrodes were placed at C_4, C_6, T_4, and T_8 and at CP_4, CP_6, $T_{4½}$, and $T_{8½}$ (Fig. 2). All recordings were made with common reference, but the choice of a relatively inactive reference site was confounded by both the ERG and VECP. Investigation of commonly used reference sites shows that the midfrontal (F_z) was affected by the ERG and both the earlobe and mastoid were highly active for the P_{22}-N_{27}-P_{35} component. Indeed it is likely that the active nature of this site[6] is probably responsible for some so-called early components of the visually evoked potential. It was found that the vertex site (C_z) was relatively inactive at the latency of the early components and had the added advantage of being equidistant from all the electrodes in the anterior-posterior chain.

This site was also used for the transverse topographic study, but since the rules of equal interelectrode distance are negated, a further reference on the anterior neck was used for comparison. The subjects were seated in a dimly lit room, and flash stimulation was delivered by a Grass PS22 photostimulator 25 cm from the eyes. Silver–silver chloride electrodes were affixed with collodion, and the resistance was maintained below 5 Kohm. A PDP8E computer was used to average the response from each of the eight channels of the electroencephalogram recorded on an Elema Schonander machine. The analysis time was 100 msec, and the bandpass of the equipment was from 66 to 700 Hz.

To maximize the signal, it was found necessary to average the response to 500 stimuli delivered at

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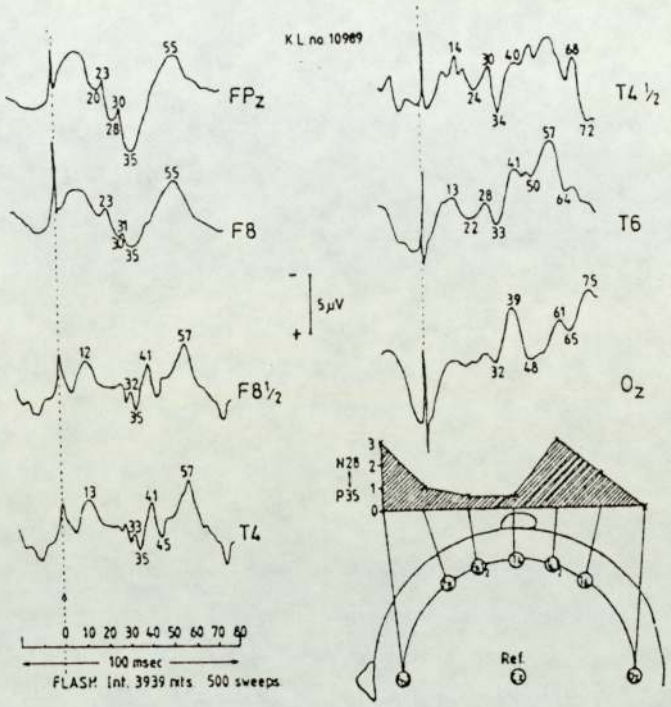

Fig. 1. Topographic distribution of potentials recorded in an anterior-posterior chain of electrodes from frontal to occipital pole, referred to vertex (C_z). The activity of this frontal pole (FP_z) shows the inverted ERG and its oscillatory potentials, and each subsequent site shows the decreasing amplitude of these components. At $T_{4½}$, however, the VESP consisting of a P_{24}-N_{30}-P_{34} components appears, and this reduces in amplitude at more posterior sites and almost disappears at the occipital pole, which shows the N_{39}-P_{48} component of the VECP.

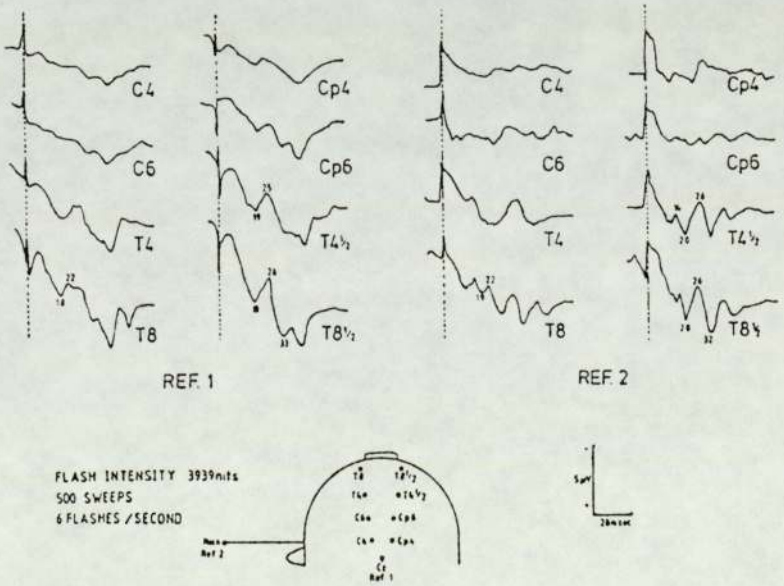

Fig. 2. Topographic distribution of potentials recorded in transverse chains of electrodes referred to vertex (*Ref. 1*) and to an anterior neck site (*Ref. 2*) as a comparator. With either reference, the amplitude of the VESP is shown to be maximal at (or around) electrode $T_{8½}$, i.e., an area level with the cocha but behind the external auditory meatus.

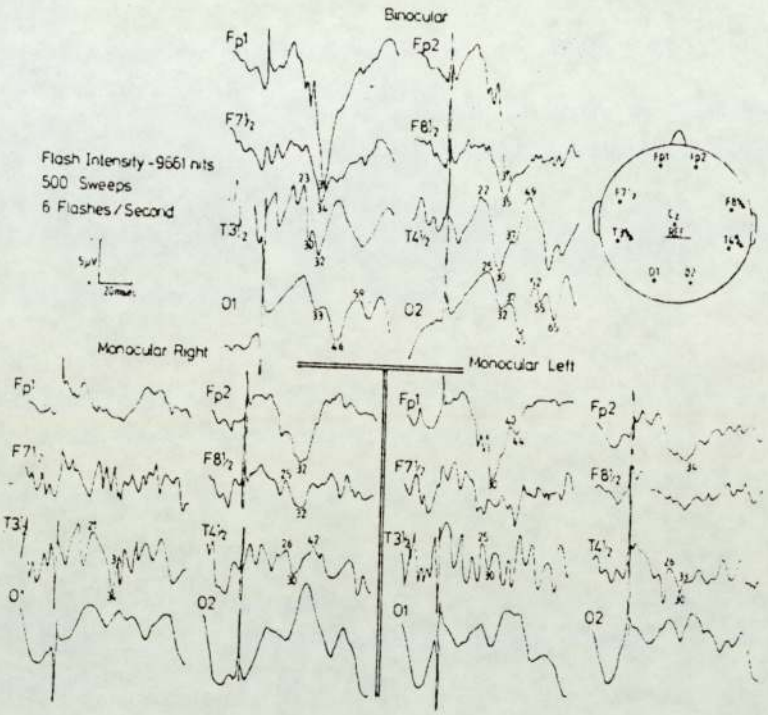

Fig. 3. During binocular stimulation the VESP at N_{23}-P_{32} is seen bilaterally at $T_{3½}$ and $T_{4½}$ and equal to approximately 7μV peak to peak. When the left eye is occluded, the ERG is reduced from the left scalp electrodes (F_p1 and $F_{7½}$), but the VESP is still present at the left (posttemporal, $T_{3½}$) as it is on the right ($T_{4½}$). Similar findings are obtained when the right eye is occluded with a reduced VESP recorded bilaterally.

high intensity (3939 nits) at a rate of 6/sec. Since the photostimulator produced a "click" with each discharge, trials included a series with the lamp occluded and a further series with white noise delivered through earphones. Under the former conditions no response of similar latency was elicited, but when white noise obscured the click, the visually evoked subcortical potential (VESP) was unchanged.

Results. In the anterior-posterior topographic study, the midfrontal ERG (inverted for comparison) recorded from electrode FP_z was seen to be widely distributed and recordable at more posterior electrodes (Fig. 1). Its recorded amplitude gradually diminished until an area of relative inactivity was obtained at electrode T_4. A similar phenomenon occurred with the midoccipital VECP, which was maximal at O_z and gradually decreased in amplitude when recorded at more anterior sites. At electrode $T_{1½}$ just behind and above the ear, a triphasic wave was seen to develop. The mean latencies of this wave (in milliseconds) were $P_{21.30}$ ($\pm$1.63), $N_{28.1}$ ($\pm$2.07), and $P_{35.90}$ ($\pm$1.10); the mean amplitude of P_{22}-N_{27} was 1.09 μV, and that of N_{27}-P_{33} was 2.05 μV.

These waveforms were recorded in 12 out of 14 subjects. It is clear that this wave was independent of both ERG and VECP, and its origin was almost certainly subcortical. We have, therefore, termed this triphasic wave the VESP. To clarify whether it arises from the optic nerve or a postchiasmal site, we compared the response to binocular and monocular stimulation. On monocular stimulation (Fig. 3), the ERG on the side ipsilateral to the occluded eye was almost totally abolished. However, the VESP was reduced bilaterally to approximately half the amplitude obtained by binocular stimulation. Such a finding would indicate that the VESP is not related to the ERG or optic nerve activity and must be of postchiasmal origin. The fact that the ipsilateral ERG recorded from the skin was not totally abolished is related to the transdermal conduction of the signal from the contralateral unoccluded eye, which produces a wide field of electrical activity.

In the transverse topographical study it was

found that the maximal amplitude of the VESP occurred at a site below the temporal electrode chain and around a point level with the cocha but behind the pinna, i.e., around the mastoid process. Since this point was at a maximum interelectrode distance from the C_z reference, we have also compared the findings using an anterior neck reference. Fig. 2 clearly shows that the amplitude of the signal is greatest, with either reference, at or around the mastoid.

Discussion. The VESP has probably not been previously identified for three reasons.

1. Inappropriate stimulus and recording parameters were used.[2] From our studies, a large number of responses to high-intensity flash stimulation need to be averaged over a short sampling time.

2. The confounding nature of the scalp-recorded ERG and its associated oscillatory potentials have not always been recognized. Indeed the illustrations of some authors appear to show mainly oscillatory potentials derived from an ERG recorded with very short time constants.[3] It is of interest to note that in our search for a common reference for the transverse distribution, both the tip of the nose and the chin were found to be highly active for ERG signals.

3. Some authors have assumed that the mastoid process is inactive for visually evoked potentials[3, 7] However, other authors agree with us that the mastoid process is highly active for early components.[2, 6] Our studies demonstrate this site to be the point of maximum amplitude of the VESP in an anterior-posterior and transverse direction, irrespective of reference site. It is certainly not true that the potential is maximal at the vertex.[3]

The VESP elicited under our standard conditions appears to be a relatively stable phenomenon present in a larger proportion of subjects (86%) than previously reported. Because its lateralization is not changed by the occlusion of an eye, its origin cannot be prechiasmal, from either the retina or the optic nerve, and must arise from postchiasmal centers. The most obvious choice would be the lateral geniculate bodies. The VESP may have some clinical utility because at present the combination of the ERG and VECP recordings is the best that can be achieved in ophthalmic electrodiagnosis and this new technique may allow a further degree of differentiation of lesions of the optic pathway.

We are most grateful to Miss Kim Lyons for the continued technical help throughout all stages of this project. We are also grateful to Miss Jennifer Pullan and Mrs. Ann Davies for graphic and secretarial assistance. Mr. Neville Drasdo provided frequent advice and encouragement.

From the Department of Ophthalmic Optics, University of Aston in Birmingham, Gosta Green, Birmingham, England. Submitted for publication May 23, 1979. Reprint requests: G. F. A. Harding, Dept. of Ophthalmic Optics, University of Aston in Birmingham, Gosta Green, Birmingham B47ET, England.

Key words: electroretinogram, reference, subcortical, topography, visual evoked potential

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The visually evoked subcortical potential: is it related to the electroretinogram?

M. P. Rubinstein and G. F. A. Harding

The visually evoked subcortical potential (VESP) of mean latencies P_{21}-N_{28}-P_{36} has previously been recorded at an electrode site around the mastoid process. An initial topographical study of the potential indicated that it was independent of the electroretinogram (ERG), and monocular stimulation showed bilateral reduction, which suggests that the VESP is of postchiasmal origin. A more detailed topographical study of the scalp and facial distribution of the ERG and its oscillatory potentials has been carried out, with simultaneous recording of the VESP. Two monocular fields of ERG activity have been demonstrated, each having a wide area of distribution and interacting medially. Remnants of the ERG b-wave have been detected at many electrode sites, but they were of different amplitude and morphology from the VESP. Results are also presented from two atypical control subjects and two patients, providing further evidence of the separate genesis of the ERG and VESP.

Key words: electroretinogram, gold-foil electrode, noncorneal, oscillatory, topography, visual evoked subcortical potential

The existence of short latency components of the visual evoked potential (VEP) has been known for many years (Cobb, 1950[1]; Cobb and Dawson, 1960[2] and Ciganek, 1961[3]), but their detailed investigation has remained unattractive due partly to their extreme variability and partly due to their low amplitude as compared with the more consistent middle-latency components, especially the major positive component (P100 or P2) that is more routinely considered in clinical electrodiagnosis. More recently, several reports have been presented suggesting as origins for these components the electroretinogram (ERG) (Allison, 1977[4]), the visual evoked cortical potential (Nakamura, 1978[5]), the lateral geniculate body or geniculo-calcarine tract (Picton, 1974[6]) and the optic nerve (Honda, 1977[7]).

In a previous communication (Harding and Rubinstein, 1980[8]) a human Visually Evoked Subcortical Potential (VESP) was described, having a triphasic configuration of mean peak latencies, P21.3 m.secs., N28.1 m.secs., P35.9 m.secs. Topographically this potential was found to be of maximum amplitude at or around the mastoid process and functionally independent of the electroretinogram (ERG) or optic nerve activity, therefore appearing to be of post-chiasmal origin.

During evaluation of reference sites, an ERG-type signal was detected at certain scalp and facial sites distant from the cornea. In order to confirm independence of the VESP and ERG a topographical study of the ERG has been carried out with simultaneous recording of the VESP. In addition, results are presented from two atypical control subjects and two patients.

Materials and Method

For the topographical study, observations were made on 12 normal volunteer subjects (6 male and 6 female) aged between 20 and 28 years (mean 23 years). All had visual acuities of 6/6 or better and full visual fields. Electrodes were placed according to the International 10/20 system (Jasper, 1958[9]) in a modified form, the standard sites used being FP_z, F_z, FP_2, F_8, F_4, T_4. Additional electrodes were placed at N_z, F_{12}, T_8 (being 10% lower than FP_z, F_8 and T_4 respectively) and at M_2 and F_{16} (being 20% lower than FP_2 and F_8 respectively). One electrode was placed in the centre of the right lower lid as close as possible to the lid margin, at LL (Figure 1).

The VESP was monitored using our standard electrodes sited at $T_{4\frac{1}{2}}$ and $T_{3\frac{1}{2}}$ (mid-way between T_4 and T_6 and T_3 and T_5 respectively) and referred to the vertex, C_z.

A gold-foil electrode (GFE) was used to record a base-line ERG (Arden et al. 1979[10]). During preliminary evaluation of this electrode, comparison was made on several subjects between the GFE and a standard Henkes contact lens electrode. High correlation of both 'a' and 'b' wave amplitude and latency was found and the GFE was chosen for use in this study since it proved easily manageable and well tolerated by all subjects. In order to ensure an accurate topographical assessment, common reference recordings were made using the vertex (C_z), the contralateral occiput (O_1) and the anterior neck, as comparator reference sites.

Standard silver/silver chloride EEG electrodes were affixed with collodion to the scalp and with adhesive discs to the face, and the resistance maintained below 5Kohms. The subjects were seated in a dimly lit room and flash stimulation was delivered by a Grass PS22 Photostimulator 25cms. from the eyes. Direct viewing of the Photostimulator was maintained during all the recordings. The stimuli were presented binocularly and then monocularly to each eye. The unstimulated eye was carefully occluded.

Five hundred stimuli at high intensity (3939 nits) at a rate of 6/sec. were used (Harding and Rubinstein, 1980[8]) and a PDP8E computer averaged the response from each of 8 channels of the EEG recorded on an Elema Schonander machine. The analysis time was 100 m.secs. and the bandpass of the equipment was from 66 to 700Hz.

Results

Control ERG signals recorded with the GFE referred to the vertex revealed a mean 'a' wave latency of 14.82 m.secs. (± 1.16 m.secs.) and mean amplitude of 15.40uV. (±4.71uV.) and a mean 'b' wave latency of 37.36 m.secs. (± 1.85 m.secs.) and mean amplitude of 57.58uV. (± 16.67uV.). Two oscillatory potentials (OPs) were seen on the 'b' wave of the ERG in most subjects with mean latencies of 17.22 m.secs. (± 1.09 m.secs.) and 25.22 m.secs. (± 1.48 m.secs.).

The use of either an anterior neck or contralateral occipital reference site produced negligible effect on amplitude or latency of the ERG, indeed the anterior neck site produced increased myogenic artifact in the response, making the identification of OPs more difficult.

Amplitude and latency measurements of the waveforms derived from the various electrode sites were made manually and the mean values of the amplitude of any detectable ERG-type signal expressed as a percentage of the corneal ERG amplitude (Table 1).

The amplitude of the ERG response from skin electrodes was found to diminish acutely as distance from the eye increased and artifact became accentuated but latencies however remained almost identical to those of the GFE. The amplitude of the response from the lower lid was found to be the highest of the non-corneal sites, that of the 'a' wave being 26.8% and that of the 'b' wave being 31.16% of the control ERG signal.

Figure 2 illustrates the scalp and facial distribution of ERG - type signals in five subjects with various amplitudes of corneal ERG. As distance between the cornea and the recording electrode increased, the 'a' wave was abolished earlier than the 'b' wave as would be expected from their relative amplitudes. A remnant of the 'b' wave was however detectable in most subjects at almost all electrode sites, although often appearing as an extremely low amplitude deflection difficult to discern from myogenic artifact except by the superimposition of consecutive tracings. Similarly, the amplitude of the OPs reduced rapidly as the distance from the cornea increased.

Myogenic and lid-blink artifact varied between subjects and in some cases confounded the ERG signal at skin electrodes relatively close to the cornea. The extent of the field of activity produced was directly proportional to the amplitude of the corneal ERG (Figure 2), subject 5 demonstrating a wider distribution of ERG type signals than subject 2.

On binocular stimulation the response at sites N_z and FP_z was found to be twice that produced on monocular stimulation of either eye, and the response at FP_2 was around one and a half times the monocular response from the right eye, indicating interaction of the two monocular ERG fields. The response at LL was not enhanced on binocular stimulation nor was that at any other electrode site.

The results of simultaneous recording of corneal ERG and VESPs in the same five subjects are shown in Figure 3. Subjects 1, 2, 3 and 5 demonstrate well formed bilateral VESP components all with clear triphasic configurations. The latencies of the VESPs recorded in subjects 1, 2 and 3 are clearly unrelated to those of the ERG, but in subject 5 there is a closer relationship between the peak of the ERG 'b' wave and the final, positive peak of the VESP. The results from subject 4 are atypical. This is a subject from whom no VESP has ever been recorded despite repeated attempts on a number of occasions over a period of 14 months and the use of variations in electrode montage and stimulus parameters. A normal corneal ERG, however, was recorded in this subject, as was a visual evoked cortical potential (VECP) to both flash and pattern-reversal stimulation. No neurological or ophthalmological abnormality could be detected.

Later components were seen at certain electrode sites consisting, in 10 subjects, of a positive peak around 45-55 m.sec. latency. In 3 subjects a negative peak of latency around 60-70 m.secs. was also seen. The origin of these components was determined by comparison of response using the three reference sites. The positive component around 45-55 m.secs. was present on recordings from electrodes F_{12}, T_8, T_4 and M_2 when using C_z as a reference (Figure 2), but was absent when an anterior neck reference was used, although ERG topography remained the same. The use of O_1 as reference revealed similar responses to those obtained using the vertex site. This would suggest that the component may be surface negative around C_z, and therefore probably of cortical origin, possibly spreading from the occiput. In accordance with EEG convention, when the electrode connected to Grid 1 (in this case the "active" electrode) becomes electropositive in relation to the electrode connected to Grid 2 (in this case the "reference" electrode C_z), there will be a downwards deflection of the recording pen.

Thus, if C_z becomes relatively electronegative compared with the active electrode, a similar deflection will occur. Indeed, this component may well constitute the N_1 component of the visual evoked cortical potential, trials in our laboratory using flash stimulation showing that the N_1 component has a mean latency of 56.1 m.secs. (± 6.8 m.secs.).

The second atypical control subject was a 20 year old male who revealed markedly asymmetric ERG responses, the amplitude of that from the right eye being almost half that from the left eye, although the latencies were approximately the same, (Figure 4). The VESPs were however found to be of approximately equal amplitude and of similar latency, as were the initial VECP components detected using occipital electrodes. This was a consistent, repeatable asymmetry, which was not found to be due to the electrodes or recording technique and the subject on examination had visual acuities of 6/5 in both eyes, full visual fields and ophthalmoscopic examination was normal.

Two patients with distinct and discrete pathologies have also been examined. Case 1 was a 39 year old male who during a fall sustained a fracture of the left zygoma and orbit, with an associated left optic nerve injury. Vision in the left eye was reduced to no light perception and the optic disc was pale and atrophic. Electrophysiological assessment (Figure 5) revealed normal photopic ERGs from both eyes. Stimulation of the affected eye failed to elicit any consistent VESPs, and VECPs were also absent even when high intensity flash stimulation was used. These responses were of normal latency and amplitude from the unaffected eye, and despite the VECPs being of higher amplitude over the left occiput, there was no significant asymmetry in the monitoring EEG.

Case 2 was a 22 year old male who suffered a penetrating wound with a metallic intra-ocular foreign body in the left eye. Subsequent to its removal the retina detached, involving the macular area and reducing the vision to accurate projection of light. Electrophysiological assessment (Figure 6) revealed abolition of the ERG of the affected eye. VESPs were present bilaterally at normal latency and of normal amplitude for monocular stimulation and a VECP could be consistently recorded bilaterally using flash stimulation, although no response could be elicited using pattern-reversal stimulation of any check size. The VECPs from the affected eye were slightly delayed compared with those from the unaffected eye, although the VESPs were of compatible latency and amplitude.

Discussion

It is clear that the ERG signal produced under the same conditions used to elicit the VESP is distributed over a wide field around the orbit and this is in agreement with other authors (Nakamura, 1978[5]).

The measureable extent of the field of activity of the ERG is dependent partly on the amplitude of the corneal signal and partly on the degree of myogenic artifact present. The fields from either eye clearly overlap medially, but are separated by the nasal insulator. Since the interaction of the fields does not extend to the lower lid site, the recording of monocular responses without occlusion of the opposite eye is possible and this may be of value in the clinical situation.

At the more posterior sites used in this study, namely T_4 and T_6, any measureable remnant of the ERG 'b' wave takes the form of a small monophasic deflection generally much less than 1 microvolt in amplitude, dependent on corneal ERG amplitude. The VESP however assumes a triphasic P-N-P configuration and its peak to peak amplitudes are of the order of 1.5uV. and 2.5uV. respectively.

The subject (Figure 2, No.4.) from whom VESP signals could not be recorded is unusual and is one of 3 out of 60 seen in our laboratory, all being neurologically normal. The ERG from the cornea is of equally high amplitude when compared with other subjects, scalp and facial distribution of the ERG-type response also being similar to other subjects.

The existence of amplitude asymmetries of ERG and VEP is well known (Armington, 1974[11]; Kooi, 1979[12]; Harmony, Ricardo, Otero, Fernandez, Llorente and Valdes, 1973[13]), but the co-existence of an almost 50% asymmetry in ERG with symmetrical VESP and VECP must indicate independence of the respective evoked potentials.

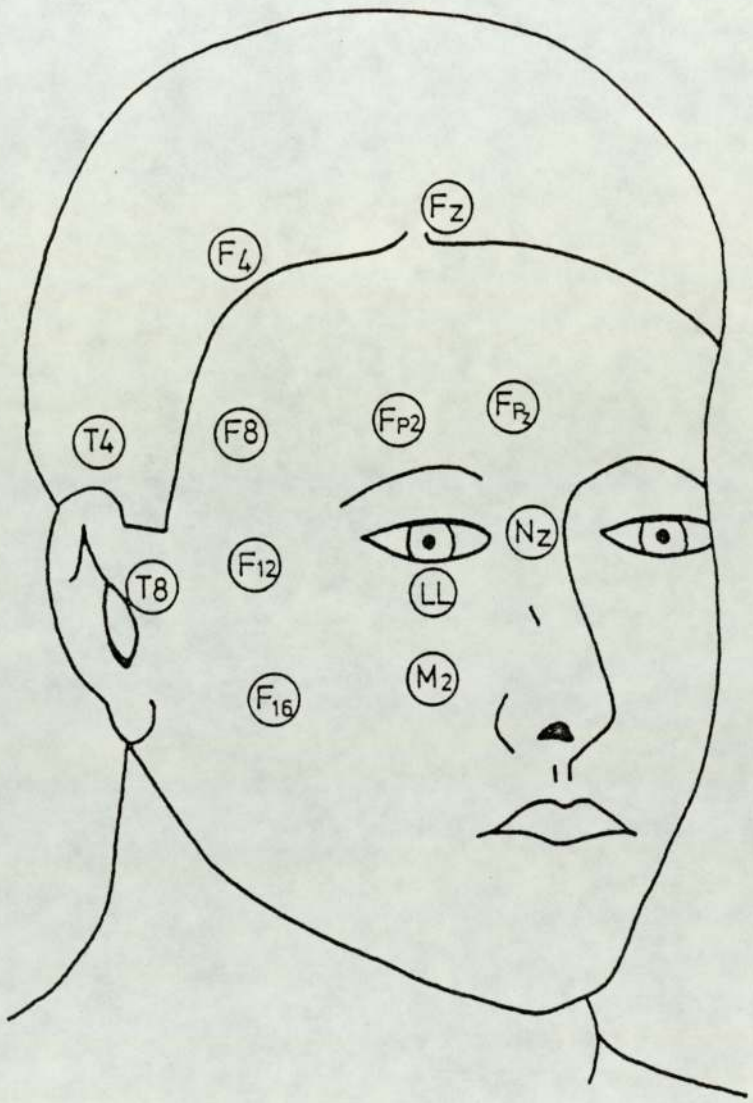
The results obtained from the two patients reported demonstrate that in Case 1 due to unilateral optic nerve trauma despite the survival of an ERG of normal amplitude and latency from the affected eye, the VESP and VECP are absent. Case 2 shows that extinction of the ERG in one eye due to retinal detachment can co-exist with bilateral survival of both VESP and VECP from the same eye.

Cobb and Morton (1952[14]), noted an early component of the occipital response to high intensity flashes and excluded direct spread of the retinal potential over the scalp, but did not discount spread across the base of the brain. Cobb and Dawson (1960[2]) using a bipolar recording technique reported early components of the occipital response beginning 20-25 m.secs. after stimulation and on comparison with a simultaneously recorded ERG suggested these components were unrelated to current spread from the ERG, although from their illustration the location of the signal appears more anterior than the occiput.

Monnier (1946[15]) observed that a negative wave resembling the ERG 'c' wave could be recorded from the non-illuminated eye in response to light stimulation of the contralateral eye and the activity of the efferent centrifugal pathway of the optic nerve was regarded as its origin. Horsten, Wildboer-Venema and Winkelman (1961[16]) showed in cats and in one patient that when one eye was enucleated and replaced with a saline-soaked gauze pad an inverted complete ERG signal could be recorded from the socket when the intact eye was very strongly illuminated. These findings were also reported in cats after transection of the optic nerve or coagulation of the chiasma, and it was concluded that this transmission of signals did not take place via the nervous pathway, but by direct electrical spread via the surrounding tissues. Similar results were reported in cats by Yonemura, Strzyzewski and Jacobson (1965[17]). Honda (1977[7]) described the recording of high frequency wavelets in the region of the lateral canthus whilst the eye was rotated nasally, and postulated their origin was probably the optic nerve. Siegfreid (1979[18]) reported similar findings of possible optic nerve potentials around the temple and discounted passive conduction of the ERG at this site.

The distinct difference in morphology between the VESP and the ERG 'b' wave remnant recordable at the temporal sites described and the relative disparity in amplitudes strongly suggests that the VESP is not attributable to a volume conducted ERG response.

In conclusion, on the basis of the evidence of the present topographical study; the co-existence of intact ERG and extinct VESP and vice versa in pathological states; the results presented of atypical control subjects; and the effect of monocular versus binocular stimulation on the VESP (Harding and Rubinstein, 1980[8]); we suggest that the VESP and ERG are distinct and unrelated electrophysiological phenomena.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M2
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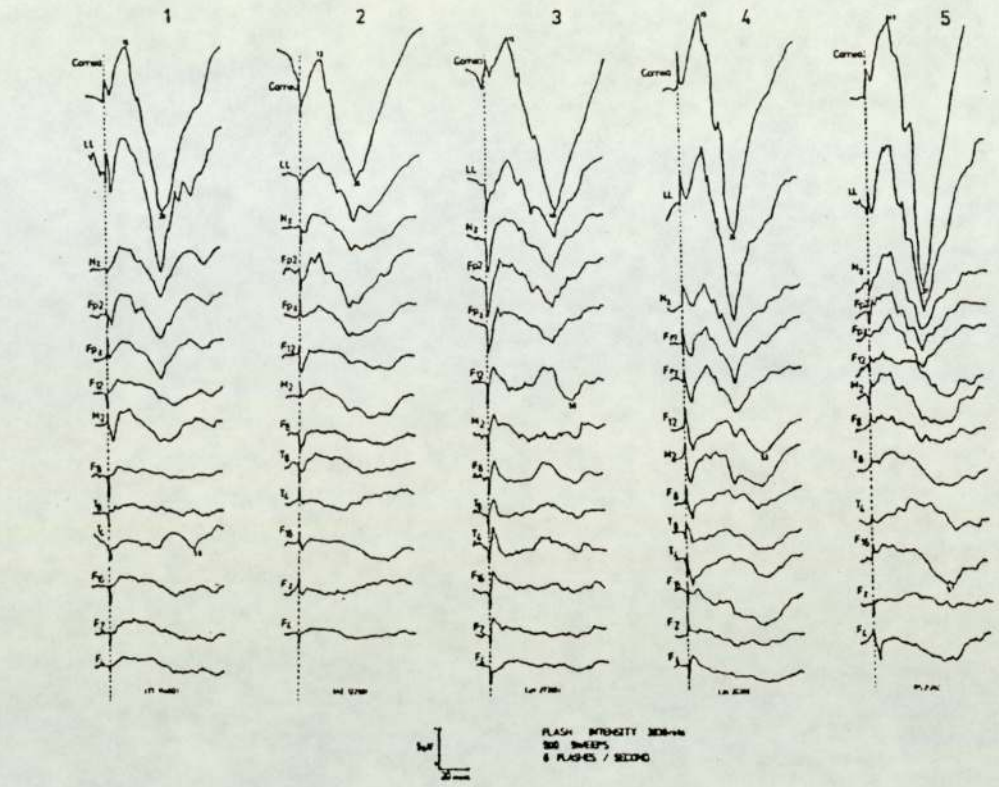
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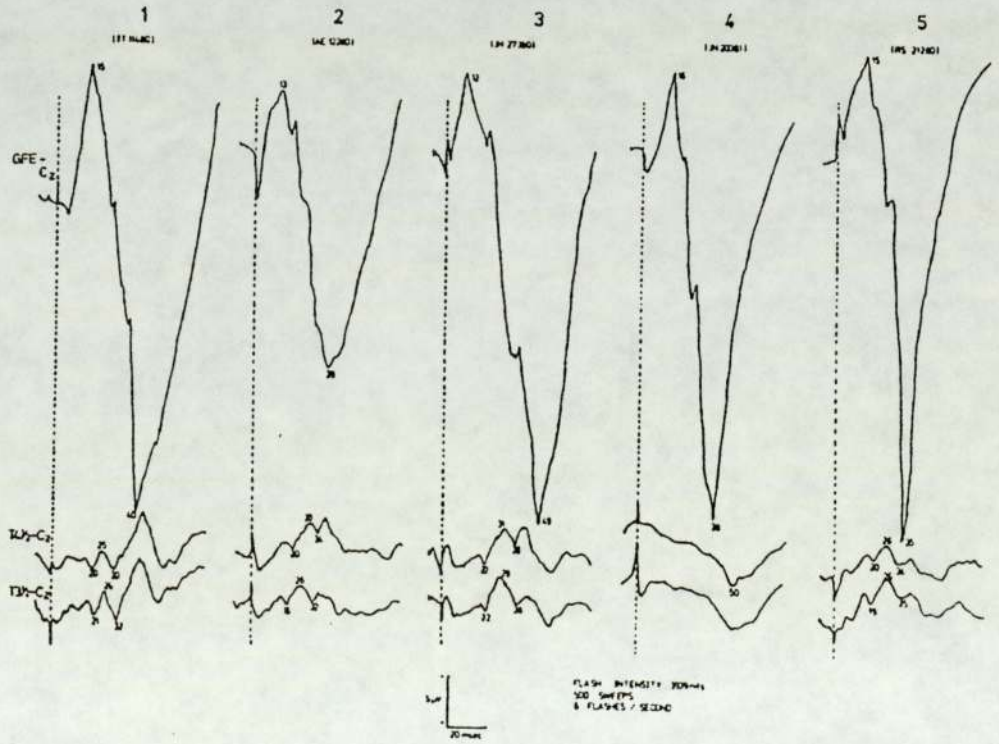
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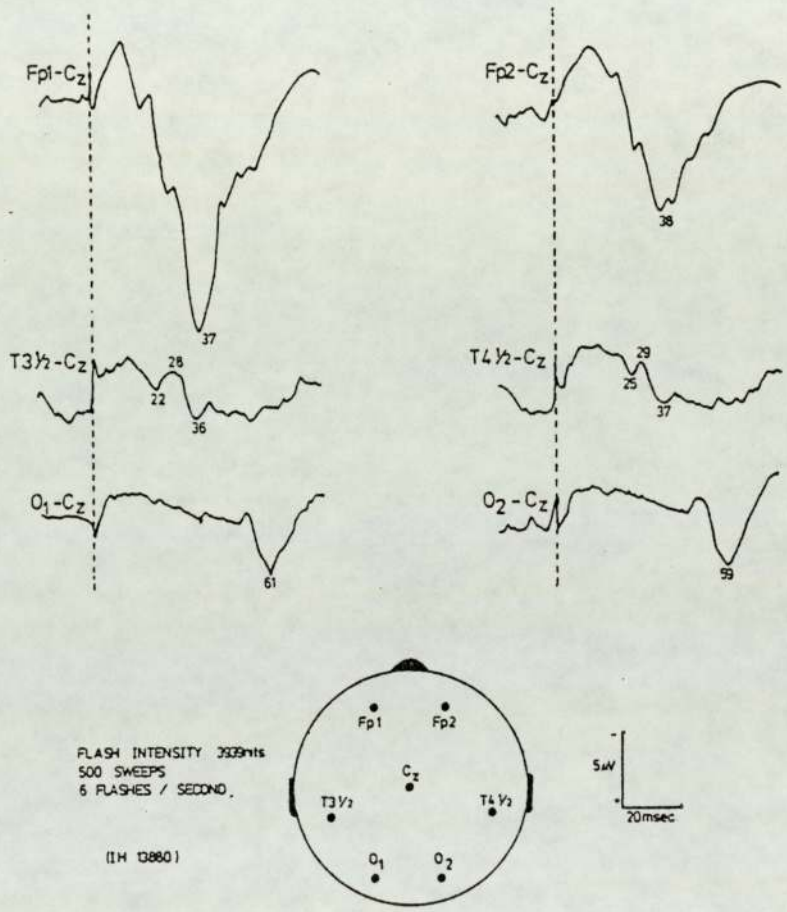
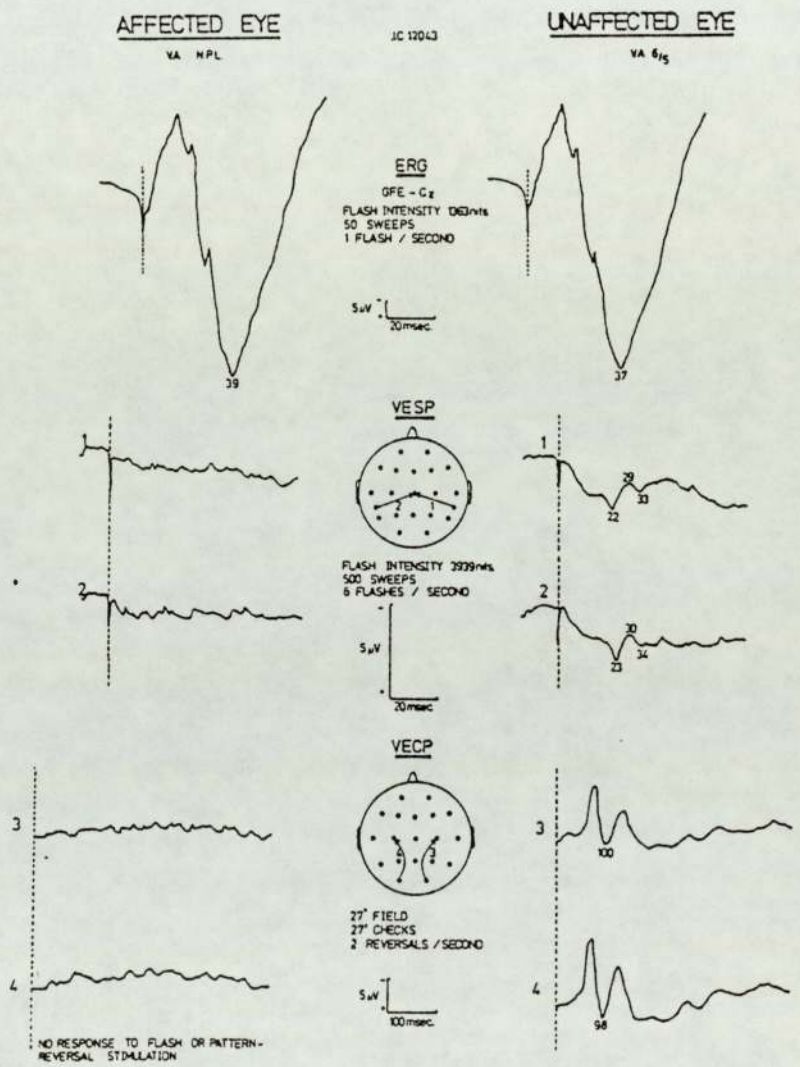
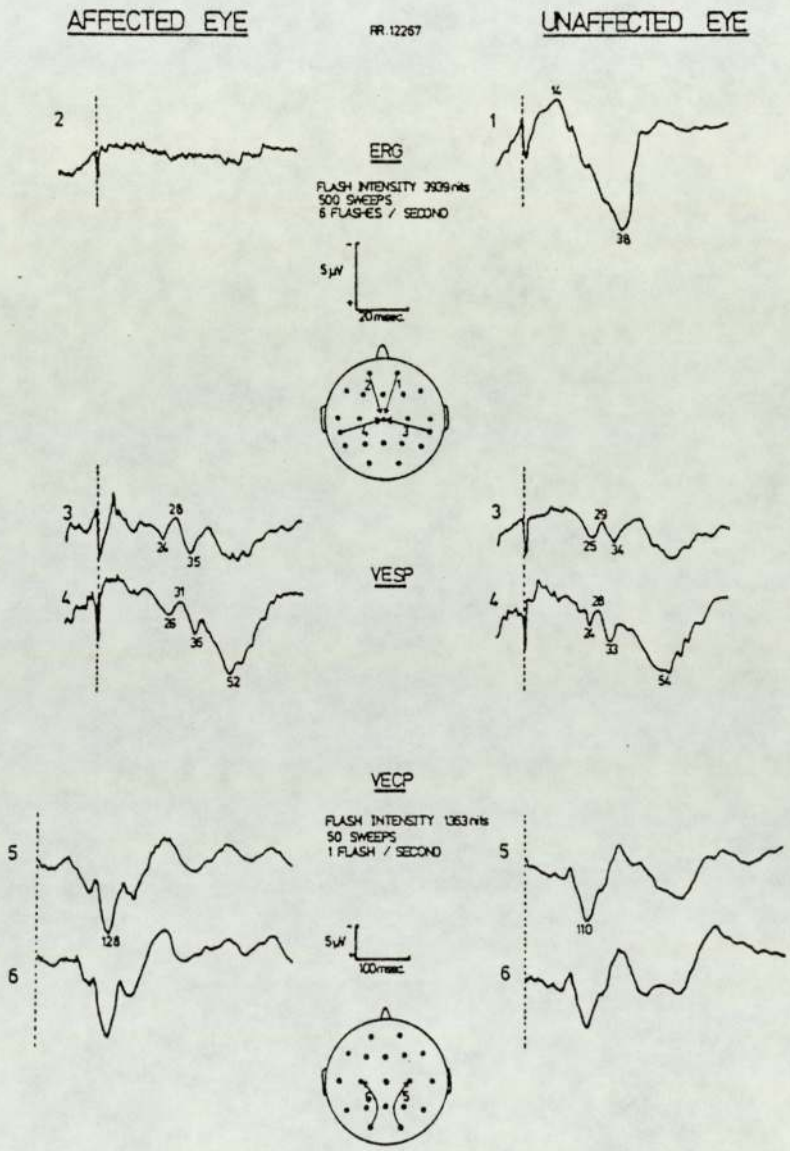
FLASH INTENSITY
SWEEPS
FLASHES / SECOND

	'a' WAVE			'b' WAVE		
ELECTRODE SITE	LATENCY (m.sec)	AMPLITUDE (uV)	% CONTROL AMPLITUDE	LATENCY (m.sec)	AMPLITUDE (uV)	% CONTROL AMPLITUDE
CORNEA	14 ± 1.16	15.40 ± 4.71	100	37.36 ± 1.85	57.58 ± 16.67	100
LL	18.83 ± 1.46	4.13 ± 3.20	26.8	37 ± 3.45	17.94 ± 12.8	31.16
N_z	12.75 ± 2.38	1.75 ± 0.55	11.38	33.75 ± 2.82	9.69 ± 5.36	16.82
Fp_2	12.75 ± 4.41	1.11 ± 0.63	7.21	35.83 ± 2.3	6.88 ± 2.66	11.96
Fp_z	11.5 ± 5.37	1.12 ± 0.71	7.27	35.66 ± 2.74	5.85 ± 1.78	10.16
F_{12}	-	-	-	36.62 ± 3.61	1.27 ± 1.31	2.20
M_2	14.5 ± 1.25	0.36 ± 0.44	2.32	35.9 ± 2.54	4.91 ± 3.80	8.53
F8	12.1 ± 2.4	0.05 ± 0.19	0.37	36.67 ± 1.79	1.54 ± 1.85	2.67
T8	-	-	-	36.8 ± 2.13	0.58 ± 0.86	1.01
T4	-	-	-	35.25 ± 2.38	0.35 ± 0.54	0.60
F16	-	-	-	34.2 ± 0.74	1.07 ± 1.27	1.87
F_z	-	-	-	-	-	-
F4	-	-	-	36.4 ± 3.25	0.4 ± 0.95	0.69


Fp1-Cz
37
Fp2-Cz
38
T3½-Cz
28
22
36
T4½-Cz
29
25
37
O1-Cz
61
O2-Cz
59
FLASH INTENSITY 3939nits
500 SWEEPS
6 FLASHES / SECOND.
(IH 13860)
Fp1
Fp2
Cz
T3½
T4½
O1
O2
5uV
20msec


AFFECTED EYE
VA HPL
JC 12043
UNAFFECTED EYE
VA 6/5
ERG
GFE - Cz
FLASH INTENSITY 1063mrls
50 SWEEPS
1 FLASH / SECOND
5μV
20msec.
39
37
VESP
FLASH INTENSITY 2939mrls
500 SWEEPS
6 FLASHES / SECOND
5μV
20msec
1
2
29
30
22
30
34
23
VECP
27' FIELD
27' CHECKS
2 REVERSALS / SECOND
5μV
100msec
3
4
100
98
NO RESPONSE TO FLASH OR PATTERN-REVERSAL STIMULATION


AFFECTED EYE
RR 12267
UNAFFECTED EYE
2
ERG
FLASH INTENSITY 3909 mls
500 SWEEPS
6 FLASHES / SECOND
5 µV
20 msec
1
38
3
28
24
35
4
31
26
36
52
VESP
3
29
25
34
4
28
24
33
54
VECP
FLASH INTENSITY 1363 mls
50 SWEEPS
1 FLASH / SECOND
5
128
6
5 µV
100 msec
5
110
6

LEGENDS

TABLE 1 Mean amplitude and latency measurements of ERG-type waveforms derived from the various electrode sites (all referred to the vertex, C_z) during monocular stimulation of the right eye of 12 subjects. Amplitude value of any detectable 'a' and 'b' wave remnant is expressed as a percentage of the corneal ERG amplitude. Latency of components remains remarkably constant, but amplitude diminishes acutely at non-corneal sites in proportion to the cornea-electrode distance. 'a' wave remnants are abolished at electrodes relatively close to the cornea, but a vestigial, low amplitude 'b' wave remnant is present at most electrode sites.
A dash (-) indicates no measureable response.

FIGURE 1 Facial and scalp electrode sites used in the topographical study of the ERG. Standard 10/20 system sites being FP_z, F_z, FP_2, F_8, F_4, T_4. Additional electrodes at N_2, F_{12}, T_8 (being 10% lower than FP_z, F_8, T_4 respectively, and at M_2 and F_{16}) being 20% lower than FP_2 and F_8 respectively).

FIGURE 2 Scalp and facial distribution of ERG-type signals in five subjects. Note that the corneal signal is recorded with a Gold-foil electrode at half the gain of all other channels. All electrodes are referred to the vertex and recordings made in accordance with EEG convention, positive at Grid 1 downwards. All subjects show similar distributions of signals the extent of the field being in direct proportion to the amplitude of the corneal signal. At temporal sites T_4 and T_8 a very low amplitude 'b' wave remnant is seen in some cases.

FIGURE 3 Simultaneous recording of corneal ERG and the VESP in the same five subjects. Subjects 1, 2, 3 and 5 demonstrate well formed VESPs bilaterally. Subject 4 is atypical - although being neurologically normal repeated attempts to record VESPs have been unsuccessful, although normal ERG signal was present.

FIGURE 4 Recordings in a normal control subject showed ERG signals recorded from electrode sites FP_1 and FP_2 to be consistently asymmetrical, that from the right eye being of almost half the amplitude of that from the left eye. However, simultaneously recorded VESPs recorded at electrodes ($T_{3\frac{1}{2}}$ and $T_{4\frac{1}{2}}$) were of almost identical amplitudes. The early components of the occipital response (recorded at electrodes O_1 and O_2) were also symmetrical.

FIGURE 5 Recordin gs from a 39 year old male who sustained a left optic nerve injury. Normal photopic ERGs were recorded from either eye, but stimulation of the affected eye failed to reveal any consistent VESP or VECP. Recordings of VESP and VECP from the unaffected eye were normal.

FIGURE 6 Recordings from a 22 year old male with retinal detachment of the left eye following a penetrating injury. The ERG from the affected eye was totally extinguished, VESP and VECP (to flash stimulation) being present bilaterally, although no VECP could be elicited from the affected eye using pattern-reversal stimulation. Recordings of ERG, VESP and VECP from the unaffected eye were normal.

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EEG and Clinical Neurophysiology.
International Congress Series 526:464-474
Excerpta Medica, Amsterdam.

COMPONENTS OF THE VISUALLY EVOKED SUBCORTICAL POTENTIAL (VESP) TO FLASH STIMULATION IN MAN

G.F.A. Harding and M.P. Rubinstein

Neuropsychology Unit, Department of Ophthalmic Optics, University of Aston in Birmingham, Birminghom, U.K.

The early components of the visual evoked potential, that is components before 50 msec latency, are poorly documented due to their minute amplitude, inter-subject variability, and poor repeatability under the standardized experimental conditions used for eliciting the visual evoked cortical potential (1). The earliest description of a short latency visual evoked potential was that of Van Hasselt (2), who recorded a potential occurring at 10 msec latency, of maximal amplitude around the ear and mastoid and only obtainable in four out of ten subjects. He concluded that this potential arose from structures peripheral to the optic chiasma since it was only clearly recorded ipsilaterally to the stimulated eye, and suggested that since the latency was longer than the "a" wave of the ERG, it was probable that the potential arose from the optic nerve. Cracco and Cracco (3), described early oscillatory potentials at around 100 Hz recorded from a wide scalp distribution of electrodes referred to the earlobes. These components, had latencies between 9 and 24 msec and were of maximal amplitude in the midline and parasagittal recording locations. They suggested that on the basis of present information the potentials probably ranged from those originating in the ERG and optic nerve, to additional potentials arising in the lateral geniculate body, optic radiation or the cortex.

In 1978 we identified a triphasic complex recorded by farfield techniques and consisting of a positive peak at 22 msec, negative at 27 msec and a positive at 35 msec latency (4). It appeared important to delineate this component from both the scalp recorded ERG and its oscillatory potentials, and also from the visually evoked cortical potential (VECP).

MATERIAL AND METHODS

The studies were made on 20 normal young volunteers, age range 19-38 years. All the subjects had visual acuities of 6/6 or better. They were seated in a dimly-lit room and flash stimulation was delivered using a Grass PS 22 Photostimulator placed 25 cm from the eyes. High intensity stimulation was given, the luminance being 3939 cd/m^2. The signals were recorded on an Elema Schonander EEG ma-

chine and averaging was performed by a PDP8E computer simultaneously on 8 channels of the EEG.

The computer averaged the responses to 500 stimuli presented at a rate of 6/sec. The analysis time of the computer was 100 msec and the band pass filtering was from 66 to 700 Hz. Since the photostimulator produced an audible click, control trials were always included with white noise delivered through ear-phones and with the lamp occluded.

Initial investigation of commonly used cephalic reference sites revealed that any site anterior to the vertex was markedly contaminated by the flash-evoked ERG and its oscillatory potentials, and that both the earlobe and mastoid were highly active at latencies around 20-40 msec. Locations posterior to the vertex were affected by VECP but it was found that the vertex electrode C_z was relatively inactive at these early latencies and also had the added advantage, as a common reference, that it was equidistant from all electrodes placed in an anterior-posterior temporal chain. Since in studies of the transverse topography of the VESP the C_z electrode would not be equidistant from all active electrode sites, an anterior neck reference was used as further comparator.

For the study of the anterior-posterior distribution of the potential a series of electrodes were placed according to the international 10/20 system at FP_z, F_8, T_4, T_6 and O_z (5). Additional half-distance electrodes were placed at $F_{8.5}$ and $T_{4.5}$ (Fig.1).

In the study of the transverse distribution, electrodes were placed at C_4, T_4, T_8 and additional half-distance electrodes at C_6, CP_4, $T_{4.5}$ and $T_{8.5}$ (Fig.1). Silver-silver chloride electrodes were fixed with collodion and resistence maintained below 5 K Ω.

RESULTS

In the anterior-posterior topographic study the midfrontal ERG (which was recorded inverted to follow normal EEG conventions) from electrode FP_z was found to be conducted posteriorly along the scalp and recordable at electrodes as posterior as the rolandic and sylvian fissures (Fig.2). However, its amplitude gradually diminished in a posterior direction until this site was relatively inactive compared to the reference. At a point just posterior to this region, a clear potential was observed which was of maximal amplitude at electrode $T_{4.5}$, immediately behind the ear, and gradually decreased in amplitude posteriorly. This VESP consisted of a triphasic wave the mean latencies of which were: positive 20.55±2.06 msec, negative 26.83±2.28 msec, positive 34.22±1.73 msec. The mean amplitude of the wave, measured peak to peak, were positive to negative 1.53±0.71μV; negative to positive 2.41±1.02μV. The response was recordable in 18 of the 20 subjects.

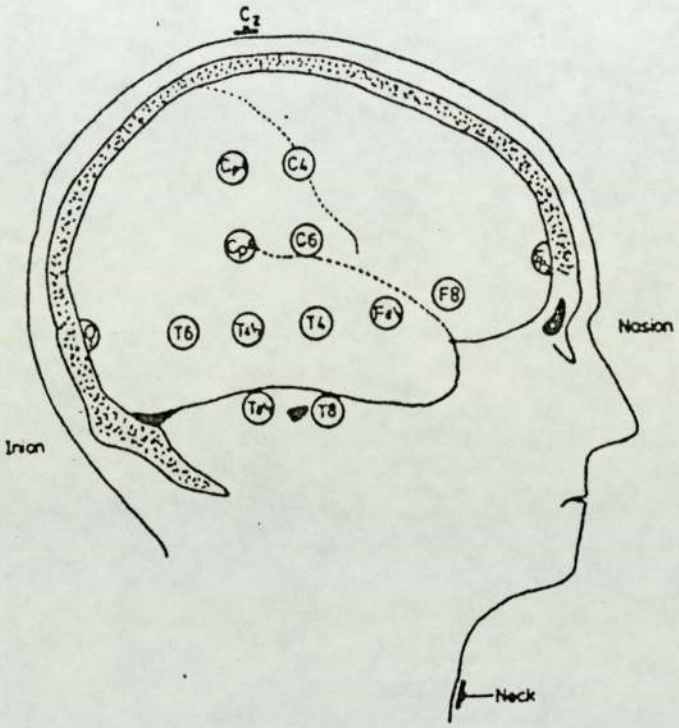

Figure 1. Location of electrodes used in the topographical studies of the visual evoked sub-cortical potentials (VESPs). Most of the electrodes are denominated by the standard international 10/20 system. Additional half-distance electrodes are indicated at electrodes $F_{8.5}$ (midway between F_8 and T_4) and $T_{4.5}$ (midway between T_4 and T_6) for the posterior study. For the transverse study additional electrodes were placed at CP_4 midway between C_4 and P_4, CP_6, and $T_{4.5}$. Electrode T_8 is placed below T_4 at 10% of the distance between the cochas. Electrode $T_{8.5}$ is level with this electrode and below $T_{4.5}$.

In the transverse topographical study the amplitude of the VESP was found to be maximal at sites below the temporal electrode chain and at a point level with and behind the pinna, i.e. around the mastoid process (Fig.3). This finding was irrespective of whether the vertex or anterior neck reference site was used and so the amplitude distribution could not be explained on the basis of dis-

tance between the active electrode and the reference.

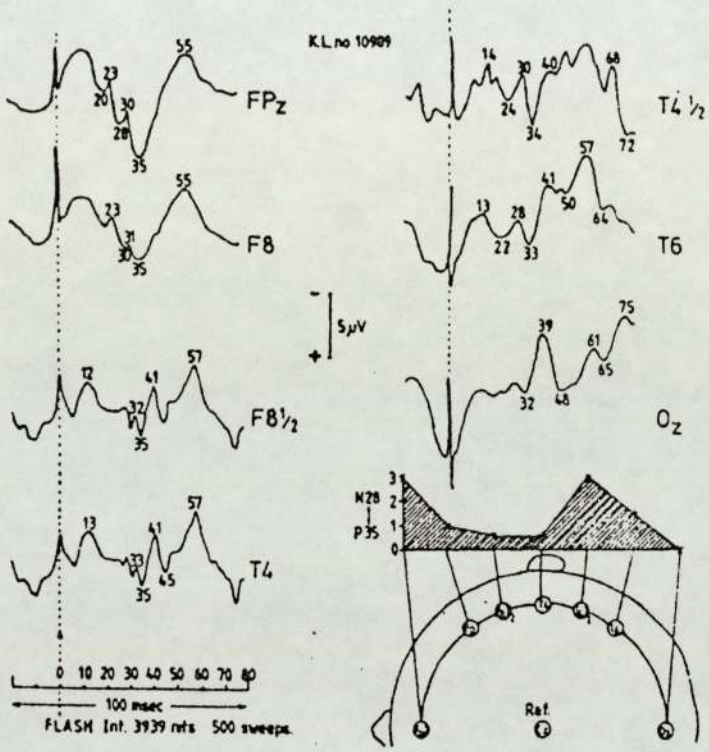

Figure 2. Distribution of potentials recorded from an anterior-posterior chain of electrodes from frontal to occipital pole all referred to the vertex C_z. The activity at FP_z is dominated by the inverted ERG and its oscillatory potentials and subsequent posterior sites show the decreasing amplitude of these components. At $T_{4,5}$ however, the VESP consisting of a positive 24, negative 30, positive 34, triphasic wave appears. This component reduces in amplitude at more posterior sites and almost disappears at the occiput which shows the negative 39, positive 48 components of the visual evoked cortical potential. The flash artifact is clearly shown at 0 msec. The amplitude topogram of potentials between 28 and 30 msec is shown alongside the head.

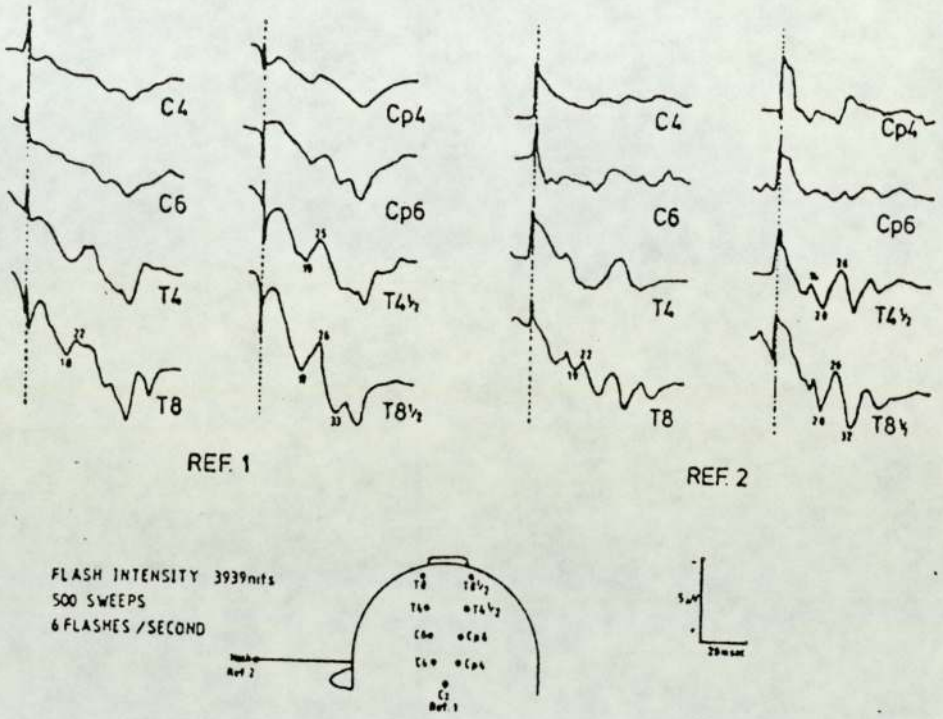

Figure 3. Topographic distribution of VESP recorded in transverse chains of electrodes all referred to either the vertex (Reference 1) or to an anterior neck site (Reference 2). Whichever reference is used the VESP is clearly seen as a positive 19, negative 26, positive 33 component maximal around $T_{4.5}$ and $T_{8.5}$, that is, at about the mastoid.

When the sound of the click of the photostimulator was masked by white noise delivered to the ear-phones an identical potential was recorded and no potential of similar latency was recordable when the lamp was occluded.

In one of our subjects the ERG was markedly asymmetric. This finding was entirely reliable and consistent but was not correlated with any detectable retinal abnormality. If the VESPs were related to the ERG and its oscillatory potentials, one would expect the VESPs to be of lower amplitude, ipsilateral to the reduced ERG. It can be seen from Figure 4, that although the ERG was clearly

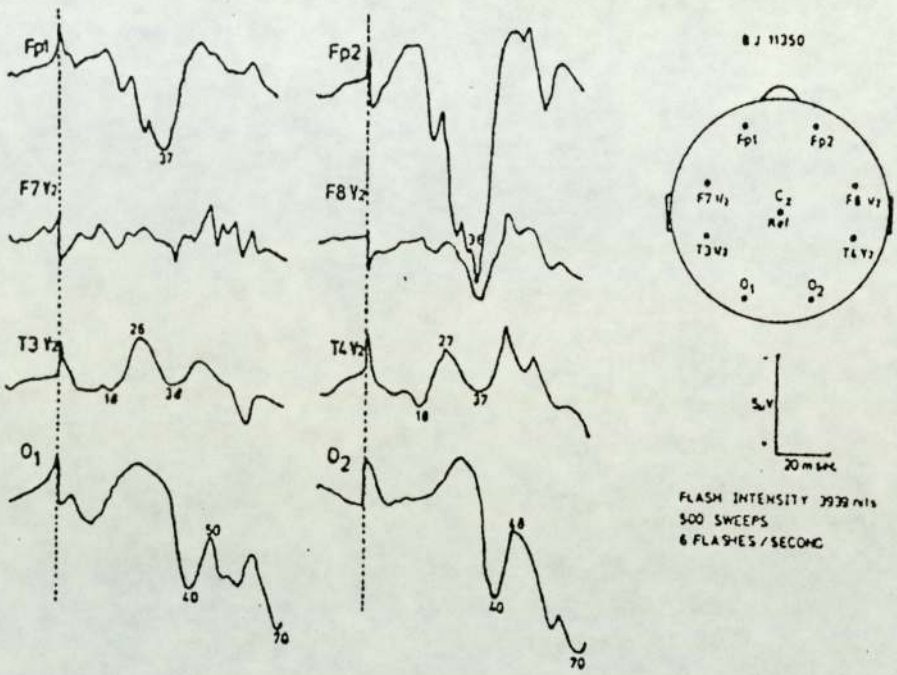

Figure 4. Scalp recorded ERG and the VESP in a subject with a nonpathological asymmetry of the ERG. Although the scalp recorded ERG is markedly reduced at the left frontal pole (FP_1) compared to the right (FP_2), the VESP consisting of positive 18, negative 26, positive 38, triphasic wave is of equal amplitude at electrodes $T_{3.5}$ (left) and $T_{4.5}$ (right).

reduced on the left in this subject and scarcely spread posteriorly along the scalp at all, a clear VESP was obtained on this side. It was of equal amplitude to the potential recorded on the right, i.e. the side with the normal amplitude ERG.

This finding indicated that this wave was independent of the ERG, and since its latencies did not coincide with those of the VECP and its topographical location did not suggest that it was arising from the visual cortex, it appeared that this component was possibly of postchiasmatic subcortical origin.

To clarify whether this component arose from the optic nerve or a postchiasmatic site we compared the response to binocular and monocular stimulation. On monocular stimulation, (Fig.5) the scalp recorded ERG was

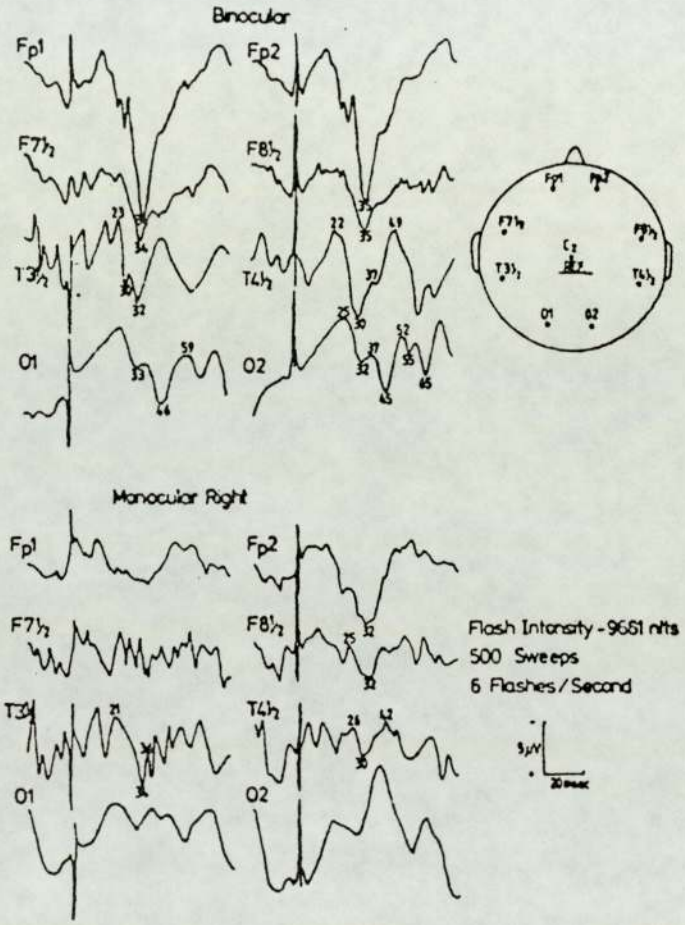

Figure 5. Potentials recorded to binocular flash stimulation are shown in the upper traces. The VESP can be seen as a negative 22, positive 30, potential recorded bilaterally at electrodes $T_{3.5}$ and $T_{4.5}$. The scalp recorded ERG and its oscillatory potentials are seen at FP_1 and FP_2. When monocular stimulation is given to the right eye only the ERG is clearly reduced from the left frontal pole (FP_1) but the VESP seen at $T_{3.5}$ on the left is equal or greater than that seen at $T_{4.5}$ on the right, and the amplitude of the potentials tends to be bilaterally reduced from that obtained by binocular stimulation.

clearly reduced on the side ipsilateral to the occluded eye. If the VESP arose from the optic nerve, this component should also be reduced ipsilaterally to the occluded eye. However, if the component arose from post-chiasmatic sites it would tend to be reduced bilaterally. This latter finding was consistently obtained in each subject and bilateral reduction observed, irrespective of which eye was occluded.

We have only recently begun to study patients with lesions of the visual pathway using these techniques. A recent patient presented with a right homonymous hemianopia, following a brain stem vascular disturbance of the basilar and posterior cerebral arteries. The patient was fully conscious and dysarthric. There was a clear right homonymous hemianopia, horizontal nystagmus on lateral gaze to either side, and a mild right sided facial weakness.

There was bilateral ataxia of all four limbs, more evident on the right than on the left, the tendon reflexes were brisk and the plantars were flexor. CAT Scan showed global atrophy involving the left cerebral hemisphere and also the cerebellum. The VECP as recorded by our standard technique (6), showed some reduction in amplitude, contralateral to the field defect (Fig.6). The VESP was clearly reduced on the side contralateral to the field defect and this reduction was even more marked than the reduction in the VECP (Fig.7). This finding would be entirely consistent with the clinical history.

DISCUSSION

The VESP elicited under our standardized conditions appears to be a relatively stable phenomenon in 90% of normal subjects. The potential is of low amplitude but of relatively consistent latency and indeed the test-retest reliability over periods of days or weeks is good, the P_{34} wave only varying by a mean difference of 0.2 msec.

The topographical distribution of the component indicates that it is maximal around the mastoid process and indeed it may constitute the explanation for some of the so-called early components of the VECP where this site was used as an "inactive" reference (3,7-10). Other authors agree that the mastoid process is highly active for early components (2,11).

Previous studies have neglected the confounding nature of the scalp recorded ERG and the oscillatory potentials. Indeed illustrations of other authors (3) appear to show oscillating potentials derived from filtering the ERG with short time constants. In our search for a non-active cephalic reference, we noted that the ERG could easily be recorded at both, the tip of the nose and chin. Since the VESP, as described in this paper, is

unrelated to the amplitude of the ERG and its oscillatory potentials, it is unlikely that it arises from this source. Equally since it does not reduce ipsilaterally to an occluded eye it is unlikely to arise from an optic nerve site and must be postchiasmatic. The most likely explanation is that this potential arises from a thalamic or optic radiation site and such an origin would be entirely consistent with all our findings.

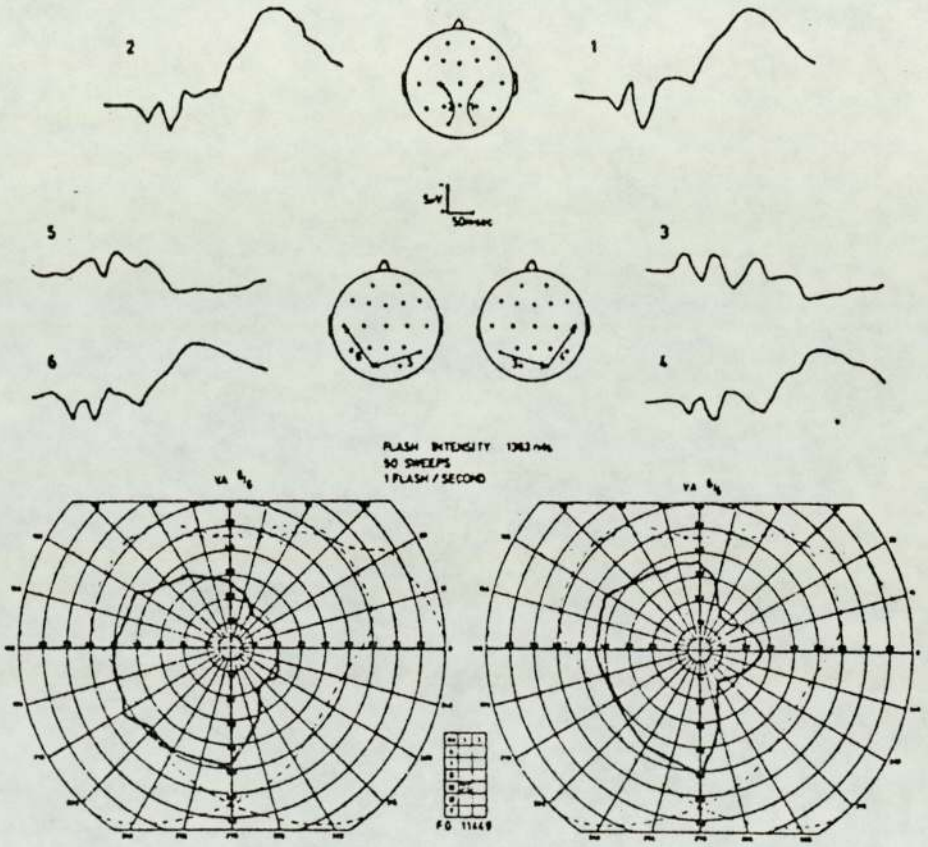

Figure 6. Visual fields and visual evoked cortical potential in a patient with a right homonymous hemianopia. It can be seen that the components from the left occiput (channel 2) are slightly reduced, particularly the earlier components, when compared to the right occiput (channel 1). Phase reversal is seen slightly better at the right occiput (channels 3 and 4) than at the left occiput (channels 5 and 6).

It is possible that this technique may supplement the ERG and the VECP in electrodiagnosis of lesions of the visual pathway.

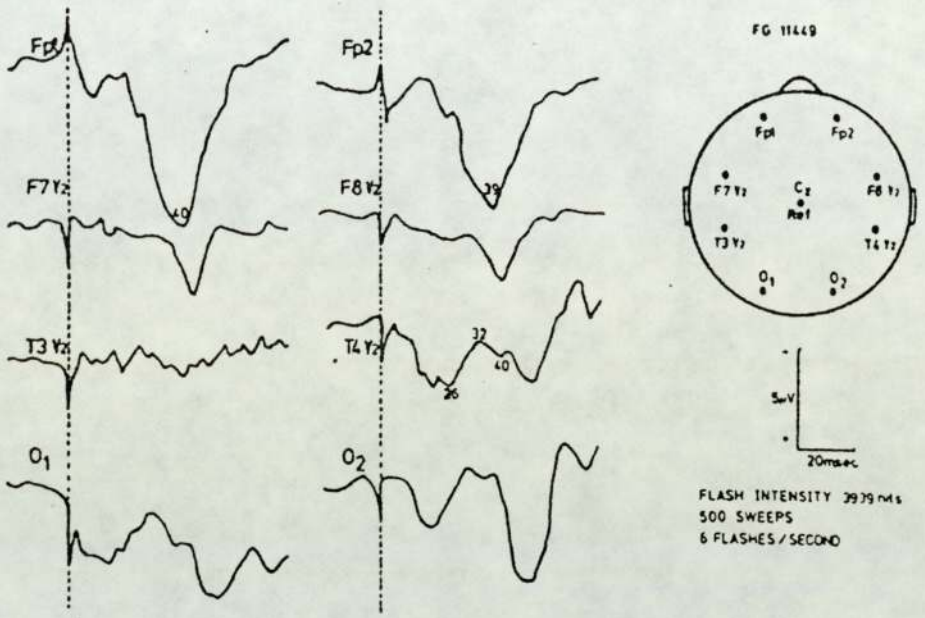

Figure 7. VESP results in the same patient as in Fig.6. Although the ERG is seen bilaterally at FP_1 and FP_2, the VESP is only seen unilaterally as a positive 26, negative 32, positive 40 msec triphasic wave on the right ($T_{4.5}$). Only a vague outline of the response can be seen on the left ($T_{3.5}$) which is the side contralateral to the hemianopia.

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ACKNOWLEDGEMENTS

We are grateful to Dr.M. Anderson for allowing us to study his patients. Miss K. Lyons provided expert technical assistance and Mrs. A. Davies typed the manuscript. We are grateful for the support of the Medical Research Council and the West Midland Regional Health Authority and for the helpful suggestions and encouragement of Mr. N. Drasdo.

Electroenceph. Clin. Neurophysiol. (1980)
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14. The "visually evoked subcortical potential" to flash stimulation in man. — G.F.A. Harding and M.P. Rubinstein (Birmingham)

Early components (before 50 msec) of the VEP have previously received little attention due to their minute amplitude, inter-subject variability and poor repeatability under the generally established clinical situation for recording the cortical potential. In our study, stimulus and analysis parameters have been adjusted to provide optimum conditions for producing and recording these components: large numbers of high intensity flashes are delivered at a fast rate and instrument/computer settings are altered accordingly.

A composite triphasic wave of mean latency P23-N28-P34 has been recorded in 90% of subjects from an electrode slightly posterior to the Rolandic fissure, topographic studies revealing this normally to be maximal at electrodes midway between T3 and T5, and T4 and T6 respectively, when referred to either vertex (C_z) or non-cephalic common reference sites.

Simultaneous recording of a lid electroretinogram and occipital Visual Evoked Cortical Potential has shown a spread of the ERG backwards along the scalp and the VECP forwards, but that these components are independent of these sources and presumably generated at a subcortical site. We have termed these components "visually evoked subcortical potentials".

Monocular stimulation has shown abolition of the ERG ipsilateral to the occluded eye but bilateral reduction of the amplitude of the VESP, indicating that the wave is independent of the ERG and optic nerve and must be arising from a post-chiasmal site. The findings in relation to patients with visual lesions will also be discussed.

EARLY COMPONENTS OF THE VISUAL EVOKED POTENTIAL IN MAN

Are they of sub-cortical origin?

G.F.A. HARDING & M.P. RUBINSTEIN
(Birmingham, England)

ABSTRACT

Stimulus and analysis parameters have been adjusted to provide optimum conditions for producing and recording the early components of the flash VEPs. A visual evoked potential of mean latency P20-N26-P34 has been recorded in 93% of normal subjects maximally from an electrode position slightly posterior to the Rolandic/Sylvian fissure and around the upper mastoid process.

This potential is topographically separated from the lid ERG and the occipital VECP. Monocular stimulation shows abolition of the ERG ipsilateral to occlusion but bilateral reduction of the amplitude of the P20-N26-P34 potential, indicating that the wave is independent of the ERG and optic nerve and must be arising from a post-chiasmal site.

Patients with homonymous hemianopia of both cortical and subcortical origin, and bitemporal hemianopia have been studied and the results obtained are consistent with potentials arising from a post-chiasmal but infra-cortical site. In view of these results and those of the topographical studies indicating a non-retinal and non-optic nerve origin we have entitled these components 'visual evoked subcortical potentials' (VESPs).

INTRODUCTION

The early components of the visual evoked potential, that is components before 50 milliseconds latency, are poorly documented due to their minute amplitude, inter-subject variability and poor repeatability under the standardised experimental conditions used for eliciting the visual evoked cortical potential. (Desmedt 1977).

Surprisingly, early components of the visual evoked potential are often mentioned by early evoked potential workers and can often be seen in their early crude averaged records. Cobb and Morton (1952), Ciganek (1961) and Cobb and Dawson (1960) all show these low amplitude components. These early workers all used high intensity flash stimuli and the reduction in use of this technique may explain the loss of interest in early components.

The earliest specific description of a short latency visual evoked potential

Doc. Ophthal. Proc. Series, Vol. 27, ed. by H. Spekreijse & P.A. Apkarian

was that of Van Hasselt (1972), who recorded a potential occurring at 10 milliseconds latency of maximal amplitude around the ear and mastoid and only obtainable in four out of ten subjects. He concluded that this potential arose from structures peripheral to the optic chiasma since it was only clearly recorded ipsilateral to the stimulated eye, and suggested that since the latency was longer than the 'a' wave of the ERG, it was probable that the potential arose from the optic nerve.

Cracco and Cracco (1978) recently described oscillatory potentials at around 100 cycles per second recorded from a wide scalp distribution of electrodes all referred to the ear-lobes. These components had latencies between 9–24 milliseconds and were of maximal amplitude in the mid-line and parasaggital recording locations. They suggested that on the basis of present information the potentials probably ranged from those originating in the ERG and optic nerve, to additional potentials arising in the lateral geniculate body, optic radiation or the cortex.

The possibility that some of the early components of the visual evoked potential were of sub-cortical origin first attracted us in 1978. Our work on the auditory evoked brain stem potentials convinced us of the possibility of recording visually evoked sub-cortical potentials by far-field techniques.

In 1978 a pilot study was carried out on a small group of normal volunteer controls. By increasing the number of responses averaged to bright stroboscopic flashes by multi-channel recording from a variety of cephalic sites we eventually identified a small, less than 3 microvolt complex, recorded by far-field techniques. This complex consisted of a positive wave at 22 milliseconds, a negative at 27 milliseconds and a positive wave at 35 milliseconds (Harding 1979) and appeared to be located around the mid-temporal region. It was essential to topographically define this component and to demonstrate its independence from both the scalp recorded electroretinogram or ERG and its associated oscillatory potentials and also from the visually evoked cortical potential.

MATERIALS AND METHODS

Observations were made on thirty normal young volunteers, 16 male and 14 female, mean age 23.2 years. All had visual acuities of 6/6 or better. The subjects were seated in a dimly-lit room and flash stimulation delivered by a Grass PS22 Photo-stimulator ranged from 1363 to 9661 nits. A PDP8E computer was used to simultaneously average eight channels of responses to 500 stimuli which were usually presented at a rate of 6 per second, although slower presentations have been used. The band-pass of the equipment was 66–700 Hz. Since the photo-stimulator produced an audible 'click', control trials were performed with white noise delivered through earphones and with the lamp occluded.

Investigation of commonly used cephalic reference sites revealed that any site anterior to the vertex was markedly contaminated by flash-evoked ERG and both the earlobe and mastoid were highly active at latencies around 20–40 milliseconds. Indeed, it may be that the active nature of this reference

site may be responsible for some so-called early components of the visual evoked cortical potential.

In our investigations of possible reference sites we found that the vertex electrode Cz was relatively inactive at early latencies. It is, of course, well known that the vertex site is highly active at later latencies and indeed many late nonspecific components of both the auditory and visual evoked potentials are maximal at this site. The vertex site has the added advantage that it is approximately equidistant from a temporal chain of active recording sites. Since the anterior-posterior location of the source of the signal would be determined from this chain and since the amplitude of the signal is partially proportional to the inter-electrode distance, this constituted a major advantage in using the vertex reference. (Fig. 1) All the electrode positions were

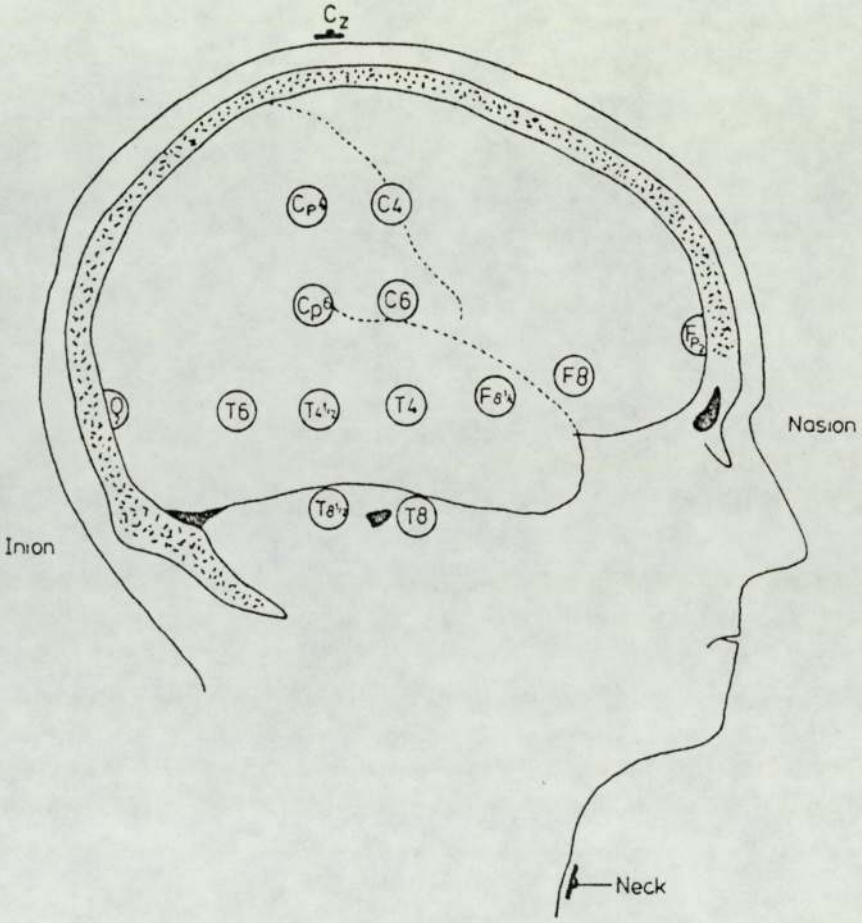

Fig. 1. Scalp distribution of electrodes used in topographical study of the visually evoked sub-cortical potential, consisting of an anterior-posterior chain and two transverse chains of electrodes. Most electrodes are placed according to the International 10/20 System but electrodes CP4, CP6, T4½, T8½, C6, T8 and F8½ are additional electrodes placed midway between the standard placements. The vertex (Cz) and the neck electrodes are used as the common reference.

determined according to the International 10/20 System, using additional half distance electrodes.

In the anterior-posterior study half distance electrodes were placed at F8½ and T4½. For the study of the transverse distribution additional electrodes were placed at C6, CP4, and CP6, that is, midway between the central and parietal positions and T4½ and T8½. (Fig. 1).

Unfortunately, in the study of the transverse distribution of the amplitude of the potential, it is impossible to find a site for the reference electrode that is both inactive and equidistant from all recording electrodes. Obviously, both the frontal and occipital poles, which are equidistant from the electrodes, are highly active and therefore it was decided to use inactive reference sites which were not equidistant from all members of the electrode chain. To obtain direct comparability with the anterior-posterior study the vertex was again used as one reference site. This site is nearest the centrorolandic electrodes and furthest from the lower mastoid. To control for this factor as far as possible, the anterior neck was used as a comparator reference site. This site was found to be completely uncontaminated by the electroretinogram and is, of course, nearer to the lower electrodes than to the rolandic ones.

RESULTS

The anterior-posterior distribution of the visually evoked sub-cortical potentials of the VESPs is shown in Fig. 2. The activity at the frontal pole is dominated by the ERG which is widely distributed, but which decreases in amplitude to a trough around the Rolandic-Sylvian fissure. At a point just behind the ear, at electrode T4½ a triphasic wave is seen. The mean latencies of this wave are positive 20.1 (± 2.03), negative 26.3 (± 2.10), positive 33.9 (± 1.87) milliseconds, and its mean amplitudes positive to negative 1.6 (± 0.78) and negative to positive 2.3 (± 0.99) microvolts. It does not occur at similar latencies to any components of the visual evoked cortical potential recorded at the occiput (Oz). When the lamp was occluded similar potentials could not be recorded. When trials were performed with white noise delivered through earphones a clear response to the photic stimulus was elicited.

Although the VESP is of a different latency to that of known myogenic components, control trials were performed with subjects relaxed and also maintaining high muscular tension as monitored by the on-going EEG. Neither of these actions altered the amplitude or latency of the VESP. This visual evoked potential was successfully recorded in 28 of the 30 subjects. Unlike auditory brain stem evoked potentials there was no significant difference in latency between males and females. In nine subjects the trial-retrial repeatability was tested over a period of between 1 and 12 months. (Fig. 3.). The mean variability in latency over time is relatively small being 1.11 milliseconds for the P20 wave, 1.88 milliseconds for the N26 wave and 1.11 milliseconds for the P34 wave.

The variation in amplitude is far greater although only two scores are shown since the amplitude measures are made peak to peak, that is, P20–N26

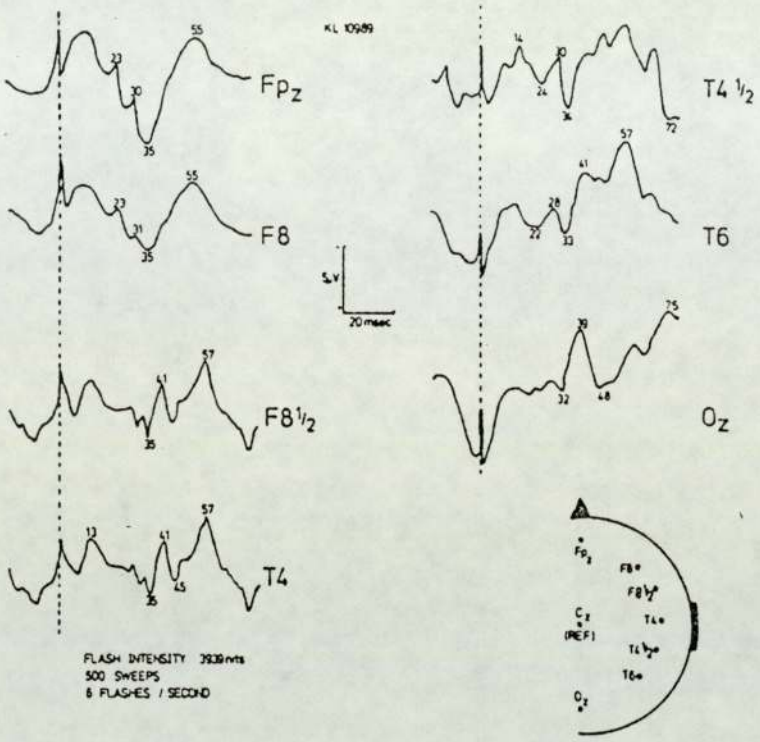

Fig. 2. Distribution of potentials recorded in an anterior-posterior chain of electrodes from frontal to occipital pole all referred to the vertex (Cz). The activity of the frontal pole (Fpz) shows the inverted ERG and its oscillatory potentials, and each subsequent site shows the decreasing amplitude of these components. At T4½ however, the VESP consisting of a P24, N30, P34 complex appears and this reduces in amplitude at more posterior sites and almost disappears at the occipital pole (Oz) which shows the N39, P48, N75 components of the VECP.

and N26–P34. Peak to peak measures of amplitude are more liable to variation and variation in background noise will also affect the averaged amplitude and reduce its repeatability.

In the transverse topographical study, the amplitude of the VESP was maximal at sites below the temporal electrode chain and at a point with, but behind the pinna, that is, around the mastoid process at electrodes T4½ and T8½. This finding was irrespective of whether the vertex or neck electrode sites are used. (Fig. 4). This would indicate that inter-electrode distance was not a confounding factor.

Since the VESP is recorded bilaterally, it is possible that the response might be related to the ERG and the oscillatory potentials. However, the topographical distribution of the VESP contrasts markedly with that of the scalp recorded ERG when referred to the same vertex site. (Fig. 5).

The amplitude of the ERG as recorded at half gain by a Gold Foil electrode (Channel 1) is markedly reduced when recorded at sub-lid, nasal,

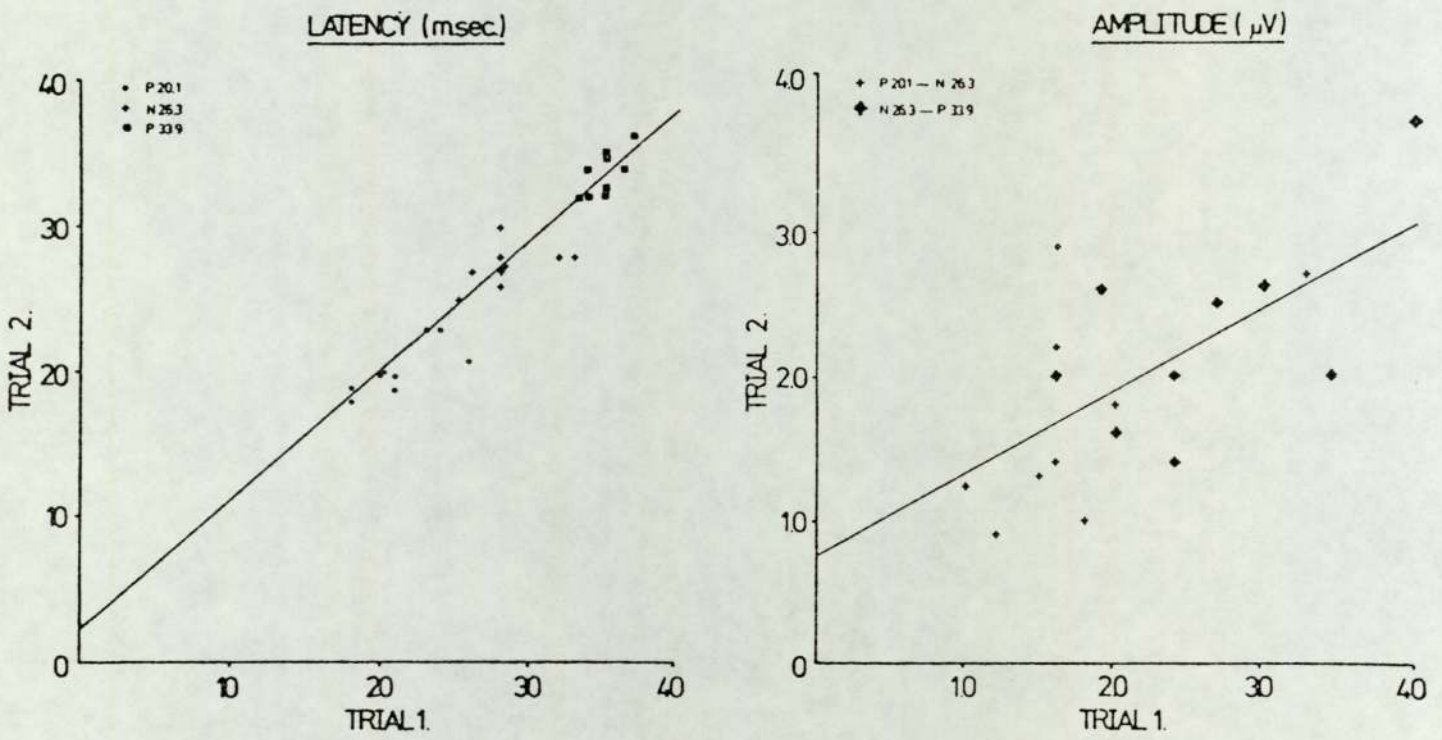

Fig. 3. Scattergram of trial-retrial repeatability of VESP latency and amplitude over periods of between 1 and 12 months. The regression line of y (trial 2) on x (trial 1) is calculated and considered as a 'best-fit' line.

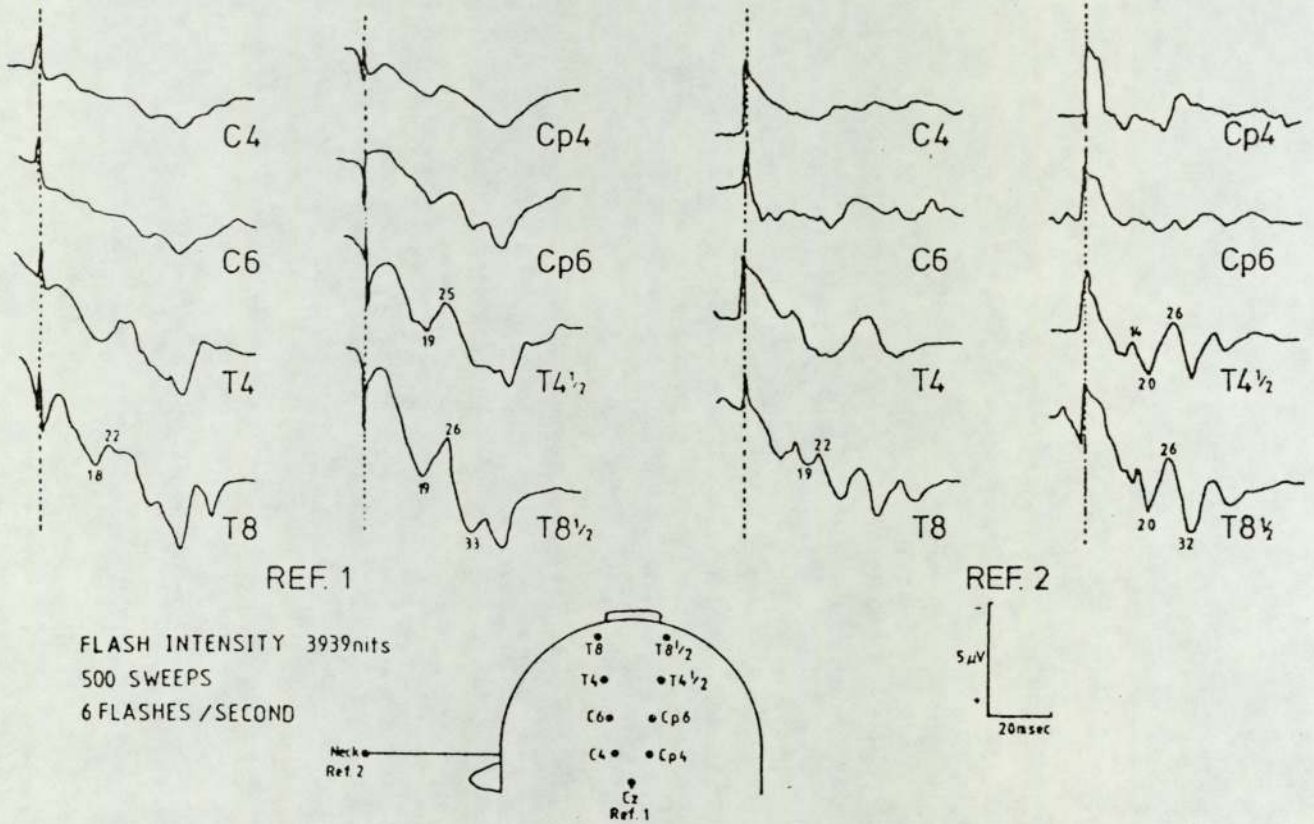

Fig. 4. Topographic distribution of potentials recorded in transverse chains of electrodes referred to vertex (Ref. 1) and to an anterior neck site (Ref. 2) as a comparator. Using either reference, the amplitude of the VESP is shown to be maximal at (or around) electrode T8½, that is, an area level with the cochlea but behind the external auditory meatus.

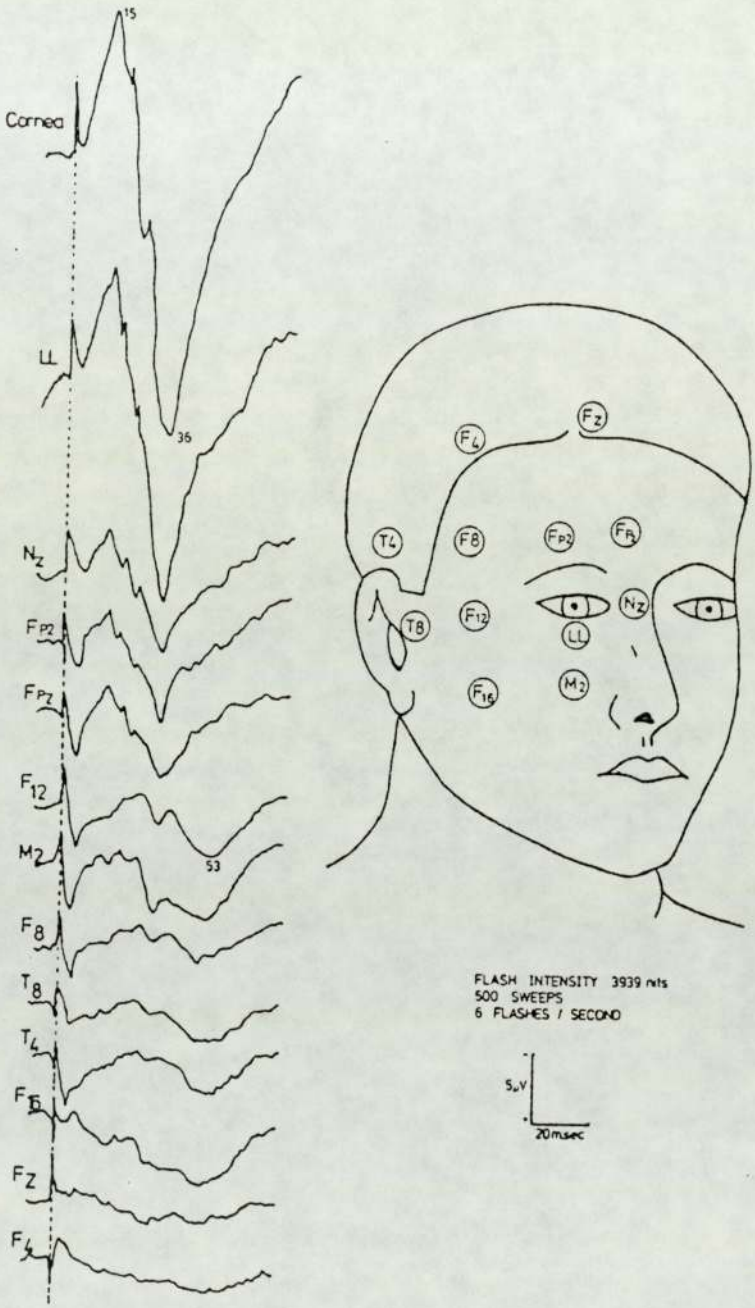

Fig. 5. Facial and scalp topography of electroretinogram in one subject. All electrodes are referred to the vertex (Cz) and recordings made in accordance with EEG convention (Positive at Grid 1. downwards). The corneal signal is recorded at half gain from a Gold Foil Electrode, with a peak of the 'a' wave at 15 milliseconds and a peak of the 'b' wave at 36 milliseconds. The amplitude of the signal rapidly decreases as cornea-electrode distance increases. At electrodes T8 and T4, the ERG is almost absent, only a vestigial 'b' wave appearing as a slight deflection.

frontal pole and frontal sites. The reduction is even more marked at fronto-temporal sites and at the electrodes where the VESP is maximal, that is, electrodes T4 and T8 the ERG is almost non-existant. During simultaneous recording with all electrodes referred to the vertex (Cz) it can be seen that the latency of the 'b' wave of the ERG contrasts with latency of the VESP, (Fig. 6). The former having a peak positive latency of 39 milliseconds and

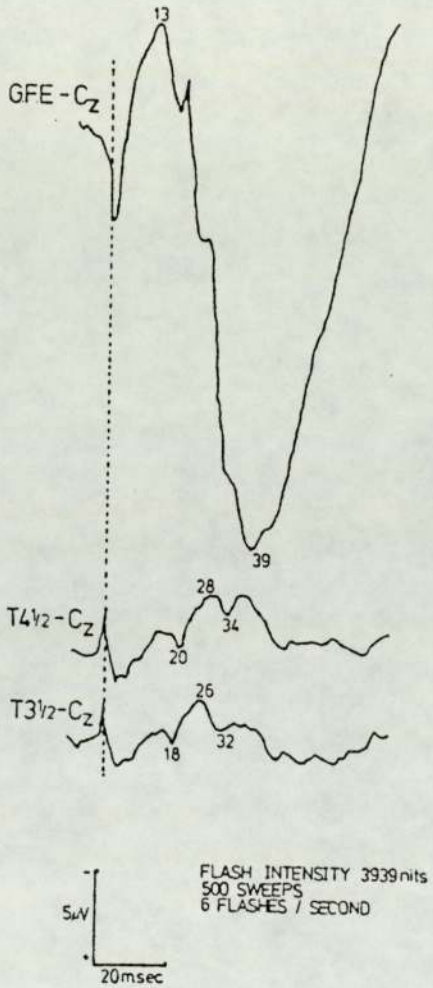

Fig. 6. Simultaneous recording of the electroretinogram and VESP. The peak of the ERG 'a' wave is seen at 13 milliseconds and that of the 'b' wave at 39 milliseconds. The VESP was seen bilaterally at T4½ and T3½ at latencies unrelated to those of the ERG in its oscillatory potentials.

the latter latencies of positive 18–20, negative 26–28 and positive 32–34. Neither do the latencies and morphology of the oscillatory potentials of the ERG appear to coincide with the VESP.

Equally, if the VESP were part of the oscillatory potentials of the ERG or arose from the optic nerve, when stimulation is changed from binocular to monocular the response should reduce ipsilateral to the occluded eye.

It can be seen that in Fig. 7, although the ERG potential on the scalp is

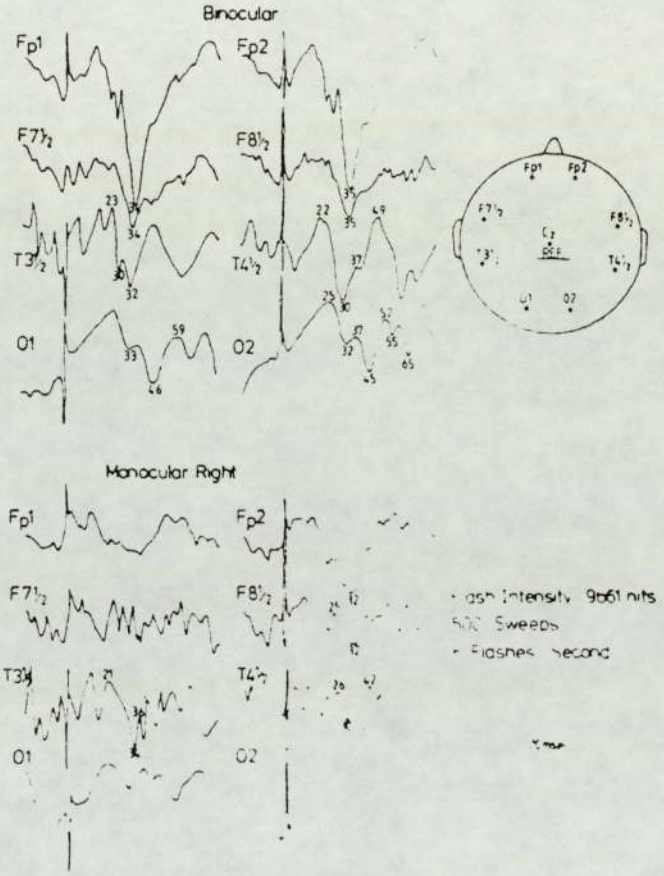

Fig. 7. During binocular flash stimulation the VESP at N23, P32 is seen bilaterally at T3½ and T4½ and equal to approximately 7 uVs peak to peak. When the left eye is occluded the ERG is reduced from the left scalp electrodes (Fp1 and F7½) but the VESP is still present at the left (T3½) as it is on the right (T4½). Similar findings are obtained when the right eye is occluded, with a reduced VESP recorded bilaterally contrasting with an ipsilateral reduction of the ERG.

reduced ipsilateral to the eye which is occluded, the VESP, which in this individual is early at negative 23, positive 32, is reduced bilaterally. These results can only be explained by the response arising from a post-chiasmal site.

We have begun to study patients with lesions of the visual pathway using these techniques. A recent patient presented with a right homonymous hemianopia following a vascular disturbance of the basilar and posterior cerebral arteries. The patient was fully conscious and was dysarthric. There was a clear right homonymous hemianopia, horizontal nystagmus on lateral gaze to either side, and a mild right sided facial weakness. There was bilateral ataxia of all four limbs which was more evident on the right than the left, the tendon reflexes were brisk and the plantors were flexor. CAT scan showed global atrophy involving the left cerebral hemisphere and also the cerebellum. The visual fields are shown in Fig. 8 together with the visual evoked cortical potential. Using flash stimulation and our standard montage it can be seen that the VEP is partly reduced contralateral to the field defect and phase-reversals and amplitudes differ between the two sides.

If the VESP does arise from a thalamic or post-thalamic site it should be reduced on the side of the head contralateral to the field defect. This is clearly demonstrated in Fig. 9 in which the component is absent or markedly reduced on the left, that is, contralateral to the right homonymous hemianopia. In patients with a recent cortical deficit, the VESP should remain preserved. We have investigated a child with cortical abnormality who presented with sudden loss of co-ordination of right limbs and head movements and reduced amplitude of the EEG over the left hemisphere. Unfortunately, due to the young age of the patient accurate field studies could not be obtained. The VESPs were well maintained bilaterally and showed clear components (Fig. 10). The visual evoked cortical potential however showed a clear reduction over the left hemisphere of both the P1 and P2 components. Such a finding would suggest cortical involvement without involvement of subcortical visual pathways.

The final patient was a 66 year old lady with bitemporal hemianopia. The CAT scan showed a large supra-sellar cystic space occupying lesion with expanded pituitary fossa and erosion of the floor and posterior clinoids. The VESP is clearly reduced over the right cerebral hemisphere on left eye stimulation with flash. On right eye stimulation the converse is seen with reduction over the left hemisphere (Fig. 11).

We have compared the VESP to visual evoked cortical responses obtained by pattern-reversal of half the visual field using a 56 minute checkerboard. When the left half field of the left eye was stimulated no response was obtained. Stimulation of the nasal field however produced a clear response of higher amplitude over the left hemisphere. When the temporal half field of the right eye was stimulated no cortical response was seen whereas the nasal field produced a clear response.

DISCUSSION

The visual evoked sub-cortical potential elicited under our standardised conditions appears to be a relatively stable phenomenon recorded in 93% of normal subjects.

The potential is of low amplitude but the confidence limits for test-retest

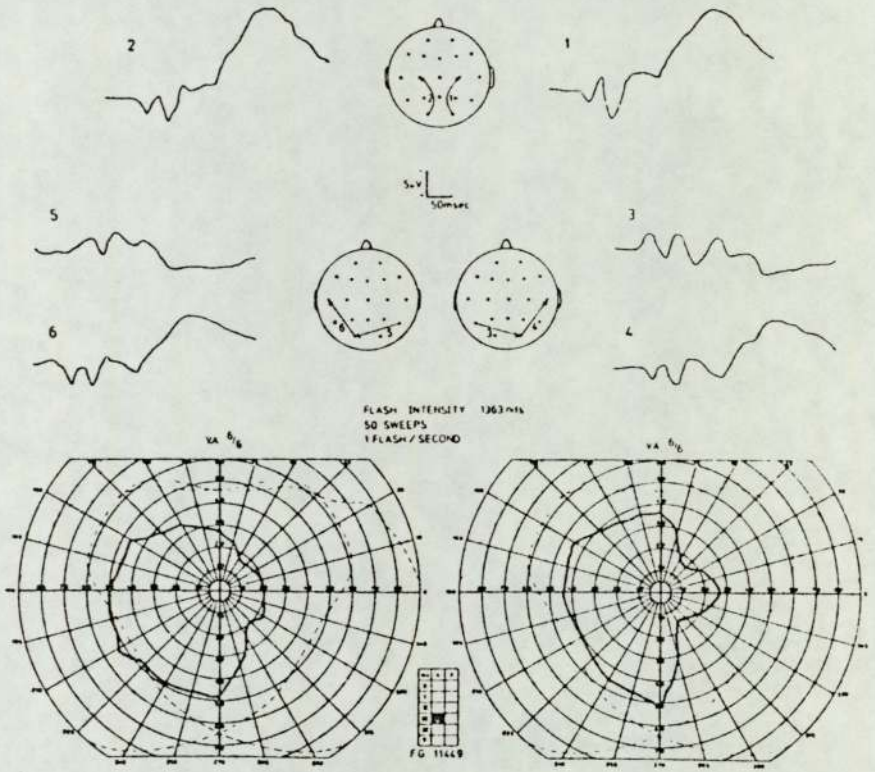

Fig. 8. Patient with a right homonymous hemianopia (and macular sparing) as shown in the field plots following brain stem vascular disturbance. Binocular flash stimulation showed the major positive component of the visual evoked cortical potential P2, at 120 milliseconds. The amplitude being 10 uVs on the right (Channel 1) and 5 uVs on the left (Channel 2). Phase reversal was seen more clearly to the right occiput than to the left (Channels 5 and 6).

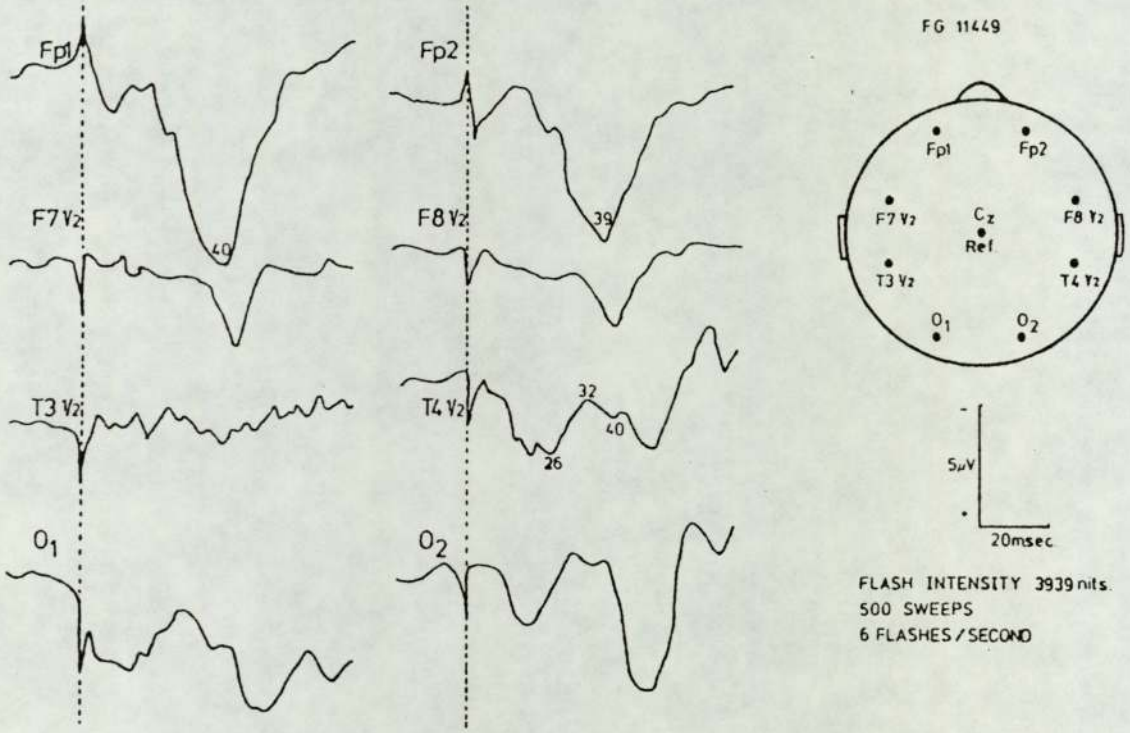

Fig. 9. VESP technique used on the same patient with right homonymous hemianopia following brain stem vascular disturbance. A clear VESP complex is seen on the right at T4½ (P26, N32, P40) but such a complex is absent on the left (T3½). It is interesting to note that the ERG from the left eye (Fp1) is of higher amplitude than that from the right eye (Fp2).

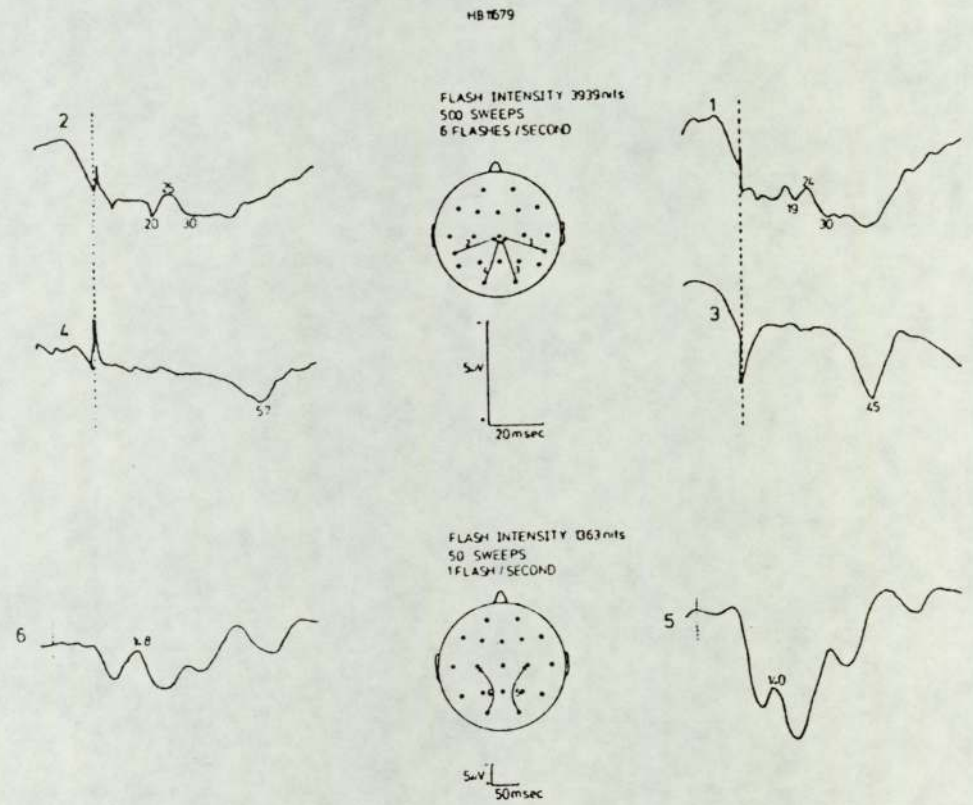

Fig. 10. Patient with cortical abnormality. The VESP is clearly preserved bilaterally. (Channels 1 and 2). The P1 component of the VECP is delayed and reduced on the left (Channel 4) compared with the P1 component of the right (Channel 3). The VECP on the left (Channel 6) is markedly reduced in amplitude and slightly delayed, compared with the VECP on the right (Channel 6), during binocular stimulation.

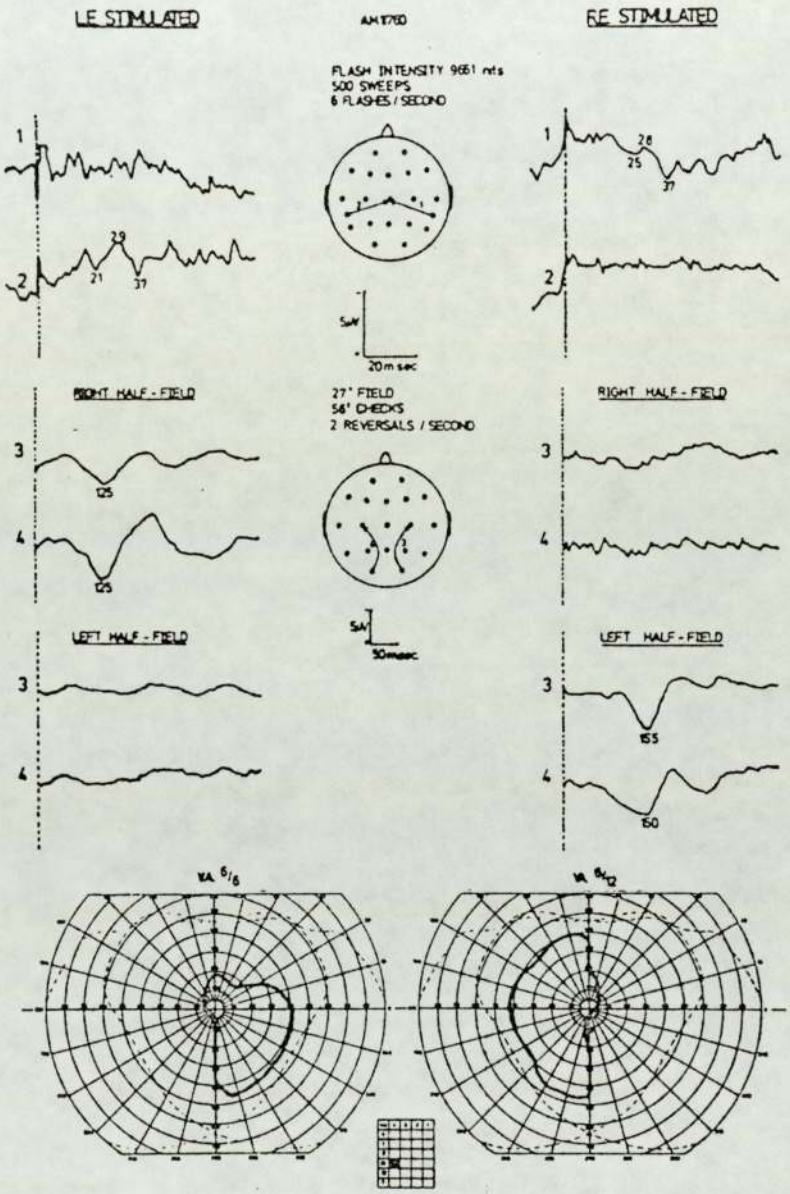

Fig. 11. Patient with pituitary adenoma producing chiasmal compression and associated bitemporal hemianopia. The VESP technique on monocular stimulation of the right eye showed a P25, N28, P37 complex on the right (Channel 1) but absence of any response on the left (Channel 2). On monocular stimulation of the left eye, no response was seen on the right (Channel 1) but a P21, N29, P37 complex as seen on the left (Channel 2). Half-field pattern reversal stimulation shows absence of response when the right half-field of the right eye was stimulated but a major positive component at 150–155 milliseconds when the left half-field was stimulated. When the right half-field of the left eye was stimulated a major positive was seen at 125 milliseconds but was absent on left half-field stimulation. The field plots are shown at the bottom of the figure.

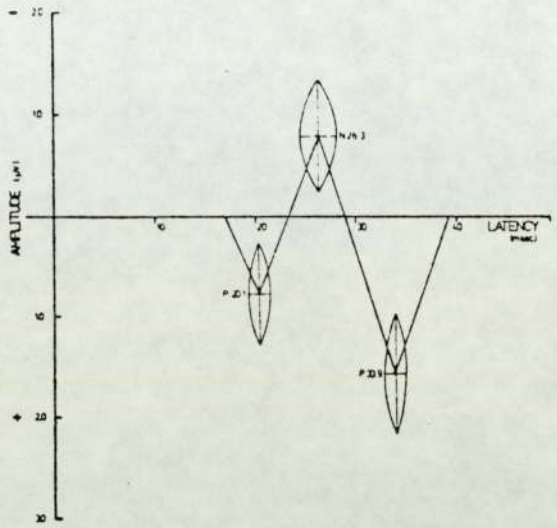

Fig. 12. Graphical representation of the mean VESP in normal subjects (N = 30). The mean difference in amplitude and latency of the VESP between recording on two occasions on nine subjects are shown as elipsoids. It is clearly seen that the mean amplitude differences are considerably greater than the mean latency differences of all three components of the complex. The mean latency variations are 1.11, 1.88, and 1.11 for the P20, N26, P34 wave respectively.

reliability over months, shows remarkably little variation in latency (Fig. 12). The latency of the P34 component is the least variable, only varying in latency by a mean of 1.11 of a millisecond.

The topographical distribution of the component indicates that is maximal around the mastoid process and indeed it may constitute the explanation for some of the so-called early components of the visual evoked cortical potential where this site was used as an 'inactive' reference. (Ciganek 1961; Kooi & Bagchi 1964; Gastaut, Regis, Lyagoubi, Memo & Simon 1967; Allison Matsumiya, Goff & Goff 1977; Cracco & Cracco 1978).

Since the VESP as described in this paper is unrelated to the amplitude of the electroretinogram and its oscillatory potentials, it is unlikely that it arises from this source. Equally since it does not reduce ipsilateral to an occluded eye it is unlikely to arise from an optic nerve site and must be post-chiasmal. The findings from patients support the suggestion that the origin of the signal is post-chiasmal and the finding of reduced cortical potentials co-existing with preserved sub-cortical potentials would indicate that the signal is not of cortical origin. In this connection it should be noted that Corletto et al. reported in 1967 preservation of an early N23, P28 millisecond wave following an occipital lobectomy.

The most likely explanation is that this potential arises from a thalamic or optic radiation site and such an origin would be entirely consistent with

all our findings. It is possible that this technique may supplement the electroretinogram and the visually evoked cortical potential in ophthalmic electro-diagnosis of lesions of the visual pathway.

ACKNOWLEDGEMENTS

We are most grateful to Mr Bernard Williams and Dr Milne Anderson of the Midland Centre for Neurosurgery for allowing us to study their patients.

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Authors' address:
Clinical Neurophysiology Unit
Dept. of Ophthalmic Optics
University of Aston in Birmingham
Birmingham, England

In: Courjon, J., Mauguiere, F., Revol, M. (Eds.)
Clinical applications of evoked potentials in neurology.
Raven Press, New York (in press).

THE VISUALLY EVOKED SUBCORTICAL POTENTIAL TO FLASH STIMULATION IN NORMAL SUBJECTS AND PATIENTS WITH LESIONS OF THE VISUAL PATHWAY.

Harding, G.F.A. and Rubinstein, M.P.

The Clinical Neurophysiology Unit, Department of Ophthalmic Optics,
University of Aston in Birmingham, Gosta Green, Birmingham B4 7ET, England.

Running Title: VESP in Normals & Neuro-ophthalmic Patients.

INTRODUCTION

Although short latency components of the VEP are often described by early workers and can be seen in their records (3, 4 and 2) they have received relatively little attention. Early workers used high intensity flash and the later trend towards the use of structured stimuli without overall luminance change may well have contributed to this neglect. The early components of the visual evoked potential, that is, components before 50 milliseconds latency, are poorly documented due to their minute amplitude, inter-subject variability and poor repeatability under the standardised experimental conditions used for eliciting the visual evoked cortical potential (6).

The earliest specific description of short latency VEP was that of Van Hasselt (10) who recorded a potential occurring at 10 milliseconds latency of maximal amplitude around the ear and mastoid and only obtainable in 40% of subjects. Cracco and Cracco (5) described oscillatory potentials at around 100 Hz recorded from a wide distribution of scalp electrodes referred to the earlobes. The latencies were between 9-24 milliseconds and of maximal amplitude in the mid-line and parasaggital locations.

In 1978 we carried out a pilot study on a small group of normal volunteer controls. By increasing the number of responses averaged to bright stroboscopic flashes and by multi-channel recording from a variety of cephalic sites we identified a small, less than 3 microvolt complex, recorded by far-field techniques. This complex consisted of a positive wave at 22 milliseconds, a negative at 27 milliseconds and a positive wave at 35 milliseconds (8) and appeared to be located around the mid-temporal region.

MATERIALS AND METHODS

Observations were made on forty five normal young unversity volunteers, twenty-two male and twenty three female, mean age 23.1 years. All had visual acuities of 6/6 or better. The subjects were seated in a dimly lit room and flash stimulation delivered by a Grass PS22 Photostimulator at 3939 candelas per square metre, that is, intensity 8, placed 25 cms from the yes. A PDP8E computer was used to simultaneously average eight channels of responses to 500 stimuli which were usually presented at a rate of 6 per second, although slower presentations have been used. The band pass of the equipment was 66-700Hz.

Cephalic reference sites revealed that sites anterior to the vertex were contaminated by flash-evoked ERG and both the earlobe and mastoid were highly active at latencies around 20-40 milliseconds. We found that the vertex electrode Cz was relatively inactive at early latencies. It is, of course, well known that the vertex site is highly active at later latencies. The vertex site has the added advantage that it is approximately equidistant from a temporal chain of active recording sites. Since the anterior-posterior location of the source of the signal would be determined from this chain and since the amplitude of the signal is partially proportional to the inter-electrode distance, this constituted a major advantage in using the vertex reference. Electrode positions were determined according to the International 10/20 System, using additional half-distance electrodes. In the anterior-posterior study half-distance electrodes were placed at F8½ and T4½. For the study of the transverse distribution additional electrodes were placed at C6, CP4, CP6, that is, midway between the central and parietal positions at T4½ and T8½.

RESULTS

The distribution of the visually evoked sub-cortical potentials (VESP) is shown in Figure 1. The activity at the frontal pole is dominated by the ERG which is widely distributed, but which decreased in amplitude to a trough around the Rolandic-Sylvian fissure. At a point just behind the ear, at electrode T4½ a triphasic wave is seen. The mean latencies of this wave are positive 20.61 ± 2.14, negative 26.22 ± 2.16, positive 33.80 ± 1.98 milliseconds, and its mean amplitudes positive to negative 1.32 ± 0.71 and negative to positive 2.33 ± 0.98 microvolts. It does not occur at similar latencies to any components of the visual evoked cortical potential recorded at the occiput (Oz).

FIGURE 1

In the transverse direction, the amplitude of the VESP was maximal at sites below the temporal electrode chain and at a point level with, but behind the pinna, that is, around the mastoid process at electrodes T4½ and T8½. This finding was irrespective of whether the vertex reference or a neck electrode reference site was used. This would indicate that inter-electrode distance was not a confounding factor.

Since the photostimulator produces an audible click, control trials were performed both with the lamp occluded and with white noise delivered through ear-phones. When the lamp was occluded similar potentials could not be recorded. When trials were performed with white noise delivered through ear-phones a clear response to the photic stimulus was elicited.

Although the VESP is of a different latency to that of known myogenic components, control trials were performed with subjects relaxed and also maintaining high muscular tension as monitored by the on-going EEG. Neither of these actions altered the amplitude or latency of the VESP. The visual evoked subcortical potential was successfully recorded in forty-three of the forty-five subjects. Unlike auditory brainstem evoked potentials there was no significant difference in latency between males and females. In fifteen subjects the trial-retrial repeatability was tested over a period of between 1 and 12 months. The mean variability in latency over time is relatively small being 1.06 milliseconds for the P20.6 wave, 1.64 milliseconds for the N26.2 wave and 1.43 milliseconds for the P33.8 wave. The variation in amplitude is greater although peak to peak measures of amplitude are more liable to variation and variation in background noise will also affect the averaged amplitude and reduce its reliability.

RESULTS ON PATIENTS

Although we have only recently begun to use these techniques in patient investigations it has been possible to study patients with lesions at various levels of the visual pathway.

Three patients with optic nerve lesions have been examined. For example, a patient presented with a fracture of the left orbit and zygoma following a fall. The visual acuity of the left eye was reduced to no light perception and the optic disc was pale and atrophic. ERGs were found to be of normal and equal amplitude in both eyes (Figure 2). The VECP from the right eye was of normal latency and amplitude as was the VESP. However, no VECP or VESP could be elicited on stimulation of the left eye. No significant abnormality was seen in the monitoring EEG to suggest cerebral damage. Similar results have also been seen in a case of optic nerve tumour and in macular trauma due to a metallic intraocular foreign body.

FIGURE 2

Patients with bitemporal hemianopia arising from chiasmal compression would be expected to show a reduction in both the VESP and visual evoked cortical potential (VECP) contralateral to the eye stimulated by flash stimuli. A 66 year old patient with bitemporal hemianopia presented for investigation. The CAT scan

showed a large supra-sellar cystic space occupying lesion with expanded pituitary fossa and erosion of the floor and posterior clinoids. The VESP was reduced over the right cerebral hemisphere on left eye stimulation with flash. On right eye stimulation the converse was observed with reduction over the left hemisphere (Figure 3).

FIGURE 3

We have compared the VESP to visual evoked cortical responses obtained by pattern reversal of half the visual field using a 26' checkerboard. When the left half field of the left eye was stimulated no response was obtained. Stimulation of the nasal field however produced a clear response of higher amplitude over the left hemisphere. When the temporal half field of the right eye was stimulated no cortical response was seen, whereas the nasal field produced a clear response. Similar results have been produced in one other patient we have studied with bitemporal hemianopia.

In patients with a post-chiasmal lesion, if the VESP does arise from a thalamic or post-thalamic site it should be reduced on the side of the head contralateral to the field defect. Six patients with such lesions have been studied. A recent patient presented with a right homonymous hemianopia following a vascular disturbance of the basilar and posterior cerebral arteries. The patient was fully conscious and was dysarthric. There was a clear right homonymous hemianopia, horizontal nystagmus on lateral gaze to either side, and a mild right sided facial weakness. There was bilateral ataxia of all four limbs which was more evident on the right than the left, the tendon reflexes were brisk and the plantors were flexor. CAT scan showed global atrophy involving the left cerebral hemisphere and also the cerebellum. The visual fields are shown in Figure 4 together with the visual evoked sub-cortical potential. Using flash stimulation and our standard montage it can be seen that the VESP is reduced contralateral to the field defect. In the four other patients similar findings were obtained, but one patient with a hemianopia due to a recent cortical trauma showed preservation of the VESP coexisting with reduced flash VECP contralateral to the field defect.

FIGURE 4

Initial investigations have been carried out in 6 patients with unilateral retrobulbar neuritis. We have failed to show any significant increase in latency of the VESP even though the VEP shows clear evidence of a delay of the P100 component when the affected eye is stimulated.

DISCUSSION

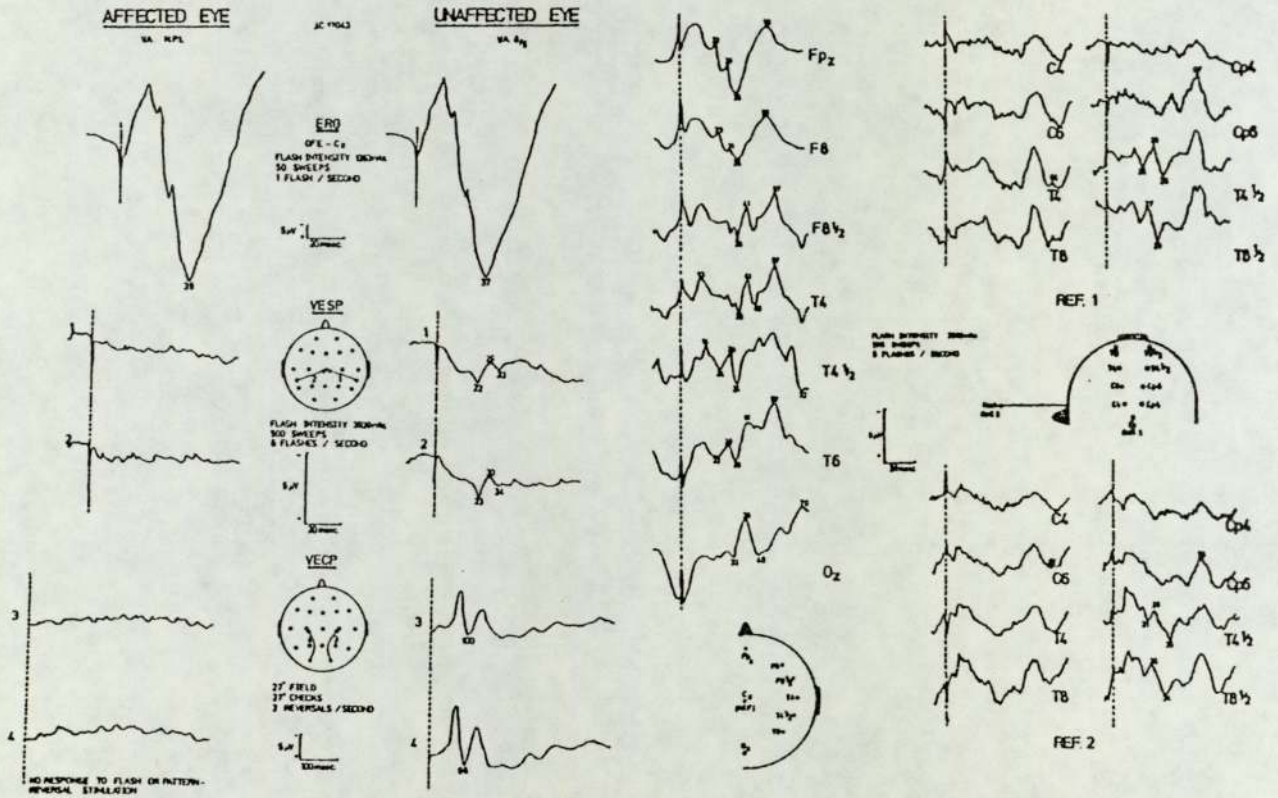
The visual evoked sub-cortical potential elicited under our standardised conditions appears to be relatively stable phenomenon recorded in 96% of normal subjects. The potential is of low amplitude but the confidence limits for test-retest reliability over months shows remarkably little variation in latency, the P34 component only varying in latency by a mean of 1.43 milliseconds.

The topographical distribution of the component indicates that it is maximal around the mastoid process and indeed it may constitute the explanation for some of the so-called early components of the visual evoked cortical potential where this site was used as an "inactive" reference. (2,9,7,1 and 5).

Since the VESP as described in this paper is unrelated to the amplitude of the electroretinogram and its oscillatory potentials, it is unlikely that it arises from this source. The findings from normals and patients support the suggestion that the origin of the signal is post-chiasmal and is not of visual cortex origin. The most likely explanation is that this potential arises from a thalamic or optic radiation site and such an origin would be entirely consistent with all our findings. It is possible that this technique may supplement the electroretinogram and the visually evoked cortical potential in ophthalmic electro-diagnosis of lesions of the visual pathway.

ACKNOWLEDGEMENTS

We are grateful to Mr Bernard Williams and Dr Milne Anderson of the Midland Centre for Neurosurgery and Neurology for allowing us to study their patients.


AFFECTED EYE
UNAFFECTED EYE
ERG
VESP
VECP
NO RESPONSE TO FLASH OR PATTERN-REVERSAL STIMULATION
Fpz
F8
F8½
T4
T4½
T6
Oz
C4
Cp4
C6
Cp6
T4
T4½
T8
T8½
REF. 1
REF. 2

LE STIMULATED
AMBIENT
RE STIMULATED
RIGHT HALF-FIELD
27° FIELD
56' CHECKS
2 REVERSALS / SECOND
RIGHT HALF-FIELD
LEFT HALF-FIELD
LEFT HALF-FIELD

LEGENDS

FIGURE 1. Scalp topographical distribution of VESP. In anterior-posterior direction ERG is shown to dominate frontal sites (FPz, F8) and VECP at posterior site (Oz). At electrode T4½ a trough develops with triphasic complex P24-N30-P34 being generated, independent of ERG or VECP.
In transverse direction, using either Cz or neck reference, VESP is shown to be of maximal amplitude around the upper mastoid area, at electrodes T4½ and T8½.

FIGURE 2. Patient with left optic nerve trauma exhibiting bilaterally intact ERG (FP1,FP2). On stimulation of the affected eye, no VESP or VECP could be elicited, although stimulation of the unaffected eye showed normal VESP and VECP thus contradicting the ERG-origin of the VESP.

FIGURE 3. Patient with pituitary adenoma and associated bitemporal hemianopia. The VESP technique on stimulation of the right eye showed a P25, N28, P37 complex on the right (Channel 1) but no response on the left (Channel 2). On stimulation of the left eye no response was seen on the right (Channel 1) but a P21, N29, P37 complex was seen on the left (Channel 2). Pattern reversal stimulation of the right half field shows no response, but a major positive at 150-155 milliseconds was seen when the left half field was stimulated. Stimulation of the right half field of the left eye showed a major positive at 125 milliseconds, but no response on left half field stimulation.

FIGURE 4. Patient with brainstem vascular disturbance, showing a clear VESP complex on the right (T4½) at latencies P26, N32, P40 but which is absent on the left (T3½). The visual fields show a well defined right homonymous hemianopia with macular sparing.

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