THE EFFECTS OF VIGABATRIN ON THE VISUAL SYSTEM

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Abstract

This thesis considers the visual electrophysiological effects of vigabatrin (an anti-epileptic drug, which acts by increasing the levels of the inhibitory neurotransmitter GABA) on the retina of the eye compared to the concentric visual field defects which have been found associated with the drug. Flash & pattern ERG's, EOG's multifocal ERG's (VERIS), flash & pattern VEP's and visual fields were tested. Although VEP's have been shown not to be affected by vigabatrin, these were recorded to complete the testing.

Initially, of the eight vigabatrin patients with known visual field defects, 7 showed abnormally delayed 30Hz flicker a-wave latencies, 5 abnormally delayed 30Hz b-wave latencies and 6 abnormally low 30Hz amplitudes. Also 7 showed an abnormally prolonged latency of oscillatory potential 1 (OP1). The two patients taking vigabatrin at the time of testing showed low EOG Arden index values. The VERIS results correlated well with the severity of the visual field defects.

Following this finding, eleven healthy subjects received vigabatrin over a 10-day period. No changes were seen in the visual fields, however, the photopic ERG b-wave latency significantly increased (although not to abnormal values).

A matched pairs study with eleven vigabatrin, patients and eleven epileptic patients, who had never taken vigabatrin supported the findings of abnormal 30Hz flicker b-wave and OP latencies associated with vigabatrin, again with the VERIS results correlating to the severity of the visual field defect.

The abnormal 30Hz flicker and VERIS responses indicate involvement of the cone photoreceptors and the OP's show an effect on the amacrine cells. The ERG increase in the photopic b-wave latency also suggests involvement of the bipolar cells, however, this effect and the reversible effect on the Arden index after cessation of the drug may be unrelated to the visual field defect.

To conclude this thesis, a field specific VEP stimulus was developed to assess the retinal function in the peripheral field of paediatric patients. It comprises of a dartboard stimulus with a central 0-5 degree black and white chequered stimulus, a blank 5-30 degree annulus and a 30-60 degree peripheral chequered stimulus. When optimised on four vigabatrin patients it was found that no peripheral response can be evoked with a field loss exceeding 30-35 degrees. Co-operation was found to be successful in children as young as four years old.

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Introduction

Epilepsy is a term used to describe a variety of disorders classified by the Commission on Classification and Terminology of the International League against Epilepsy (ILAE). Epilepsy is thought to affect approximately 620 people out of 100,000 of the population (Granieri et al 1983, Keränen et al 1989). The different seizure types manifest with differing frequencies and affect different age groups of the population. A proportion of these patients suffer with partial seizures for which the first line of treatment is usually the antiepileptic drugs carbamazepine, phenytoin or sodium valproate (Walker 1996). Complex partial seizures may be particularly difficult to control and many of these patients are prescribed combination drug therapy.

Vigabatrin is an antiepileptic drug, which was introduced in 1982 and used in studies with patients suffering from 'resistant epilepsy' (Dam 1991), usually as an 'add-on' drug to the current therapy. The anti-convulsant properties of vigabatrin are based on the mechanism of increasing the whole brain concentration of Gamma-amino butyric acid (GABA). GABA is a major inhibitory neurotransmitter and vigabatrin has a very similar chemical structure to GABA and acts by irreversibly binding to GABA-transaminase (the enzyme that degrades GABA) therefore increasing the neurotransmitter concentration.

Initial 'add-on' drug studies using vigabatrin reported approximately a 50% decrease in seizure frequency (Loiseau et al 1986, Riekkinen et al 1989, Michelucci & Tassinari 1989). A more recent study by Kälviäinen et al (1995) reported that 60% of newly diagnosed patients were successfully treated (being seizure free or with acceptable seizure control) using vigabatrin monotherapy.

At this time side effects of vigabatrin were reported as mild mainly consisting of drowsiness, dizziness, mood instability, headaches and weight gain. In 1995, however, Harding et al reported a prolonged b-wave of the photopic electroretinogram (ERG) after the addition of vigabatrin to the therapy of epileptic patients and in 1997 Eke et al reported visual field constriction, low electroculogram (EOG) Arden indices and reduced ERG oscillatory potentials associated with vigabatrin.

During the development of vigabatrin preliminary toxicological animal studies had shown neuropathological changes, with rodents exhibiting myelin vacuolation in various parts of the brain including the visual pathways. Dogs had developed intramyelinic oedema although the changes were reversible on cessation of the drug (Graham 1989). No comparative neuropathology was found in monkeys.

Following these findings post-mortem and post-surgical tissue examinations were carried out on human specimens, however these showed no evidence of myelin microvacuolation associated with vigabatrin (Cannon et al 1991).

Other studies investigated the effect on the visual evoked potential (VEP) after the addition of vigabatrin to the patients' therapy but no significant difference in the latencies of the main components were seen compared to the baseline pre-treatment phase (Hammond & Wilder 1983, 1985, 1987, Hammond et al 1988a, 1988b).

Following the three cases of visual field constriction reported by Eke et al (1997), other research groups (Wilson & Brodie 1997, Blackwell & Hayllar 1997, Wong et al 1997) reported similar findings associated with vigabatrin. During this period however the manufacturers Hoechst Marion Roussel had only received rare reports of visual field defects associated with vigabatrin, a frequency of less than 0.1% of the 140,000 patients who had received the drug since 1989 when it was first licensed (Backstrom et al, 1997).

It was unknown whether the visual field defects were purely associated with vigabatrin, associated with the epilepsy itself, somehow affected by other antiepileptic drugs, or was the result when vigabatrin was taken in combination with other drugs. At that time no adult study had investigated the visual effects of monotherapy with vigabatrin.

Of the above factors, it was also unknown which were associated with the visual electrophysiological findings of Harding et al (1995) and Eke et al (1997). Although involvement of the ERG, EOG and oscillatory potentials responses indicated retinal involvement, probably at the levels of the ganglion cells, bipolar cells and retinal

pigment epithelium, it was also unknown whether these abnormal responses were directly associated with the visual field defects.

As the treatment of epilepsy does not routinely include ophthalmological testing, the true incidence of the patients affected by vigabatrin was not known nor was whether the condition was permanent or reversible.

Since visual field constriction, ERG and EOG abnormal responses had been reported associated with vigabatrin, these tests were completed in all parts of this study. Although VEP and pattern ERG responses have not been reported to be affected by vigabatrin, these tests were completed only in the patient groups in order to complete visual electrophysiology.

This thesis aims to address four main aspects associated with the side effects of vigabatrin treatment.

1. In order to establish the effect of vigabatrin on the electrophysiological responses, initially eight vigabatrin patients (6 who had been withdrawn from the drug and 2 that were currently taking vigabatrin), with known visual field defects (three of which had been the cases previously reported by Eke et al, 1997) were referred to Aston for testing and their results were compared to the Aston normal databases.

2. To investigate whether normal healthy subjects developed any changes in the visual fields or electrophysiology after receiving a short-term dose of vigabatrin. The effects of a short-term intake of carbamazepine, (the usual first line drug of choice for patients with complex partial seizures) were also tested. This was undertaken as a double blind cross over placebo controlled study. In this study any changes in the responses would not be associated with the presence of epilepsy or other drugs.

3..In order to try and assess whether the presence of epilepsy and the combination of other antiepileptic drugs with vigabatrin may affect the visual responses a matched pairs study was carried out. Eleven vigabatrin patients were matched by sex, age, seizure type and drug therapy with eleven other epileptic patients who had never

taken vigabatrin. Any changes in the responses of the vigabatrin group, which did not occur in the control group, would indicate an association with the drug.

4.The visual fields of the vigabatrin patients were showing a loss of the peripheral vision, more evident nasally than temporally and of varying severity through out the patient group. Unfortunately, visual field testing requires a lot of concentration and valid results are not usually obtained in paediatric patients under ten years old or in patients with behavioural and learning difficulties. The final aim was to develop a system/ diagnostic test, which could detect peripheral visual field loss and could be used reliably with these patients.

A field specific VEP stimulus ('dartboard stimulus') was developed. It consists of a central area of alternating checks that extend from 0-5 degrees radius, a blank annulus from 5-30 degrees and a peripheral annulus of alternating checks from 30-60 degrees. Responses were recorded monocularly from the central and peripheral stimuli using electrodes positioned at O1 & O2 with reference to Fz. By testing 4 vigabatrin patients with peripheral visual field loss that extended to 15-20 degrees, it could be seen that no peripheral responses were evoked. A normal database of 47 children aged between 3 and 10 years was then collected for comparison with future patient results.

Currently the manufacturers agree that vigabatrin appears to be associated with the visual field defects and approximately 31% of adult patients treated with vigabatrin for epilepsy are thought to be affected.

CHAPTER 1 INTRODUCTION TO EPILEPSY

1.1 Classification of Epilepsy

Epilepsies and epileptic syndromes are terms used to describe a variety of disorders classified by the Commission on Classification and Terminology of the International League Against Epilepsy (ILAE) as ' an epileptic disorder characterised by a cluster of signs and symptoms customarily occurring together; these include such items as type of seizure, aetiology, anatomy, precipitating factors, age of onset, severity, chronicity, diurnal and circadian cycling, and sometimes prognosis' (1985,1989).

There are two main types of epilepsies, a). those with generalised seizures and b). those with partial or focal seizures. Another common method of dividing the epilepsies is in terms of their aetiology in which there are three major categories 1).Primary (idiopathic) epilepsies which do not follow or are not associated with another disorder. 2). Secondary (symptomatic) epilepsies which are thought to have developed in relation to a previous disorder of the central nervous system. 3). Cryptogenic epilepsy which is often considered to be secondary epilepsies although the cause of the disorder is not known or hidden.

Although the International classification defines a large number of groups and sub-groups of epileptic disorders, every patient with epilepsy may not necessarily conform to one group of seizure type. Loiseau et al (1991) attempted to classify 986 patients recruited from an adult neurology unit and a private practice. They reported that in 97% of the cases, a clearly defined syndrome could be classified. However, they did experience some difficulties in the classification of a group of children diagnosed as having infantile psychosis, mental retardation and experienced generalised, or partial and generalised seizures with either bilateral spike-wave discharges or functional foci. They also stated that a small number of patients remained unclassified, some owing to the fact that the clinical symptoms did not fit the International Classification of Epilepsies and Epileptic Syndromes (ICE).

1.2 Incidence and prevalence of epilepsy

The incidence and prevalence of epilepsy has been studied throughout the world. There has, however, been some discrepancy in the figures presented in different

studies mainly due to the parameters used in defining whether a certain disorder or syndrome is classified as epileptic. Keränen et al (1989) studied the incidence and prevalence of epilepsy in patients equal to or older than sixteen years, in an area of Eastern Finland covered by the Kuopio University Central Hospital district between 1960 and 1979. They defined epilepsy as 'a condition with at least two unprovoked, non febrile epileptic seizures separated by a minimum time interval of 24h. An epileptic EEG was not prerequisite for the diagnosis of epilepsy.' Keränen et al reported an incidence of epilepsy of 24 per 100,000 and a prevalence of 629 per 100,000.

A previous study carried out in the Copparo district of Italy by Granieri et al (1983) reported a similar prevalence value of 6.2 per 1000 but a slightly higher incidence value of 33.1 per 100,000. This study followed the World Health definition of epilepsy, this being 'Epilepsy is a chronic brain disorder of various aetiologies characterised by recurrent seizures due to excessive discharge of cerebral neurones (epileptic seizures), associated with a variety of clinical and laboratory manifestations'. They then classified the disorders according to the ILAE.

The higher incidence value in the study by Ganieri et al (1983) could be related to the classified group where the majority of the patients were under the age of 19yrs. In contrast it could also be argued that this is not the case since Hauser et al (1991) reported an increase in prevalence in elderly patients possibly due to an increase in survivorship or as a secondary disorder to disease such as a cerebral vascular accident. Forsgren (1990) also found the highest age-specific incidence rate was in the patients over sixty years of age in a study investigating the characterisation of epilepsy in newly diagnosed patients. He also stated that up until this age males showed a higher incidence ratio than females with the rate of initial diagnosis being 38.5 per 100,000 for males and 28.7 per 100,000 for females.

Different types of seizure manifest with differing frequencies and appear to affect different age groups in the population. Keränen et al (1988) investigated the distribution of seizures in Eastern Finland in a sample of 1,220 patients over the age of 15 years. They obtained the information from hospital case records, area health centres and EEG records. Classification was in accordance with the International Classification of Epileptic Seizures (ICES). They were able to clearly classify 82.5%

of cases according to the dominant seizure type and found that of these 56% of patients suffered with partial seizures (7.5% simple partial, 23% complex partial and 25.5% partial seizures leading to secondarily generalised seizures). Twenty-six and a half percent suffered from generalised seizures of which 1% experienced absence seizures and 23% had tonic/clonic seizures. A further 2% experienced both partial and generalised seizures.

Regarding age-specific prevalence of epileptic seizures, Hauser et al (1991), Keränen et al (1989) and Granieri et al (1983) all state that the incidence and prevalence of generalised onset epilepsy is higher in childhood and in early adult life, whereas in the more mature adult there is a higher incidence and prevalence of partial epilepsy. Granieri et al (1983) suggested that this may either be associated with the good prognosis of generalised seizures in childhood or the increase in incidence of partial seizures in older patients being related to the increased occurrence of brain tumours and cerebrovascular disorders. Hauser et al (1991) also described a gradual increase in active prevalence of epilepsy from birth up to 20yrs, a stable adult prevalence and then another increase in the elderly (over approximately 70yrs)

1.3 Diagnosis of seizure type

The differential diagnosis of the seizure type, as well as the knowledge of the symptoms experienced, are important for the management of the disorder. The electroencephalogram (EEG) along with details of the symptoms and family history are required.

Sometimes for chronic uncontrolled epilepsy neuroradiology and neurophychology tests are undertaken.

1. Positron emission tomography (PET) which measures regional blood flow and metabolic rate. Epileptic foci are associated with ipsilateral regions of hypoperfusion and hypometabolism between seizures (interictally) and hyperperfusion and hypermetabolism during seizures. This technique, however, does not localise the foci (Fish, 1989).
2. Computerised tomograhy (CT) can measure an altered density in tissue which may be caused by atrophy or a lesion. This, however, is currently more accurately measured by magnetic resonance imaging (MRI)

1.3.1 The EEG recording

The EEG is recorded from electrodes placed at set locations on the scalp, measured by the bony landmarks of the skull and according to the International 10-20 system. The electrical potentials in the brain are recorded as a change in the voltage corresponding to the potential difference between the recording electrode and the reference electrode (Fz). A continuous trace is recorded and any abnormal activity can be seen. During a seizure the brain exhibits abnormally excessive activity which usually will become apparent on the EEG. Generalised seizures will show a spread of this increased activity through out the brain and partial seizures will show activity on the channels relating to the focal area which may spread to adjacent regions or become generalised. Some patients may also exhibit abnormal EEG recordings between seizures.

1.4 The EEG and epilepsy

Intensive monitoring of the patient may take place in a hospital setting with 24hr EEG and video monitoring to record the type of seizure and visual events relating to the ictal event. Alternatively, a 24hr recording can be completed with ambulatory monitoring with the patient keeping a diary and noting the times of the symptoms which can later be related to the EEG recording. During the EEG monitoring, a single channel electrocardiogram (ECG) is often recorded as epileptic seizures may be associated with a change in the ECG i.e. a change in heart rate. Alternatively, a disturbance with the cardiovascular system may result in a change in the EEG. However, unlike cardiovascular patients, those with epilepsy, when between seizures, show no more ECG abnormalities than the normal population (Binnie et al, 1989).

The differential diagnosis of whether epilepsy is the cause of the patient's problem and if so, the type of seizure he/she is suffering from is a complex procedure. Seizures occurring at the time of EEG monitoring will most often show whether they are epileptic in nature or not, with the different seizure types showing different patterns of EEG change. Together with studying the rhythm and frequency of the discharge, areas in which this occurs (with partial seizures), whether it is associated with impaired consciousness, psychic or viscerosensory symptoms and whether a partial seizure becomes generalised, amongst other factors, the clinician is able to classify the type/types of epilepsy the patient is suffering from.

Accurate classification of the seizure type is essential as different types respond to different drug therapies. Dreifuss (1997) categorised the symptoms and EEG changes typically associated with each seizure type. He described how absence (generalised) seizures and complex partial seizures may both present with the patient describing 'a short period of unawareness and unresponsiveness' and yet both seizure types are very different and require different drug therapies.

1.5 Complex partial seizures

The majority of the patients in this study suffer from complex partial seizures. These mainly differ from simple partial seizures by the association of an impairment of consciousness at the onset of the seizure or as a symptom following a simple partial onset. Also complex partial seizures frequently involve both hemispheres whereas simple partial seizures are usually unilateral.

Prior to the revised edition of the commission on classification and terminology of the International League Against Epilepsy (ILAE) in 1981, the term 'complex partial seizure was used interchangeably with 'temporal lobe seizure' and 'psychomotor seizure'. However, it has been found that not all seizures with psychic symptoms had motor involvement, not all temporal lobe seizures had psychomotor symptoms, some seizures that initiate outside the temporal lobe may spread to the limbic system and some temporal lobe seizures may have complex symptoms without involving the limbic system (Williamson & Engel Jr. 1997). Therefore, the term complex partial seizure was chosen to classify a seizure type that differs from a simple partial seizure by the association of impaired consciousness.

Although the first line of treatment for partial seizures is usually carbamazepine, phenytoin or sodium valproate (Walker, 1996), views of the efficacy of monotherapy with sodium valproate for complex partial seizures have been varied and carbamazepine remains the drug of choice. Between a fifth and two thirds of complex partial seizure patients are not controlled by antiepileptic drugs and many are prescribed a combination drug therapy with the effects of new drugs often studied as an 'add-on' trial. Since 1982, vigabatrin has been used in studies with patients suffering from resistant epilepsy (Dam 1991) and when used as an 'add-on' drug to

the current therapy, it appeared to have a positive effect in reducing the frequency of the seizures.

Meldrum (1989) suggested three hypotheses for the factors resulting in the intractibility of chronic epilepsy.

1. A defect of the neuronal membrane and it's ionic conductive properties.
2. A defect in the GABA-ergic inhibitory system or in other endogenous anticonvulsant agents.
3. A defect in the excitatory mechanisms, especially with the excitatory amino acids.

Different drugs are developed to counteract these different defects and one or a combination of drugs may be used to threat the different seizure types.

CHAPTER 2 VIGABATRIN

2.1 Structure and metabolism of vigabatrin

The anti-epileptic properties of vigabatrin are based upon the mechanism of increasing the whole brain concentration of gamma-amino butyric acid (GABA) which is a major inhibitory neurotransmitter. Vigabatrin has a very similar chemical structure to that of GABA (fig. 1) enabling it to bind to the GABA-Transaminase (GABA-T) enzyme (the enzyme that degrades GABA). The slight difference in the chemical structure ensures vigabatrin binds irreversibly to the enzyme, therefore increasing the concentration of available GABA. The inhibition of GABA-T as a result of vigabatrin treatment has been found to be dose dependent in the rat brain with comparable dose response curves with the dose range used in man (Bolton et al 1989).

Fig. 1 shows the similarity in the structures of vigabatrin and GABA which enables vigabatrin to bind with GABA-T. (Reprinted from Richens, 1991).

Vigabatrin is taken orally and is very water soluble (33 mg/ml), (Ben-Menachem, 1995). It is rapidly absorbed, reaching a maximum plasma concentration after approximately 2 hr and having a plasma concentration half life of between 5-7 hrs (Schechter, 1989). The drug is eliminated mainly via the kidneys with approximately

70% being excreted as an unchanged compound, (Ben-Menachem , 1995, Ben-Menachem & French 1997).

Following absorption, vigabatrin does not bind to plasma proteins. It is minimally metabolised and does not induce the action of liver enzymes which may result in the reduction of efficacy (by increased or decreased rate of metabolism) of other current drug treatments (Mumford, 1988). Rimmer & Richens (1989) did find that the addition of vigabatrin to the therapy of patients taking phenytoin as part of their prescribed medication resulted in a decrease of plasma phenytoin concentrations. This only occurred four weeks after the addition of vigabatrin (weeks 2-4 having the maximum dose of vigabatrin (3g/day)). However due to the 4 week delay they concluded that this effect was unlikely to be associated with vigabatrin. Vigabatrin appears to have few drug interactions and mild side effects. The most common side effects experienced with vigabatrin are drowsiness, dizziness, mood instability, headaches and weight gain. These effects are relatively mild and are tolerated by most patients.

2.2 Efficacy of vigababtrin

Due to the difficulties in treating these patients, the majority of the research in this area has involved the use of vigabatrin as an 'add-on' drug to concomitant therapy. Riekkinen et al (1989) studied 75 patients suffering from complex partial seizures. In every patient , 3g/day of vigabatrin was 'added on' to their medication for a period of three months. After this time they found a decrease in seizure frequency of over 50% in 41 cases. The responders were then divided into equal numbers, one group of patients continued on 3g/day of vigabatrin for a further three months and the others were reduced to 1.5g/day. They found that the reduction in dose resulted in an increase in seizure frequency.

Other studies, mainly investigating the change in seizure frequency after the addition of vigabatrin have also reported reductions of approximately 50% (Loiseau et al (1986), Michelucci & Tassinari (1989)). Although nearly half the patients decreased in frequency of seizures and nearly one fifth improved Michelucci & Tassinari (1989) describe these figures as low in comparison to other studies reported since the accumulated data was more representative of the population suffering with partial seizures.

More recently vigabatrin monotherapy has been studied in newly diagnosed patients with epilepsy. In a randomised controlled study by Kälviäinen et al (1995), patients suffering from partial seizures and /or generalised tonic clonic seizures were randomly administered either carbamazepine or vigabatrin. The control group consisted of patients who had experienced one epileptic seizure but were given no drug treatment. Sixty percent of patients were successfully treated (being seizure free or with acceptable seizure control) in each group, over a period of twelve months. The main failure with vigabatrin treatment was the occurrence of seizures, 26% of patients experiencing unacceptable seizure control. Although 52% of patients taking carbamazepine became seizure free, failure of 24% was reported to be due to intolerable side effects. As mentioned earlier the side effects of vigabatrin appeared to be mild and no patients dropped out of the study by Kälviäinen et al (1995) for these reasons.

2.3 Neuropathological results with animal studies

Preliminary animal studies have reported neuropathological changes in rodents and dogs associated with vigabatrin. Rodents given vigabatrin at doses of 100-300 mg/kg/day for a year exhibited myelin vacuolation, although this was limited to the visual pathways, hypothalamus, fornix columns and cerebellar white matter. Electron microscopy suggests that this neuropathology is associated with the separation of the outer layer of the myelin sheath leading to microvacuolation. Dogs, however, treated with doses of 200/kg/day for one year only developed intramyelinic oedema (which did not progress to separation of the lamellae), limited to the areas of the fornix columns, optic tract and chiasm and hypothalamus. These were reversible on cessation of the drug (Graham 1989). In general, monkey studies have not reported a finding of microvacuolation in the CNS comparative to those of rodents and dogs. Post-mortem and post-surgical tissue of human patients previously receiving vigabatrin show no evidence of myelin microvacuolation associated with the drug (Cannon et al 1991).

Although the animal studies reported neuropathological conditions associated with the drug, the majority of the patients who are prescribed vigabatrin have experienced severe seizures, unable to be sufficiently controlled by other AED's. Therefore the risk of developing a neuropathological condition whilst taking vigabatrin has to be weighed up against the improvement in the quality of life, that the patients would gain, from a reduction in seizure frequency.

2.4 The effect on the visual system in humans

Although the main side effects of vigabatrin in patients have been found to be associated with drowsiness, headaches and weight gain, usually of a mild form and well tolerated, the neuropathological findings in animal studies (with high doses of vigabatrin) are still of concern.

It may be that the neuropathological findings are in some way associated with the increased concentration of GABA whilst taking vigabatrin. GABA is ubiquitous (being everywhere at once, everywhere) in the retina and the increase in concentration due to vigabatrin may also have an effect on the retinal function. Evoked potentials of the brain can be easily recorded non-invasively with the use of surface electrodes and a suitable stimulus, and measure the time taken from the retina to the brain.

Studies by Hammond and Wilder (1983, 1985, 1987) and Hammond et al (1988a, 1988b) investigated the effect of vigabatrin as an 'add-on' therapy' to the components of the VEP. They concluded in 1987 and 1988 there was no significant change when compared to the baseline values (pre-treatment phase) in the latencies of the main components in any of the evoked potentials recorded. This is a view shared by Mervaala et al (1987) when studying patients with complex partial seizures being administered vigabatrin as monotherapy after previously having received monotherapy with carbamazepine. They reported no significant prolongations of the latencies for the VEP responses after the therapy with vigabatrin.

By 1995 however Harding et al had reported a prolonged b-wave latency of the photopic ERG after the addition of vigabatrin to the therapy of epileptic patients. Eke et al (1997) then reported visual field constriction, low EOG Arden indices and reduced oscillatory potentials of the ERG associated with vigabatrin. Therefore although therapeutic doses of vigabatrin did not appear to affect the visual system in the same manner as the doses given to animals there still appeared to be an adverse effect.

CHAPTER 3 VISUAL ELECTROPHYSIOLOGY AND VISUAL FIELD TESTING

3.1 Composition of the retina and electroretinograms

3.1.1 The retina

Externally the choroid layer supplies the nutritional requirements for the underlying pigment epithelium and photoreceptors, the blood supply coming from the central retinal artery. The photoreceptors (rods and cones) are situated below the pigment epithelium and their nuclei form the outer nuclear layer.

Deeper into the retina lie the bipolar cells and their nuclei form the inner nuclear layer. Below the inner nuclear layer there is the ganglion cell layer. Between the outer and inner nuclear layers, horizontal cells are situated at the outer plexiform layer. These horizontal cells send information to other horizontal cells and to both the photoreceptors and the bipolar cells. A layer of amacrine cells is located between the ganglion cells and the bipolar cells at the inner plexiform layer, these cells contain many neurochemicals and synapse with other amacrine cells, the bipolar cells and the ganglion cells. Large glial cells termed Müller cells occupy the extracellular spaces. The organisation of the retina can be seen in fig.2.

The organisation of the cells is not uniform throughout the retina. The highest density of cones is at the fovea having approximately 150,000 cells/mm^2. The cones contain either blue, green or red pigments for colour vision, no blue cones are present at the fovea (Ikeda, 1987). About 20 degrees from the fovea the density of the cones decreases and the density of the rods peak with a value of approximately 150,000 cells/mm^2. Towards the periphery of the retina the density of the rods decreases, although in the far periphery there are still around 60,000 cells/mm^2. At the fovea the photoreceptors synapse singularly with a bipolar cell and a fewer ganglion cells , however towards the periphery many photoreceptors synapse with less bipolar cells and even fewer ganglion cells. The axons from the ganglion cells receiving information from the central retina eventually occupy approximately 60 percent of the visual cortex whereas those arising from the peripheral retina only occupy a small area (Ikeda, 1987).

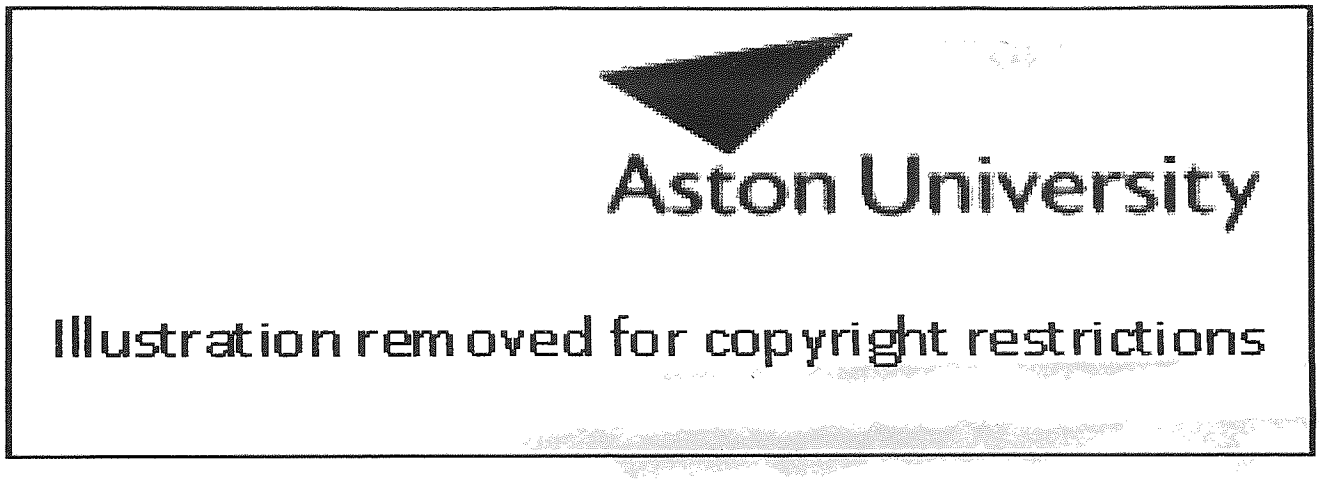


Fig.2. shows the structure of the retina as viewed through an electronmicroscope.
(Reprinted from an illustration by Ikeda (1987).

3.1.2 Components of the flash electroretinogram

The ERG was defined by Noell (1954) as 'the retinal response to illumination measured from cornea (or corpus vitreous) in reference to the outside of the eye'. The retinal response to a single flash of light produces a biphasic waveform, with a dominant positive b-wave preceded by a negative a-wave and lastly a slow positive c-wave. An early receptor potential can sometimes be seen immediately prior to the a-wave taking the form of a positive peak and a larger negative component. This is thought to be associated with the initial response to the bleaching of the retinal photopigment. Small wavelets can also be seen on the rise of the b-wave, these multiple positive components were first described by Cobb & Morton in 1954 and were termed oscillatory potentials. The ERG is a mass response made up of the a, b, c, components, oscillatory potentials and the early receptor response. The retina is composed of multi-layers of cells, different cell types give rise to certain aspects of the ERG wave.

The a,b and c waves

The negative a-wave is thought to be mainly produced from the hyperpolarisation of the photoreceptors in response to the flash of light . This response is made up of a fast cone component and a slower rod response (Ikeda, 1987). The positive b-wave is generally accepted as being associated with the depolarisation of the bipolar cells in the inner nuclear layer. Miller and Dowling (1970) argue that although the peak of the bipolar response is similar to the b-wave of the ERG, the absolute and peak latency of the bipolar response occurs too early when compared with that of the b-wave. After recording ERG responses from the eyes of 100 mud puppies, then recording the response of the Müller cells to the same stimulus using microelectrodes, Miller and Dowling (1970) reported that the light-induced responses of the Müller cells were always positive (depolarising) and that they were identical to the b-wave of the ERG. It may be that the Müller cells contribute in the formation of the b-wave, but the disappearance of the b-wave when the blood supply is clamped to the bipolar cells strongly suggests involvement of these cells (Ikeda, 1987). The c-wave of the ERG is thought to originate in the pigment epithelium (Miller and Dowling, 1970).

This view is supported by Noell (1954), he studied retinal illumination of the retina in rabbits and the effect of intravenous administration of poisonous agents (azide, sodium iodate, iodoacetic acid) on the different components of the ERG. He then compared these effects to the structural damage produced. After investigating the origin of the c-wave of the ERG (the most prominent component in the ERG of the rabbit), he concluded that 'the initial event for the generation of the c-wave must be a change in the ion concentration at the retinal side of the pigment epithelium'.

The oscillatory potentials

The oscillatory potentials are thought to arise from the inner part of the retina, evidence to support this theory is the abolishment of the potentials after the circulation to this area is prevented, as with central retinal artery occlusion (Galloway, 1981). The oscillatory potentials have been localised to the inner nuclear layer but are thought to be a separate response to that of the b-wave. Particularly large oscillatory potentials have been reported, when recorded from species with many cone receptors in the retina and a well developed inner nuclear layer (the pigeon). An absence of the OP's along with the b-wave has also been reported in patients with congenital achromasia (rod monochromatism, Algarve, 1968). Wachtmeister and Dowling (1978) further studied the origin of the oscillatory potentials in the mud puppy. They described the mud puppy OP's as having many similar properties to those of human and other vertebrate OP's. They stated that although the interstimulus interval required to produce the OP's of maximum amplitude in the human were much shorter (30sec) than in the mud puppy (60sec), in both species up to seven OP's could be seen with a similar appearance and latency for a given stimulus. They investigated the effect on the responses of different depth penetration of the retina. They recorded a transretinal ERG with the active electrode in the vitreous and the reference electrode behind the eye cup, the intraretinal potentials were recorded via micropipettes, a spot stimulus was used. They found that the oscillatory potentials reversed in polarity in relation to retinal depth, they also reported this to be a feature of the b-wave, indicating that it was generated by structures which extended radially through the retina. They described the different OP's reversing in polarity at different depths of the retina (with the surface nearest ganglion cells being termed 0% depth and the surface nearest the photoreceptors being termed 100%). They reported the first OP

(OP1) to reverse at approximately 20% depth (at the border of the inner plexiform layer and the inner nuclear layer), the OP2 and OP3 components reversing at a 30% depth (in the middle of the inner nuclear layer), the b-wave reversing at 35% depth (in the inner nuclear layer) and the OP4 and OP5 components reversing at a 40% depth (still within the inner nuclear layer). Wachtmeister and Dowling (1978) also investigated the effect on the b-wave and OP responses after applying increasing concentrations (0.1mM to 10mM) of GABA to the open eye cup. They found a decrease in the amplitudes of the OP's approximately 1 minute after the addition of GABA. The OP1 component was found to be particularly sensitive. They reported hardly any effect to the b-wave. They suggested that since the polarity OP1 component had been seen to reverse at the retinal depth where the amacrine cells and inner plexiform layer are located, the generation of OP1 may be initiated by a synaptic feedback mechanism from the amacrine cells and/or inner plexiform layer to the inner nuclear layer and bipolar cells. They concluded that the application of GABA (an inhibitory neurotransmitter usually found at this site in the retina) would selectively depress the OP's.

3.1.3 The ERG and vigabatrin

Vigabatrin increases the whole brain concentration of the GABA (Bolton et al, 1989). Since GABA is a known constituent of retina (Ehinger and Falck, 1971), treatment with vigabatrin may result in an increase in the retinal GABA levels which could have an effect on the ERG response. Ehinger and Falck (1971) studied GABA levels of the rabbit retina and the mechanism of uptake of GABA in the retina by injecting radioactive (^{14}C) GABA into the vitreous. The retina was sectioned and the radioactivity of the different depths measured. They found that after 4hrs the radioactivity appeared mainly in the amacrine cells, the inner part of the nuclear layer and the inner plexiform layer. They suggested that this demonstrated an uptake of the GABA by the cells in these layers since other cell layers located nearer to and further from the site of the injected GABA did not show such a high level of radioactivity, thus ruling out the mechanism of a simple diffusion gradient across the retina. The components of the ERG responses, particularly those thought to arise from these areas or in part from these areas, may be subjected to an increase in the inhibitory response of GABA during vigabatrin treatment. The most sensitive response of the ERG

would probably be the OP's although the b-wave of the ERG may also be affected. Even if the functioning of these layers of the retina were to be affected by the increased levels of GABA, this may not be electro-physiologically evident.

3.1.4 Recording of the flash ERG

Under the official standards of the International Society for the Clinical Electrophysiology of Vision (ISCEV) 1989, the full field ERG should be recorded to include the following responses:

- 1) A maximal response in the dark adapted eye.
- 2) A response developed by the rods (in the dark adapted eye).
- 3) Oscillatory potentials
- 4) A response developed by the cones.
- 5) Responses obtained to a rapidly repeated stimulus (flicker)

The responses maybe recorded with a DTL fibre electrode consisting of filaments of spun nylon impregnated with silver (Thompson and Drasdo, 1987). One end of the fibre is connected to a metal hook, which is positioned at the lateral canthus of the eye. The fibre is then drawn across the sclera of the eye below the cornea so that it is floating on the tear film and the other end secured with tape to the side of the nose. Both a report by Celesia et al (1993) recommending the International Federation of Clinical Neurophysiology (IFCN) standards for ERG and VEP and the approved ISCEV (1994) standards state that the recording electrode should consist of a corneal contact lens which supports the eyelids. Unlike the contact lens electrode the DTL fibre does not require corneal anaesthesia, the fibre is also less likely to disturb the surface of the cornea which may affect the quality of the response. The DTL fibre can also be worn comfortably over quite a long period of time, while maintaining the patient's ability to blink (Thompson and Drasdo, 1987).
The reference electrode is also positioned near the outer canthus of the eye and an earth electrode is placed on the forehead. The impedance of the skin electrodes is kept to a minimum with a recommended upper limit of 5000 ohms (Celesia et al, 1993). The flash stimulus is presented from a full field Ganzfeld bowl to ensure

uniform illumination of the retina. The flash stimulus strength used was 3.0 cds/m^2 except for the response developed by the rods, in which to obtain a pure rod response, the intensity of the stimulus must be lower than the level required to stimulate the cones. ISCEV (1994) standards recommend a dim white flash 2.5 log units below the white standard flash, which they indicate must be within the range of 1.5-3.0 cds/m^2. Flash ERG recordings are recommended to be undertaken in the maximally dilated eye with at least 20 minutes dark adaptation prior to the recording of the scotopic responses as suggested by Celesia et al (1993). The pure rod response has been omitted in this study as the 2.5 log filter function was unavailable with the equipment used.

The ERG's in this study were recorded using a Medelec Sapphire 4E recording system and a Ganzfeld stimulator and bowl.

Figures 3, 4, 5 & 6 show the responses obtained from a normal subject for photopic, 30Hz flicker, oscillatory potentials and scotopic (maximal) ERG response.

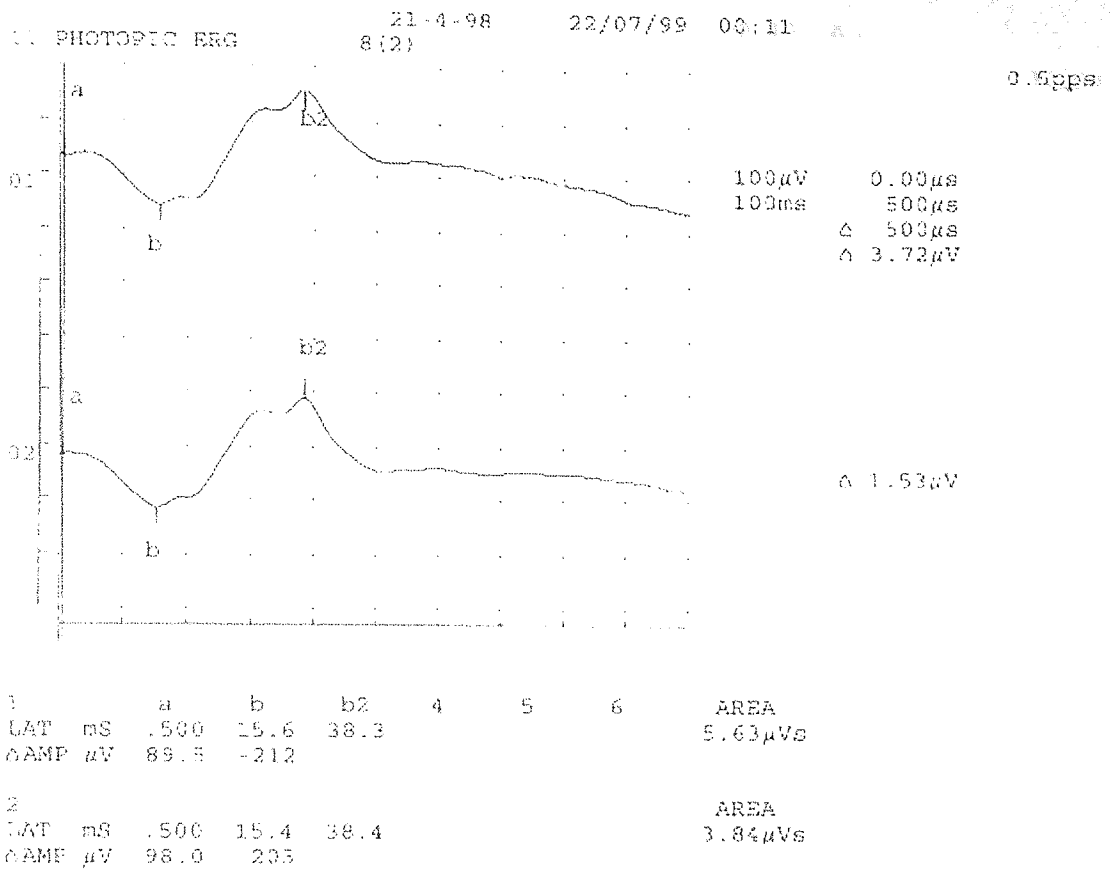


Figure 3 shows the photopic ERG responses of a normal subject. The top trace is that recorded from the right eye and the bottom trace from the left eye. The a wave is labelled 'b' and the b-wave 'b2'. The latencies and amplitudes of these components can be seen below the traces.

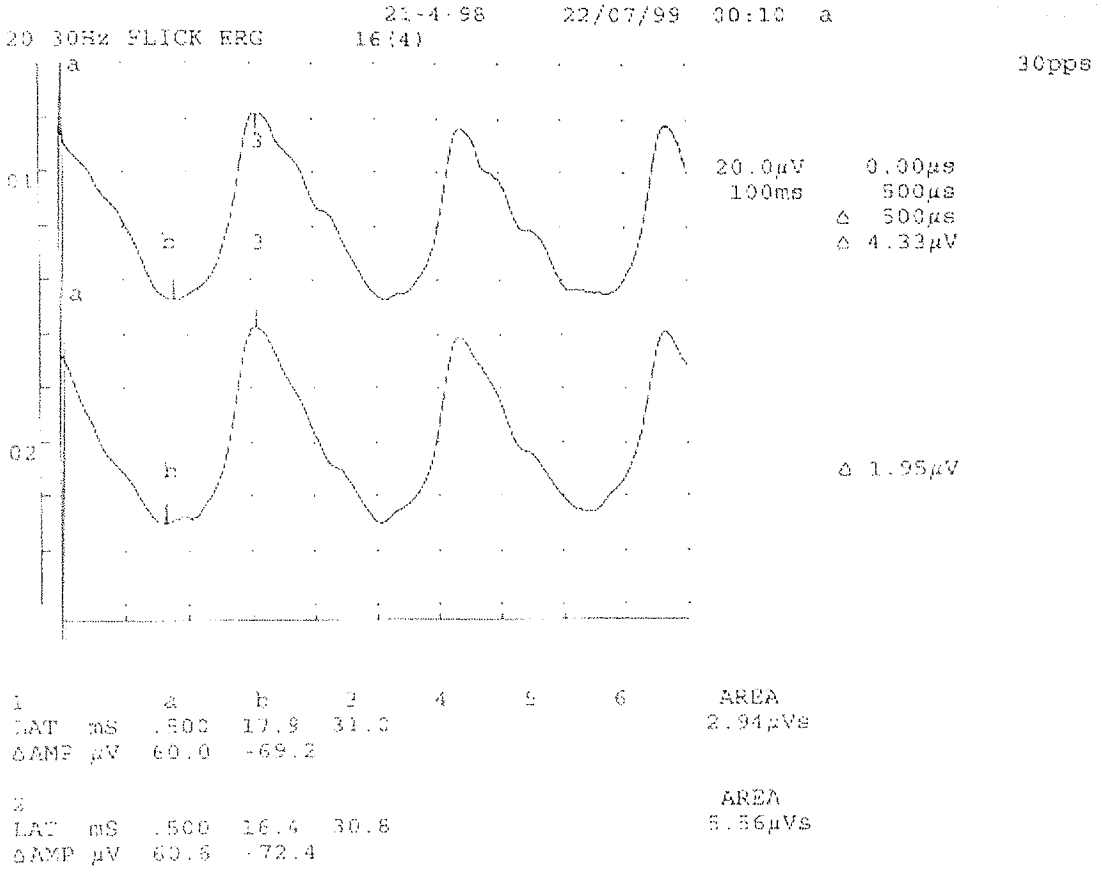


Figure 4 shows the 30Hz flicker ERG responses of a normal subject. The top trace is that recorded from the right eye and the bottom trace from the left eye. The a wave is labelled 'b' and the b-wave '3'. The latencies and amplitudes of these components can be seen below the traces.

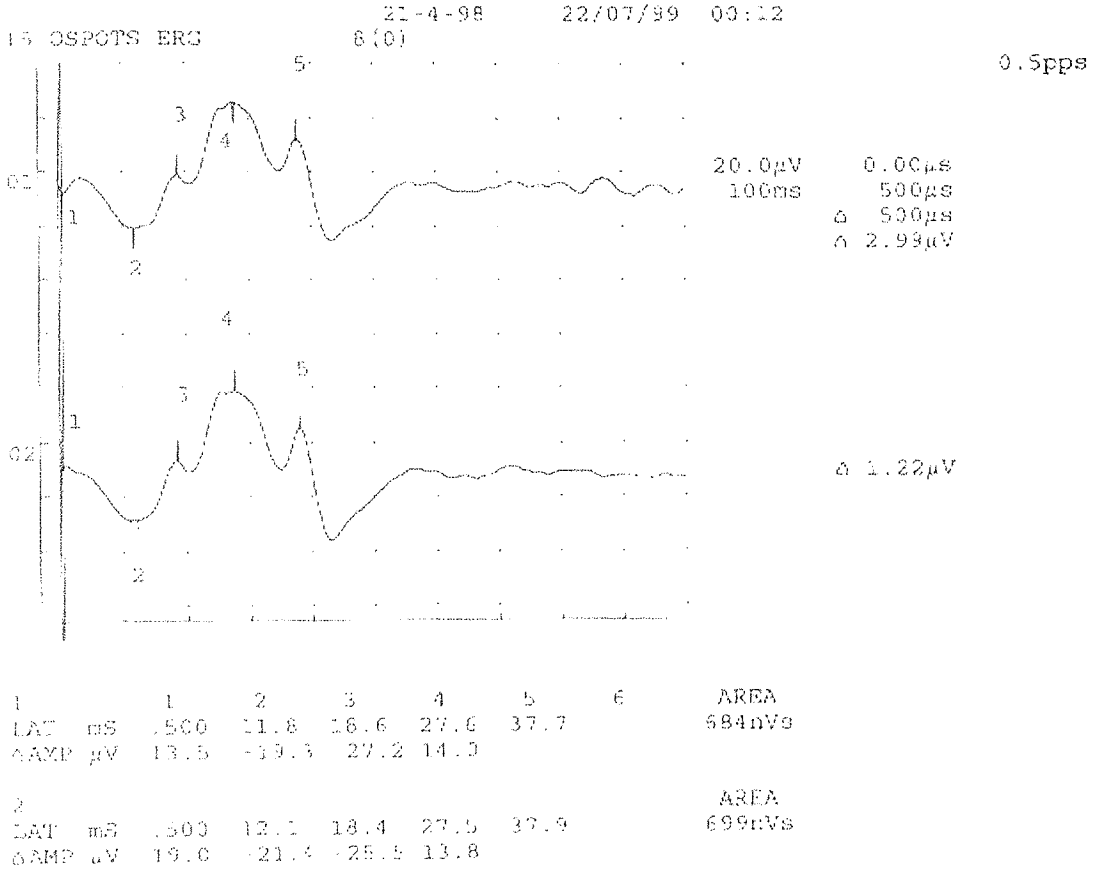


Figure 5 shows the oscillatory potential responses from a normal subject with the right eye above and the left below. The a-wave is labelled 2, OP1 labelled 3 and OP2 labelled 4. The latencies and amplitudes can be seen in the table below the trace.

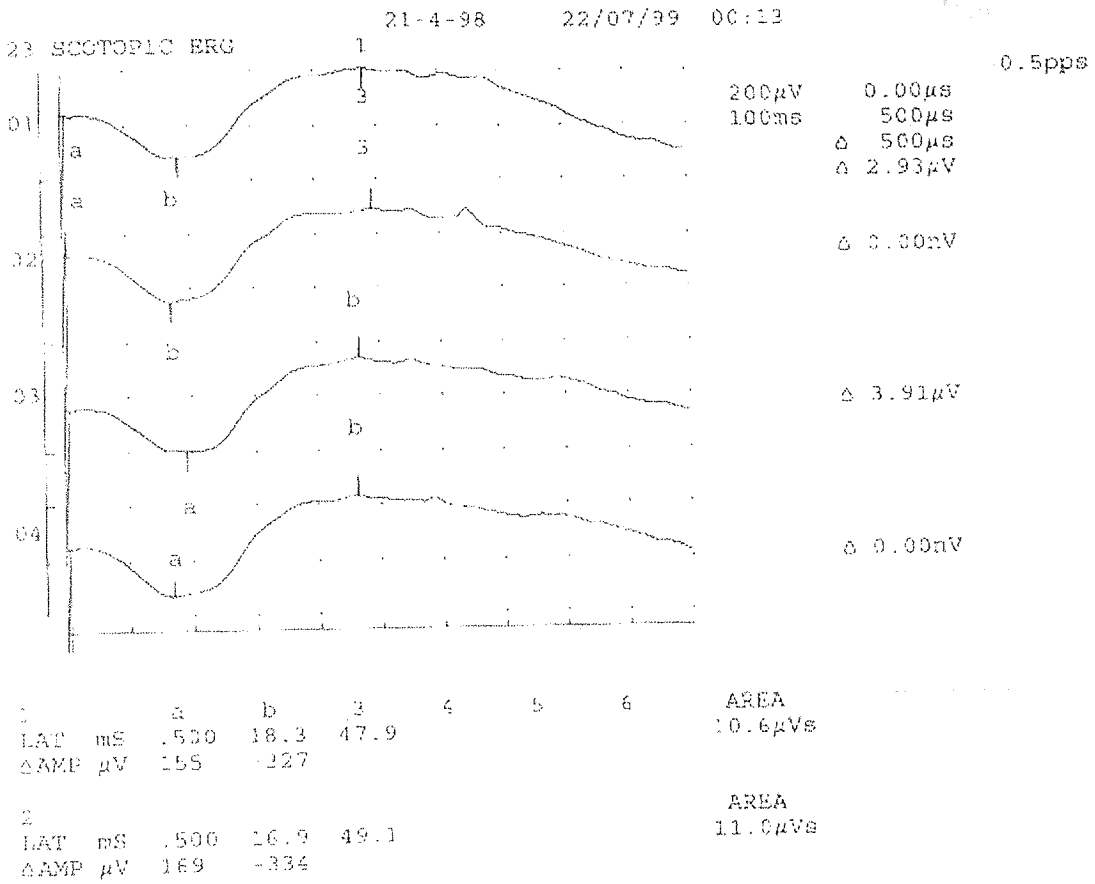


Figure 6 shows the scotopic (maximal) ERG responses of a normal subject. The traces are ordered downwards right, left, right, left. The a wave is labelled 'b' and the b-wave '3'. The latencies and amplitudes of these components can be seen below the traces.

3.1.5 The pattern ERG

The pattern ERG is recorded with the same electrode positions as the flash ERG. In this study the pattern reversal stimulus of constant total luminance is presented on a television screen with a reversal rate of 2Hz. The normal response produced presents on the monitor as a waveform with a negative component at approximately 35ms (N35), a positive peak at approximately 50ms (P50) and a negative component at approximately 95ms (N95). The latencies of the N35, P50 and N95 components are measured together with the N35-P50 and P50-N95 amplitudes. The PERG records a response which indicates the level of functioning of the inner retina. Lesions that may only affect a small central area of the retina may not be obviously apparent in a mass flash ERG of the whole retina. Recommendations for ISCEV standards (Marmor et al, 1996) suggest that the stimulus parameters be 'a black-and-white reversing checkerboard with a stimulus field size between 10 and 16 degrees, and a check size of approximately 40 degrees'. The 'contrast should be maximal (but no less than 80%)'. The photopic luminance levels of the white areas should be greater than $80cd/m^2$ since PERG's are difficult to record with a low stimulus luminance. The luminance should also not alter during the reversals. The responses should also be recorded with the patients' pupils undilated with refractive errors corrected for the viewing distance if required. This study will adhere as closely as possible to the recommendations. Responses will also be recorded binocularly which is preferred in the recommendations. To obtain a clear recording of this small response many wave forms must be averaged. This study uses the pattern reversal checkerboard with 256 averages. The 'interrupted recording technique' is applied to allow the subject to blink and briefly rest in order to assist in maintaining fixation and reducing the artefacts produced from movement and blinks.

3.2 The electroculogram

The electro-oculogram (EOG) is an indirect recording of the potential difference between two electrodes taped to the skin at the medial and lateral canthi of the eye, this was first demonstrated by Du Bois-Reymond in the 19th century.

The eye has an ocular dipole (a positive corneal pole and negative pole of the fundus), the standing potential of which is approximately 60mv and generated mostly from the retinal pigment epithelium. Recordings are obtained by applying two

surface electrodes to the skin, one each to the medial and lateral canthi of the eye. A third electrode (an earth) is applied, usually to the forehead. The resistance between the skin and electrode is kept to the lowest level possible to minimise interference and artefact on the trace. The EOG continually records the changes in the corneo-retinal potential. As the eyes are moved there is a large change in the potential difference recorded, mainly due to the change in the orientation of the ocular dipole. The amount of change in potential difference from before to after the movement depends upon the degree of movement. The electro-oculographic technique performed in this study uses fixation lights 30 degrees apart. The eyes fixate on the illuminated red light for approximately 1 second and the 30 degree movement occurs to the other light when that in turn becomes active. The sweep speed (recording time) is set at 10 seconds resulting in a trace consisting of 5 saccades (see fig 7). Irregular or incomplete saccades can then be disregarded. The potential difference between the two eye positions can be measured between the base and peak of the saccade (see fig.7).

The potential difference is not only altered by eye movement but also by retinal illumination. Both the rods and cones contribute to the electro-oculogram (Galloway, 1981), however, Arden and Kelsey (1962) state that most of the potentials are generated from the pigment epithelium. Increases in illumination cause a light rise in potential difference and a period of darkness results in a fall to a dark trough. The dark trough is thought to be an 'all or nothing' response irrespective of the previous illumination. The light peak however, does appear to depend upon the intensity of the light and upon the amount of time spent in the dark prior to this (Arden and Kelsey, 1962). As well as the light peak and dark trough responses, the EOG is thought to exhibit a slow oscillation. Arden and Kelsey (1962) found that after the light peak at around eight minutes, the potential difference fell independently of the light. They also reported that after the dark trough (which occurred at approximately thirteen minutes after the lights had been turned off), there was a peak appearing at approximately 22 minutes and they concluded that the EOG has the form of a slow oscillation.

Since the intensity of illumination has been shown to affect the magnitude of the light peak, all EOG recordings in the light phase in this study are undertaken at 600cdsec/m^2 (International standards). In order to achieve a total retinal response the

'Ganzfeld' stimulator is used. Since the dark trough value appears independent of previous light intensity, there should be no effect on this value.
A study by Arden and Barrada (1962), on normal subjects found the ratio of the light peak divided by the dark trough to be a more reliable value than the actual measured potentials. They reported that any value under 185% i.e. Light Peak/Dark Trough x 100 (which they termed the Arden Index) is pathological. They also stated that any peak time over 11 minutes was associated with a low ratio. They also suggested that the effect of the intensity of illumination on the light peak value may partially be compensated for by the reflex pupillary constriction.

The EOG is usually recorded under 3 conditions:

- a). 5 minutes of constant illumination
- b). 13 minutes of dark adaptation
- c). 15 minutes of light adaptation

The 5 minutes pre-adaptation allows the recording of a steady baseline although small rises and falls may occur in some subjects. After studying the characteristics of the electro-oculogram over many hours, Kris (1960) suggested that this may be related to diurnal variation.

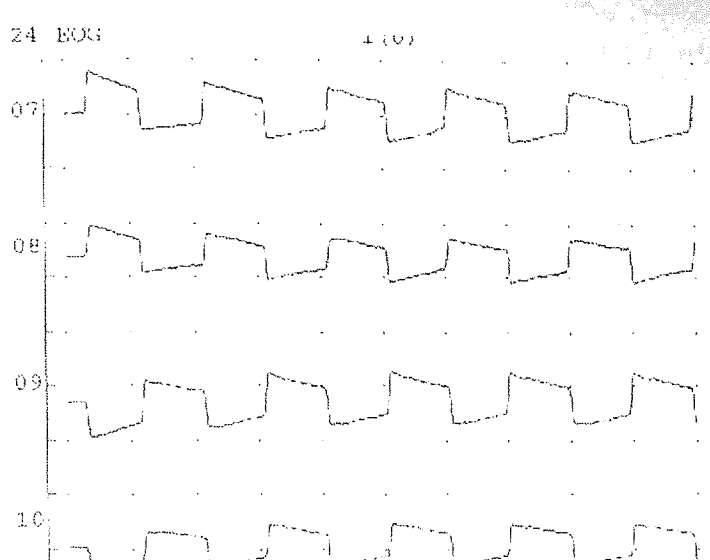


Fig.7. shows the EOG traces recorded from the right (R) and left (L) eyes of a 19yr old healthy male subject. Traces 1-4 show recordings for the RLRL eyes respectively. The movements of the eyes between two fixation lights situated 30 degrees a part form saccades of which five have been recorded on each trace.

Chapter 3.3 Visual field testing

3.3.1 Introduction

Since the report by Eke et al (1997) of three case reports of patients taking vigabatrin exhibiting visual field defects, there have since been numerous publications supporting the findings (Harding 1997, Daneshvar et al 1999, Hardus et al 2000, Wilton et al 1999) and the incidence of the affect has been reported to be as high as 29% in adults (Wild et al, 1999). More recently the visual field loss characteristic of the vigabatrin defect has been reported in children taking the drug (Vanhatalo & Pääkkönen 1999). However, research of the visual field effects in children has only recently been reported and another study found no affect of vigabatrin on paediatric visual fields after three months (Duckett et al, 1998).

3.3.2 The visual field

The visual field is all the space that one eye can see at any given instant. The normal monocular visual field extends 60 degrees upwards, 75 degrees downwards, 100 degrees temporally and 60 degrees nasally. The normal binocular visual field is 200 degrees horizontally but has the same extent as monocular vision vertically. With the gaze of the eye fixed on one point, each direction of the visual field corresponds to a different point on the retina, with the fovea corresponding to the point of fixation. As an image is inverted and reversed by the eye the temporal retina reflects the nasal visual field and the inferior retina reflects the superior visual field and vice versa. At about 10-15 degrees on the nasal side of the fovea the optic nerve head is formed to carry the information via the optic nerve to the brain. At this point no images or light can be detected and this is reflected by a blind spot on the temporal visual field. The visual field is also described as a hill of vision and was termed by Traquair in 1927 as an 'island of vision in a sea of darkness'. The height of the hill at any point represents the sensitivity of the vision. The sensitivity of the vision also changes with adaptation of the eye to light with the hill being higher in the dark-adapted eye than in photopic conditions. Therefore when testing visual fields the background light must be kept constant and the subject should be adapted to the background luminance prior to testing.

3.3.3 Presenting visual field stimuli

There are two main ways of presenting the stimuli to the subject.

1. A set intensity stimulus is moved towards the hill of vision until it is noticed, then this is repeated with either a higher or lower intensity stimulus. The sensitivity is tested at many points over different meridians and represented by isopters (lines joining the points of equal sensitivity). The different intensities used will form the different isopters described above, which form a type of contour map of the hill of vision. This is the basis of kinetic perimetry.

2. A stimulus is presented at one set point on the hill of vision. After the presentation, the stimulus intensity is altered until it is noticed and then decreased until it is no longer seen in a staircase manner (discussed later). As the stimulus does not move on presentation this is termed static perimetry.

3.3.4 The absolute threshold

The absolute threshold value is the minimum stimulus required to produce a sensation. This varies across the visual field but also with different background illumination, different stimulus size and the duration of the presentation of the stimulus. The threshold is represented by an S-shaped curve, which measures the reliability of the results. The x-axis is a measure of the stimulus intensity and the y-axis measures the percentage of times that the stimulus was seen (0-100%). The gradient of the curve indicates the intra-subject variability. The threshold point is taken as the 50% value of seeing or not seeing the stimulus. When the stimulus is observed above the 95% value it has reached the suprathreshold point. Below the 5% value is the infrathreshold point (Lieberman and Drake, 1992)

Outside the fovea and macula the process of summation occurs whereby the rod and cone responses converge on to the horizontal cells which further communicate between themselves and converge further to smaller numbers of bipolar cells and then to even fewer ganglion cells (Ikeda 1987). From this process the more peripheral

ganglion cells receive information from many rods and cones. Due to this convergence, two small spots of light stimulating simultaneously on the receptive field should require less luminance than one spot to produce a sensation. With perfect spatial summation the relationship would be as in the equation below, known as Ricco's Law

Ricco's law states-

Intensity x Area = constant

This law however only holds in some areas of the retina, at certain eccentricities and stimulus size, where complete summation occurs. Beyond these areas the summation is only partially achieved. Piper's law (seen in the equation below) holds in the areas of partial summation where the larger area of the stimulus requires a higher luminous intensity than a smaller one.

$(\text{Area})^{0.5} \times \text{Intensity} = \text{constant}$

Beyond 24 degrees, partial summation of large areas is not thought to increase further and with any additional increase in area not requiring any further decrease in intensity (Davson, 1990). However the validity of these laws has been questioned and Hallett et al (1962) suggested that they do not consider the non-uniformity of the retina with arguments including local fluctuations in sensitivity over small fields, the variability of sensitivity of the small fields to different retinal positions and the variation in the summation properties over the retina.

3.3.5 Stimulus size

The stimuli can also be presented in different sizes. The size is determined by the angle it subtends (minutes of arc) on the fixated eye. When using a bowl perimeter the sizes are classed into six sizes (0, 1, 11, 111, 1V & V) following the size terminology of the kinetic Goldmann bowl perimeter and expressed in Roman numerals.

With regard to Ricco's and Piper's laws of spatial summation discussed in chapter 3.3.4, overall two threshold stimuli are said to be related by the equation

$A^K \times I = C$

Where A = Area

I = Intensity

K= an exponent value that varies from 0.05 to 0.9 depending on the retinal position of the stimulus.

For the purposes of perimetry stimulus size, Goldmann chose an intermediate value for k being 0.8, and with each increase in Goldmann standard size (which doubles the diameter) the intensity is increased by 5dB.

The relative size of the Goldmann classification and the minutes of arc subtended to the eye can be seen in table 1. Another more informal method of kinetic plotting of isopters is by the use of a tangent screen. With this method the central 30 degrees of the visual field is represented on a large black screen with the centre positioned at a distance of one metre from the patient's eye. The stimuli (small coloured discs on the end of a black wand), which are of constant intensity, (ensured by constant background luminance) are moved along a chosen tangent towards the fixation point until the patient reports seeing the stimulus. Both the colour and size of the stimulus can be altered as can the distance of the patient from the screen, however the test is usually completed using white stimuli and a distance of one metre. With this technique, the size of the stimulus relates to the actual size in millimetres. The size is expressed as a fraction of the stimulus diameter over the distance i.e. 4/1000 = a size of 4mm at a one metre distance. The relative sizes to the Goldmann stimulus can also be found in table 1.

Goldmann	mm^2	M' of arc
0	0.0625	3.78
I	0.25	7.68
II	1	15.36
III	4	30.71
IV	16	61.3
V	64	122.56

Table 1 shows the relative sizes of the Goldmann stimuli to the size measured by the angle subtended to the fixated eye (seen in the third column expressed as minutes (M') of arc when using a perimetry bowl, and to the size of the stimulus used at a distance of one metre when using the tangent screen method.

Automated static perimetry (as used in this study) is usually undertaken using the Goldmann size 111 stimulus ($4mm^2$) with the resulting threshold values then being compared to those of the age related normal population. Some disorders e.g. severe macular opacities may make testing with size 111 impractical if the stimulus is too small and unable to be seen by the subject. Choplin et al (1990) investigated the relationship between mean retinal sensitivity in the central 30 degrees of the visual field using stimulus sizes 111, 1V & V in normal subjects and found that there may be a 'factor' to correct the differences between the sensitivity values obtained from these three tests. This would allow patients tested with large stimuli to be compared to the normal database of the size 111-stimulus and follow-up tests of one patient compared to a previous test using a different size (if severe visual deterioration warranted this). However it still remains unclear whether their results could be generalised to all disorders.

3.3.6 Recording and display of sensitivity values

The sensitivity of vision is inversely proportional to the intensity of the stimulus i.e. the higher the luminance required to evoke a response from the patient, the lower the sensitivity is at that point. Both the stimuli and the background are measured in

luminance units of candelas per square metre (cd/m^2) or apostilbs (asb) where 1 cd/m^2 is equal to 3.14asb.

The units of sensitivity are devised in the same manner for both kinetic and static perimetry although the exact units differ by the maximum intensity of the stimulus each perimeter can produce. The Humphrey visual field analyser (used in this study) has a maximum intensity of 10,000 asb. The intensity of the stimulus is then attenuated by neutral density filters on a logarithmic scale and expressed in decibels (dB). Therefore 0dB expresses no attenuation (an intensity of 10,000asb), 1 log unit expresses 10dB (1000 asb), 2 log units expresses 20 dB (100 asb) etc. In this manner the sensitivity at a location can be expressed as decibels with the higher figures indicating higher attenuation of the intensity.

The duration of the stimulus also has an effect on the sensitivity level. A stimulus with a luminance at threshold level appears brighter with a longer duration of stimulation up to approximately 100ms in the human eye. This is termed 'the critical duration of vision'. Before this time temporal summation occurs, a process that can be considered as many repeated responses to successive stimuli with an additive effect for the duration of the stimulus presentation. This is represented by Bloch's law

Luminance x duration = constant

With respect to perimetry, the duration of the stimulus presentation should be greater than the 'critical duration of vision' thus avoiding the necessity of including both duration and luminance into the equation (with a duration above this time, luminance is the only essential factor).

The duration should also be kept below the reaction time of the subject. The time between presentation of the stimulus and the first eye movement in response to the stimulus is approximately 250ms.

Although temporal summation depends upon different factors (mentioned in 3.3.4), the process of summation is thought to have decreased by a presentation time of 0.06s and under most conditions be complete by 0.1s (Anderson 1992). However, with regard to retinal location, temporal summation does take a little longer in the

peripheral visual field leading to a slightly extended 'critical duration of vision'. The Humphrey visual field analyser used in this study has a stimulus duration of 0.2s.

3.3.7 The variability/reliability of the responses

The variability of a subject's responses can be detected by plotting a 'frequency of seeing curve'. A few points are selected across the visual field and at each point the sensitivity is assessed. For each point 6 intensities are chosen, some of which are above the threshold point and some are below. The stimuli of different intensities are then randomly presented to the subject on numerous occasions and the number of times the stimulus is seen is recorded. When the results are plotted with the x-axis as a measure of intensity and the y-axis a measure of the percentage of times the stimulus was seen (0-100%), an s-shaped curve is formed. The gradient of the curve indicates the intra-subject variability with a steeper curve indicating a more reliable result. The variability in results differs between subjects; the eccentricity of the point tested (increasing in the periphery) and with the type of perimeter used (Lewis et al (1986). The reliability of the result does however improve with co-operation and experience of the subject.

3.3.8 Kinetic perimetry and static perimetry

Kinetic perimetry

As mentioned briefly in chapter 3.3.3, kinetic perimetry is expressed in isopters, which are oval lines, that join points of equal sensitivity across the meridians. Areas central to the isopter (in the normal visual field) will be suprathreshold values with the sensitivity of these points increasing towards the point of fixation. Peripherally to the isopter, the stimulus of that particular intensity is infrathreshold and unseen.
The most broadly reported kinetic perimeter is the Goldmann, which can test up to 90 degrees of the visual field. Scotomas are detected when an observed stimulus disappears on continued movement towards the centre of the field.

An aspect of kinetic perimetry, which does not affect static perimetry, is the speed of the movement of the stimulus. The speed of the stimulus is related to the reaction time and to the fluctuation of sensitivity over a small field as reported by Hallett et al (1962). If the movement of the stimulus is too fast, the subject may not react until it

has moved further towards the centre of the visual field signifying a lower sensitivity than should have been recorded. Also, if the movement of the stimulus is too slow, the subject may lose attention, which increases the fluctuation and will give rise to more variable responses. The Goldmann technique recommends 5 degrees/ second in the peripheral field (Henson 1998).

Although since the 1970's computerised static perimetry has surpassed kinetic perimetry this did produce a loss in the main advantage of kinetic perimetry, that of flexibility. Manual kinetic perimetry allowed the perimetrist total control over the test with the option of concentrating on one specific location of the visual field or repeating a stimulus presentation as often as required. However, this may also be a disadvantage if repeated tests are performed by different perimetrists.

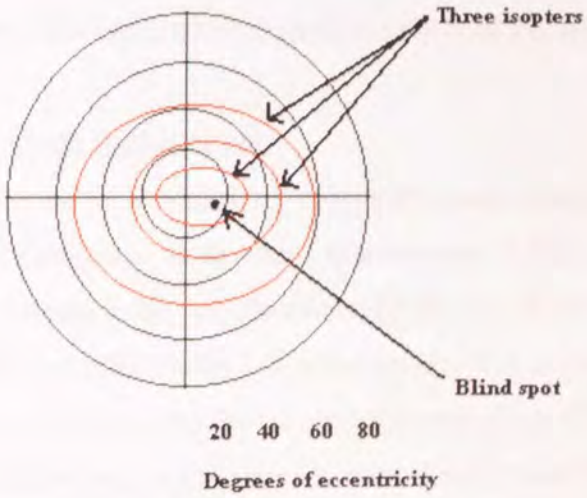


Figure 8 shows a schematic diagram of the right eye of a Goldmann visual field. The blind spot can be seen on the temporal (right) side and three isopters can be seen in red. The inner isopters resemble the highest sensitivity values and the outer those of less sensitivity.

Computerised static perimetry

The introduction of computerised static perimetry has increased the sensitivity of detecting defects, introduced computerised analysis of the sensitivity data recorded and reduced the need for highly trained operators. The automated standardised tests have also reduced the variability in the results produced when testing with different operators.

Static perimeters may produce stimuli by a variety of methods.

1. By projecting a light source on to the back of the bowl (as with the Goldmann perimeter)
2. By the use of light emitting diodes (LED's) embedded into the bowl.
3. By video monitor presentation although with this method the stimuli are presented on a flat screen and testing can not exceed 30 degrees eccentricity similar to the tangent screen test described in 3.3.4.

With the LED's, the diodes are set at a fixed point and a fixed size. This produces less flexibility in stimulus presentation than with the projection system. The Humphrey visual field analyser used in this study is of the favoured projection design.

The Humphrey visual field analyser.

The Humphrey visual field analyser is a computerised automated static perimeter with which stimuli are projected on to a bowl at a distance of 33cm. The projection is normally white although this may be altered by the use of colour filters. The stimuli can range in size from Goldmann 1-V although size 111 is usually preferred. The presentation time is 200ms and the maximum intensity is 3138 cd/m^2. The intensity step is 1dB and the stimuli are presented on to a background illumination of $10cd/m^2$.

Basic Testing strategies

There are three basic testing strategies used in static perimetry

1. Suprathreshold screening

A stimulus is presented at a set intensity at all points over the visual field and then this is repeated using a dimmer stimulus around the point of fixation. This is a crude but

simple method, which may be of best use for basic time efficient screening procedures.

2. Threshold related screening

The stimulus presentation follows the contour of the hill of vision. The intensities of all stimuli are suprathreshold but are presented at an intensity related to the normal threshold value at any particular point. In this manner the true sensitivity values over the visual field are not represented although it is a useful technique for the gross detection of defects.

3. Full Threshold determination testing

The full threshold determination test (as used in this study) is the most accurate although most time consuming estimation of threshold values over a large number of retinal locations. This technique differs from the two above in that rather recording a yes/no (seen/unseen) response, this test aims to determine the approximate threshold value at each point.

Estimation of the threshold value at different visual field locations

For the 30-2 test the automated static perimeter contains a database of normal age-related visual field results. This not only allows comparison of the subject's results after completion of the test but also provides information for which intensity would be optimal to begin testing at each location. For example, the first stimulus may be set at 2-4dB above or below the normal age-related threshold value for that particular location. Depending on the response (seen/unseen) of the subject the intensity of the stimulus is altered and presentation repeated in a 'staircase' or repetitive up and down method, a technique first developed by Bebie et al (1976).

The 'staircase' or repetitive up and down method

The most popular variation of this method is the 'two reversal staircase technique'. After the initial response the stimulus intensity is either increased or decreased by 4dB until the opposite response is given i.e. a previously unseen stimulus is seen and vice versa. The intensity is then altered by 2dB in the opposite direction (first reversal) until the second opposite response is given (second reversal). The threshold value is then taken as half way between these two points. Depending on the responses

given this method enables detection of false positive and false negative responses (discussed later). The order of the stimulus presentation is randomised over the retinal locations tested of which there are 76 for the Humphrey (30-2) programme (measuring the central 30 degrees of the visual field) and 68 for the peripheral 60/30-2 programme measuring 30-60 degrees eccentricity. After the threshold values have been recorded for a location, the automated programme completes a second threshold value test for any location which appears irregular to the normal expected value or when compared to the neighbouring points. The Humphrey visual field analyser completes a second threshold test to any value 4dB below the expected threshold (Humphrey Instruments, 1983).

Fluctuation and reliability parameters

There are three main reliability parameters, fixation losses, false positives and false negatives. However; intra-test fluctuation (short-term fluctuation) and inter-test fluctuation (long term fluctuation) must also be taken into account.

The short-term fluctuation (SF) is defined as 'any scatter that occurs during a visual field examination of approximately twenty minutes duration' (Flammer et al, 1984). The SF is calculated by re-testing 10 pre-chosen points in the visual field. By assessing the differences between each pair of threshold values, an approximate error value can be calculated for the visual field. It has been reported however that the variability in threshold values has been found to increase with eccentricity (Parrish et al 1984, Heijl et al 1987) and Brenton & Phelps (1986) suggested that small defects in the periphery may not be detected. It would not be feasible however to re-test all locations and visual field testing needs to be a balance of accuracy and efficiency.

Long term fluctuation is defined as the 'variation in the measurement over time, when the variation due to repeated measurements at a given time (SF) has been removed' (Flammer et al, 1984). The long-term fluctuation is mainly of use when comparing slowly progressive defects on a number of occasions over a period of time and will not be dealt with further.

Fixation

During testing, the subject is asked to maintain fixation on a continually visable spot on the back of the bowl. Once the subject is aligned, the centre of the pupil can be tracked on the Humphrey visual field analyser monitor. Initially there is an optional foveal threshold test where the subject fixates in the centre of a diamond shaped area situated approximately 10 degrees below the central point of fixation. A stimulus of 30dB is then presented in the centre of the diamond with the following stimulus intensity being altered in the 'staircase' manner, the direction depending on the response of the subject. The foveal threshold value is taken as the dimmest stimulus to which the subject responded positively.

Fixation is then returned to the central point and the test stimuli presented. Fixation is checked using the Heijl-Krakau technique whereby a stimulus is presented in the area of the blind spot. If fixation has been maintained this stimulus is normally not seen and the analyser is programmed to check periodically approximately twenty times throughout the test with a higher frequency at the beginning of the test. A loss in fixation is recorded as the number of stimuli seen out of the number of presentations in that area. When this fraction is expressed as a percentage, any test with a value of 20% or more is classed as unreliable. The maintaining of fixation improves with practice, encouragement and regular rest breaks however Sanabria et al (1991) suggested that the fixation loss values contained in many reports appeared higher than expected. They concluded that fixation losses could be reduced if the test was paused when the losses were first recorded and the blind spot relocated before continuing. They also suggested vigilant monitoring of eye movement tendencies with appropriate instruction to the subject. A significant correlation between fixation losses and false positive responses (discussed later) was also reported. Although reassurance and encouragement decrease these values, there is always the possibility that the anatomical blind spot of the subject is not in the same area as that of the average normal population, and after relocation of the blind spot not improving results and the other factors thought not to affect it, a test with a high fixation loss value may have to be interpreted.

Of all the reliability parameters, fixation losses account for the majority of the tests with unreliable results. Katz and Sommer (1988) and Bickler-Bluth (1989) report

these figures as being as high as 30% and 35% in normal subjects which has led to the suggestion of altering the cut-off point from 20% in order to increase the number of reliable test results achieved.

False positives

A false positive response is recorded when the subject responds positively to seeing a stimulus at a time when the analyser had paused and not presented one. This may occur if the subject responds to the audible sound of the analyser as the projector system moves before a stimulus is presented. The subject may also be 'trigger happy,' either feeling anxious or trying to respond to the stimulus too quickly, and does so before it is presented. Similarly to fixation losses, these values are recorded as a fraction (the number of responses divided by the number of non-presentations). The results are then taken as unreliable if the relative percentage is 33% or above. As mentioned earlier, a false positive response during the Heijl-Krakau procedure of testing fixation may lead to the recording of a fixation loss. False positives however, are usually the least recorded response of the reliability parameters (Katz & Sommer 1988).

False negatives

False negatives are recorded when a stimulus presented at an intensity 9dB above a previously recorded threshold value at a location is not seen (Anderson, 1992). This may be due to blinking, loss of attention or fatigue and are more likely to be recorded in areas adjacent to defects where the threshold values are more variable (Katz and Sommer, 1988) and the location more prone to fatigue (Henson, 1998). Hudson et al (1994) decribed the fatigue effect as resulting in an overall decrease in sensitivity, this being more extensive in the periphery.

Statistical indices of reliability and ageing

The Humphrey visual field analyser uses the normal database collected from age-related subjects which is incorporated into a Humphrey Statpak package

Aging and perimetry

Age is a significant factor when assessing visual fields as sensitivity and therefore threshold values decrease with age. Brenton & Phelps (1986) reported that the

sensitivity values decrease –0.5dB/decade at fixation, -0.6dB/decade in the central visual field and –0.6dB/decade in the peripheral visual field with intersubject variability increasing in the periphery over 60 years of age. These changes have been suggested as being associated with an age related change in pupil size (the decrease in pupil size reducing the amount of light entering the eye), the development of opacities of the lens, cellular changes in the corneal epithelium and a decrease in photoreceptors and nuclei in the outer nuclear layer and ganglion cells in the retina (Jaffe et al, 1986).

Statpac Indices

From the normal age-related database, the mean deviation (MD), pattern standard deviation (PSD), corrected pattern standard deviation (CPSD) and short term fluctuation (SF) can be calculated for the central visual fields.

Mean Deviation

This represents the measure of the mean depression of the visual field compared to that of a normal age matched person. Since the comparison takes into account the variance (although expressed in standard deviation i.e. the square root of the variance) of the normal database it shows a deviation value rather than a defect. The deviation can also be expressed as total deviation plots where the deviation values for each location are rounded to the nearest whole figure (either positive or negative) and a total deviation plot can be seen. For a convenient interpretation, a value of –5dB or less is taken as an unreliable response, however, the Statpac programme holds the exact abnormal limit for each location and this may differ slightly over the visual field. The total deviation can also be plotted as a probability symbol map where abnormal locations are shaded on a grey scale according to the severity. The severity is scaled into four classes, the probability of the defect being either $p<5\%$, $p<2\%$, $p<1\%$ & $p<0.5\%$ i.e. a location with a probability of $p<1\%$ symbolises that less than 1% of the normal population had a sensitivity value that low. Therefore, the most severe defects are shaded black symbolising $p>0.05\%$.

Pattern Standard Deviation

This is a measure of the uniformity of the shape of the visual field whilst taking into account the variance (in terms of standard deviation) of the normal database. A perfectly uniform 'hill of vision' would produce a deviation of zero, however, this is rarely the case and small values in the positive direction are more usual for a normal visual field. 'The PSD is an index of the standard deviation of the difference of each sensitivity value from the expected value (based on the normal value at that location and the mean deviation index)' (Anderson, 1992). Therefore, it is a measure of local field loss and represents whether the numbers in the total deviation plot are similar or very different. In this manner, diseases that cause an overall decrease in the height of the 'hill of vision' will become less evident allowing more localised defects to be identified. As with total deviation, pattern deviation can be expressed as both numerical and symbol probability plots.

Corrected pattern standard deviation (CPSD)

This measures the pattern standard deviation after an adjustment has been calculated to correct for the variability in threshold values represented by short term fluctuation (SF -discussed earlier). After correcting for local fluctuations the CPSD shows differences between adjacent points more clearly. The CPSD is calculated from the square root of the following equation-

$(CPSD)^2=(PSD)^2-k(SF)^2$

k= a constant to adjust for the non uniform fluctuation

The constant differs between a 24-2 and 30-2 test. The 30 degree visual field constant- k has been calculated to be 1.28 and is related to the spatial distribution of the points used to calculate the SF. The CPSD is measured in decibels and a probablility value is shown if less than 10% of the normal population have the calculated value or higher.

Refractive Error, lens rim artefacts and anatomical artefacts

When testing the central visual field, it is essential that the stimulus is in focus and the general rule is that any refractive error in excess of one diopter should be corrected for. Without correction, the stimulus will appear blurred resulting in an increase in the size of the retinal image with a decreased luminance at the edges. Henson (1998)

reported that when a hyperopic blur of 5.00 diopters was simulated and a size III stimulus presented, the central sensitivity was reduced by 6dB. Although refractive error correction is necessary, this does introduce the problem of possible lens rim artefact at approximately 25-30 degrees of eccentricity. This is a particular problem with automated perimetry as the artefact does not become apparent until after completion of the test especially as the stimuli are presented in a pre-programmed manner with the more peripheral points generally being tested towards the end of the examination. Zalta (1989) studied lens rim artefact using a Humphrey 30-2 programme both retrospectively and prospectively (with particular attention to lens positioning) and found an incidence of 10.4% and 6.2% respectively. He found that the lens rim artefact typically affected the temporal quadrant at the points at 27 degrees resulting in a combination of absolute and relative defects and often in combination with another quadrant. Lens rim artefact can lead to misdiagnosis either by identifying the artefact as a true defect or by not identifying a scotoma obscured by the artefact. Lens rim artefact was found to increase with increasing age where subjects fatigue more rapidly, may adjust their position due to discomfort and anatomically aging may change the facial features with the eyes becoming sunken making close placement of the lens difficult.
Zalta (1989) also reported an increase in lens rim artefact associated with an increase in hyperopic corrective lens prescription and recommended the use of the Humphrey 24-2 programme for high prescriptions.

When testing the peripheral field it is not possible to correct the refractive error, however, defocus affects the resulting threshold values less in the periphery and the main concerns are prominent eyebrows and droopy eyelids which may obscure a superior defect, a problem less easy to resolve. An example of the central 30-2 visual field printout and 60-30/2 print out can be seen in figures 9 and 10.

Perimetry in children

As mentioned earlier in the introduction, vigabatrin is often prescribed to children and studies have recently shown visual field loss characteristic of that associated with vigabatrin in some patients (Vanhatalo & Pääkkönen 1999). As well as the difficulty of compliance with young children, visual field defects associated with vigabatrin may still be difficult to detect. Lakowski and Aspinall (1968) studied the visual fields

(with static perimetry) of children aged between six and eleven years and compared them to those of young adults. In the group of children they found the younger the child, the lower the sensitivity both in the foveal and peripheral (eccentricities above 20 degrees) regions. They also found that the visual field for the 6 year old only extended up to 15 degrees each side of the fovea. The field was found to increase with increasing age with the 11 year olds exhibiting a similar field to the young adults. The reason for the gradual increase in sensitivity and eccentricity may be due to an increased understanding of the required task with maturity but Lakowski and Aspinall (1968) also discussed the possibility that the young child may have cortically suppressed the peripheral information in order to encourage development of the foveal processes. When further studying children using adapted tests and forewarning the child of areas where the stimulus may appear, Aspinall (1976) found that the differences in the sensitivity values between the adults and children decreased. This, however, does question whether visual field constriction associated with vigabatrin could be identified in young children, especially if the development of some patients is delayed compared to healthy children.

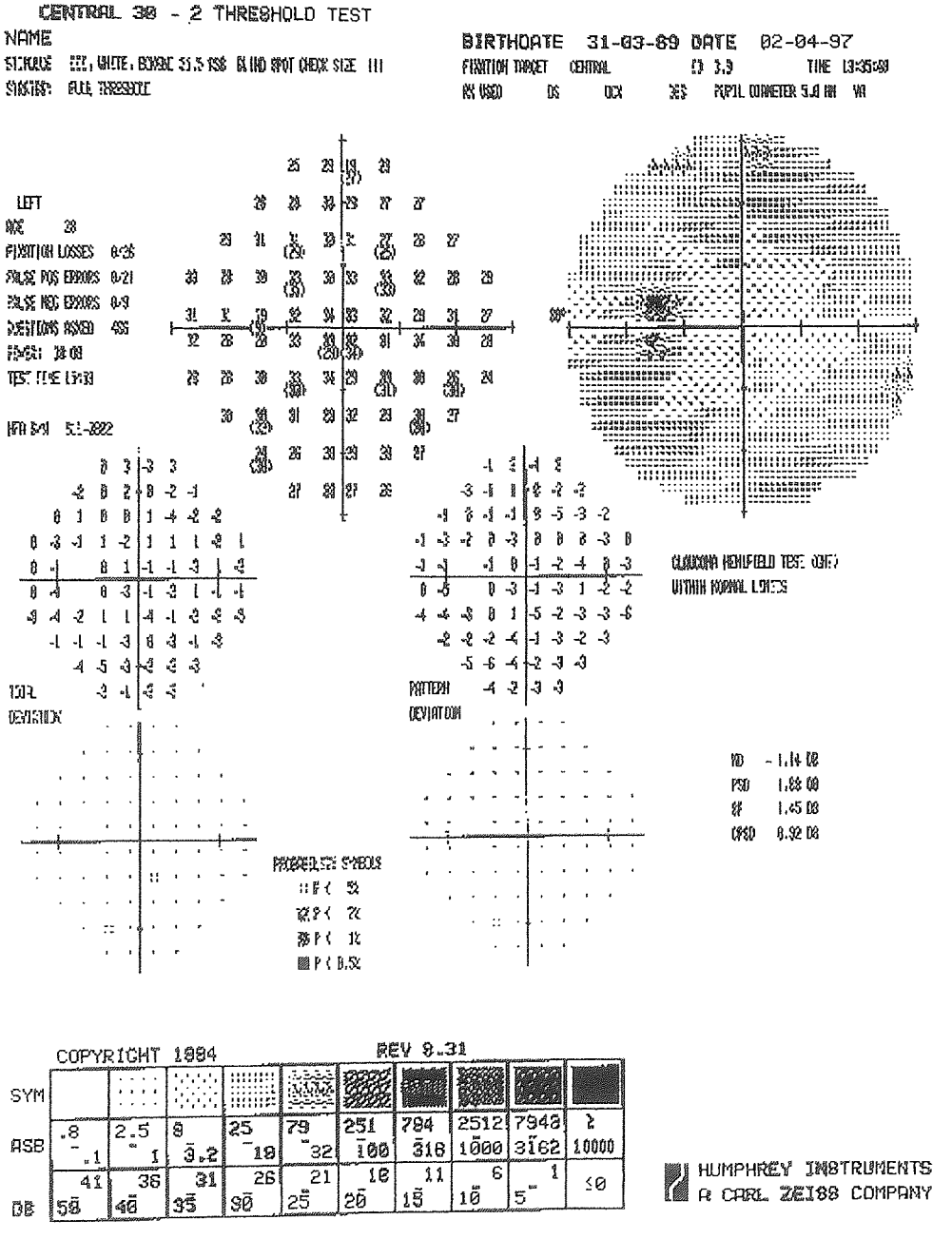


Figure 9 shows the central 30-2 print out of the left eye of a normal subject. The grey scale can be seen at the top with the sensitivity values below. At the bottom the total and pattern deviations from the normal age related database can be seen.

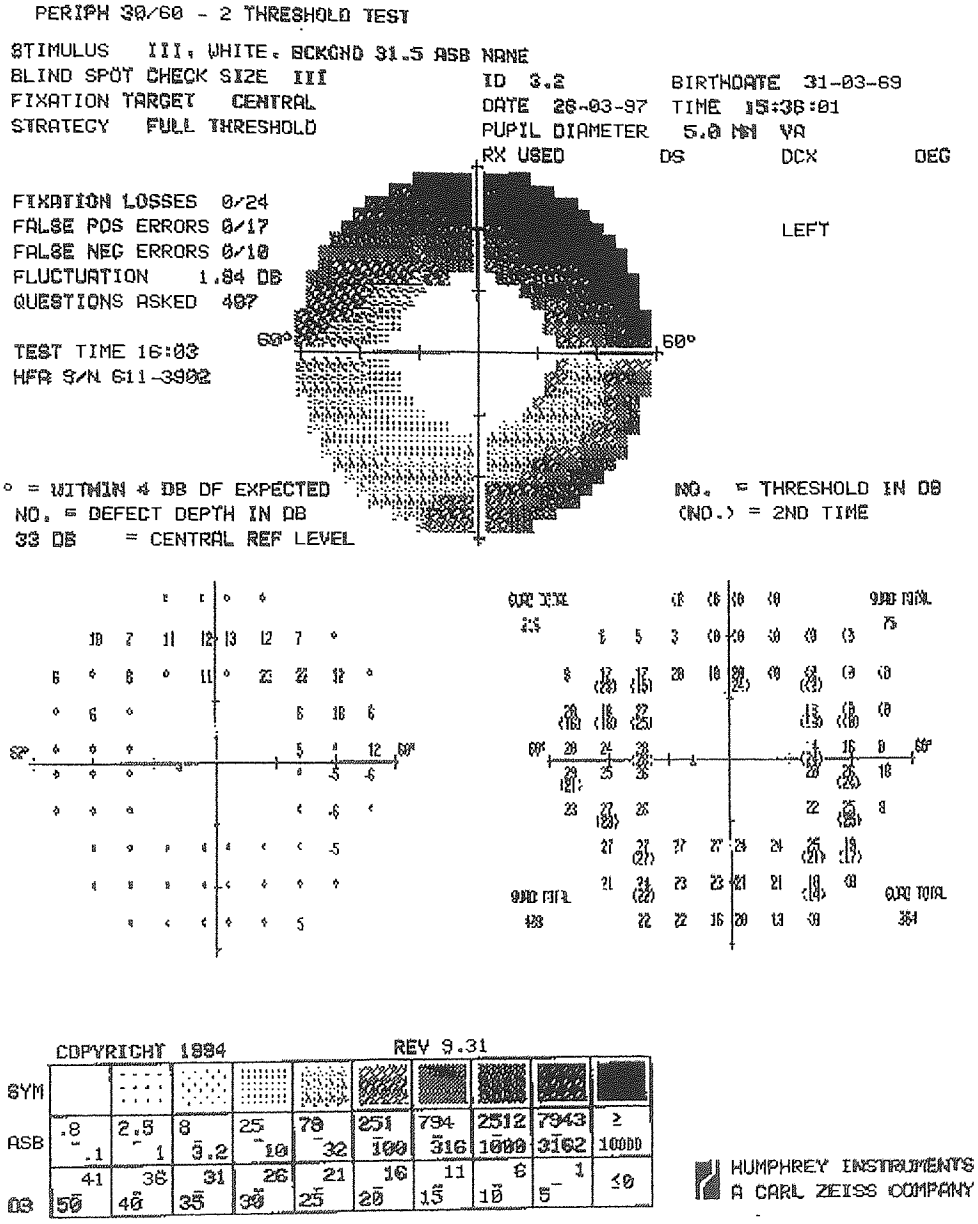


Figure 10 shows the 60-30/2 printout of the left eye of a normal subject. The large black area at top right of the grey scale plot shows the area of vision obscured by the eyebrow and upper nasal regions.

3.4 Flash and pattern visual evoked potentials (VEP's)

Visual Evoked Potentials (VEP's) are produced in the visual cortex of the brain as a response to a specific visual stimulus. These potentials can be recorded using a non-invasive technique where electrodes are taped (with Blenderm tape) to the scalp and/or more firmly attached with an adhesive. The position of the electrodes are ascertained by measuring the head at certain bony landmarks of the skull using the International 10-20 system. Positions O4, O2, O1, O3, Cz and Fz are used for the recording of the VEP. (O3 being midway between O1 and T5 and O4 being midway between O2 and T6). O4, O2, O1 and O3 lie over the visual cortex of the brain, Cz is the reference electrode lying over a non-visually active part of the brain and Fz is the earth. The position Cz is preferred to Fz as the reference since it is less affected by muscle activity and blinks which may cause interference and artefact on the trace. A fraction of a second after the stimulus is produced (this usually being either diffuse flash or a reversing checkerboard pattern), the response is recorded and is presented on the monitor as a waveform). Since the response is smaller than background EEG activity several responses are averaged. This process relies on the assumption that the VEP to a set stimulus should form a response, with the components at subsequent stimulations having very similar latencies and amplitudes. The averaging technique will cancel out the majority of the irregular background activity, showing a more defined waveform. The subject being tested must not be allowed to become tired since rhythmical alpha activity may also be recorded which will not be diminished by averaging. These wave forms are larger than the VEP response and make analysing the VEP very difficult.

3.4.1 Flash VEP's

The stimulus consists of bright flashes of light which are produced from either a stroboscope (connected to a Medelec OS5 stimulator Int. 4) which is positioned 30cm from the patient's eye, or from a Ganzfeld stimulator where the flashes are presented in the Ganzfeld bowl. The flash is presented at a rate of 1 flash per second.
The visually evoked response consists of a series of negative and positive components the nomenclature given by Harding in 1974 being P0, N1, P1, N2, P2, N3. The N2 and P2 components have been found to be the most consistent components of the waveform with latencies of approximately 75ms and 110ms respectively (Harding 1991). Responses can be recorded with each eye individually or binocularly. Age has an increasing effect on the latency of the P2 component which needs to be considered when interpreting the responses. Wright and Harding (1985) and Wright et al (1985)

reported an increase of 20ms in P2 latency between the second and eighth decade of life. Flash VEP is thought to be unrelated to visual acuity. Harding (1991) reported the VEP to be insensitive to refractive errors of up to 5 Diopters.

3.4.2 Pattern VEP's

Specific patterns are displayed on a television screen to act as a visual stimulus in order to elicit a response. Patterns are usually checks of differing size or a sine wave or square wave grating. These may either be presented as pattern on-off or pattern reversal, the pattern reversal checkerboard being more widely used. This study uses the pattern reversal checkerboard with a reversal rate of 2/sec. The checkerboard is made up of black and white squares so on reversal, the black squares become white and the white squares become black. Therefore there is no overall change in luminance. The visual evoked response to pattern stimuli is derived mainly derived from the central macula area (Galloway, 1981). The response can be affected by resolution therefore any refractive errors of the patient's vision must be corrected for, prior to testing. Fixation must also be maintained at the centre of the screen since if the patient defocuses their eyes the resolution of the pattern would be lost and the resulting response attenuated. The patient must also be instructed to concentrate, giving the individual a mental task to complete during the test may assist with this. If the patient becomes tired, alpha waves produced mainly during relaxation will be recorded along with the VEP. However these alpha waves are a lot larger than the visual evoked response and the averager contains an artefact rejection where larger input voltages than a pre-selected level will be rejected to prevent contaminated responses.
As with the P2 component of the flash VEP, the P100 component of the pattern VEP increases in latency with age, although to a lesser extent. Data published by Wright et al (1985) shows a mean increase latency of the major positive component (with 56 minute checks) from 108.56ms for the age range 10-19yrs to 111ms for the age range 70-79yrs.

Pattern reversal stimulates approximately the centre 15 degrees of the retina, depending on the size of the checks (larger checks stimulating more to the periphery). The amplitude and latency of the VEP may be of use in detecting visual field defects, although this method is not thought to be as sensitive as perimetry (Galloway, 1981).

Although VEP testing was performed in this study in order to complete the visual electrophysiology, there is no evidence to show that these responses are affected by vigabatrin.

3.5.1 Introduction to the multifocal ERG

The Visual Evoked Response Imaging System (VERIS) is a retinal function analyser developed by Sutter and Tran (1992) which is capable of recording multifocal ERG's. The technique allows recording of ERG responses from 103 separate locations of the retina in approximately 4 minutes. The anatomy of the retina varies with eccentricity, differences in acuity relating to the photoreceptor density (cells/mm^2) in the region. The cones have a density as high as 150,000 cells/mm^2 at the fovea decreasing to 10,000 cells/mm^2 at 20 degrees eccentricity. The maximum rod density is found at 20 degrees with approximately 150,000 cells/mm^2 but only decreasing to 60,000 cells/mm^2 in the periphery (Ikeda 1987). The ganglion cell to receptor cell ratios also alter with eccentricity being 4:1 at the centre, reducing to 1:1 at approximately 15 degrees (Wassle et al, 1989). The VERIS records cone ERG's with each hexagonal location being stimulated independently and with the stimulus elements being presented in a predetermined pseudo-random sequence (termed a binary m-sequence). The response from each location contributes to the total corneal ERG response with stimulation to 50 degrees eccentricity horizontally and 40 degrees vertically.

3.5.2 Multifocal ERG responses

The multifocal responses although less than 1/10,000 times of the size of the full field ERG (Mohidin et al, 1997), resemble the ERG with a trough followed by a positive peak. When all the traces are summed to form one waveform the trough is very similar to the a-wave of the ERG, although the positive peak has a shorter latency than the b-wave. The summed waveform also lacks the oscillatory potentials seen on ERG, a schematic of these waveforms can be found in figure 11 (Hood et al 1997b). These components have been suggested as being produced from the same cells that generate the a-wave and b-wave of the standard ERG (Hood & Li 1997a), the origins of these components can be found in chapter 3.1. However this suggestion remains controversial. Kondo et al (1995) compared the results of full-field, focal and multifocal ERG's in patients with known retinal diseases. Although they reported comparability of the three tests for the dysfunctional areas of the retinas tested, they

described discrepancies between the conventional focal ERG and the multifocal ERG with the negative and positive waves of the responses of one patient with branch retinal arterial occlusion. Therefore the origins of the multifocal ERG components may not be identical to those of the ERG. However Kondo et al suggested that the lack of the negative wave in the multifocal ERG response in that particular case, may have been influenced by the filter settings as reported by Keating et al (1997).

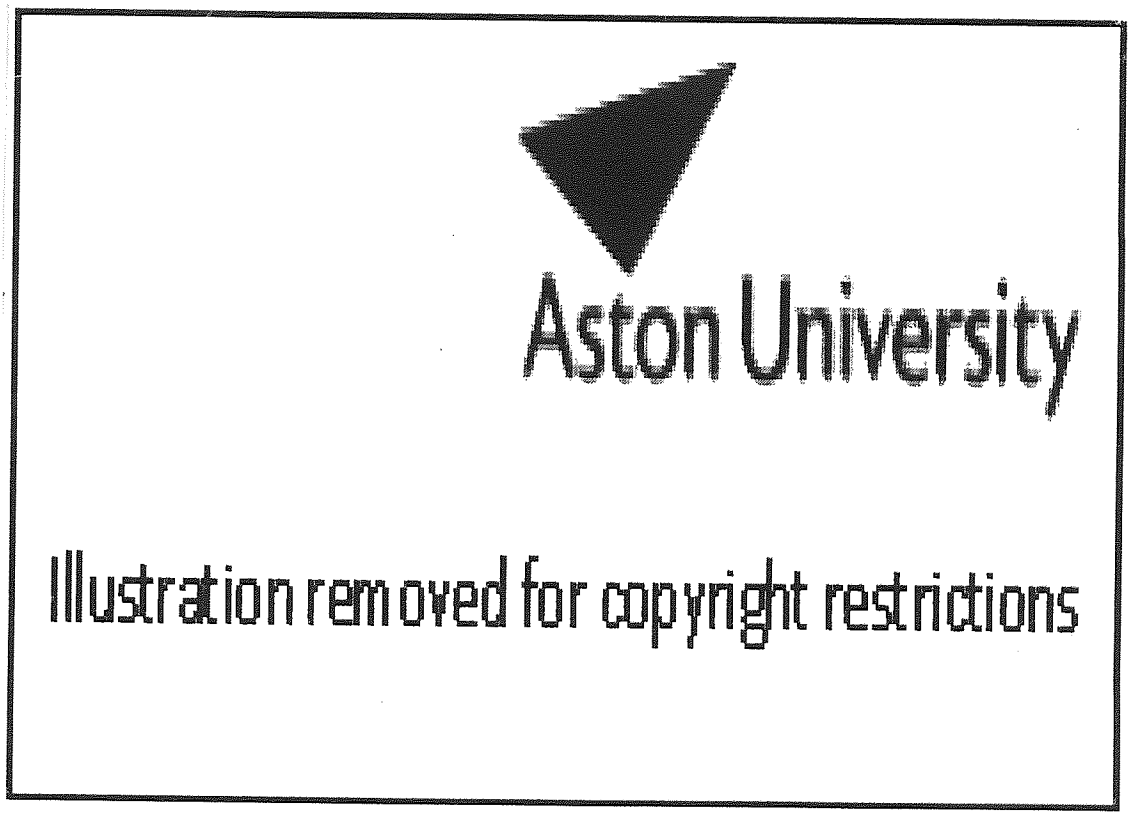


Figure 11 shows a schematic diagram of the full-field ERG response compared to that of the multifocal ERG response. The peak of the multifocal ERG has a slightly shorter latency than that of the full-field ERG and the waveform also lacks oscillatory potentials. (Reprinted from Hood et al, 1997b)

Hood et al (1997b) further investigated the components of the multifocal and full-field ERG's on three healthy subjects. They reported that when 7 frames of background intensity were inserted between the white hexagon stimulation at each location i.e. slowing the sequence, an oscillatory potential (they termed PC1) became evident, a component similar to that of the full-field ERG. They also described how increasing the background intensity of the multifocal ERG decreased the peak (b-wave) latency and increased the PC1 latency resulting in a single waveform, resembling the standard multifocal ERG response. They acknowledged the proposal by Keating et al (1996, 1997) that low frequency filtering of 10Hz (as compared to the 1Hz filter of the full-field ERG) may have affected the waveform morphology, but reported only minor differences in the appearance of full-field ERG's recorded with the low frequency filter setting at 1Hz and 10Hz. Contrary to the view of Sutter and Tran (1992) that the influence of the neighbouring hexagons on the response of one location would be small if the locations were uncorrolated, Hood et al (1997b) suggested that a steady-state adaptation may occur with the high frequency of stimulation, but reported little effect of this with the 7 background frame programme. They proposed this to be the main reason for the differences in the morphology of the two waveforms.

3.5.3 Advantages of the multifocal

The full-field ERG is the total response of different cells in different locations of the retina. Different cells appear more vulnerable to different disease processes and therefore the affect on the retina is not always evenly distributed. The multifocal ERG records responses from the outer retinal layers with the distribution of the responses corresponding to that of the density of the cones (Sutter and Tran 1992). Some localised lesions i.e. small maculopathies cannot be detected by the full-field ERG. Prior to the development of the VERIS, small areas of defect of the retina could be assessed by focal ERG. However with the focal ERG, the small stimulus used produces responses with small amplitudes and the procedure is sensitive to stray light and poor signal to noise ratio (Kretschmann et al, 1996). Also with the focal ERG, mapping many areas of the retina is time consuming. The multifocal ERG allows many areas to be stimulated in a short time and with the elements being stimulated independently. With the ERG response, if two flash stimuli of equal intensity are given in quick succession, the second response is known to have a decreased

amplitude compared to the first. With the VERIS, the small responses produced require a large number of averages to obtain a valid response. The VERIS system overcomes this problem by producing 16,384 stimuli pictures within the 3.6 minute testing time. The comparison of the multifocal ERG results and those of a visual field test can be of benefit in detecting the area of defect. If the pattern matches that of the visual field, the defect probably involves the outer retinal layer.

3.5.4 The stimulus array

The stimulus consists of an array of 103 hexagons. The hexagons are scaled with eccentricity, the smaller hexagons being presented in the centre and larger ones towards the periphery. The scaling produces similar amplitudes and signal to noise ratio for each location. With the subject's eye situated 33cm from the centre of the screen the stimulus extends 50 degrees horizontally and 40 degrees vertically. The layout of the array can be seen in figure 12. At any one time each hexagon has a probability of 0.5 of being black or white and the frames change at a rate of 75Hz in a predetermined pseudo-random order. The sequence of the colour change is the same for each hexagon although this change is time lagged by a different amount for each location (Hood et al, 1997b, Hood and Li, 1997a). The luminance of the white segments is 200cd/m^2 and that of the black less than 3cd/m^2 (as suggested by Sutter and Tran, 1992). The filter bandwidth is 10-300 Hz and the amplification is 100,000.

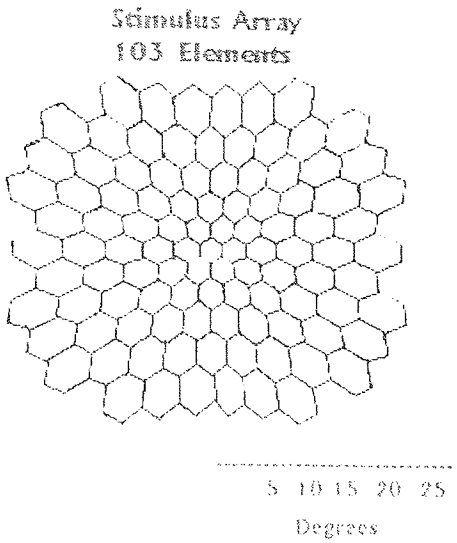


Figure 12 shows the layout of the stimulus array of the 103 densely packed hexagons.

3.5.5 Recording the multifocal ERG

Responses are recorded monocularly using DTL fibre electrode lying in the conjunctival fluid along the lower tarsal membrane. A gold reference electrode is taped to the outer canthus of the eye with a gold ear-clip as the earth. Prior to testing the pupils are fully dilated (to a diameter of 6mm or above) using 0.5% tropicamide and vision corrected for the viewing distance using a full aperture trial lens. The position of the chin rest is centred according to the interpupillary distance and the non-tested eye is patched. During recording a continuous horizontal trace represents the raw data from which muscle artefact, eye movements and blinks can be detected. The total recording is divided into 16 segments of 15 seconds where the subject maintains fixation on a spot in the centre of the screen. Any segments containing artefacts are discarded and repeated.

Although the procedure stated above uses 103 hexagonal locations with recording divided into 16 segments of approximately 15 seconds, the VERIS system provides an alternative stimulus array of 61 hexagons (also extending 50 degrees horizontally and 40 degrees vertically) and a recording sequence of 8 segments of approximately 30 seconds. Studies have been reported using both the 103 and 61 location stimulus arrays, however, when recording with 61 locations, small visual defects may not become apparent. As for the duration, many studies describe results from healthy

subjects under differing stimulatory conditions (Kondo et al 1995, Kondo et al 1998, Hood et al 1999). For a practised subject 30-second segments can often be completed with little or no artefact contamination, although in a clinical setting this is often not feasible.

3.5.5.1 Artefact rejection procedure

Although theoretically all segments containing artefacts should be rejected and repeated to obtain the optimum response, in reality this is not always practical, and fatigue from repeated testing may also detrimentally affect the result. The VERIS software provides an off-line artefact reject procedure. Since the VERIS system relies on computation of all location responses, simply discarding contaminated data is not possible. With the test completed, the off-line rejection procedure compares the resultant waveform for each location to that of the predicted response. If the segment containing the artefact is more than 2SD away from the predicted response it is replaced by it. The predicted response has been estimated from the entire recording i.e. all 103 locations (Sutter and Tran, 1992, Verdon, et al 1998). It is recommended however not to incorporate the artefact rejection more than four times (Tomey) as the process reduces the original validity of the result.

3.5.5.2 Types of recording electrodes

As with the full-field ERG, the VERIS can be recorded using different types of electrode. Many research departments favour the contact lens electrode with the resultant responses of larger amplitude and a higher signal to noise ratio. However other recording electrodes including gold foil, the DTL fibre and carbon glide electrodes may also be used with the advantage of avoiding unnecessary discomfort and possible corneal abrasion. Mohidin et al, (1997) studied the differences in the responses obtained by these four different types of electrode. After recording responses in twelve subjects with the different electrode types, on three occasions, they found that the largest mean amplitudes were obtained with the JET contact lens electrode, followed by the gold foil, then the DTL fibre and lastly the carbon glide. For the comparison of patient responses to the normal database and for ongoing patient monitoring, repeatability/ test retest reliability and reproducibility are also of importance. Mohidin et al 1997 found that the variation in test retest results were significantly higher with the carbon glide electrode than with the other three types

which showed no significant differences between them. Parks et al (1997) further discussed the repeatability and reproducibility of the test in terms of eccentricity of the visual field, reporting larger variation in the peripheral responses than those in the central area did. However inter-subject variation has been found to be greatest within the central one degree (Sutter & Tran, 1992).

3.5.5.3 Normal data collection and presentation of responses

Normative data for the right and left eyes were collected separately and the databases held the mean waveform at each of the 103 locations. After a test has been completed the response densities were calculated using the scalar product method. The computer programme compares the resultant waveform point by point with the mean normal waveform. Calculations using the differences between the two, either in latency or amplitude, produce a scalar product (a correlation coefficient). The scalar product of an element, when divided by the area of that element produces the response density (nV/deg^2). This is used to design 3-D and 2-D pseudocolour plots. As the waveforms produced at each location are very small and the signal to noise ratio low, the scalar product and response densities are preferred as measurements rather than the a-b amplitude and a wave and b-wave latencies used for the full-field ERG. Figure 13, 14, 15, 16 & 17 show the resultant trace array, 2D and 3D pseudocolour plots for the right eye of a normal subject.

3.5.6 Detection of disease using the VERIS

The VERIS has been successful in identifying areas of disease affecting the retinal pigment epithelium and the cones of the retina. Disease can affect both the latency and the amplitude of the multifocal ERG responses. The VERIS Clinic computer analysis allows the resultant responses to be displayed in groups of either quadrants or five concentric rings (grouping with eccentricity) to enable specific areas of defect to become more apparent. The multifocal ERG has been widely used to map retinal disorders that may affect the cones and/ or the outer retinal layer. Kretschmann et al, (1996) reported the multifocal ERG responses of patients with retinal and choroidal diseases. These included a patient with age related macular degeneration with central scotomas in both eyes. They described the multifocal ERG traces to have central responses close to noise level. They also reported another patient with Stargardt's disease and one with a chorioatrophic scar in each eye, for both patients they reported

abnormal multifocal ERG responses closely matching the visual field defects found with perimetry. Multifocal ERG testing has also recently been found to be affective in the assessment of retinitis pigmentosa. This disorder has been found to produce full field ERG cone responses with decreased amplitudes and prolonged latencies (Seelinger et al 1998, Hood et al 1999). The multifocal ERG characteristically shows intact central responses with abnormal peripheral responses, the extent of which is dependent on the severity of the disorder. Hood et al (1998) reported however that the summed response from the retinitis pigmentosa patients showed a normal latency differing from the findings of the full field ERG response. They explained this finding to be due to the high relative contribution of the central responses and the stimulus array only stimulating less than one quarter of the cones of the full field ERG. When separating the central and peripheral (above 7.5 degrees eccentricity) responses they reported that the abnormal latencies became evident. This shows the importance of the concentric ring analysis discussed earlier.

3.5.7 Multifocal ERG and vigabatrin induced visual field loss.

Since vigabatrin has been reported to affect the EOG response (probably affecting the retinal pigment epithelium) and abnormal 30Hz flicker ERG responses have also been reported in vigabatrin patients, the multifocal ERG would be a useful tool to investigate the distribution of the abnormal responses over the visual field. The topography of the defects may not appear to match the perimetry results as well as with the patients with other retinal disorders discussed by Kretschmann et al, (1996) as vigabatrin is thought not to solely affect these regions of the retina. Full field ERG testing has also shown prolonged photopic ERG b-wave latencies after the addition of vigabatrin (Harding et al, 1995) and oscillatory potentials have also been reported to show abnormal responses after administration of vigabatrin (Eke et al, 1997). This indicates an effect of vigabatrin on the amacrine cells and ganglion cell layer. The inner nuclear layer, although thought to contribute to the multifocal ERG response, has been suggested as only reflecting a small component of the response (first-order component) which is the mean local response to all the flashes occurring in a stimulus cycle.

3.5.8 Contributions of the inner retinal layer to the multifocal ERG

Palmowski et al (1997) investigated the contribution of the inner retina to the multifocal ERG by deriving a second order component. They describe this as 'the interaction between two focal flashes (white frames) separated by an integral number of stimulus base intervals (steps in the m-sequence)'. The second order component is further derived into two parts termed the first and second slice. The first slice shows the difference in the response of two successive m-sequences. With the pseudorandom sequence of the stimulus there are four possible combinations that can be produced.

1. A white frame followed by a black frame.
2. A black frame followed by a white frame.
3. A black frame followed by a black frame.
4. A white frame followed by a white frame.

The second slice is derived in a similar manner although one background frame (50% black and 50% white) is shown between the frames. Although the second order component still contains an outer retinal component (Palmowski et al, 1997), the component is thought to be largely produced from the inner retina and optic head, with changes in these structures altering the adaptive effect of the retina to the focal stimulation on subsequent flashes (Sutter et al, 1999).

Hood et al (1999) also reported to have identified the inner retinal contributions to the multifocal ERG using the first order response. By using tetrodotoxin (a drug that blocks all sodium based action potentials) they altered the multifocal ERG response from monkeys by preventing the action potential in the ganglion cells and amacrine cells. On testing diabetic and glaucoma patients with inner retinal disorders, they found that when the stimulus contrast was reduced from 100% to 50%, similar responses to the treated monkeys were produced.

These techniques of testing inner retinal function were not available during this study and an analysis of abnormality was used for the test with 2SD and 3SD from the normal mean database being taken as the 95% and 99% levels as described in chapter 4.6

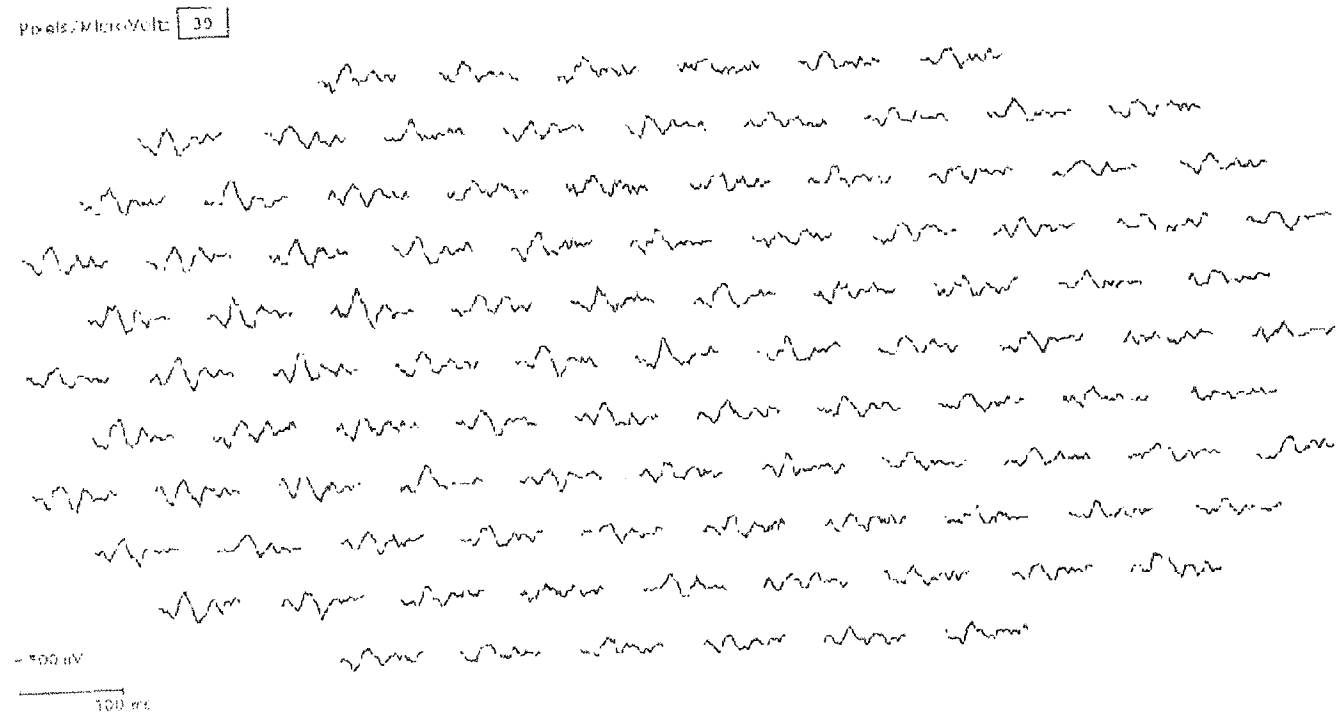


Figure 13 shows the trace response produced by the right eye of a normal subject. The value of 39 pixels/ microvolts reflects the maximum amplitude response obtained at the central location.

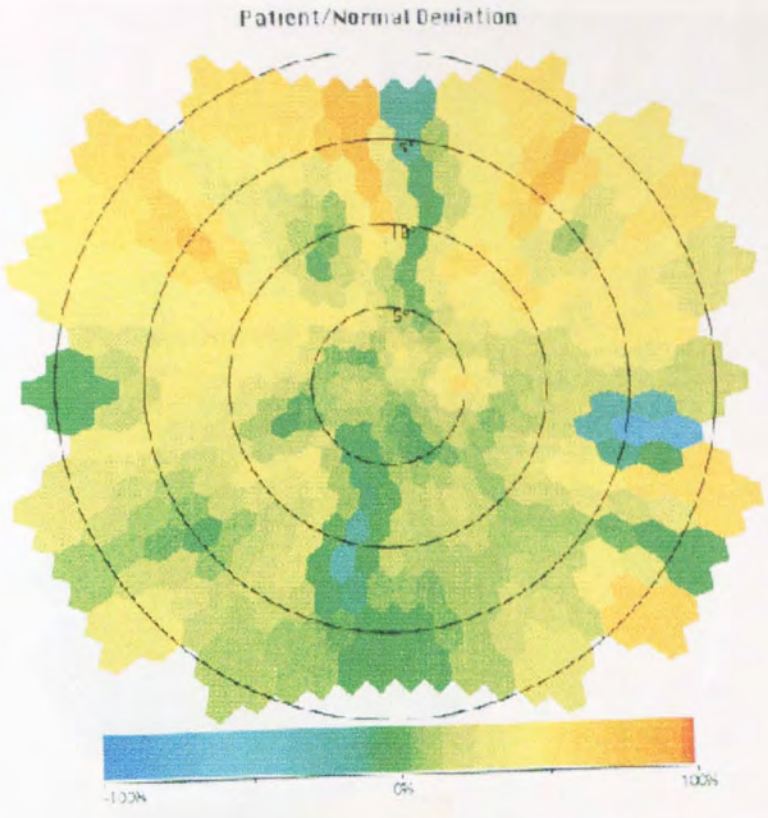


Figure 14 shows the 2 Dimensional deviation from the normal database mean value of the right eye of a normal subject. The colur bar at the bottom rates the severity by colour. The centre colour signifies 0% deviation from the mean, the far right 100% above and the far left 100% below the mean.

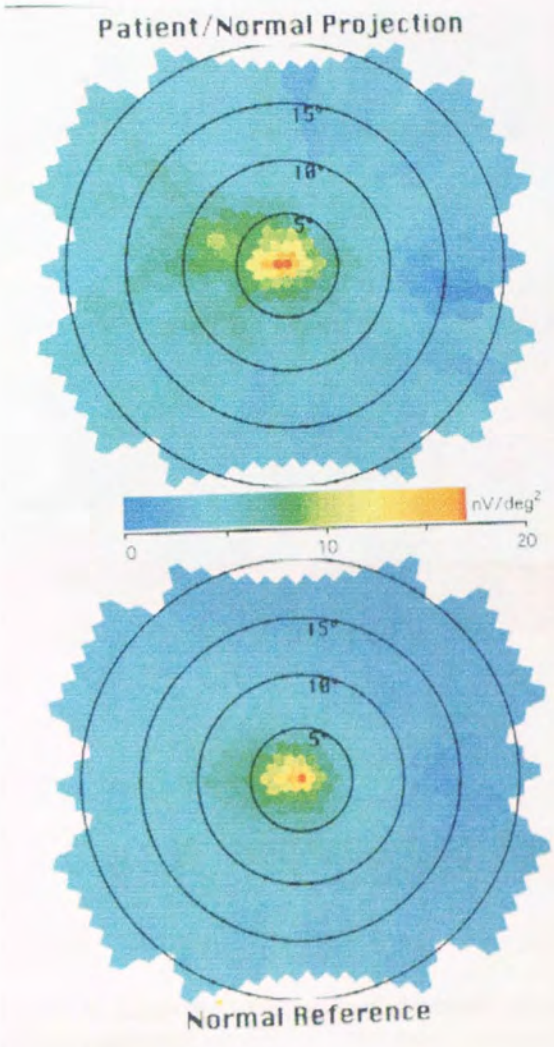


Figure 15 shows the normal 2 Dimensional mean response (bottom) and the response of the right eye of a normal subject (above). The colours represent nv/deg^2, the scale of which can be seen in the centre. To the right of the colour spectrum is above normal and to the left below normal.

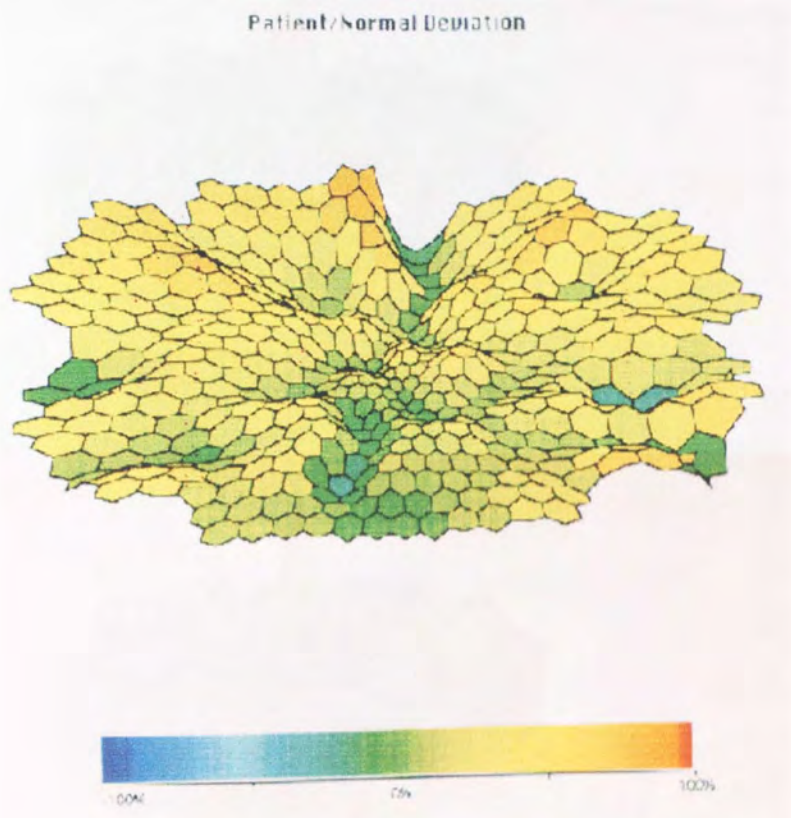


Figure 16 shows the 3 Dimensional deviation plot of the right eye of a normal subject compared to the normal database.

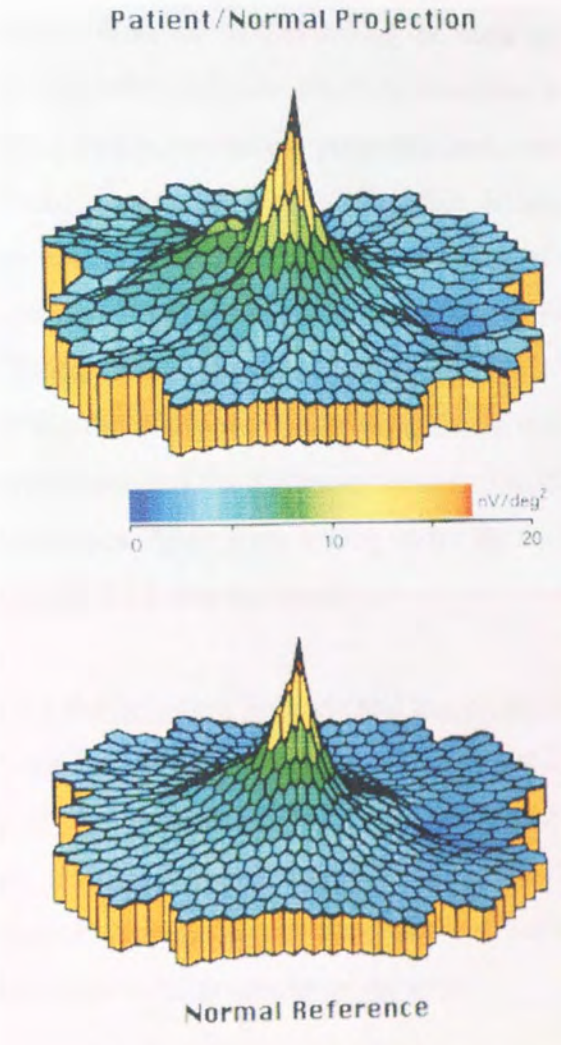


Figure 17 shows the 3 Dimensional response of the right eye of a normal subject (above) and that of the normal database (below).

CHAPTER 4 COLLECTION OF ERG AND VERIS NORMAL DATABASES

4.1 Introduction

4.1. The collection of normal flash ERG and VERIS databases

The main aims of this study were to collect a database of normal ERG and VERIS results. With the VERIS testing the same protocol was followed as would be used for the vigabatrin patients, which is described in chapter 3.5.6. For the ERG, photopic, 30Hz flicker, oscillatory potentials and scotopic (maximal rod) responses were recorded using the Medelec Sapphire 4E and Ganzfeld stimulator and bowl. These were done under both dilated and undilated conditions using the same subjects. Although vigabatrin patient testing was to follow the International Standards for the Clinical Electrophysiology of Vision (ISCEV) with the pupils dilated (Marmor et al 1996), this study was undertaken also to observe the changes in mean latencies, amplitudes and the difference in variation of the components under these two conditions. Apart from testing under the two conditions the protocol described in chapter 3.1.3 was followed.

4.2.1 Participating Subjects and test procedures for the ERG and VERIS

Fourteen healthy subjects (11 females and 3 males), with no known retinal disorders took part in the study. Their ages ranged between 20-32yrs with a mean age of 23.0 yrs. Ethical approval was given and before testing, the subjects gave an informed consent. A qualified optician prior to dilation examined the anterior chamber angles and intraocular pressures of the eyes.

Undilated ERG's were recorded, first using a DTL fibre as the recording electrode and silver-silver chloride electrodes placed at the lateral canthi of the eyes (reference) and on the forehead (earth). Testing was performed binocularly. The pupils were then dilated with 0.5% tropicamide (a mydriatic agent) and the ERG tests were repeated.

Following the dilated ERG, the subject was prepared for VERIS testing. The silver-silver chloride electrodes were removed, and a gold electrode placed at the lateral canthi as the reference and a gold ear-clip attached to the earlobe for the earth. The

DTL fibre was retained for the recording electrode. VERIS testing was then performed monocularly with the non-tested eye patched.

4.2.2 Collection of a normal EOG database

Although for the EOG response, the 185% Arden index, introduced by Arden and Barrada (1962), is generally taken as the standard limit below which values are classed as abnormal, fourteen healthy subjects (different from those who participated in the ERG and VERIS testing) underwent EOG tests. The group consisted of 7 males and 7 females with an age range of 18-44 yrs and a mean age of 28.2 yrs. Since vigabatrin has been reported to affect the EOG response with a decrease in the Arden index (Eke et al, 1997), normal values for the light peak and dark trough were collected to establish a normal database and to see whether vigabatrin affects either or both of these components. Informed consent was obtained from the subjects prior to testing and the EOG was carried out according to the protocol described in chapter 3.2.3.

4.3 Comparison of the dilated and undilated ERG responses

In order to compare the two conditions, the latencies (ms) of the a and b-waves and the amplitudes (μv) of the a-b waves were measured for the photopic, scotopic and 30 Hz flicker. For the oscillatory potentials the latencies of the a-wave, OP1 and OP2 were measured along with the a-OP1 and trough of OP1-peak of OP2 amplitudes.

4.3.1 Changes in latency

After dilation, the mean latencies of all the components measured decreased. When analysed with a paired two-tailed t-test these were all significant to a $p<0.01$ level except the latency of OP2 which significantly decreased ($p<0.05$). This decrease was probably due to the increase in light entering the eye, since the pupil size increased by an average of 3mm after application of tropicamide.

4.3.2 Changes in amplitudes

The mean amplitudes measured increased significantly ($p<0.01$) with the exceptions of the photopic a-b wave, and OP1-OP2 amplitudes. These amplitudes decreased after dilation.

Since the photopic amplitudes were measured from the trough of the a-wave to the peak of the b-wave, the a-wave amplitude was also measured from the baseline to establish whether this decrease in amplitude was also associated with a decrease in the a-wave rather than purely with the b-wave. The a-wave amplitude from baseline was also measured for 30Hz flicker, scotopic and oscillatory potential responses. All the amplitudes increased in the dilated responses. A significant increase ($p<0.01$) was seen for the photopic, scotopic and oscillatory potential responses. The mean +/- 1SD of the a-wave amplitudes from the baseline can be found in table 3. The values of the photopic amplitudes under both conditions were extremely similar- see table 2.

For the decrease in the oscillatory OP1-OP2 amplitude in the dilated responses, it may be that the effect of dilation on the OP1 component, producing the large increase in the a-OP1 amplitude, only produced a small additional increase to the peak of the second component. The a-OP1 and OP1-OP2 amplitudes were summed to give the a-OP2 amplitude. In this case the amplitude increased from 37.2 μv before dilation to 42.9 μv after dilation, this increase being significant ($p<0.05$).

4.3.3 Changes in the waveform appearance

It appears, therefore, that the morphology of the waveform may be altered by dilation of the pupils, with certain components being more strongly affected than others. Janaky et al (1996) reported that OP1 was thought to be of cone origin as the component was present when the dark adapted eye was stimulated by a white flash of 30cd/m^2 intensity, although absent when stimulated by a blue flash. With the data in table 2,the OP1 component appeared more sensitive to the increase in pupil size. In some subjects changes could also be seen visually with the scotopic responses, where the scotopic oscillatory potentials became more prominent, leading to an apparent double trough at the a-wave. The a-wave of the ERG in dark adaptation has been previously reported as splitting into two or three peaks (Algarve, 1968). It has been considered that they are the first wavelets in a series resembling the photopic OP's. The mean values, standard deviation and significance values of the results can be found in table 2.

4.4 The necessity of dilating the pupils prior to ERG testing

The significant decreases in latency and increases in amplitude after dilation (with the exception of the a-b wave amplitude) show the necessity of collection of dilated normal ERG data prior to testing patients. The normal undilated data was also required, as no normal database had been collected using the Sapphire 4E and Ganzfeld stimulator and bowl, and some future clinical referrals may be required to be tested with the pupils undilated. With 2SD of the mean being taken as the abnormal value, a slightly delayed latency or decreased amplitude may not be identified when comparing undilated results to the dilated normal database. Although the ISCEV standards make comparison of results between different testing centres more comparable, the use of other published normal data, even with those centres using the same equipment, may also be unable to detect small abnormalities.

It can be seen that although the mean differences between the components of the oscillatory potentials in the two conditions is relatively small, the variation of the results as expressed by the standard deviation is much less in the dilated condition. The importance of these subtle differences is shown in table 12 of chapter 5.6.6 where the dilated ERG results of 8 patients with known visual field loss who had been, or were currently, taking vigabatrin were compared to both the dilated and undilated normal ERG databases.

ERG Test	Undilated mean	Undilated SD	Dilated mean	Dilated SD	p value
Photopic					
Latency a-wave	15.37	0.6	14.81	0.75	2.04E-05
Latency b-wave	37.29	2.04	34.10	1.71	3.52E-07
amplitude a-b wave	139.6	36.55	136.88	44.04	0.69
30Hz Flicker					
Latency a-wave	16.43	1.07	14.25	1.46	1.58E-07
Latency b-wave	30.64	0.73	27.73	1.20	8.59E-14
amplitude a-b wave	70.41	22.36	95.04	27.87	1.71E-06
Scotopic					
Latency a-wave	17.02	1.90	15.25	0.78	4.94E-06
Latency b-wave	44.98	2.94	42.32	5.83	0.0027
amplitude a-b wave	304	95.5	348.75	112.49	0.003
Oscillatory Potentials					
Lat a	11.63	2.21	10.40	0.87	9.34E-08
Lat OP1	18.51	0.76	18.24	0.54	0.00065
amp a-OP1	20.95	12.92	31.63	10.67	6.54E-07
Lat OP2	25.85	2.34	25.23	0.64	0.013
amp OP1-OP2	23.67	8.50	20.93	6.44	0.058

Table 2 shows the mean latencies (ms) and amplitudes (μv) +/- 1SD for the major components of the ERG with the pupils either dilated or undilated. The same subjects where used for both conditions. The p-value showing the difference between these values can be seen in the last column.

ERG test	Undilated mean	Undilated 1SD	Dilated mean	Dilated 1SD	P value
Photopic	73.43	28.66	110.18	57.35	1.06E-05
30Hz flicker	52.33	14.84	54.16	22.19	0.297
Scotopic	175.54	62.07	233.89	84.56	5.90E-08
OP	14.22	5.45	21.37	9.56	3.23E-06

Table 3 shows the mean +/- 1SD amplitudes (μv) from baseline to the a-wave for photopic, 30Hz flicker scotopic and OP responses. The mean values are shown before and after dilation. The p-value (from a one-tailed t-test) is shown, a significant increase in amplitude can be seen in all responses except the 30Hz flicker.

4.5 Normal EOG results

Table 4 shows the mean values of the 28 eyes for the light peak, dark trough and Arden index values. The abnormal value, taken as 2SD below the mean value for the Arden index, approximates well with the Arden index lower limit of 185% (Arden and Barrada, 1962). The light peak and dark trough mean +/- 2SD values, when compared to those of the vigabatrin patients, may show an effect on one or both of these components which, if both components are affected in the same direction (i.e. both decreased), would not be evident from the Arden index.

Light peak	Mean	869.75	Dark Trough	Mean	350.64	Arden Index	Mean	249.37
	SD	210.43		SD	84.12		SD	31.16
	2SD	420.86		2SD	168.24		2SD	62.33
	minus 2SD	448.89		minus 2SD	182.40		minus 2SD	187.05

Table 4 shows the normal mean values for the components of the EOG. The mean, 1SD, 2SD and mean minus 2SD (which is taken as the lower normal limit) can be seen for the light peak, dark trough and Arden index.

4.6 Collection of the normal VERIS database

Although the VERIS clinic software system contained a normal database of 103 subjects for both the left and right eyes, to ensure an accurate comparison between patients tested at Aston and the normal population, it was necessary to compile a normal database for the right and left eyes within the department. The fourteen subjects who undertook the normal ERG testing also completed the VERIS test. Although the VERIS is not a psychophysical test, as with the visual field tests, there appeared to be a 'practice/learning effect' (Wood et al, 1987). Due to this factor, with limited time for the subjects to practice, some responses were discarded and replaced by those of other subjects. The normal database consisted of 15 responses for the right eye and 13 responses for the left eye. The subjects' ages ranged between 18 and 34 years. Owing to time limitations, age grouped normal responses were unable to be obtained.

4.6.1 Presentation of the normal results with VERIS Clinic software

As explained in chapter 3.5.6.3, the VERIS clinic software expresses the responses from a single test as a response density (nV/deg^2), which is devised from a scalar product (a correlation coefficient obtained from a comparison of the waveform at each location with the mean normal waveform). These results are then depicted as either waveforms (103 waveforms or grouped waveforms (concentric rings, quadrant groups or a mean response)), or as 2D or 3D pseudocolour plots. With this software obtaining amplitudes or latencies for waveforms at individual locations was not possible, although the response density values at each location could be exported.

4.6.2 Appearance of the 3SD pseudocolour plots

The VERIS 3D pseudocolour plot of the right eye of a normal subject can be seen in chapter 3.5. The thickness of the orange base indicates the amplitude value of the waveforms. It can be seen from all three plots, (the main plot being the VERIS response, the lower left plot showing the mean 3D plot of the normal database and the upper left plot showing the response of the subject compared to the mean plot) that the amplitude is slightly reduced on the temporal side. This was also the case for the left eyes in the subjects. It was not evident whether this was a normal physiological response of this test or a technical problem and the latter could not be solved without exchanging the equipment. This, however, was not possible, as time limitations would not allow another normal database collection on replacement equipment. Vigabatrin patients characteristically show more severe visual field loss in the nasal region but also have some degree of involvement temporally. The main 3D pseudocolour plots from the seven patients tested in chapter 5 showed more abnormalities in the amplitudes of the temporal hemifield than in the nasal hemifield. This posed the question of whether the plot showed the retinal field rather than the visual field. Monocular responses were then obtained from the normal subject seen in chapter 3.5 with the right and left hemifields of the stimulus obscured. These 3D pseudocolour plots can be seen in figures 18, 19, 20 & 21. Figure 5 also shows the trace array responses from the right eye viewing the left hemifield. From these results it could be seen that the plots did show the visual fields rather than the retinal fields and the problem appeared technical. Although this somewhat invalidates the diagnostic value of the 3D-pseudocolour plot, since the decrease in the amplitude of

the temporal responses occurred in all tests performed, the comparison between the patient's response and the normal mean response still produced an accurate result.

4.6.3 2D pseudocolour plots and the response density plots

As with the 3D-pseudocolour plot, the appearance of the colour scale of the 2D plot would be partly affected by the reduced amplitude of the temporal responses. Diagnostically, due to the subtle changes in colour over the plot, it was also difficult to see the extent of the abnormality in the different locations over the field. Since the valid results are those when the responses were compared to the normal mean database, a 2D-response density plot was devised. After each test, the response density values from the 103 locations were exported into Excel and these were compared to the normal mean values for the relevant eye. Locations that presented with response density values 2SD and 3SD less than the normal mean value were identified. The stimulus array (seen in figure 12 of chapter 3.5.5) was then grey scale shaded. Locations with response densities less than 2SD of the mean were shaded grey and those less than 3SD of the mean were shaded black. This composed a plot, which could be more easily compared to the mean and pattern deviation plots of the central visual field tests. The response density plots for eight vigabatrin patients with known visual field loss can be found in figure 24 of chapter 5.

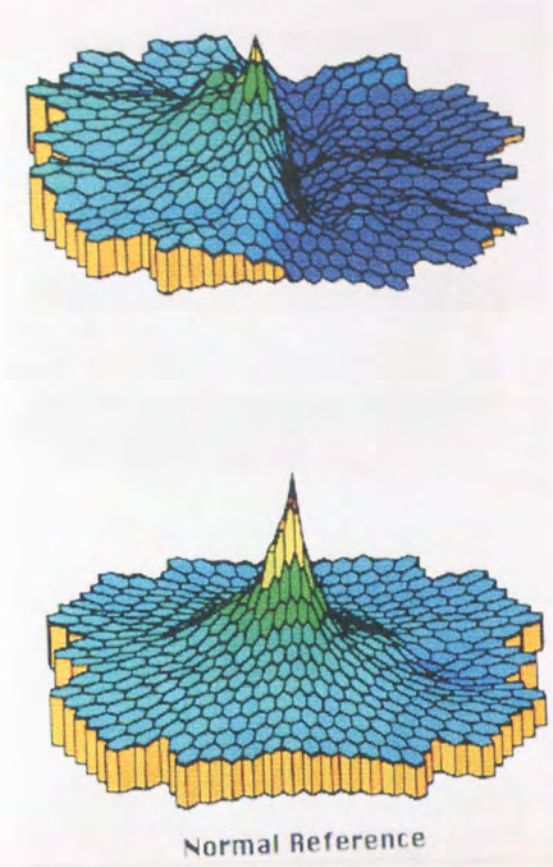


Figure 18 shows the responses of the right eye of a normal subject with the right hemifield obscured compared to the mean normal database response (below).

Patient/Normal Projection

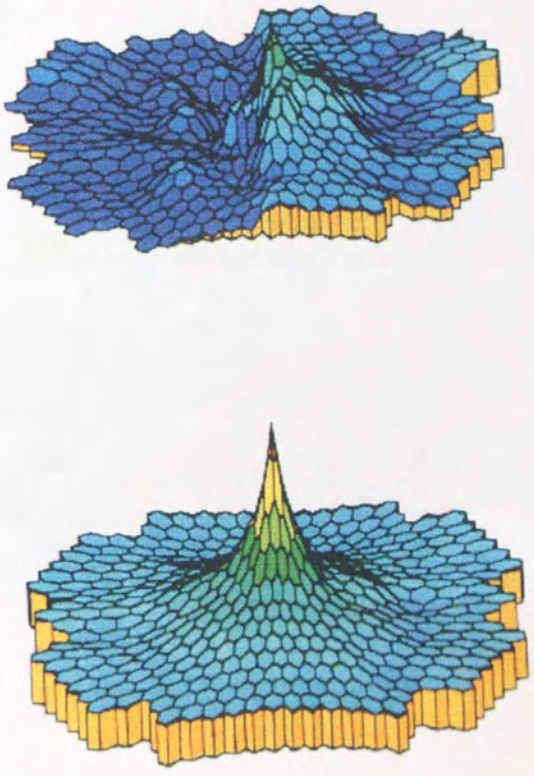


Figure 19 shows the responses of the right eye of a normal subject with the left hemifield obscured compared to the mean normal database response (below).

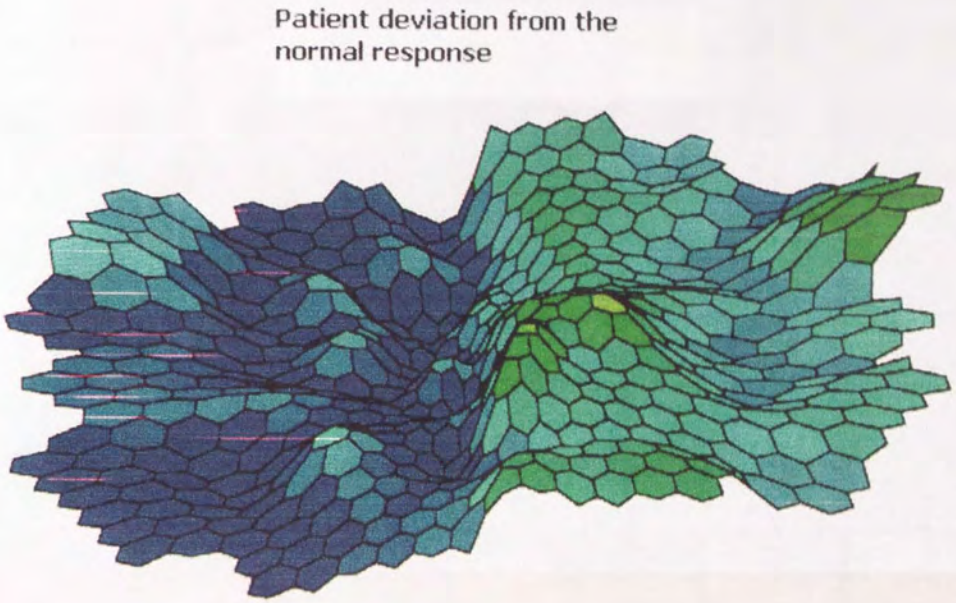


Figure 20 shows the deviation from normal of the response of the right eye of a normal subject with the left hemifield obscured

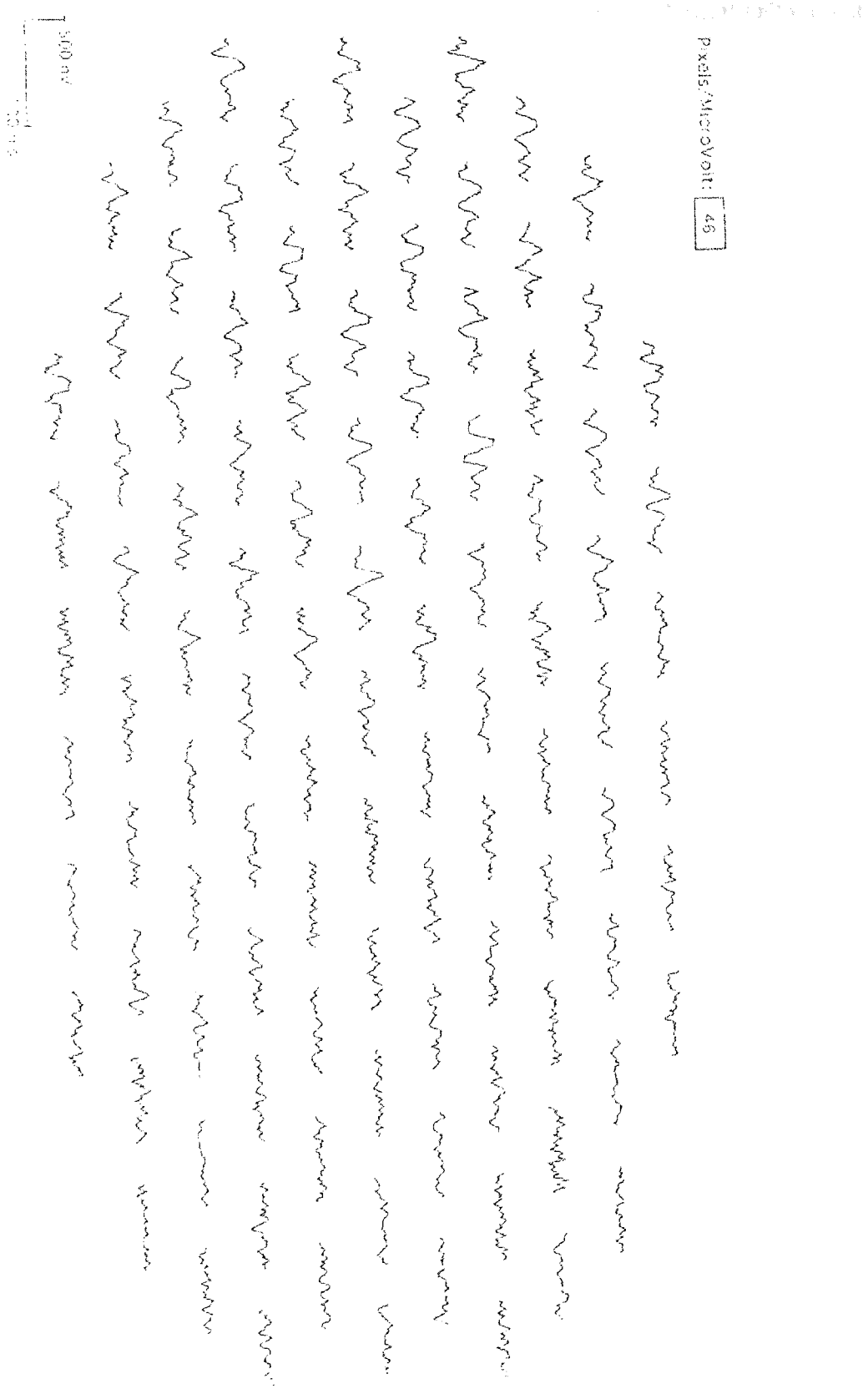


Figure 21 shows the trace array of the right eye of a normal subject with the right hemifield obscured

CHAPTER 5 VISUAL FIELDS AND VISUAL ELECTROPHYSIOLOGY OF 8 VIGABATRIN PATIENTS

5.1 Referral of patients and patient histories

5.1.1 Referral and ethics

Eight patients with known visual field defects associated with vigabatrin were referred to Aston for visual field and visual electrodiagnostic testing. Dr. Lawden (from the Leicester Royal Infirmary in Leicester) referred four patients, three cases of whom had previously been reported by Eke et al (1997). In addition Dr. Betts (from the Queen Elizabeth psychiatric hospital in Birmingham) referred four more patients. Following referral, informed consent was obtained from the patients.

5.1.2 Patient details

The patient group consisted of 4 males and 4 females ranging from 25-50 yr in age with a mean age of 37.1 yr. All patients had been found to have visual field loss associated with vigabatrin, in six the drug had been withdrawn and two were continuing with the treatment. The patient histories are briefly outlined below and the maximum dose of vigabatrin taken, the duration and the time since it was withdrawn for each patient, are summarised in table 5.

Patient Histories (Ages at the time of testing, 1997)

Pt. 1. (LCC)

- This patient is a 50yr old male who developed complex partial seizures at the age of 2 yrs. At the age of 26yrs, he developed secondary generalisation.
- He was first treated with Tridione for 2yrs in 1949, between 1969 and 1973 he was taking a combination of phenobarbitone, phenytoin, Ospolot and carbamazepine. Between 1974 and 1981 he was prescribed phenobarbitone, phenytoin, Ospolot, Benuride and sodium valproate, and after 1989 until 1994 he took phenytoin, sodium valproate and vigabatrin. The maximum dose taken of vigabatrin was 4g.
- In February 1994 he underwent a left temporal lobectomy and is now seizure-free. He continued on sodium valproate until 1996.
- Constriction of his peripheral vision was first reported in October 1991.

Pt. 2. (LMN)

- This patient is a 48yr old female who developed complex partial seizures at the age of 28yrs. These seizures appear to be associated with her menstrual cycle and usually occur a couple of days before her period.
- She was commenced on sodium valproate and carbamazepine in 1983. The sodium valproate was stopped in 1991 and vigabatrin begun in August 1991. Vigabatrin was continued until October 1994 with 3.5g being the maximum dose taken. She is currently taking Lamotrogine (commenced August 1997) and continues to take the carbamazepine.
- Severely constricted peripheral vision was first reported in October 1994.

Pt.3. (LLK)

- This patient is a 25 yr old female who experienced prolonged febrile seizures at 2yrs. At the age of 10yrs she was classified with complex partial seizures with occasional secondary generalisation.
- She was commenced on valproate in July 1989 and on vigabatrin in April 1990. In May 1993 the vigabatrin was stopped and carbamazepine started. In October 1993 the valproate was stopped and Lamotrogine started. She is currently taking slow release carbamazepine and topiramate. The maximum dose of vigabatrin taken was 2g.
- Severely constricted peripheral visual fields were first reported in May 1993.

Pt. 4. (LCS)

- This patient is a 36yr old male who first experienced a febrile convulsion at the age of 6yrs. At the age of 10 he developed complex partial seizures with secondary generalisation.
- He was commenced on phenobarbitone in 1970 which was stopped in 1990. A combination of the following drugs was taken prior to 1990, Phenytoin, Carbamazepine, Primidone and sodium valproate. All except phenytoin were stopped in 1990, although exact dates are not known: In April 1990, he was started on vigabatrin and was still taking phenytoin. This was combined with Lamotrigine in May 1995, the Lamotrigine then being stopped in October 1995. The vigabatrin and phenytoin were then combined with Gabapentin in February

1996. The vigabatrin was withdrawn in May 1996, the maximum dose he took was 1.2g. His current treatment is phenytoin and Gabapentin.

- He complained of distorted vision in his left eye in 1994. He was diagnosed with cellophane maculopathy, the symptoms resolved spontaneously over a few months and he is reported as being currently asymptomatic. Visual field examinations in 1996 showed constricted peripheral fields.

Pt. 5. (BCH)

- This patient is a 33yr old male. He developed generalised tonic-clonic seizures at the age of 18months. At the age of 11yrs he became seizure-free and remained seizure-free for a further 6yrs. At the age of 17 he experienced petit-mal seizures approximately twice yearly. Towards 1989 he was experiencing seizures one day per fortnight (with a maximum of 6-7 seizures in the day).
- Between 1989 and 1991 he underwent two temporal lobectomies. Since 1992 he has developed simple partial seizures.
- Before 1989 he was taking carbamazepine and phenytoin. The phenytoin was stopped in 1991. In April 1992 he was commenced on vigabatrin, which was combined with the carbamazepine. The vigabatrin was begun to be withdrawn in July 1995 and was totally withdrawn by May 1997. The maximum dose taken was 2g. In July 1995, he started Lamotrogine and has remained on this and the carbamazepine since.
- He describes 'tunnel vision' which he first noticed in 1993. Visual tests after the surgery in 1991 showed no peripheral visual loss.

Pt.6. (BBS)

- This patient is a 41yr old female who developed epileptic absences in her 'teens'. This progressed to falls at the age of 20. She describes an aura which warns her to sit down to prevent her falling. The seizures occur monthly with her menstrual cycle. She also experiences 10-20 'small fits' a month which she describes as 'funny feelings'.
- When diagnosed in her 'teens' she was prescribed phenytoin. About ten years ago her medication was changed to valproate, during this time she was commenced on vigabatrin and tried carbamazepine for a period of 4 months. About 4 years ago

the vigabatrin was reduced from 1.5g to 1g as she was worried about the side effects. She is currently taking valproate and vigabatrin.

- She is anxious about the side effects of vigabatrin but has not noticed any disturbance in her vision.

Pt.7. (BMG)

- This patient is a 27yr old female. She first experienced epileptic seizures at the age of 17. She describes tonic-clonic seizures at a frequency of 1 per week- although this sometimes increases to 2-3 per week. (In January 1997 she experienced 7 seizures over 5 days and was hospitalised). She also suffers from 'minor' fits in which she does not lose consciousness.
- She was prescribed sodium valproate in 1988 which was stopped 1 year ago. She took vigabatrin for approximately 4-5years which was finished in mid-1996, the maximum dose being 4g. She has in the past found benefit from phenytoin and carbamazepine although they were stopped due to allergic reactions. She is currently taking Lamotrigine and Gabapentin.
- She does not describe any visual symptoms but was reported as having a visual loss by Dr. Betts 1996.

Pt. 8. (BDJ)

- This patient is a 37yr old male. He suffers from complex partial seizures rising in the left temporal lobe. He first experienced epileptic seizures at the age of 13, they took the form of 'absences' which decreased in frequency after the age of 24. He currently experiences seizures approximately 4 times a week, they last about 10-15 seconds and are sometimes accompanied with clapping of hands.
  At the age of 13yrs he was prescribed phenobarbitone although this was discontinued after 12-18months due to excess fatigue. In his 'mid-twenties' he tried phenytoin, this was stopped after about one year as the seizures showed no improvement. He has been taking valproate and carbamazepine for 15yrs, the valproate is now gradually being withdrawn. He was commenced on vigabatrin in 1995 which he continues to take at a dose of 2.5g.
- So far no damage to his peripheral vision has been reported.

Patient	Max. dose of vigabatrin (g)	Duration (months)	Withdrawn (Yr)
1	4.0	60	3
2	3.5	34	3
3	2.0	37	4
4	1.2	73	1
5	2.0	39	2
6	1.5	120	0
7	4.0	50	1
8	2.5	30	0

Table 5 shows the maximum (Max.) dose of vigabatrin taken for each patient, the duration in months and time (to the nearest year) since withdrawal. The final column shows that at the time of the study both patients 6 and 8 were continuing on vigabatrin.

5.2 Visual testing undertaken

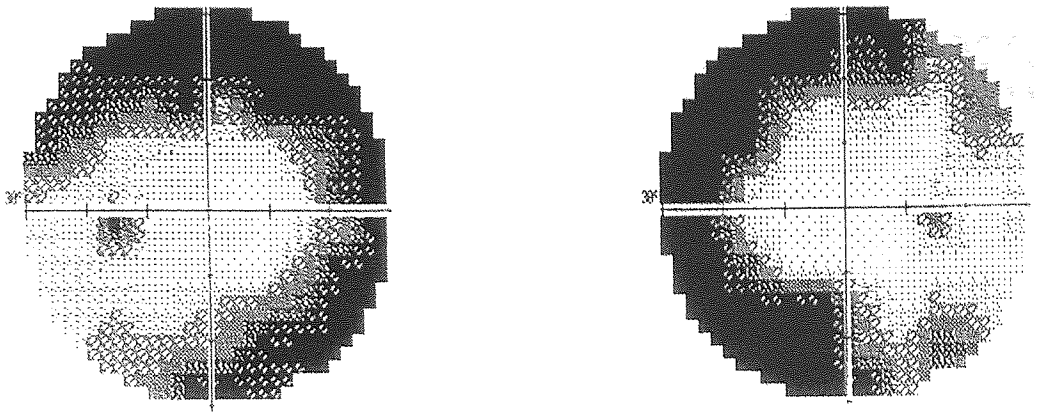
Initially full threshold perimetry was completed under the care of Dr. Wild. Both central 30-2 and peripheral 60/30-2 visual fields were tested. Full visual electrophysiology was then performed. The protocols for each test can be found in the following sections. Dilated flash ERG (3.1.4), pattern ERG (3.1.6), EOG (3.2.3), flash VEP (3.4.4), pattern VEP (3.4.7) and VERIS (3.5).

5.3. Severity of visual loss with Visual Field Testing

The results were analysed using the STATPAC™ programme. The reliability parameters of the tests- fixation losses, false-negative and false-positive responses were within normal limits for all eight patients. The eight patients were all found to have marked peripheral field loss, although this varied in severity. The visual loss appeared binocularly with approximately equal severity in the right and left eyes. The visual field had a characteristic loss of a peripheral constriction which was more marked nasally than temporally in 7 out of the eight and appeared more concentric in one patient (patient 3). The reduction in threshold sensitivity seen was frequently an absolute loss (0 dB) in the periphery and encroached less severely to 15-20 degrees in all patients. The interpolated grey scale print out of a 30-2 central visual field in figure 22 shows the characteristic pattern of concentric loss exhibited in these patients. Table 6 shows the more clinically useful total deviation values for each patient. These values indicate the deviation in height of the central visual field from the normal value expected from a person of that age. The values in table 6 are the average of 2 visual field tests for each patient. The values ranged between –3.78dB

and -19.47dB in the right eye and between -4.92dB and -20.62dB in the left eye. The average across the group was -11.39dB (SD 5.25) and -12.05dB (SD 4.69) for the right and left eyes respectively. The value is usually classed as abnormal if it is 5dB less than the normal mean database value for that age (Anderson, 1992). Seven of the eight patients showed abnormal mean deviations in both eyes and one patient (patient 8) was within normal limits. Figure 23 shows the pattern deviation plot for each patient. This is the deviation in shape of the central field after an adjustment has been made for the overall height of the hill of vision.

The mean and pattern deviations can be expressed both numerically and as plots (as seen in figure 23). The plots are expressed in probability symbols that indicate less than 5%, 2%, 1% or 0.5% of normal visual fields in the normal database had a value that low. When the mean deviations were expressed as plots, they appeared very similar to those of the pattern deviations (the right eye mean deviation plots of patient 3 (labelled LLK) and patient 7 (labelled BMG) can be seen in chapter 8.6.3). It can be seen in figure 23 that the sensitivity of the field appears not to be affected until approximately 15-20 degrees, where there is a steep drop to the severely affected regions. This is characteristically seen with all eight patients and, particularly, in the nasal hemifield.



Left Eye Right Eye

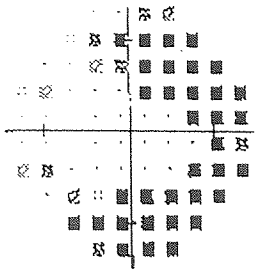
Figure 22 shows the constriction of the bilateral central 30-2 visual fields of a vigabatrin patient.

Patient	Mean Deviation Right Eye	Mean Deviation Left Eye
1	-13.24	-12.24
2	-13.38	-11.69
3	-19.47	-20.62
4	-8.56	-12.29
5	-11.09	-14.34
6	-5.61	-7.22
7	-15.98	-13.11
8	-3.78	-4.92

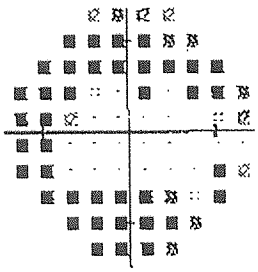
Table 6 shows the mean deviation values for the right and left central visual fields for the eight patients. A value is classed as abnormal if it is less than 5dB from the expected age-related value (Anderson, 1992). Abnormal values can be seen in all patients except patient 8. The reduction in sensitivity also appears less marked in patient 6.

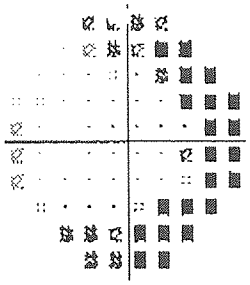
Left

Right

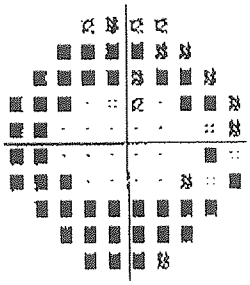


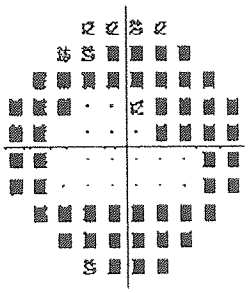
Patient 1



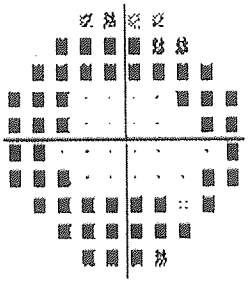


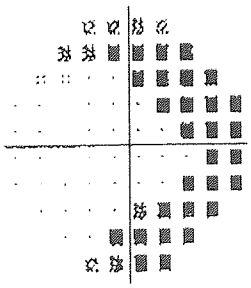
Patient 2



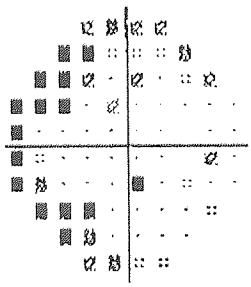


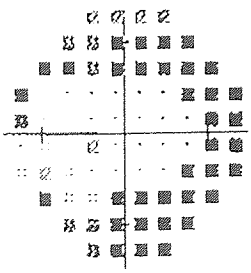
Patient 3



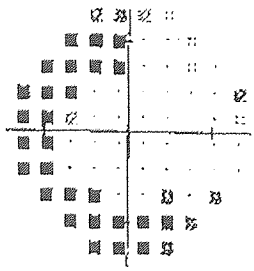


Patient 4



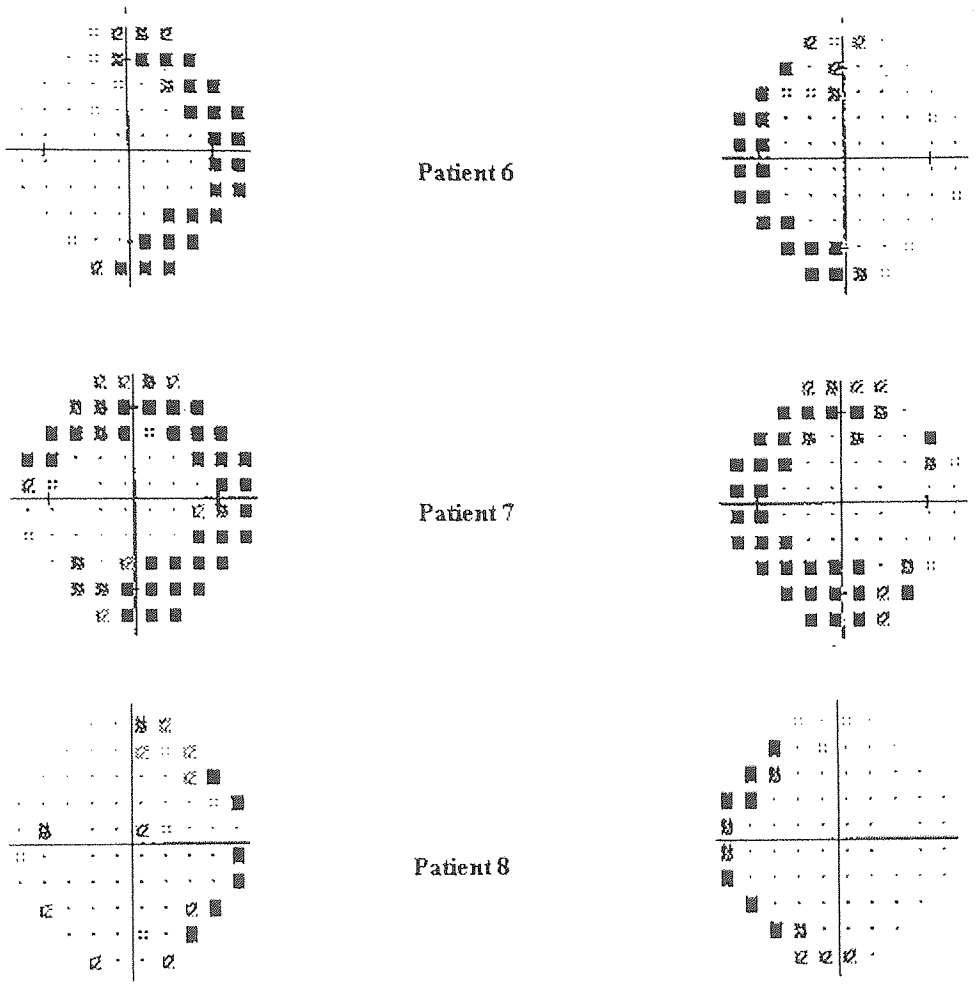


Patient 5



Left

Right



Probability Symbols

Figure 23 shows the pattern deviation plots (the deviation in shape of the central visual field after an adjustment has been made for the overall height of vision) for all patients. The probability symbols of the plots indicate that less than 5%, 2%, 1% or 0.5% of normal visual fields in the normal database for that age group had a value that low.

Results of the visual electrophysiology

The values of all components of the visual electrophysiology (excluding VERIS) can be found in tables in the appendices.

5.4 Results of the Multifocal ERG's (VERIS)

The multifocal ERG measures the cone response at 103 locations to 40 degrees vertically and 50 degrees horizontally of the visual field. The VERIS clinic software then computed the response density (nV/deg^2) at each point. The response density value at each location was then compared to the mean value in the normal database. Responses that were less than 2SD and 3SD from the normal value were classed as abnormal. The abnormal hexagonal areas can be seen in figure 24 (grey indicates 2SD and black 3SD).

All eight patients showed multiple areas of abnormality with response densities less than 2SD of the normal mean. As with the visual field testing, these varied with severity across the patient group. Seven patients were outside the 3SD normal limit with only one patient (6) showing no abnormal values. With 3SD from the mean, patient 8 only showed one area in each eye outside this limit and patients 1 & 7 showed one area monocularly. Owing to the large number of locations tested these single results could be due to chance. The number of locations with response densities less than 2SD and 3SD of the normal means for the right and left eyes of each patient can be found in table 7.

5.4.1 Pattern of cone involvement

The VERIS results are very varied across the group and a characteristic pattern of visual loss (as seen with the peripheral constriction with predominantly nasal involvement of the visual fields) is not so evident. It is clear from table 7 and figure 24 that the amount of involvement is very similar in the left and right eyes. The less severely affected patients (1,6, & 8) show abnormal areas scattered across the visual field, however, with the most severely affected patients (3 & 4) the VERIS plot shows the abnormal areas predominantly in the nasal hemifield.

Patient	No. of elements < 2SD of mean (Right eye)	No. of elements < 3SD of mean (Right eye)	No. of elements < 2SD of mean (Left eye)	No. of elements < 3SD of mean (Left eye)
1	18	4	14	1
2	26	7	26	6
3	50	11	50	14
4	51	16	58	19
5				
6	19	0	20	0
7	23	1	30	4
8	13	1	8	1

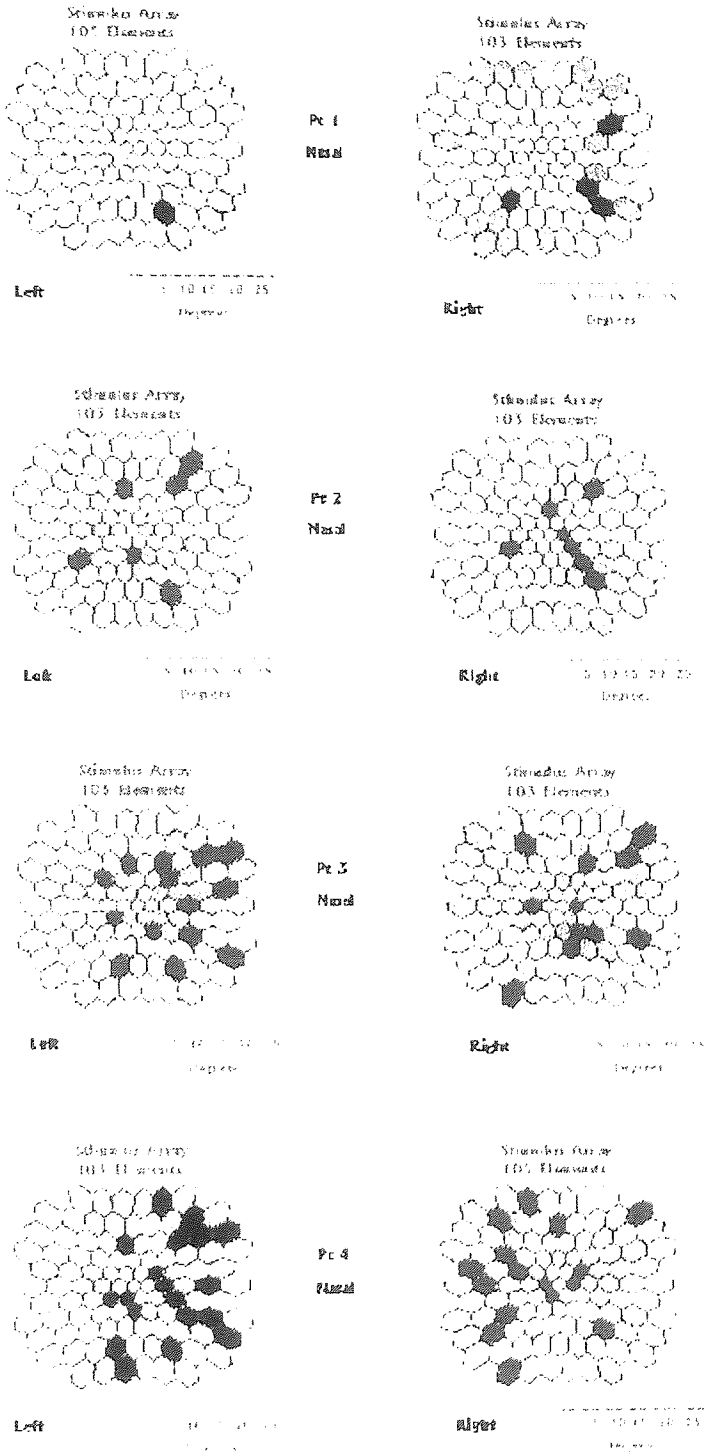
Table 7 shows the number of hexagonal areas in the 103 element array that had response densities 2SD or 3SD less than the normal mean value. Patient 5 was not available at the time of testing.

5.4.2 Severity of visual field involvement compared to that of the VERIS response.

Although the VERIS responses did not show a characteristic field loss pattern, there was a trend for the patients with severely affected visual fields to have more abnormal density responses. Table 8 shows a comparison of the severity of the effect of vigabatrin on the visual fields and VERIS responses of the eight patients. The patients (excluding patient 5) were put in order from the most severely to least severely affected. The visual fields are measured by the mean deviation value and the VERIS responses from the amount of locations with value less than 2SD from the normal mean. Although there is some agreement in the severity between the two tests, differences such as patient 4 being the most affected with the VERIS response but less severe with the visual fields, indicate that vigabatrin may affect different mechanisms in the retina to different extents. A Spearman's rank correlation coefficient showed no significance between the severity of the VERIS and visual fields in either eye. The severity of the effect also does not appear to have a direct link to the maximum dose of vigabatrin taken or the duration of treatment shown in table 5, and the two patients who were still taking vigabatrin (6 & 8) appeared two of the least affected patients. Although the group number was small it appeared that some individuals are less susceptible to this adverse affect which may be associated with differences in genetical or physiological make-up.

	Order of severity (VF mean deviation) RE	Order of severity (VERIS no. of elements < 2SD) of mean RE	Order of severity (VF mean deviation) LE	Order of severity (VERIS no. of elements < 2SD) of mean LE
Most affected	3	4	3	4
	7	3	7	3
	2	2	4	7
	1	7	1	2
	4	6	2	6
	6	1	6	1
Least affected	8	8	8	8

Table 8 shows the order of severity of the 8 patients with the central visual field tests (measured by the mean deviation) compared to the order of severity shown by the VERIS responses (measured by the number of elements outside the 2D limit). Patient 5 has been omitted since VERIS testing was not completed.



Patient 5 was unavailable at time of testing

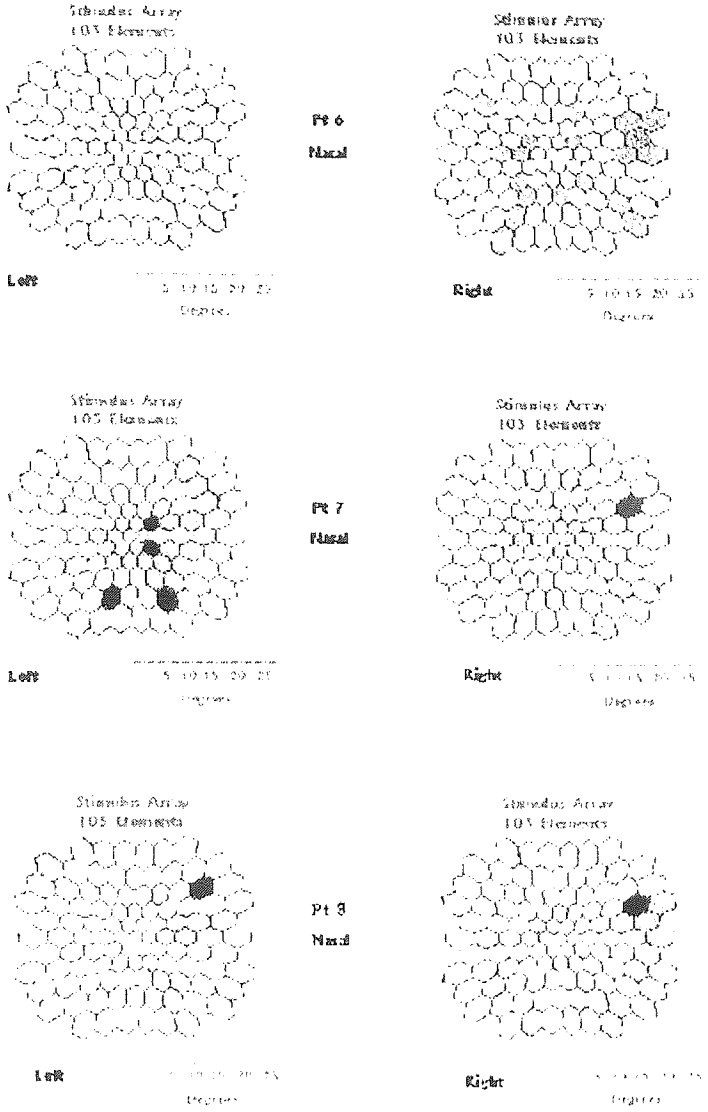


Figure 24 shows the VERIS plots for the left and right eyes of all patients except patient 5 who was not available at the time of testing. The plot shows the 103 element array, a density response that was 2SD less than the normal mean response is coloured grey and a response 3SD from the mean is coloured black.

5.5 VEP's and pattern ERG's

5.5.1 Flash and pattern reversal VEP's

Although it has been widely recognised that vigabatrin in therapeutic doses does not affect VEP's (Hammond & Wilder 1983, 1985, 1987, Hammond et al 1988a,1988b, Cosi et al 1989, Celesia et al, 1993, Harding et al 1995a, Harding et al 1995b) both pattern reversal and flash VEP's were recorded. When the waveforms were compared to the departmental normal age-related database all N2 and P2 components of the flash VEP were within normal limits. With the pattern reversal VEP, in seven of the patients the N75 and P100 components were within normal limits. The latency of the P100 component in the left eye of patient 5 however did exceed the upper normal limit.

5.5.2 Pattern reversal ERG's

When the pattern reversal ERG responses were compared to the departmental normal database, the amplitudes and latencies of the P50 and N95 components were all within normal limits, supporting the findings of Harding et al 1995.

5.6 Electroculography results

With the EOG, the light peak and dark trough responses were recorded and the Arden Index was calculated (light peak divided by the dark trough and multiplied by 100). Abnormal Arden Indices (less than 185%, Arden & Barrada, 1962) were found in the left eye of patient 5 and binocularly in patient 8. A low but normal value of 186% was also seen in the left eye of patient 6. The Arden index values of all the 8 patients can be found in table 9. The three patients reported by Eke et al (1997) as having abnormal or low EOG responses, were all found to have Arden indexes within normal limits when tested in this study. Although testing in two different centres may have influenced some differences in the responses, two of the patients were still receiving vigabatrin at the time of the first test, but had withdrawn from the drug at the time of the repeat test in this study. The patient in this study (patient 8) who showed abnormal responses binocularly, was still receiving vigabatrin, as was patient 6, who showed a low monocular response. It is unclear whether the abnormal monocular response in patient 5 was related to vigabatrin. It does however appear that the EOG is affected by taking vigabatrin but the response returns to within the normal range after cessation of the drug. As the effect on the EOG appears reversible, and as six of

the eight patients had stopped taking the drug, it was not possible to assess the severity of the effect on the EOG compared to that of the visual fields. Also, due to the reversibility of the effect on the EOG after withdrawal of the drug, it appears that different mechanisms affects this response compared to that of the continuing visual field loss.

Subject	Arden Index (%)
1-R	327
1-L	333
2-R	218
2-L	231
3-R	274
3-L	261
4-R	249
4-L	260
5-R	192
5-L	179
6-R	216
6-L	186
7-R	194
7-L	191
8-R	183
8-L	166

Table 9 shows the Arden Index (light peak divided by the dark trough and multiplied by 100) of the EOG responses from the right (R) and left (L) eyes of the eight patients. Results below 185% are considered abnormal (Arden & Barrada, 1962). Abnormal responses can be seen in the left eye of patient 5 and binocularly in patient 8. Patient 6 also shows a low value just within the normal range.

5.7 Electroretinography Results

With the ERG's, photopic, 30Hz flicker, oscillatory potentials (OPs) (under photopic conditions) and scotopic (maximal response) were recorded for all 8 patients. For photopic, 30Hz flicker and scotopic responses, the latencies of the a and b waves were measured as was the a-b amplitude. For the OPs the latencies for the a wave, OP1 and OP2 and the amplitudes for a-OP1 and OP1-OP2 were measured. All components were compared to the dilated ERG normal database, the mean values +/- 1SD of which are tabulated in chapter 4.3.3. Abnormal values have been classed as latencies greater than 2SD from the normal mean and amplitudes less than 2SD from the normal mean. The number of abnormal components for the responses for each patient can be found in table 10 and the total number of abnormalities in the patient group (from a total of 16 eyes) can be found in table 11.

Patient	Phot Lat a	Phot Lat b	Phot amp a-b	30Hz Lat a	30Hz Lat b	30Hz amp a-b	Scot Lat a	Scot Lat b	Scot amp a-b	Lat OP a	Lat OP 1	Lat OP 2	Amp a-OP1	Amp OP1-OP2
1	2	-	-	2	2	2	-	-	-	-	2	-	-	-
2	1	2	-	2	-	1	2	-	-	-	2	1	-	-
3	-	-	-	2	-	1	-	-	-	-	1	1	1	-
4	2	2	-	2	2	2	2	-	-	1	2	1	-	-
5	2	2	-	2	2	2	2	-	-	-	2	2	-	-
6	2	-	-	2	2	2	2	-	-	1	2	2	-	-
7	-	-	1	-	-	2	-	-	-	-	2	-	-	-
8	2	-	-	2	2	2	2	-	-	1	2	2	-	-

Table 10 shows the abnormal components of the ERG responses for all 8 patients. Abnormal responses have been taken as a latency values greater than 2SD of the normal mean and an amplitude less than 2SD of the normal mean. Binocular abnormal responses have been labelled '2', monocular '1' and '-' indicates a binocular response within normal limits.

Total No.	Phot Lat a	Phot Lat b	Phot amp a-b	30Hz Lat a	30Hz Lat b	30Hz amp a-b	Scot Lat a	Scot Lat b	Scot amp a-b	Lat OP a	Lat OP 1	Lat OP 2	Amp a-OP1	Amp OP1-OP2
abnormal	11	6	1	14	10	14	10	-	-	3	15	9	1	-

Table 11 shows the total number of abnormal responses for each component of the ERG responses with all the 8 patients tested i.e out of a total of 16 eyes.

5.7.1 Photopic ERG's

The photopic a wave latency appeared to be the most severely affected component with 11 of the 16 eyes showing abnormal responses (only patients 3 & 7 showed binocular normal a wave latencies). The b wave latency showed only 7 abnormal responses with binocular responses within the normal range for patients 1, 3, 6, 7 & 8. Although the photopic b-wave latency has been reported to increase after the addition of vigabtrin (Harding et al 1995a), neither of the patients receiving vigabatrin at the time of the study showed abnormal responses. It could be that the increase in b wave latency occurs transiently after the addition of vigabatrin and returns to normal after continuation of treatment. For the a-b wave amplitude only patient 7 showed an abnormal response monocularly. The 2SD value for normal mean amplitude was large (136.88μv +/- 88.09) and the normal limits were not sensitive enough to show the effect of vigabatrin. All amplitude values in the patient test group were lower than the normal mean ranging from 54.8 μv to 132 μv and with a mean 73.83μv and 1SD 21.5 μv.

Although many patients showed abnormal a-wave latencies, patient 3 (who showed the most severely affected visual fields) had normal binocular responses. This may somehow be associated with the time since the drug has been withdrawn as patient 3 had ceased vigabatrin treatment for the longest period of time. This, however, would not account for the normal responses for patient 7.

5.7.2 30Hz Flicker ERG's

The 30Hz flicker response appeared severely affected by vigabatrin even in the six who had withdrawn from the drug. The a wave showed abnormal binocular responses in seven patients with only patient 7 within the normal limits. The b-wave was less affected with five patients showing abnormal binocular responses but with patients 2,3 & 7 within normal limits. All patients in the test group showed abnormally low amplitudes but only monocularly in patients 2 & 3. The severe effect on the 30Hz

cone response is in keeping with the abnormal VERIS responses discussed in section 5.3. However, the three patients 2,3 & 7 that appeared least affected with the 30Hz flicker were rated high on the VERIS severity table 8 (in section 5.3.2).

5.7.3 Scotopic ERG's

The normal database for scotopic responses showed very varied values across the group. This was especially so for the mean +/- 2SD latency of the b-wave (42.32ms +/- 11.47) and for the a-b wave amplitude (348.75 +/- 226.89). The scotopic a wave latency however appeared more sensitive to the effect of vigabatrin in the test group, and five patients showed binocular abnormal latencies above the normal mean 15.29ms, 2SD 1.35. Although the visual fields show a characteristic peripheral loss, the rods do not appear to be severely affected and, therefore, appear not to be a main component for the visual field presentation.

5.7.4 Oscillatory Potentials

With the OPs, the latency of OP1 appeared abnormal binocularly in seven patients and monocularly in patient 3. The latency of OP2 also appeared moderately affected with 9 of the 16 eyes in the test group showing abnormal responses affecting six patients in at least one eye. The a-wave latency (3 abnormal eyes), a-OP1 (1 abnormal eye) and OP1-OP2 (no abnormal responses) amplitudes showed little effect from the vigabatrin.

5.8 The importance of a departmental normal dilated database

As discussed in chapter 4.4 all components of the normal mean ERG responses (except the photopic a-b wave amplitude) showed significant differences of at least $p<0.05$ between undilated and dilated conditions. The large number of abnormal ERG responses found in the 8 patients after treatment with vigabatrin (especially the 30Hz flicker, OP1 and scotopic a wave) has shown the importance of a normal database collected under the same conditions as the patient tests. Table 12 shows the total number of abnormal responses identified from the 8 patients when the dilated ERG results were compared to the dilated normal database and to the undilated normal database. The small differences in the reduced latencies and increased amplitudes after dilation of the pupils (with the exception of the photopic amplitude) has resulted in a larger number of abnormal responses being recognised when using

the dilated normal database as opposed to the undilated database. This was particularly evident with the scotopic a wave latency, OP1 & OP2 latencies, all 30Hz components and the photopic b-wave latency. The dilated normal mean photopic a-b wave amplitude value was greater than the undilated response, however, the SD was larger which resulted in more abnormal responses being shown in the undilated condition. This also shows that using the other condition's normal database may result in false abnormal results. The values of the two normal databases can be found in table 2 chapter 4.3.3.

Total No.	Phot Lat a	Phot Lat b	Phot amp a-b	30Hz Lat a	30Hz Lat b	30Hz amp a-b	Scot Lat a	Scot Lat b	Scot amp a-b	Lat OP a	Lat OP 1	Lat OP 2	Amp a-OP1	Amp OP1-OP2
Undilated abnormal	11	0	7	11	7	5	-	-	-	-	9	-	-	-
Dilated abnormal	11	6	1	14	10	14	10	-	-	3	15	9	1	-

Table 12. shows the total number of abnormal results (latencies greater than 2SD of the mean and amplitudes 2SD less than the mean) identified from the dilated ERG results of the 8 patients (16eyes) when compared to the the undilated ERG normal database (upper row) and the dilated normal database (lower row). Owing to a large SD for the dilated photopic a-b amplitude a false positive result can be seen in the undilated results.

5.9 EOG responses compared to the normal database

Although the Arden index is usually used to assess the EOG response, a normal database of fourteen individuals (28 eyes) was collected for comparison with the patient responses recorded under the same conditions with the same equipment, the details of which can be found in chapter 4.5. Normal mean values +/- 1SD of the light peak, dark trough and Arden index were 869.75 +/- 210.43, 350.64 +/- 84.12 and

249.37 +/- 31.16. The values of these components for the eight patients can be found in table 9. Although the Arden index values were within normal limits for patients 1 & 4, both patients showed low (values less than 2SD from the mean) binocular light peak and dark trough values, the lower normal limits for these components being 449 and 182 respectively. Patient 1 showed binocular abnormal responses and patient 4 showed an abnormal response in the left eye and a value on the lower limit for the right eye. Although six of the eight patients had light peak and dark trough responses within the normal limits, the responses were low with 14 eyes with a value less than the normal mean for light peak and 13 eyes less than the normal dark trough value. The mean values +/- 1SD for the patient group were 625.25 +/- 173.81, 289.06 +/- 103.00, 228.75 +/- 51.38 for the light peak, dark trough and Arden index respectively. Although the Arden index has been seen to return to within normal limits after cessation of vigabatrin, these results suggest those low values for the light peak and dark trough components may persist. Since EOG testing was not performed prior to vigabatrin treatment it is not known whether the values have altered during this time.

Patient	Arden Index (%)	Light Peak	Dark Trough
1-R	327	429	131
1-L	333	380	114
2-R	218	827	378
2-L	231	734	317
3-R	274	874	319
3-L	261	795	305
4-R	249	449	180
4-L	260	393	151
5-R	192	844	439
5-L	179	854	476
6-R	216	605	280
6-L	186	583	314
7-R	195	588	302
7-L	192	495	258
8-R	183	598	327
8-L	166	556	334

Table 13 shows the values for the Arden index, light peak and dark trough components of the EOG for the right (R) and left (L) eyes for all 8 patients

5.10 Overall ERG and EOG findings

The 30 Hz flicker response, especially the decrease in a-b amplitude particularly appeared to be affected by the vigabatrin. The 30Hz flicker a-wave latency also was quite severely affected, as was the 30 Hz flicker b-wave, although to a slightly lesser degree. This indicates a strong link between vigabatrin and the cone system which appears not to reverse after vigabatrin has been withdrawn. These findings may, in part, support the work of Miller et al (1999) who suggested a correlation between the visual field defects and the 30Hz flicker amplitudes of patients currently taking vigabatrin.

The oscillatory potential responses, especially the latency of OP1 and to a slightly lesser extent OP2, indicate the involvement of the amacrine cells of the retina. Janaky et al (1996) proposed that OP1 was also of cone origin, which may explain the similar severity of the effect of vigabtrin with OP1 and the 30Hz flicker response. The OP1 component (showing abnormalities in 15 of the 16 eyes) also appears unrelated to whether treatment with vigabatrin is continuing or has been withdrawn. This apparently irreversible effect may be associated with the visual field loss.

The photopic a wave latency did show 11 abnormal responses in the 16 eyes of the patients. Although the b-wave latency has been reported as delayed after initial introduction of vigabatrin (Harding et al 1995a), only 6 eyes showed abnormal responses. The photopic response has been compared more often to the VERIS multifocal ERG than the 30Hz flicker response. The trough of the multifocal ERG has been described to be very similar in latency to the a wave of the full field photopic ERG. This component may be contributing to the VERIS responses with an influence from the 75Hz flicker, producing a similar response to the decreased amplitudes seen with the 30Hz flicker responses.

For the photopic b wave latency it appears that vigabatrin affects the latency during initial treatment with the drug, although this only appears a transient effect. The EOG also appears to return to within normal limits after cessation of the drug. Therefore, it appears that vigabatrin does affect the pigment epithelium and the inner retinal layer, although it cannot be directly associated with the visual field defects.

CHAPTER 6 DOUBLE BLIND CROSS OVER PLACEBO CONTROLLED STUDY ON HEALTHY SUBJECTS

6.1 Introduction

The eight Birmingham and Leicester patients (three of which were reported by Eke et al, 1997) were confirmed as having constricted visual fields as was shown in chapter 5. A high proportion produced abnormal 30Hz latency a-wave values (7 out of the 8 binocularly), 30Hz amplitude values (all showing in at least one eye with 5 binocularly) and all showing an abnormal latency for oscillatory potential 1 (only 2 patients monocularly). The two patients still receiving vigabatrin also showed low EOG Arden indexes, one with abnormally low binocular responses (Arden index less than 185%, Arden & Barrada 1962). As the study had supported the findings of Eke et al 1997, it was necessary to establish whether these were related to the treatment of vigabatrin.

Of those taking vigabatrin, many are also taking a variety of other AED's, often with vigabatrin being prescribed as an 'add-on' drug, or during the withdrawal of a drug which may have offered little benefit to the seizure frequency or had produced undesirable side effects. In addition, patients having withdrawn from vigabatrin lost some electrophysiological abnormalities but retained others.

Due to this situation many studies have included extraneous factors such as whether the visual loss may be associated with vigabatrin combined with another drug or somehow induced by the presence of epilepsy.

Since general practitioners were becoming more reluctant to commence their patients on vigabatrin, and many were in fact withdrawing the drug, a study following the visual responses of patients before and during treatment would not have been possible.

6.2 Reported cases of field loss with vigabatrin

In 1996 Hoechst Marion Roussel reported only 28 known cases world wide of visual constriction with patients taking vigabatrin (personnel communication). They estimated that 140,000 patients had taken the drug since it was marketed in 1989 but stated that they had only received reports of visual field defects in less than 0.1% (Backstrom et al, 1997). Most clinical testing of epilepsy i.e. electroencephalography

does not routinely include visual fields or visual electrodiagnostic testing, therefore, it was probable that many patients receiving the drug may not have been identified.

6.3 Study Design

This study was a double blind cross over placebo controlled study designed to investigate the short-term effect of monotherapy with vigabatrin on visual field and visual electrodiagnostic responses. The study consisted of three 10-day periods with either vigabatrin, carbamazepine or placebo being taken in any one cycle. Carbamazepine is usually the first drug of choice in patients with partial seizures (the type of patient to be prescribed vigabatrin). Carbamazepine has not been reported to produce any visual field loss but has been found to reduce ERG b- wave amplitude and oscillatory potentials (Harding, 1997). This drug was therefore chosen to compare with vigabatrin, for any changes in the visual electrophysiological responses during the study.

6.4 Exclusion criteria

Using normal healthy subjects the study could be controlled to exclude many factors that could influence the effect of the drug. The study excluded any subjects taking any medication. Alcohol, tobacco products, and high fat foods were prohibited on the days of testing, and to ensure as accurate visual responses as possible, the subjects were limited to an age range of 18-40yrs with a corrected visual acuity of 6/6 and a prescription not exceeding +/- 5 diopter.

6.5 Ethical Aspects

The study was carried out at the Human Psychopharmocology Unit (HPRU) in Surrey University who were also psychologically testing the subjects during the cycles. Surrey University ethics committee gave ethical approval and the subjects were recruited and informed consent obtained by HPRU. Prior to enrolment the subjects had both ophthalmologic and medical examinations and during the study a qualified medical team at the unit administered the drugs. After completion or withdrawal of the study a post study medical examination was performed.

6.6 Drug Dosage and testing days

The vigabatrin and carbamazepine were increased in dose over the 10-day cycle, the maximum dose per day of vigabatrin being 2g and that of carbamazepine being 800mg. The doses were administered on the morning before testing and in the evening after testing as shown in table 14. Visual testing was undertaken initially on a baseline day (day 0) and then on days 2, 4 & 9 of each cycle. At day 2 the subjects were on half the maximum dose, at day 4 the maximum dose was being taken and on day 9 the maximum dose had been taken for six whole days. After testing was completed on day 9 the drugs were titrated down. There was a washout period of ten days where the subjects did not take any drugs before the next cycle was started.

Day of Cycle	Vigabatrin AM dose	Vigabatrin PM dose	Carbamazepine AM dose	Carbamazepine PM dose
1	0.5g	0.5g	200mg	200mg
2	0.5	1g	200mg	400mg
3	1g	1g	400mg	400mg
4	1g	1g	400mg	400mg
5	1g	1g	400mg	400mg
6	1g	1g	400mg	400mg
7	1g	1g	400mg	400mg
8	1g	1g	400mg	400mg
9	1g	0.5g	400mg	200mg
10	0.5g	0.5g	200mg	200mg

Table 14 shows to increments of the increase in the titration of vigabatrin and carbamazepine over each of the 10-day cycles.

6.7 Visual tests performed

Since both centres (HPRU & Aston) were testing the subjects on the same day, the number of electrodiagnostic tests performed were limited. There have been no reported effects of vigabatrin on VEP's (Hammond & Wilder (1983,1985,1987), Hammond el al 1988a, 1988b, Kälviäinen et al 1991). Since abnormalities have been shown in visual fields, flash ERG's and EOG's, these three tests were performed during this study.

For ERG's the photopic, 30Hz flicker, scotopic (maximal response) and oscillatory potential responses were recorded. Both central 30-2 and peripheral 60/30-2 visual fields were tested with visual acuity being corrected for the central field. At the time of the study, the VERIS was not available.

Owing to the time limitations two subjects were tested simultaneously, one having electrophysiology and the other static perimetry. Since ERG's could not always be performed first the tests were completed with the pupils undilated. The subjects were however tested throughout the study and at the same time each day to prevent possible changes in response due to circadian rhythm. Visual fields were tested using a Humphrey visual field analyser (series 6). The ERG's and EOG's were performed using a Medelec Sapphire 4E and Ganzfeld stimulator and bowl. Apart from the pupils being undilated, the electrophysiology was carried out according to the protocols described in chapter 3.1 and 3.2.

6.8 Preferable number of subjects and withdrawal Policy

It was aimed that 15 subjects would complete all three cycles of the study. If any subjects withdrew from the study another volunteer would replace them. Owing to an oversight with the study design the dropout rate was particularly high. The 800 mg dose of carbamazepine was large for the time allowed to reach maximum dose. Also the dose received was equal for all subjects resulting in lighter subjects in weight taking a higher amount of drug per Kg than heavier subjects. Due to these problems many subjects were withdrawn due to nausea and dizziness (known side effects of carbamazepine) during the cycle. With the order of the cycles being randomised this was often one of the first two cycles. Once withdrawn the subjects did not attend any other cycles.

Of the twenty subjects recruited, 14 (eight males and six females) completed at least one cycle, 8 completed the carbamazepine cycle and 11 completed the vigabatrin and placebo cycles. Seven subjects completed the whole study of all three cycles. Owing to the study design that each subject acted as their own control, with these values being the responses obtained from the baseline tests (those taken before any drugs were ingested), the fact that different subjects completed different cycles did not adversely affect the validity of the results.

6.9 Analysis procedure of results

The electrodiagnostic responses obtained from each testing day (day 0, 2, 4 & 9) were averaged separately for all the subjects completing each cycle. For the visual fields only the seven subjects that completed all three cycles were included in the analysis. The data from any subject that did not complete the whole cycle was discarded. Mean baseline data for each cycle consisted of the responses obtained from the subjects that completed that particular cycle.

6.9.1 Visual Fields

Central visual fields

For the central 30-2 visual fields the mean deviation (MD), pattern standard deviation (PSD), short-term fluctuation (SF) and corrected pattern standard deviation (CPSD) were used for the analysis. These are resultant measurements from an analysis using the value of deviation from the expected age-related normal value for each subject. Each value was averaged across the subjects +/- 1SD for baseline and days 2, 4 & 9 for each cycle.

Peripheral visual fields

For the peripheral 60/30-2 visual field, analysis was carried out using the sensitivity threshold values at the 68 points measured. The plot was divided into quadrants (superior temporal, superior nasal, inferior temporal and inferior nasal). Each quadrant contained 17 points where the threshold value had been measured. Where a value had been rechecked the two values were averaged. The threshold values were then summed with a resultant total value for each quadrant. The resultant values of each quadrant were then averaged separately for all the subjects at baseline and on days 2, 4 & 9 for each cycle.

Secondly, the field plot was divided into three concentric rings as illustrated in figure 25. The inner ring contained the central twenty threshold values; the middle and outer rings each contained twenty-four threshold values. The nasal and temporal hemifields were then analysed separately i.e. with ten inner values, twelve middle values and twelve outer values. The threshold values were averaged across the subjects (dB +/- 1SD) for baseline and days 2, 4 & 9.

6.9.2 Electrophysiological responses

Electroretinography

The responses were obtained from photopic flash, 30Hz flicker, oscillatory potentials and scotopic (maximal response) tests.

For the photopic, 30Hz flicker and scotopic responses the latency of the a-wave, b-wave and amplitude of the a-b waves were averaged across the subjects for each cycle. For the oscillatory potentials the latency of the a-wave, OP1 and OP2 and the amplitudes of a-OP1 and OP1-OP2 were analysed.

Electro-oculography

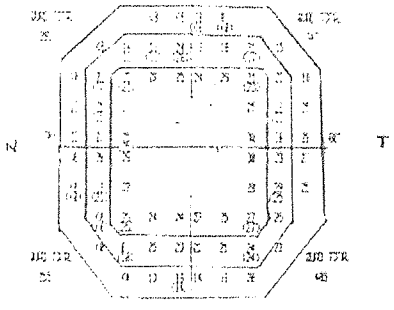
With the EOG's the light peak, dark trough values and Arden index (light peak divided by dark trough multiplied by 100) were analysed. The time taken to reach the light peak and dark trough were also recorded.

With the mean values at baseline and on days 2, 4 & 9 a two-tailed t-test was carried out between baseline and these other values.

Fig 25 shows the concentric rings into which the threshold values of the 68 points of the peripheral 60/30-2 points were divided for analysis. These outer, middle and central points were then divided into nasal and temporal hemifields for further analysis. This is a right eye visual field with nasal on the left and temporal on the right.

Superior Nasal

Superior Temporal



Inferior Nasal

Inferior Temporal

6.10 Discussion of the results

Fourteen subjects (eight males and 6 females completed at least one cycle, the mean age being 27.3 years and with a standard deviation of 6.7.

6.10.1Visual Fields

The measurements of the central visual fields, the MD, SF, PSD and CPSD showed no significant difference between baseline and any of the days for any of the cycles. These values can be found in table 15. It was not expected for the central visual field results to be affected by the vigabatrin since the visual loss with the patients taking the drug has a characteristic pattern of peripheral loss gradually encroaching towards the centre with more involvement nasally.

Drug/ Day	Mean MD	1SD	Mean PSD	1SD	Mean SF	1SD	Mean CPSD	1SD
CBZ 0	-1.29	0.79	1.77	0.26	1.24	0.30	0.97	0.50
CBZ 2	-1.82	0.66	2.19	0.72	1.23	0.60	1.51	1.05
CBZ 4	-2.03	0.68	2.36	0.94	1.25	0.30	1.77	1.19
CBZ 9	-1.83	0.90	2.24	0.79	1.31	0.49	1.56	1.12
VGV 0	-1.29	0.79	1.77	0.26	1.24	0.30	0.97	0.50
VGV 2	-0.86	0.98	1.93	0.33	1.18	0.42	1.33	0.28
VGV 4	-0.85	0.57	1.88	0.38	1.11	0.22	1.32	0.62
VGV 9	-0.81	0.90	1.98	0.58	1.28	0.29	1.40	0.57
PLAC 0	-1.29	0.79	1.77	0.26	1.24	0.30	0.97	0.50
PLAC 2	-1.56	0.73	1.93	0.64	1.39	0.26	0.94	1.00
PLAC 4	-1.05	0.66	1.88	0.44	0.97	0.17	1.49	0.51
PLAC 9	-1.38	2.02	1.76	0.37	1.21	0.29	0.96	0.74

Table 15 shows the mean values and one standard deviation for the MD, PSD, SF and CPSD measurements of the central visual fields at baseline and over each cycle (CBZ = carbamazepine, VGV = vigabatrin and PLAC = placebo).

For the peripheral 60/30-2 visual fields again there was no significant difference between baseline and days 2, 4 & 9 on any cycle. This was true for both the qradrant analysis and for the concentric ring analysis. Due to the nature of the visual loss associated with the drug, the most peripheral nasal group (N-column 1) would have been the most likely to be affected. It can however be seen by table 16 that the mean threshold showed no significant difference, the threshold being slightly increased

during the vigabatrin cycle although by an amount expected due to normal variability (Heijl et al, 1987).

Baseline

T-Column1	T-Column2	T-Column3	N-Column1	N-Column2	N-Column3
7.58	20.90	26.96	13.01	20.65	26.11
t-col 1 sd	t-col 2 sd	t-col 3 sd	n-col 1 sd	n-col 2 sd	n-col 3 sd
9.39	7.28	2.45	9.16	7.39	4.65

CBZ –Day 9

T-Column1	T-Column2	T-Column3	N-Column1	N-Column2	N-Column3
7.53	20.46	26.10	12.79	20.08	25.36
t-col 1 sd	t-col 2 sd	t-col 3 sd	n-col 1 sd	n-col 2 sd	n-col 3 sd
9.44	7.55	3.66	9.78	7.46	4.56

VGV-Day 9

T-Column1	T-Column2	T-Column3	N-Column1	N-Column2	N-Column3
7.97	21.00	26.54	13.67	20.41	26.07
t-col 1 sd	t-col 2 sd	t-col 3 sd	n-col 1 sd	n-col 2 sd	n-col 3 sd
9.15	7.49	2.26	9.47	7.66	4.33

Placebo Day 9

T-Column1	T-Column2	T-Column3	N-Column1	N-Column2	N-Column3
8.63	22.08	26.83	14.82	21.45	26.23
t-col 1 sd	t-col 2 sd	t-col 3 sd	n-col 1 sd	n-col 2 sd	n-col 3 sd
9.80	6.74	2.85	9.36	7.33	4.15

Table 16 shows the mean threshold values and one standard deviation for the concentric ring hemifield analysis of the peripheral visual fields. The mean values for the outer temporal (T-column-1) and nasal (N column-1), middle temporal (T column-2) and nasal (N column-2) and inner temporal (T column-3) and nasal (N column-3) are shown at baseline and day 9 of the three cycles. From the standard deviation (SD) it can be seen that there is no significant difference between any of these values.

It appears, therefore, that the visual field loss either requires an increased dose of vigabatrin and /or a longer period of time before any visual symptoms become apparent with visual field testing.

6.10.2 Electroretinography

The two-tailed t-test was used to analyse any differences in the baseline values of latency and amplitude and those of days 2, 4 & 9. For the carbamazepine and placebo cycles there were no significant changes for any of the tests.

During the vigabatrin cycle no significant differences were observed for the scotopic, 30Hz flicker or oscillatory potential response components, however, the photopic b-

wave latency did show a significant increase ($p<0.05$) from baseline to day 2 and ($p<0.01$) to days 4 & 9. Table 17a shows the mean latencies, 1SD and the p-values for the photopic b-wave latencies during the vigabatrin cycle. The mean latencies of the photopic b-waves during the carbamazepine and placebo cycles can be found in table 17b. Figure 26 displays the photopic b-wave latencies of all three cycles. During the vigabatrin cycle the latency shows a steep increase from baseline to day 2 further increasing though less severely to day 4, remaining fairly constant in the right eye on day 9 and slightly decreasing in the left eye.

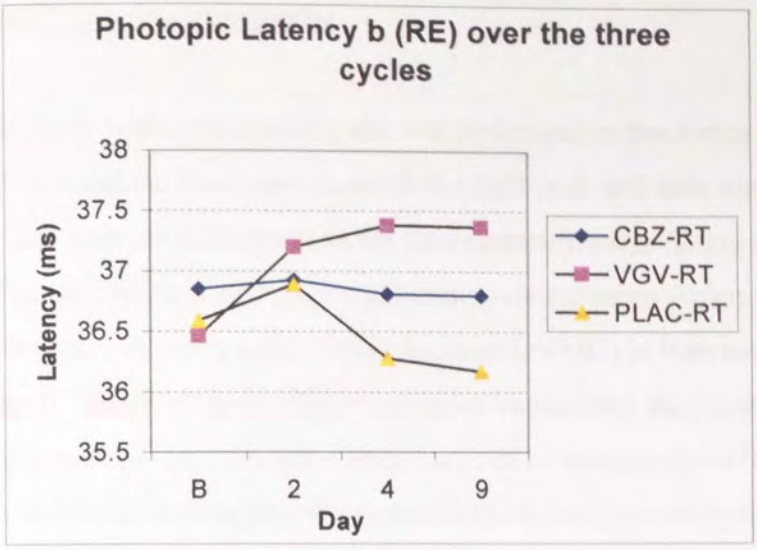
Day	RE b-wave latency	1SD	P value	LE b-wave latency	1SD	P value
0	36.46	1.49	-	36.65	1.19	-
2	37.20	0.98	0.01761	37.16	0.97	0.00066
4	37.38	0.88	0.00531	37.58	0.87	5.8553E-05
9	37.37	1.18	0.00085	37.21	1.09	0.00126

Table 17a shows the increase in photopic b-wave latency over the vigabatrin cycle. The significance can be seen by the p-values.

Day	CBZ RE Mean Photopic Lat b	CBZ LE Mean Photopic Lat b	Placebo RE Mean Photopic Lat b	Placebo LE Mean Photopic Lat b
0	36.85	36.63	36.59	36.65
2	36.92	36.88	36.89	37.29
4	36.81	36.86	36.28	36.09
9	36.80	36.78	36.17	36.35

Table 17b shows the mean latencies of the photopic b-wave in both eyes (right =RE & left = LE) during the carbamazepine and placebo cycles.

This increase in latency supports the findings of Harding et al 1995 who also found an increase in photopic b-wave latency after the addition of vigabatrin to the therapy of patients with uncontrolled epilepsy. Recently, Duckett et al (1998) have supported this finding reporting a delay in the ERG b-wave after commencing vigabatrin therapy with children without any indication of visual field loss. However, the photopic b-wave latency was not a particularly good marker for abnormal responses with the 8 Leicester and Birmingham patients, only two of these patients showed abnormally increased latencies.



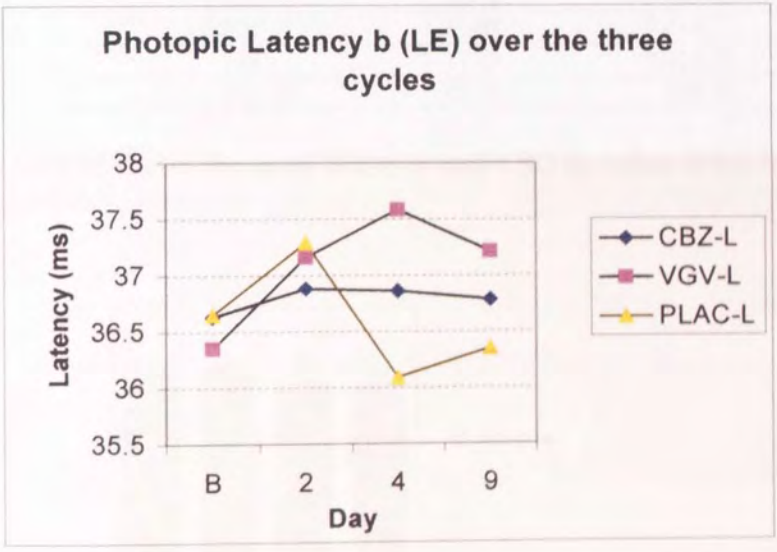


Figure 26 shows the changes in photopic b-wave latency over the three cycles. A significant increase can be seen from baseline to days 2, 4 & 9 during the vigabatrin cycle. The top graph shows the right eye responses (RT) and the bottom graph the left eye (L).

6.10.3 Electro-oculography

Analysis with a two-tailed t-test was performed on the Arden index, light peak, dark trough and the time taken to reach the light peak and dark trough.

There were no differences in the mean measurements during the carbamazepine and placebo cycles. During the vigabatrin cycle the mean Arden index gradually decreased showing a significant decrease ($p<0.05$) in both eyes between baseline and day 9. Table 18 shows the Arden index values over the vigabatrin cycle, the mean with one standard deviation error bars can be seen graphically in figure 27. The mean Arden index values over the carbamazepine and placebo cycles can be found in table 19.

Day	Mean AI (RE)	1SD	Mean AI (LE)	1SD
0	228.55	36.18	244.09	27.23
2	229	33.05	234.27	29.38
4	212	37.33	214.72	21.30
9	209.72	27.30	210.45	25.37

Table 18 shows the mean decrease and 1 SD in Arden index in both eyes during the vigabatrin cycle.

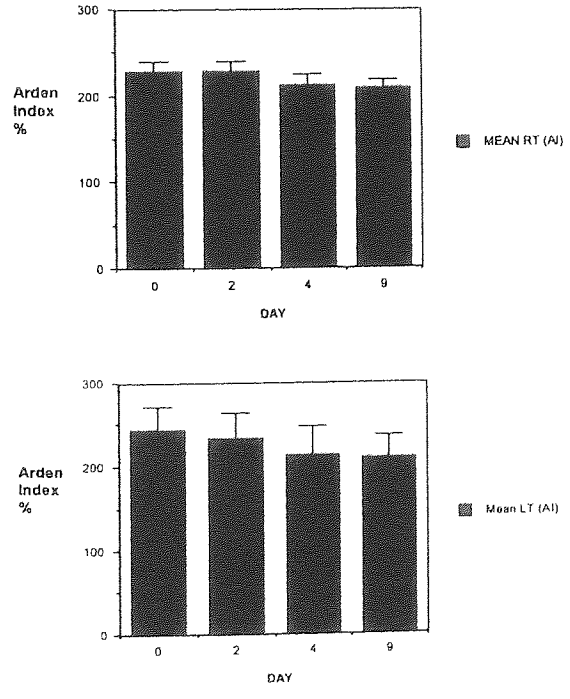


Fig 27. Shows the mean decrease (with 1 SD error bars) in Arden index in the right and left eyes during the vigabatrin cycle.

The decrease in Arden index appeared to be associated with a decrease in the light peak values. The mean right eye light peak value decreased from 900% at baseline to 838%, 817% and 803% over the cycle. The mean index in the left eye also decreased from 834% to 802%, 805% and 781% over the cycle. This decrease, however, was not significant and no change was apparent in the dark trough.

Day	CBZ RE mean Arden Index	CBZ LE mean Arden index	Placebo RE mean Arden index	Placebo LE mean Arden index
0	227.5	246.1	222.8	241.1
2	232.4	241.6	234.6	238.1
4	223.8	227.3	220.4	218.2
9	236.5	234.1	219	232.2

Table 19 shows the Arden index values for the right (RE) and left (LE) eyes over the carbamazepine (CBZ) and placebo cycles.

Eke et al 1997 reported low and abnormally low Arden indexes in two case reports of patients taking vigabatrin. After the drug was discontinued, the two patients were tested at Aston as part of the previous study. Both patients had Arden indexes within normal limits. Of the eight patients only the two currently receiving vigabatrin had low or abnormal EOG responses. It appears that after discontinuation of the drug, responses return to within the normal range.

Although the trend of the light peak to decrease was not found to be significant, the time taken (in minutes) to reach the light peak after the background intensity had been increased to 600cd/m2 did significantly increase ($p<0.05$) between baseline and day 9. Mean values and standard deviation are shown in table 20 and graphically in fig 28. This increase may somehow be associated with the decrease in Arden index since Arden and Barrada (1962) concluded that any light peak time over 11 minutes was associated with a low Arden index. On day 9 with 11 subjects completing the vigabatrin cycle, 2 eyes had a light peak time of 11 and 12 minutes.

The involvement of the EOG indicates an effect of the vigabatrin on the retinal pigment epithelium. Since it appears that the Arden index decreases due to the fall in the light peak amplitude, it is possible that there may be involvement of the photopic system with feedback to the pigment epithelium (a pathway suggested by Kolder, 1991).

DRUG B EYE	Mean	SD
LP RT-0	7.91	1.22
LP RT-9	9.45	0.82
LP LT-0	8.18	1.08
LP LT-9	9.09	1.22

Table 20. shows the mean time taken (in minutes) for the left (LT) and right eye (RT) EOG responses to reach the light peak amplitude at baseline and on day 9.

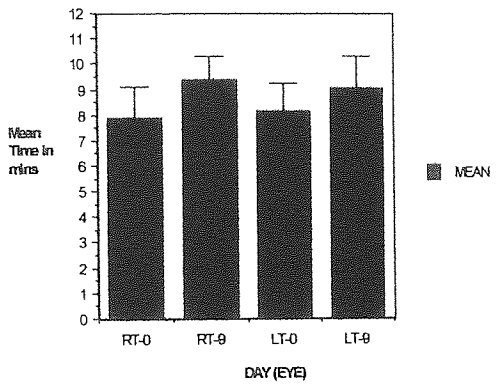


Fig 28 shows the increase in the time taken to reach the light peak from baseline to day 9 over the vigabatrin cycle.

6.11 Overall Findings

Overall during the short-term introduction of vigabatrin treatment, the ERG photopic b-wave and EOG appeared sensitive to the effect of the drug whereas the visual fields showed no change. Other authors (Harding et al 1995, Duckett et al 1998) have also reported electrophysiological changes with vigabatrin, in the absence of visual field loss.

This suggests that the increase in GABA in the retina as the result of treatment with vigabatrin, initially affects the areas of the pigment epithelium and the inner retina including the horizontal, bipolar, amacrine cells and possibly the Müller cells (Miller and Dowling (1970).

It is unclear why the changes in the EOG resolve after withdrawal of the drug and why the increase in the latency of the photopic b-wave is not characteristically associated with visual field loss. The oscillatory potentials (mainly OP1 & OP2) that appear most commonly affected by vigabatrin and associated with visual field loss (Eke et al 1997, Krauss et al 1998) are thought to be a separate response to the b-

wave, arising from slightly different depths of the retina. In animal studies, the OP1 response from the border of the inner plexiform layer and inner nuclear layer and OP2 in the middle of the inner nuclear layer, the b-wave being produced from the inner nuclear layer (Wachtmeister and Dowling, 1978). With the uptake of GABA mainly in the amacrine cells, inner nuclear layer and inner plexiform layer (Ehinger and Falck, 1971) it can be seen how both oscillatory potential and b-wave responses are affected. The cone responses affected by prolonged treatment with vigabatrin are also situated close to the pigment epithelium in the outer nuclear layer. It may be that these closely proximated cells react differently to dose and / or continued administration of the drug in terms of neurotoxicity.

This study showed that vigabatrin may affect different retinal cells initially during treatment to those after several months of the therapy. The decrease in Arden index also supported the findings of low EOG responses reported by Eke et al, 1997 and in the Birmingham and Leicester patients currently receiving vigabatrin. However, the possible factor of whether the presence of epilepsy has any influence on the effect of vigabatrin is still unknown.

CHAPTER 7 MATCHED PAIRS STUDY ON EPILEPTIC PATIENTS (HALF TAKING VIGABATRIN)

7.1 Introduction

It could be seen from the 8 patients discussed in chapter 5 that there were severe visual field constriction and abnormal visual electrophysiological responses associated with treatment of vigabatrin. However, it was not known to what extent the presence of epilepsy or the other antiepiletic drugs taken by the patients may have affected the responses (as highlighted by Harding, 1997). It is known that carbamazepine and lithium affect the ERG responses decreasing the b-wave amplitudes and oscillatory potentials with lithium also decreasing the EOG Arden index (Bayer et al 1990). Diazepam has also been found associated with visual field disorders (Takahashi et al 1989, Elder 1992). However Haas & Flammer (1985) found no significant changes in perimetry with short-term administration of diazepam in healthy young subjects. Although the presence of epilepsy would probably not affect the visual fields in the characteristic pattern associated with vigabatrin, the fields could have been affected in some patients by complex partial seizures or by treatments such as surgery. In order to assess whether these factors influenced the visual fields and visual electrophysiology a matched pairs study was carried out.

7.2 Basis of the matched pairs study

A group of patients who had taken or were currently taking vigabatrin were matched with a group of patients of a similar history who had not taken vigabatrin. As closely as possible the patient pairs were matched for seizure type and frequency, age, sex, and the antiepileptic drugs they had been prescribed. Visual field testing was carried out separately to the visual electrophysiology tests with both investigators blind to the drug histories and blind to the results of the other. Central 30-2 and peripheral 60/30-2 full threshold visual fields and full visual electrophysiology were completed. The protocols for each test can be found in the following sections. Visual fields (3.3.7), dilated flash ERG (3.1), pattern ERG (3.1.5), EOG (3.2.), flash VEP (3.4.1), pattern VEP (3.4.2) and VERIS (3.5).

7.3 Patients' referral and details

7.3.1 Recruitment, referral and exclusion criteria of the patients

The patients were referred from two centres from the Queen Elizabeth psychiatric hospital and from Birmingham City Hospital). Prior to the tests all patients completed a full visual assessment by a qualified optician. Of the 30 patients recruited, 22 (11 from each group) completed the study.
The exclusion criteria for the study consisted of the following

1. A history of amblyopia
2. Intraocular pressure of more than 22mmHg in either eye
3. Corrected visual acuity worse than 6/9
4. A refractive error exceeding 5 diopters positive sphere
5. An existing visual field defect
6. Previous or current eye disease or serious trauma /surgery or intracranial surgery
7. Abnormal pupils or use of medication affecting pupil size or reactivity
8. Presence of cataracts
9. Family history of ocular or neurological disease that affects the visual fields
10. History of multiple sclerosis

7.3.2 Patient Details

The 22 patients that completed the study (9 male and 13 females) were aged between 20 years and 58 years with a mean age of 37.4 years. Eleven of the patients had received vigabatrin for the duration of at least two years and the other eleven were matched as closely as possible for the other antiepileptic drugs taken by the 'partner' in the first group but who had never received vigabatrin. After completion of the study details of the dosage and duration of the vigabatrin patients were disclosed, these can be found in table 21.

7.4 Visual field results

As visual field testing was carried out by separately to the visual electrophysiology only the presence or not of a visual field defect in the group of

vigabatrin patients was received after completion of the study. These can be found in table 21.

CODE No.	Dose of VGV	Duration (months)	Body Weight (Kg)	Dose mg/Kg	Dose g/Kg x Duration	VF defect
OO2	2	102	74	27.03	2.76	norm
OO3	2.5	36	52.3	47.80	1.72	X
OO4	0.5	74	51.8	9.65	0.71	X
OO6	3	74	71.4	42.02	3.11	X
OO7	1.5	99	114.3	13.12	1.30	norm
OO8	2.5	108	57.5	43.48	4.70	X
O10	2	79	79.6	25.13	1.98	X
O12	1	38	67.5	14.81	0.56	norm
O13	1.5	72	94	15.96	1.15	norm
O15	2	103	82	24.39	2.51	X
O16	3.5	84	57	61.40	5.16	X

Table 21 shows the dosage and duration (months) of vigabatrin taken by the eleven patients (code numbered). The table also shows the body weight (Kg), maximum dose per body weight taken in mg/Kg and the result expressed in g/Kg when multiplied by the duration. The final column shows whether the patient exhibited a visual field loss (X) or whether the field was normal (norm).

Since the study in chapter 6 did not consider the dose and duration of vigabatrin when compared to the body weight of the subject, the two columns containing the mg/Kg and g/Kg multiplied by the duration were included in the results to see whether patients of lighter build, taking a high dose, over a long period of time would be more susceptible to visual field loss. However, no trend could be seen for the higher figures of g/Kg x duration to exhibit a visual field loss.

7.5 Results of the visual electrophysiology

7.5.1 Results of the multifocal ERG's (VERIS)

The results for the patients were exported into Excel and response density values 2SD and 3SD below the normal mean were plotted as described in chapter 5.4. None of the non-vigabatrin group showed any abnormal responses, these were taken as more than 5 locations with density values less than 2SD and more than one location less than 3SD. Two of the vigabatrin patients were unavailable at the time of testing (012 & 015) but the other VERIS plots can be seen in figure 29. Table 22 shows the

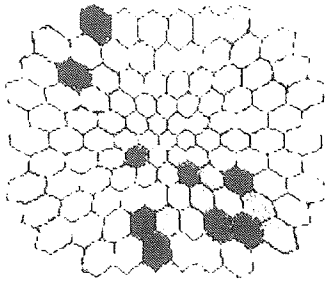
number of locations for the right and left eyes for each patient that had density responses less than 2SD and 3SD of the normal mean values.

Patient code number	Visual field	Number of element < 2SD of mean (left eye)	Number of element < 3SD of mean (left eye)	Number of element < 2SD of mean (right eye)	Number of element < 3SD of mean (right eye)
002	Norm	30	9	39	16
003	X	17	3	25	6
004	X	46	14	56	20
006	X	13	1	23	7
007	Norm	1	0	21	0
008	X	60	23	62	32
010	X	6	0	10	1
012	Norm	-	-	-	-
013	Norm	12	2	25	8
015	X	-	-	-	-
016	X	30	12	24	6

Table 22 shows the number of abnormal responses (a response density 2SD and 3SD less than the normal mean indicates an abnormal response) out of the 103 elements for the right and left eyes for each patient (patients 012 & 015 were not available at the time of testing). The table also shows whether the visual fields of these patients were considered normal (Norm) or abnormal (X).

As with the eight patients discussed in chapter 5.4.2 the patients show a differing degree of abnormality in the VERIS plots. The VERIS results do not appear to reflect the visual field results, especially with subjects 002 and 013, however, without examining the extent of involvement of the visual field this comparison cannot be determined. The VERIS plots do, however, appear very similar to those in chapter 5, particularly with the two most severely affected patients in each group (004 & 008 and pt 3 & pt 4 in chapter 5). Therefore the vigabatrin effect on the cone system may also have a characteristic effect which becomes evident in the more severe cases.

Stimulus Array
103 Elements



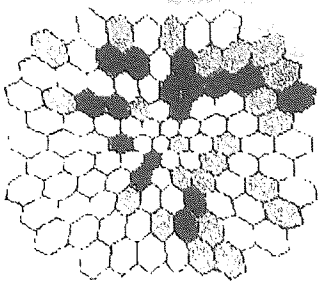
002

Nasal

Left

5 10 15 20 25
Degrees

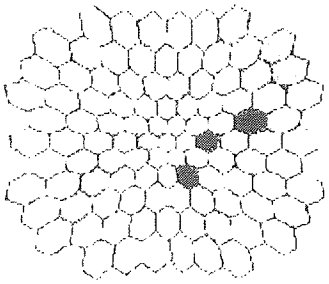
Stimulus Array
103 Elements



Right

5 10 15 20 25
Degrees

Stimulus Array
103 Elements



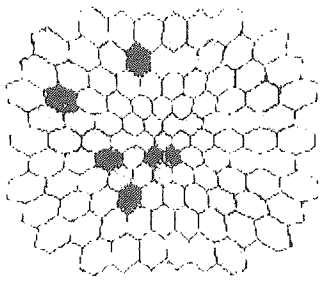
003

Nasal

Left

5 10 15 20 25
Degrees

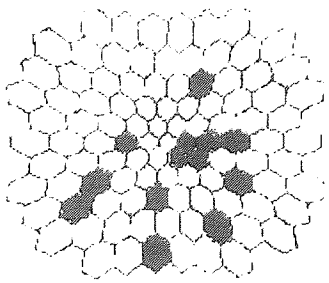
Stimulus Array
103 Elements



Right

5 10 15 20 25
Degrees

Stimulus Array
103 Elements



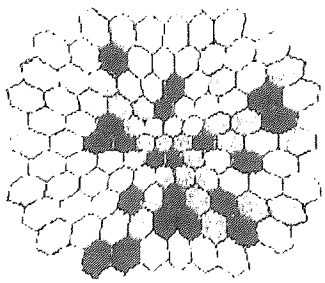
004

Nasal

Left

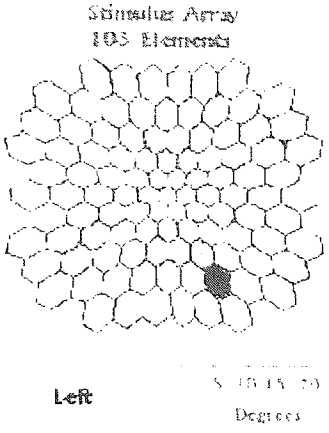
5 10 15 20 25
Degrees

Stimulus Array
103 Elements



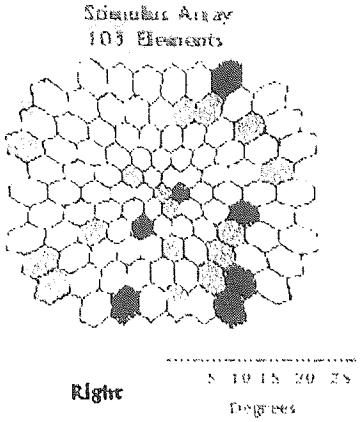
Right

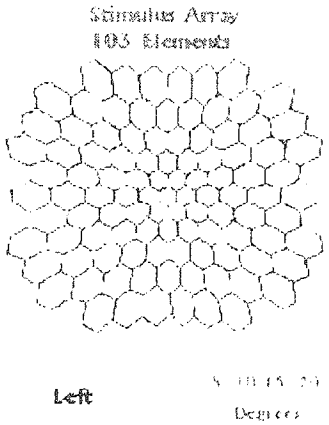
5 10 15 20 25
Degrees



006

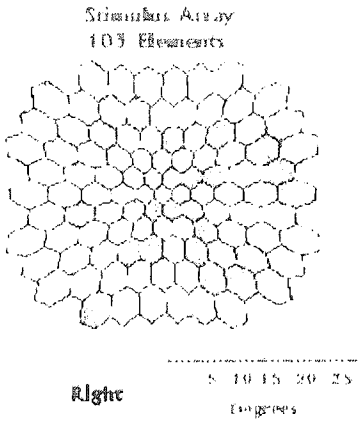
Nasal

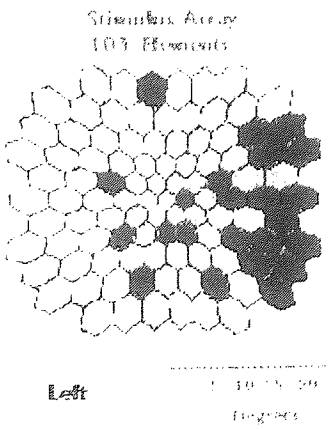




007

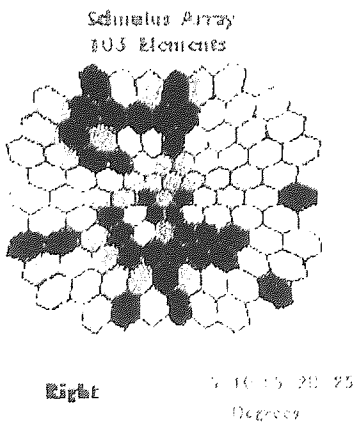
Nasal





008

Nasal



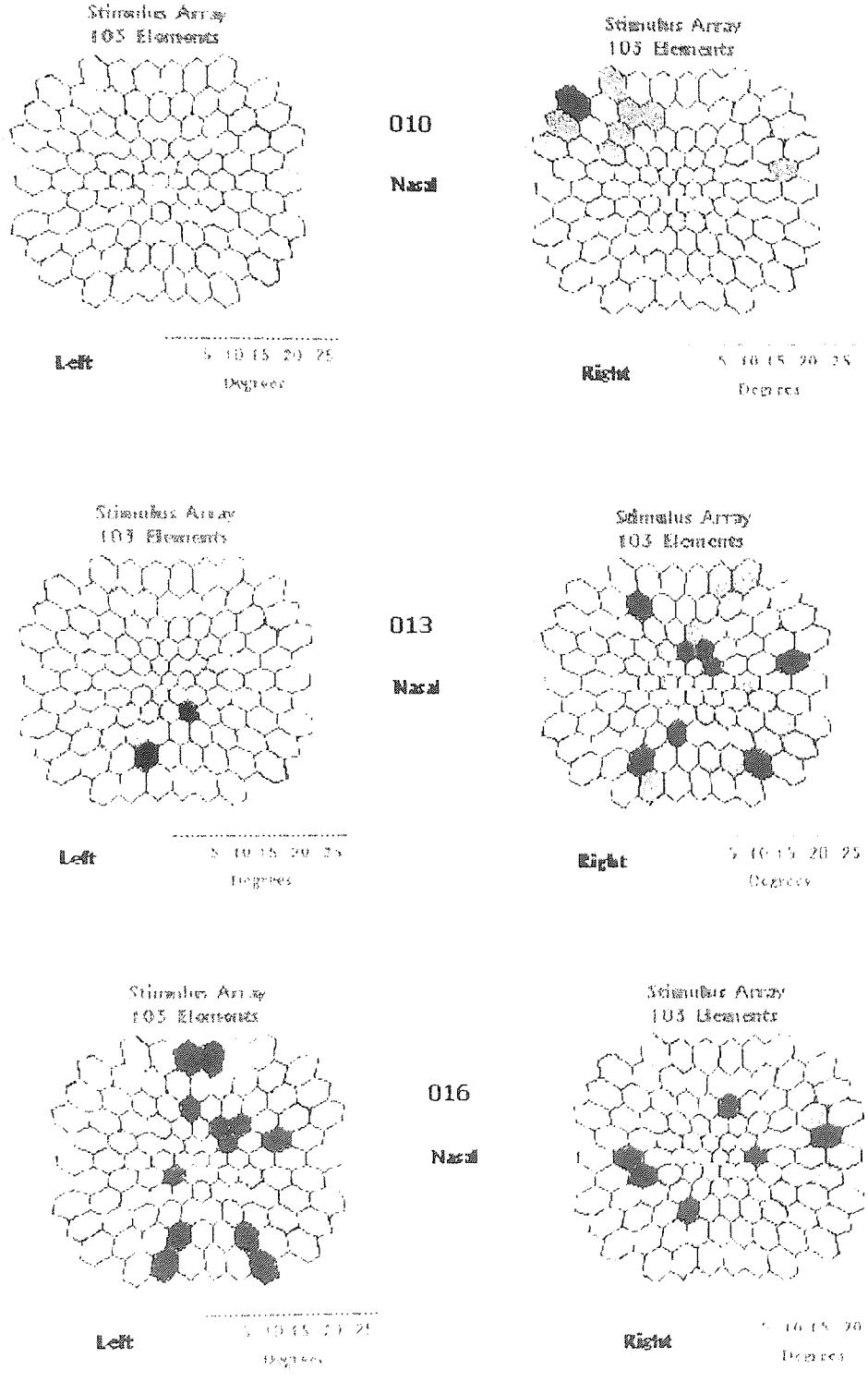


Figure 29. shows the VERIS plots for the left and right eyes for the vigabatrin group excluding patients 012 & 015 who were unavailable at the time of testing. The plot shows the 103 element array, grey segments represent a density response 2SD less than the normal mean response and black indicates 3SD from the normal mean response.

Results

Results of VEP's and PERG's

As with the eight patients discussed in chapter 5 both VEP's and PERG's showed no abnormal results in either the vigabatrin group or the matched group.

Results of EOG's

Only one vigabatrin patient showed abnormal Arden indexes, which may indicate that he may still be receiving the drug. However this information was unavailable

Results Electroretinography

It can be seen from table 23 that the 30Hz flicker ERG was the most severely affected response supporting the findings of those discussed in chapter 5. The vigabatrin group in this study appeared to have more photopic b-wave latency abnormalities in comparison to the 8 patient group. Interestingly, patient 009 was the only control to have abnormal photopic b-wave latencies which may be associated with the diazepam she is also prescribed, a caused of prolonged photopic b-wave latencies reported by Elder (1992).

Control subject 003-3 showed abnormalities for all 30Hz flicker components and a prolonged scotopic a-wave. However this was probably due to the patient age of 58 years, an age far more senior than the mean normal database age

As with the Chapter 5 study the vigabatrin group showed most abnormalities for the latency of OP1 and OP2 for oscillatory potential responses. The oscillatory potential responses can be found in table 24 and those of the EOG in table 25.

VGV/Control	CODE No.	Lat a	Lat b	Amp a-Amp b	30Hz Lat a	30Hz b	30Hz amp a-b	Scot Lat a	Scot Lat b	Scot Amp a-Ampb
v	OO2	Norm	Norm	Norm	Norm	Norm	Norm	Norm	Norm	Norm
v	OO2	Norm	Norm	Norm	Norm	Norm	Norm	Norm	Norm	Norm
v	OO3	X	Norm	Norm	...X	Norm	X	...X	Norm	Norm
v	OO3	X	Norm	Norm	...X	Norm	X	...X	Norm	Norm
v	OO4	X	X	Norm	...X	X	X	A	tech	problem
v	OO4	X	X	Norm	...X	X	X	...X	Norm	Norm
v	OO6	Norm	Norm	Norm	Norm	X	Norm	Norm	Norm	Norm
v	OO6	Norm	X	Norm	Norm	X	Norm	Norm	Norm	Norm
v	OO7	Norm	X	Norm	Norm	Norm	Norm	Norm	Norm	Norm
v	OO7	Norm	X	Norm	Norm	Norm	Norm	Norm	Norm	Norm
v	OO8	X	X	Norm	...X	X	X	...X	Norm	Norm
v	OO8	X	X	Norm	...X	X	X	...X	Norm	Norm
c	OO9	Norm	X	Norm	Norm	X	Norm	Norm	Norm	Norm
c	OO9	Norm	X	Norm	Norm	X	Norm	Norm	Norm	Norm
v	O10	X	X	Norm	...X	X	X	...X	Norm	Norm
v	O10	X	X	Norm	...X	X	Norm	...X	Norm	Norm
v	O12	Norm	Norm	Norm	Norm	Norm	Norm	Norm	Norm	Norm
v	O12	Norm	Norm	Norm	Norm	X	Norm	...X	Norm	Norm
v	O13	Norm	X	Norm	Norm	X	Norm	Norm	Norm	Norm
v	O13	Norm	X	Norm	Norm	X	Norm	Norm	Norm	Norm
v	O15	Norm	Norm	Norm	Norm	Norm	Norm	Norm	Norm	Norm
v	O15	Norm	Norm	Norm	Norm	Norm	Norm	Norm	Norm	Norm
v	O16	Norm	Norm	Norm	Norm	Norm	Norm	...X	Norm	Norm
v	O16	Norm	Norm	Norm	Norm	Norm	Norm	...X	Norm	Norm
c	O17	Norm	Norm	Norm	Norm	Norm	Norm	Norm	Norm	Norm
c	O17	Norm	Norm	Norm	Norm	Norm	Norm	Norm	Norm	Norm
c	O19	Norm	Norm	Norm	Norm	Norm	Norm	Norm	Norm	Norm
c	O19	Norm	Norm	Norm	Norm	Norm	Norm	Norm	Norm	Norm
c	O21	Norm	Norm	Norm	Not	able	to test	Norm	Norm	Norm
c	O21	Norm	Norm	Norm	Not	able	to test	Norm	Norm	Norm
c	OO1-O3	Norm	Norm	Norm	Norm	X	Norm	Norm	Norm	Norm
c	OO1-O3	Norm	Norm	Norm	Norm	X	Norm	Norm	Norm	Norm
c	OO2-O3	Norm	Norm	Norm	Norm	Norm	Norm	Norm	Norm	Norm
c	OO2-O3	Norm	Norm	Norm	Norm	X	Norm	Norm	Norm	Norm
c	OO3-O3	Norm	Norm	Norm	...X	X	X	...X	Norm	Norm
c	OO3-O3	Norm	Norm	Norm	...X	X	X	...X	Norm	Norm
c	OO4-O3	Norm	Norm	Norm	Norm	Norm	Norm	Norm	Norm	Norm
c	OO4-O3	Norm	Norm	Norm	Norm	Norm	Norm	Norm	Norm	Norm
c	OO5-O3	Norm	Norm	Norm	Norm	Norm	Norm	Norm	Norm	Norm
c	OO5-O3	Norm	Norm	Norm	Norm	Norm	Norm	Norm	Norm	Norm
c	OO8-O3	Norm	Norm	Norm	Norm	X	Norm	Norm	Norm	Norm
c	OO8-O3	Norm	Norm	Norm	Norm	X	Norm	Norm	Norm	Norm
c	O12-O3	Norm	Norm	Norm	Norm	Norm	Norm	Norm	Norm	Norm
c	O12-O3	Norm	Norm	Norm	Norm	Norm	Norm	Norm	Norm	Norm

Table 23 shows whether the responses for the photopic, 30Hz flicker and scotopic ERG's were within 2SD of the normal mean values tabulated in chapter 4.4. Normal values are represented by 'Norm' and abnormal responses by '...X'. Each patient's results are tabulated with the response of the right eye before that of the left. The first column shows whether the patient was a vigabatrin patient 'v' or a control matched pair 'c'. The scotopic response of the right eye of patient 004 was unable to be completed of the due to technical problems and the 30 Hz flicker response was not able to be completed by patient 021 as he appeared sensitive to this frequency.

Vigabatrin / control	CODE	Lat a	Lat OP1	amp a-OP1	Lat OP2
v	OO2	Norm	Norm	Norm	...X
v	OO2	Norm	Norm	Norm	...X
v	OO3	...X	...X	Norm	...X
v	OO3	...X	...X	Norm	...X
v	OO4	...X	...X	Norm	...X
v	OO4	...X	...X	Norm	...X
v	OO6	Norm	...X	Norm	...X
v	OO6	Norm	...X	Norm	...X
v	OO7	Norm	Norm	Norm	...X
v	OO7	Norm	Norm	Norm	...X
v	OO8	...X	...X	...X	...X
v	OO8	...X	...X	...X	...X
c	OO9	Norm	Norm	Norm	Norm
c	OO9	Norm	Norm	Norm	Norm
v	O10	...X	...X	Norm	...X
v	O10	...X	...X	Norm	...X
v	O12	Norm	Norm	Norm	Norm
v	O12	Norm	...X	Norm	Norm
v	O13	Norm	Norm	Norm	Norm
v	O13	Norm	Norm	Norm	Norm
v	O15	Norm	Norm	Norm	Norm
v	O15	Norm	Norm	Norm	Norm
v	O16	Norm	...X	Norm	...X
v	O16	Norm	...X	Norm	...X
c	O17	Norm	Norm	Norm	Norm
c	O17	Norm	Norm	Norm	Norm
c	O19	Norm	Norm	Norm	Norm
c	O19	Norm	Norm	Norm	Norm
c	O21	Norm	Norm	Norm	Norm
c	O21	Norm	Norm	Norm	Norm
c	OO1-O3	Norm	Norm	Norm	Norm
c	OO1-O3	Norm	Norm	Norm	Norm
c	OO2-O3	Norm	Norm	Norm	Norm
c	OO2-O3	Norm	Norm	Norm	Norm
c	OO3-O3	...X	...X	...X	Norm
c	OO3-O3	...X	...X	...X	...X
c	OO4-O3	Norm	Norm	Norm	Norm
c	OO4-O3	Norm	Norm	Norm	Norm
c	OO5-O3	Norm	Norm	Norm	Norm
c	OO5-O3	Norm	Norm	Norm	Norm
c	OO8-O3	Norm	Norm	Norm	Norm
c	OO8-O3	Norm	Norm	Norm	Norm
c	O12-O3	Norm	Norm	Norm	Norm
c	O12-O3	Norm	Norm	Norm	Norm

Table 24 shows the oscillatory potential latency of the a-wave, OP1 and OP2 as well as the amplitude of a-OP1. The first column shows whether the patient was taking vigabatrin 'v' or was a control 'c'. Eight of the eleven vigabatrin patients showed an abnormal latency bilaterally for OP2 and six of the eleven vigabatrin patients showed bilateral abnormalites for the latency of OP1 with one patient showing a monocular abnormally long latency. With the control group only patient 003-03 showed abnormally long OP1 and OP2 latencies which was probably due to the patient being 58 years of age and having slightly longer latencies than the normal database which has an average age of 23 years.

Code	Arden Index (%)	Light Peak	Dark Trough	Mins to LP
OO2	253	949	375	9
OO2	230	1120	488	9
OO3	241	681	283	12
OO3	230	842	366	12
OO4	256	925	361	11
OO4	261	1100	422	10
OO6	204	639	314	11
OO6	199	742	373	11
OO7	218	1120	515	10
OO7	208	988	476	9
OO8	154	458	297	10
OO8	171	507	297	10
OO9	259	1820	703	8
OO9	280	1700	607	8
O10	229	866	378	10
O10	247	971	393	10
O12	208	625	300	9
O12	207	615	297	10
O13	244	1330	546	8
O13	240	1140	476	8
O15	207	742	358	10
O15	197	710	361	10
O16	241	1140	473	10
O16	246	1170	476	10
O17	211	1020	483	11
O17	210	651	310	11
O19	212	954	449	10
O19	233	917	393	9
O21	Had a	seizure	during	testing
O21	Had a	seizure	during	testing
OO1-O3	184	703	383	7
OO1-O3	188	524	278	10
OO2-O3	216	1050	485	9
OO2-O3	237	1030	434	8
OO3-O3	201	385	192	11
OO3-O3	198	336	170	11
OO4-O3	203	917	451	10
OO4-O3	218	1080	495	10
OO5-O3	239	827	346	10
OO5-O3	212	732	346	8
OO8-O3	203	683	336	9
OO8-O3	219	737	336	9
O12-O3	294	717	244	9
O12-O3	297	368	124	10

Table 25 shows the Arden indecies, light peak and dark trough values. Only one vigabatrin patient 008 showed abnormally low Arden indicies.

CHAPTER 8 DEVELOPMENT OF THE CHILDREN'S H-STIMULUS

8.1 Introduction

8.1.1 Reasons for the development of the H-stimulus

Since there was an apparent association between vigabatrin therapy and visual field constriction in a proportion of adult patients (a frequency reported by Hoescht Marion Roussel of 0.1%, Backstrom et al, 1997), it was necessary to assess the extent of involvement in the child population. With children suffering from partial epilepsy and infantile spasms (West's syndrome), vigabatrin has been shown to be a highly effective treatment in reducing the frequency of episodes (Chiron et al 1991, Dulac et al 1991, Herranz et al, 1991, Uldall et al 1991). With young children and those with learning difficulties, co-operation is poor with formal perimetry and with multifocal ERG's. Since it was unknown what proportion of children may be developing visual field constriction, or whether the effect may progress more aggressively in children, it was necessary to develop a test that was quick and easy for the patient to complete, whilst assessing whether the vision had been affected by the drug.

8.1.2 Theory behind the H-stimulus and visual field testing

Since vigabatrin is thought to effect the retina, a stimulus in the periphery of the visual field would not be responded to in the affected retina, and this lack of stimulation would therefore not be recorded as a cortical evoked response. Due to this peripheral visual defects should be able to be identified just by maintaining fixation at the centre of the stimulus during the test. This would also remove the need for the patient to give more complicated 'yes/no' responses as is required during visual field testing. The traditional VEP response is commonly produced from a stimulus at approximately the central 15 degrees (radius) of the visual field. (The pattern VEP displayed on a 15-inch television displays checks 12 degrees of visual angle in height and 15 degrees of visual angle in width). As vigabatrin characteristically affects the visual field from the periphery to the centre, the effect of vigabatrin on the retina would have to be very severe before a change in the response would be detected in the traditional VEP.

With the 8 patients discussed in chapter 5, most showed predominately nasal involvement from the periphery to approximately 20-25 degrees, the most severely affected patient exhibiting involvement up to 15 degrees. The H-stimulus was designed to detect visual field loss that had effected the peripheral visual field between 30 and 60 degrees of visual angle (equivalent to the 60/30-2 visual field test). Although the H-stimulus would be a more crude measurement than the visual field, visual loss should be detected before it progressed to the central 30 degrees.

8.1.3 Theory behind Stimulus Design

A reversing black and white chequered dartboard stimulus was designed with a small central stimulus, a blank surrounding annulus and a large peripheral stimulus, which was scaled to reflect the area of cortical representation of the two stimuli. Yiannikas and Walsh (1983) however stated that the peripheral 8-32 degrees of the visual field produce a significant contribution to the P100 of the visual evoked potential. The design was based on the cortical magnification principle and the linear magnification factor first proposed by Daniel and Whitteridge (1961). They showed a ratio of more than forty to one between the fovea (0 degrees) and 60 degrees for the millimetres of cortex represented by 1 degree of visual field. The linear magnification factor in the striate cortex is inversely proportional to the eccentricity, Horton et al, 1991 adapted this formula from the macaque monkey formula of Daniel and Whitteridge (1961) for human striate cortex. Although the design of the H-stimulus did not follow a published formula for cortical magnification, the area of the segments were scaled to approximately compensate for this with the radius of the stimulus segments linearly increasing by a factor of 1.43 per 10 degrees of eccentricity, resulting in similar amplitude values for the central 0-5 degree and peripheral (30-60 degree) responses. As vigabatrin has been shown not to affect the VEP, any changes in the peripheral responses will indicate a defect further forward in the visual system and in most cases (excluding other visual disorders) will be affecting the retina.

8.2 Stimulus parameters

The stimulus consisted of a black and white reversing dartboard pattern, projected onto a back projection screen. It comprised of a central stimulus pattern 2.6cm in diameter, neutral background to 16.8cm in diameter and a peripheral stimulus up to 50cm in diameter. With the patient seated 14.5cm away from the screen, when the

central stimulus was triggered, responses would be recorded from the central 5 degrees (radius) of the visual field. With the peripheral stimulus being triggered, responses would be obtained from 30-60 degrees of the visual field.

With the diameter of the peripheral stimulus at 50cm (60 degrees of visual angle), the peripheral stimulus consisted of three rings of 18 segments (9 black and 9 white at any one time). The inner ring had an inner boundary at 30 degrees and an outer border at 40 degrees, the middle ring had segments from 40-50 degrees and the outer ring consisted of segments from 50-60 degrees. With the increase in eccentricity, the size of the segments increased as described in chapter 8.1.3.

8.3.1 Luminance and contrast of the H-stimulus

The stimulus was back-projected onto a translucent screen, the peripheral diameter measuring 50cm and with the patient's eye positioned centrally. Owing to the use of the projector and mesh effect of the screen, the maximum and minimum luminance of the stimulus varied across the field of vision to some degree being dependent on the position of the onlooker.

The luminance of the peripheral 54 segments (those in the outer 3 rings), were measured using a Minolta spot photometer. The photometer was positioned one meter from the screen and at the height of the centre of the stimulus. The segments of the central 0-5 degree stimulus could not be accurately measured due to the small size and the close proximity of the black and white segments.

8.3.2 Variability of the maximum luminance

With the peripheral stimulus divided into quadrants it could be seen that the maximum luminance was highest in the lower left quadrant, the lower right quadrant having slightly lower values, further reduced in the upper left quadrant with the lowest maximum luminance in the upper right quadrant. When the measurements for each ring were averaged, the outer 40-50 degree ring had a maximum luminance of 184.9 cdsec/m^2, the middle 40-50 degree ring had an average value of 285.3 cdsec/m^2 and the inner 30-40 degree ring had an average value of 348.5 cdsec/m^2. The maximum luminance of all 54 segments can be found in table 26. The values ranged from 100.3 cdsec/m^2 in the outer ring to 551.9 cdsec/m^2 in the inner ring.

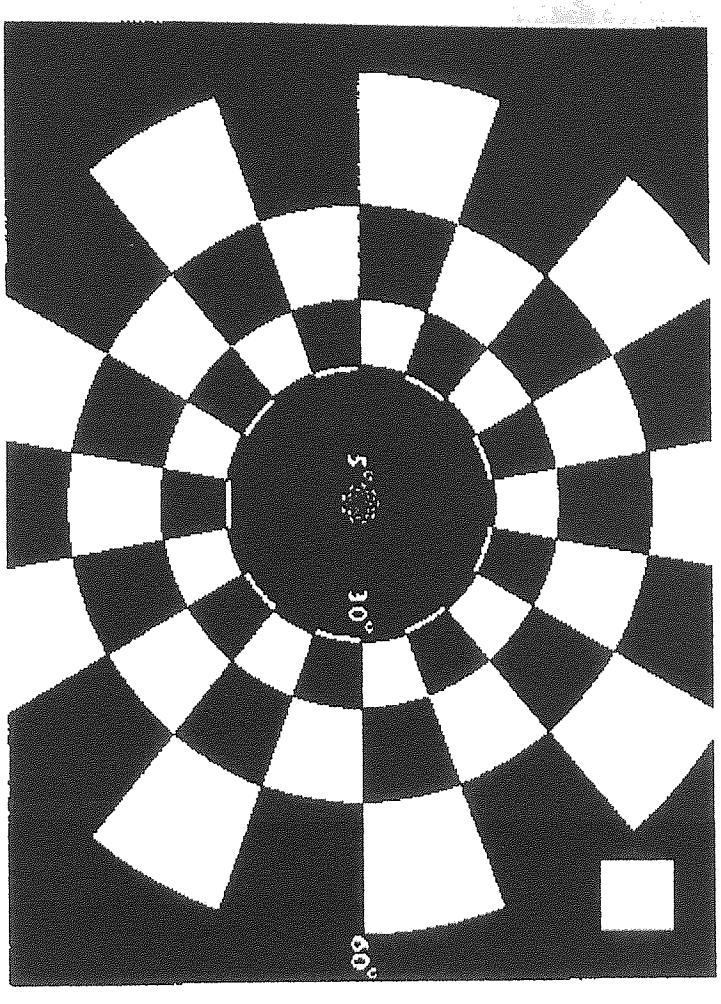


Figure 30 shows the design of the H-stimulus with a small central (5 degree radius) stimulus, a blank annulus until 30 degrees eccentricity and a peripheral stimulus from30-60 degrees.

visual angle / quadrant	L-max	L-min	Michelson's equation for contrast	Mean Luminance
Outer ring 50-60 deg				
1	130.0	31.7	60.8	80.9
2	114.4	34.4	53.8	74.4
3	107.1	34.0	51.9	70.5
4	106.7	29.3	57.0	68.0
5	100.3	25.4	59.6	62.8
6	112.3	21.4	68.0	66.8
7	146.2	18.9	77.1	82.6
8	175.5	18.1	81.3	96.8
9	202.3	17.3	84.2	109.8
10	298.3	19.1	88.0	158.7
11	308.9	18.1	88.9	163.5
12	315.9	18.6	88.9	167.2
13	278.2	19.0	87.2	148.6
14	247.7	21.2	84.2	134.5
15	207.6	21.9	80.9	114.8
16	179.3	22.8	77.5	101.0
17	157.7	24.7	72.9	91.2
18	139.4	27.7	66.8	83.6
Mean	184.9	23.5	73.8	104.2
Middle ring 40-50 deg				
1	167.2	29.0	70.5	98.1
2	163.2	30.4	68.6	96.8
3	152.1	29.7	67.3	90.9
4	155.8	28.4	69.2	92.1
5	156.2	25.3	72.1	90.7
6	210.3	23.9	79.6	117.1
7	231.8	22.8	82.1	127.3
8	291.7	21.7	86.1	156.7
9	358.1	22.3	88.3	190.2
10	421.5	23.5	89.4	222.5
11	468.5	23.5	90.5	246.0
12	468.9	23.4	90.5	246.1
13	454.1	24.0	89.9	239.1
14	376.3	24.7	87.7	200.5
15	357.2	24.4	87.2	190.8
16	268.9	25.1	82.9	147.0
17	228.8	25.7	79.8	127.3
18	204.3	27.8	76.0	116.1
Mean	285.3	25.3	81.0	155.3
Inner ring 30-40 deg				
1	239.1	28.4	78.8	133.7
2	207.9	28.5	75.9	118.2
3	210.6	28.8	75.9	119.7
4	192.2	27.7	74.8	109.9
5	247.3	26.3	80.8	136.8
6	250.8	25.3	81.7	138.0
7	329.5	24.3	86.3	176.9
8	358.8	25.0	87.0	191.9
9	449.5	25.3	89.4	237.4
10	481.5	26.5	89.6	254.0
11	551.9	26.7	90.8	289.3
12	537.6	26.8	90.5	282.2
13	501.9	26.6	90.0	264.2
14	438.3	26.5	88.6	232.4
15	391.9	26.5	87.3	209.2
16	350.1	26.5	85.9	188.3
17	278.8	27.2	82.3	153.0
18	254.9	27.4	80.6	141.1
Mean	348.5	26.7	84.2	187.6

Table 26 shows the maximum and minimum luminance measurements (cdsec/m^2), the Michelson's contrast and mean luminance values for the 54 segments of the outer 3 rings for the peripheral H-Stimulus. Each ring contained 18 segments which are labelled 1-18, segment 1 being the top segment the segment number increasing in a clockwise manner. The outer ring consisted of segments between 50-60 degrees, the middle ring segments at 40-50 degrees and the inner ring at 30-40 degrees.

8.3.3 Variability of the minimum luminance

With the stimulus divided into quadrants the lowest minimum luminance measurements were in the lower right quadrant, increasing in the lower left quadrant, with a further increase in the upper left and with the highest values in the upper right quadrant.

When the minimum luminance of the segments were averaged for each ring, the outer ring had a value of 23.5 cdsec/m^2, the middle ring value was 25.3 cdsec/m^2 and the inner ring value was 26.7 cdsec/m^2. The values of the 54 segments ranged from 17.3 cdsec/m^2 to 34.35 cdsec/m^2 and can be found in table 26.

8.3.4 Variability of the mean luminance

The mean luminance was derived from the measurement of the maximum luminance (L max) and minimum luminance (L min) of the segments as described by Brignell et al, 1998.

Mean Luminance = (L max + L min) / 2

These values were also found to vary across the segments with a range from 62.8 cdsec/m^2 to 264.2 cdsec/m^2. The average mean luminance values were 104.2 cd/m^2 for the outer ring, 155.3 cdsec/m^2 for the middle ring and 187.6 cdsec/m^2 for the inner ring, therefore showing an increase towards the centre of the stimulus. The mean luminance values for all segments can be found in table 26.

8.3.5 Variability of contrast across the peripheral stimulus

The pattern stimulus contrast was calculated using the Michelson contrast ratio as described by Brignell et al, 1998.

$$\text{Contrast} = \frac{L_{max} - L_{min}}{L_{max} + L_{min}} \quad 100\%$$

These values ranged from 51.9 % to 90.8 %. The average contrast value for the outer ring was 73.8 % with 81.0 % for the middle ring and 84.2 % for the inner ring. All

values can be found in table 26. The contrast values are all above 50% which Brignell et al, 1998 described as the contrast value over which small changes in contrast across the stimulus have little effect on the VEP response. Although there was quite a wide range of contrast values over the 54 segments, the average change in values with eccentricity was relatively small.

8.3.6 Luminance of the grey background.

The luminance of the grey background annulus was measured at four points mid-way between the central and peripheral stimuli. They were taken above and below and to the left and the right of the central stimulus. Luminance values were 67.8 cdsec/m^2 and 92.7 cdsec/m^2 for the top and bottom measurements and 93.1 cdsec/m^2 and 66. 25 cdsec/m^2 for the left and right measurements.

8.3.7 Overall luminance findings

The values for mean luminance and contrast do not follow the guidelines for the International standards for the electrophysiology of vision (Brignell et al 1998). However, the design enables a wide field of vision to be tested which was not available using a commercial monitor at that time. An alteration of the design of the stimulus for use with a large monitor may improve the quality of the mean luminance and contrast, although this would be to the detriment of the degree of eccentricity tested.

8.4 Equipment and set-up

The dartboard stimulus was produced using a PC and the Cambridge Research Systems VSG programme (version 4.02). The PC was connected to a NEC multisync MT 800 projector that projected the stimulus onto a back-projection screen. A Medelec sapphire 4E stimulus lead was attached to the PC to initiate the collection of evoked responses when the stimulus was active.

The central and peripheral stimuli both reversed at approximately 2 frames per second, though differing slightly, and time lagged so that they reversed at a slightly different point in time to each other. The testing was run on 2 programmes, one triggering from the central stimulus and the other from the periphery. Due to the time lagging of the two stimuli the response of the non-tested stimulus was cancelled out.

The N135 peripheral response was also delayed for 30msec before the stimulus was generated. Due to this and to a physiological slightly slower peripheral response, the waveform appears with a latency approximately35msec delayed when compared to the central P100 response.

8.5 Protocol for the children

Ethics committee approval was obtained from the Aston committee and informed consent was obtained from the parent or guardian before testing.

The head of the child was measured and positions O2, O1, Fz & Cz of the International 10-20 system were marked on the scalp with a soft Chinagraph pencil. These areas were cleaned using Omniprep (a mildly abrasive soap solution) and silver-silver chloride electrodes were taped to the skin with Blenderm. A small amount of gel was placed in the cup of the electrode in order to improve conductivity. The electrodes are then connected to a Medelec Sapphire 4E recording system.

The child was seated 14.5cm in front of a back projection screen on which the dartboard type stimulus was displayed. During testing the child fixated on the middle of the central stimulus whilst the pattern reversed from black/white to white/black each second.

Responses were recorded to both the central and peripheral stimuli, binocularly with 3-4 year old children and monocularly with the right and left eyes for the 5-10 year olds with the non-tested eye patched. The central and peripheral responses were recorded in an ABBA design to compensate for fatigue or learning effect.

The VEP's were recorded averaging 50 responses. The low frequency filter was set at 1 Hz and the high frequency filter at 50Hz. Responses were collected at a sweep speed of 500ms.

8.6 Pilot study

8.6.1 Subjects

The protocol was first optimised using 3 healthy young adult subjects (2 female and 1 male) with a mean age of 23 yr. These responses were then compared to those obtained from 4 vigabatrin patients (3 female and 1 male) mean age of 25.5 yr, with known visual field constriction, and previously tested at Aston. The ABBA monocular children's protocol was followed although responses in the adults were obtained from positions O4, O2, O1 & O3 of the International 10-20 system, with reference to Fz and Cz as the earth. It was observed during recording that with a time allowance for a couple of extra repeats if poor responses were produced, that the actual testing time would not exceed 10-15 minutes.

8.6.2 Waveforms

For the central response, the P100 latency and the amplitude of N75-P100 were measured. For the peripheral response the latency of the N135 and amplitude of the N135 to the following trough as described by Halliday (1982) andBlumhardt et al (1989).

The monocular central and peripheral responses obtained from one healthy subject (aged 5 yr.) in figure 31 and that of the vigabatrin patient (BMG) can be seen in figure 32. The mean deviation of the central visual field plot shown in figure 3 shows the extent of the constriction in the eye of the patient. The responses have only been shown for one eye, however, the effect of vigabatrin is systemic and the responses of the other eye are usually very similar in severity.

8.6.3 Pilot study results

Central Response

It can be seen from the waveforms in figure 31, figure 32 and from the latency values of the healthy subjects in table 27 that the central P100 latency was delayed compared to that of a standard pattern reversal VEP. The mean P100 latency for positions O4, O3, O2 & O1 of the healthy subjects ranged between 141ms-142ms for the right eye and 138ms-139ms for the left eye. The mean central responses for the patients were slightly further delayed with a mean P100 latency of between 145ms-146ms for the

right eye and 148ms –150ms in the left eye, although due to the small sample size this was probably due to individual variability. The latency of the central response should not be affected by the vigabatrin treatment however it may be associated with the presence of epilepsy or other drugs. Lücking et al (1970) described a more variable VEP response in patients with epilepsy than with those of normal subjects.
The latencies for the central P100 component can be seen in table 27 for the right and left eyes of the healthy subjects and the patients.

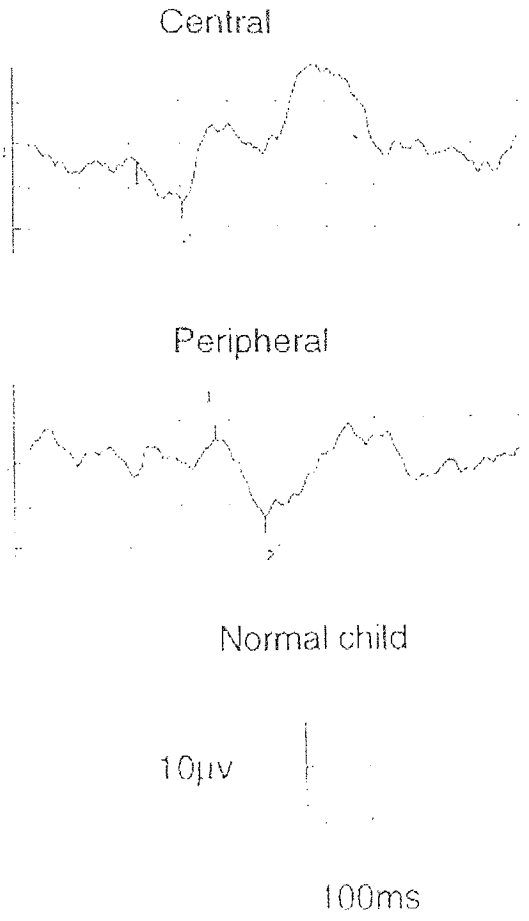


Figure 31 shows the central and peripheral responses of a healthy 5 year old male

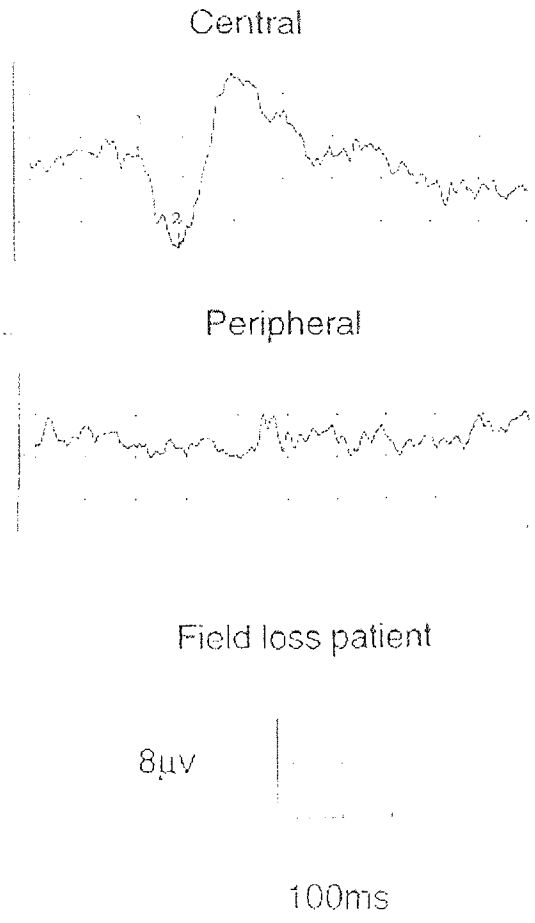


Figure 32 shows the central and peripheral responses of a 25 year old female taking vigabatrin. The peripheral response of the female patient is absent with the trace only showing background brain activity and noise.

Normal Central P100 Latencies

R-EYE	O4	O2	O1	O3		L-EYE	O4	O2	O1	O3
PM	143	143	140	140		PM	135	134	133	133
RB	144	144	146	146		RB	140	140	140	142
AT	137	138	141	141		AT	141	141	140	140
Mean	141.33	141.67	141.33	142.33		Mean	138.67	138.33	137.67	138.33

Patient Central P100 Latencies

R-EYE	O4	O2	O1	O3		L-EYE	O4	O2	O1	O3
BMG	148	148	155	155		BMG	147	147	140	139
LLK	148	147	143	143		LLK	148	147	147	147
NIHA	147	147	147	147		NIHA	155	154	152	152
SUSE	139	139	140	140		SUSE	150	150	152	152
Mean	145.5	145.25	146.25	146.25			150	149.5	147.75	147.5

Table 27. shows the P100 latencies (ms) for positions O4, O2, O1 & O3 for the central VEP response for both the 3 healthy subjects (above) and for the 4 vigabatrin patients. The mean of these responses for each recording position can be seen at the bottom of each category. The latencies are shown for responses of the right (R-eye) and left (L-eye) eyes.

Normal Central P100 Amplitudes

RT EYE	O4	O2	O1	O3		LT EYE	O4	O2	O1	O3
PM	7.34	8.02	5.27	3.13		PM	4.83	5.81	2.67	1.36
RB	12.0	12.1	10.1	7.52		RB	7.67	7.70	7.52	5.92
AT	5.4	6.64	5.16	4.86		AT	4.75	5.79	4.89	3.59
Mean	8.25	8.92	6.84	5.17		Mean	5.75	6.43	5.03	3.62

Patient Central P100 Amplitudes

RT EYE	O4	O2	O1	O3		LT EYE	O4	O2	O1	O3
BMG	7.61	8.19	6.85	6.30		BMG	7.61	8.70	6.59	5.58
LLK	9.71	10.1	11.0	9.05		LLK	4.15	6.98	7.59	5.06
NIHA	4.84	4.85	2.89	1.99		NIHA	4.86	5.01	4.84	3.68
SUSE	6.08	6.01	5.06	4.23		SUSE	8.26	7.84	7.67	7.46
Mean	7.06	7.29	6.45	5.39			6.22	7.13	6.67	5.45

Table 28. shows the P100 amplitudes for positions O4, O2, O1 & O3 for the central VEP response for the 3 healthy subjects (above) and for the 4 vigabatrin patients. The mean amplitude for these responses for each recording position can be seen at the bottom of each category.

The amplitudes for the central P100 responses for both the healthy adults and the vigabatrin patients can be seen in table 28. The amplitudes are quite varied across all individuals and the mean values at each position for the patient and vigabatrin groups appear similar.

Peripheral Response

The peripheral N135 responses can be seen clearly in figure 31 for the healthy subject, however the response of the vigabatrin patient is absent with a trace showing only background EEG activity and noise. The mean deviation for the right central visual field of this patient (BMG) shown in figure 33 and the field can be seen to be constricted to 20-25 degrees, with the peripheral stimulus at 30-60 degrees of the visual angle, the VEP response was absent.

The latencies of the peripheral N135 responses for the healthy subjects and the vigabatrin patients can be seen in table 29. For positions O4, O2, O1 & O3 the mean peripheral responses of the healthy subjects measured 162ms for the right eye and ranged between 164ms & 168 ms for the left eye. None of the vigabatrin patients showed any responses. The peripheral N135 amplitudes for the healthy subjects can be seen in table 30. The severity of the visual field constriction of these patients can be seen in figure 33. Of the four vigabatrin patients tested, three showed constriction of the central visual field. Patient SUSE showed a normal central visual field although involvement up to 30 degrees could be seen nasally in the peripheral 60-30/2 visual field and up to 35-40 degrees temporally. Figure 33 shows the mean deviation of the right central visual fields of patients BMG, LLK and NIHA. The threshold plot of the right peripheral visual field of SUSE is also shown since a normative database does not exist for the 60-30/2 test.

Normal Peripheral N135 Latencies

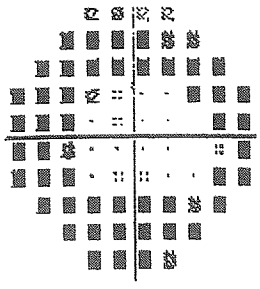
R-EYE	O4	O2	O1	O3		L-EYE	O4	O2	O1	O3
PM	152	152	152	152		PM	160	160	159	159
RB	175	175	175	176		RB	169	169	168	168
AT	159	159	158	158		AT	173	174	165	165
Mean	162	162	161.67	162		Mean	167.33	167.67	164	164

Table 29 shows the peripheral N135 for positions O4, O2, O1 & O3 for the central VEP response for both the 3 healthy subjects. The mean latency of these responses for each recording position can be seen at the bottom of each category. No responses were evident in the 4 vigabatrin patients.

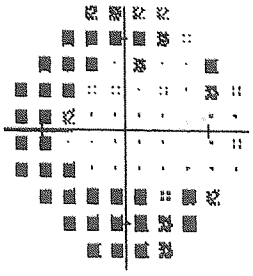
Normal Peripheral N135 Amplitudes

RT EYE	O4	O2	O1	O3		LT EYE	O4	O2	O1	O3
PM	4.27	4.23	5.66	5.18		PM	7.56	6.8	4.99	3.8
RB	3.20	3.16	2.22	1.80		RB	5.06	5.11	4.32	3.37
AT	5.59	5.2	5.15	4.39		AT	5.73	4.48	3.97	4.41
Mean	4.35	4.20	4.34	3.79		Mean	6.12	5.46	4.43	3.86

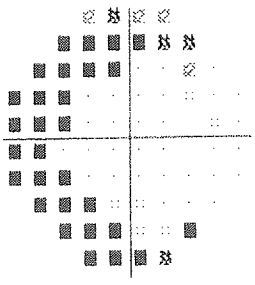
Table 30 shows the peripheral N135 amplitudes for positions O4, O2, O1 & O3 for the VEP response for the 3 healthy subjects. The mean of these responses for each recording position can be seen at the bottom of each category. No responses were evident for the vigabatrin patients.



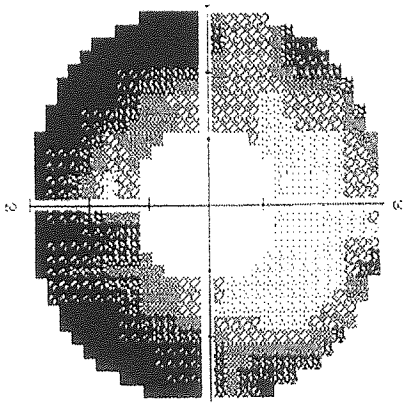
LLK



BMG



NIHA



SUSE

Figure 33 displays the mean deviation plots for central visual fields of the right eye in three vigabatrin patients tested with the H-stimulus (BMG, LLK and NIHA). Since SUSE showed no constriction in the central visual field the threshold plot for the right peripheral 60-30/2 visual field is displayed.

8.7 Simulation of peripheral constriction using a healthy subject

8.7.1 Choice of healthy subject

Ideally in order to demonstrate the degree of peripheral loss that would affect and eventually abolish the peripheral visual evoked response, a group of vigabatrin patients each exhibiting a varying degree of loss should have been recruited. Since the H-stimulus was primarily designed for children and the viewing distance set at 14.5cm, adults over the age of 25yr or with hypertropia would not achieve accurate accommodation at that distance and were excluded from this investigation. Of the consenting vigabatrin patients, only the four who took part in the pilot study fell within the criteria and visual field results were not available for two at that time, due to a continuing blind study.

Since the peripheral stimulus response was absent in the patients with visual field loss affecting 20-25 degrees, in order to try to establish the degree of constriction at which the visual evoked response becomes affected, a normal healthy subject was tested with progressive occlusion of the peripheral stimulus.

8.7.2 Method and measurements of visual constriction

Responses were recorded from positions O2 & O1 with reference to Fz. Throughout the investigation the subject remained 14.5cm from the stimulus. Initially, responses were recorded from the central stimulus and from the 30-60 degree peripheral annulus. The inner border of the peripheral stimulus was maintained at 30 degrees and peripheral responses were recorded with the outer border at 55, 50, 45, 40 & 35 degrees. At 35 degrees the lower nasal quadrant of the stimulus was occluded to simulate the characteristic visual constriction of vigabatrin. Periodically throughout the investigation central responses were recorded to ensure the results were not being affected by fatigue.

8.7.3 Effect of peripheral constriction on the responses

Clear peripheral responses were obtained from the stimulus with peripheral borders at 60, 55, 50, 45, & 40 degrees. There was no apparent change in latency from 60 to 45 degrees although the response taken at 40 degrees was slightly prolonged. Amplitudes were variable for the responses and no apparent decrease could be seen. With the peripheral stimulus at 30-35 degrees a very small wave could be seen close to the latency of the previously recorded responses. At 35 degrees with the lower nasal quadrant occluded, no response could be evoked.

It appeared that visual responses evoked from the peripheral H-stimulus could be obtained from a constricted visual field to the severity of 40 degrees, however, the pattern of involvement of vigabatrin could not accurately be replicated by this method. The lack of an H-stimulus peripheral response with patient SUSE described in chapter 8.6 supports the findings of the simulation study. With the visual constriction of the peripheral field of SUSE only showing sparing in the temporal 30-40 degrees, the loss of response corresponds to these findings.
Further investigation with normal subjects is necessary. The recruitment of a number of vigabatrin patients with varying degrees of visual constriction would be preferable, although due to the strict participant criteria an alternative protocol with a viewing distance of at least 30cm would probably be necessary.

8.8 Collection of normal child data

8.8.1Subjects

Forty-seven healthy children without the need of corrected vision completed the study. The children were aged between 3 and 10 years old (16 female and 31 male) and the protocol described in 8.5. was followed. The number of children in each year group can be found in table 6. Of the 47 children responses the mean age +/- 1 SD was 7.14yr +/- 2.09.
The waveforms for the P100 and N135 responses for children between 3yrs and 10 yrs can be found in figures 34-41.

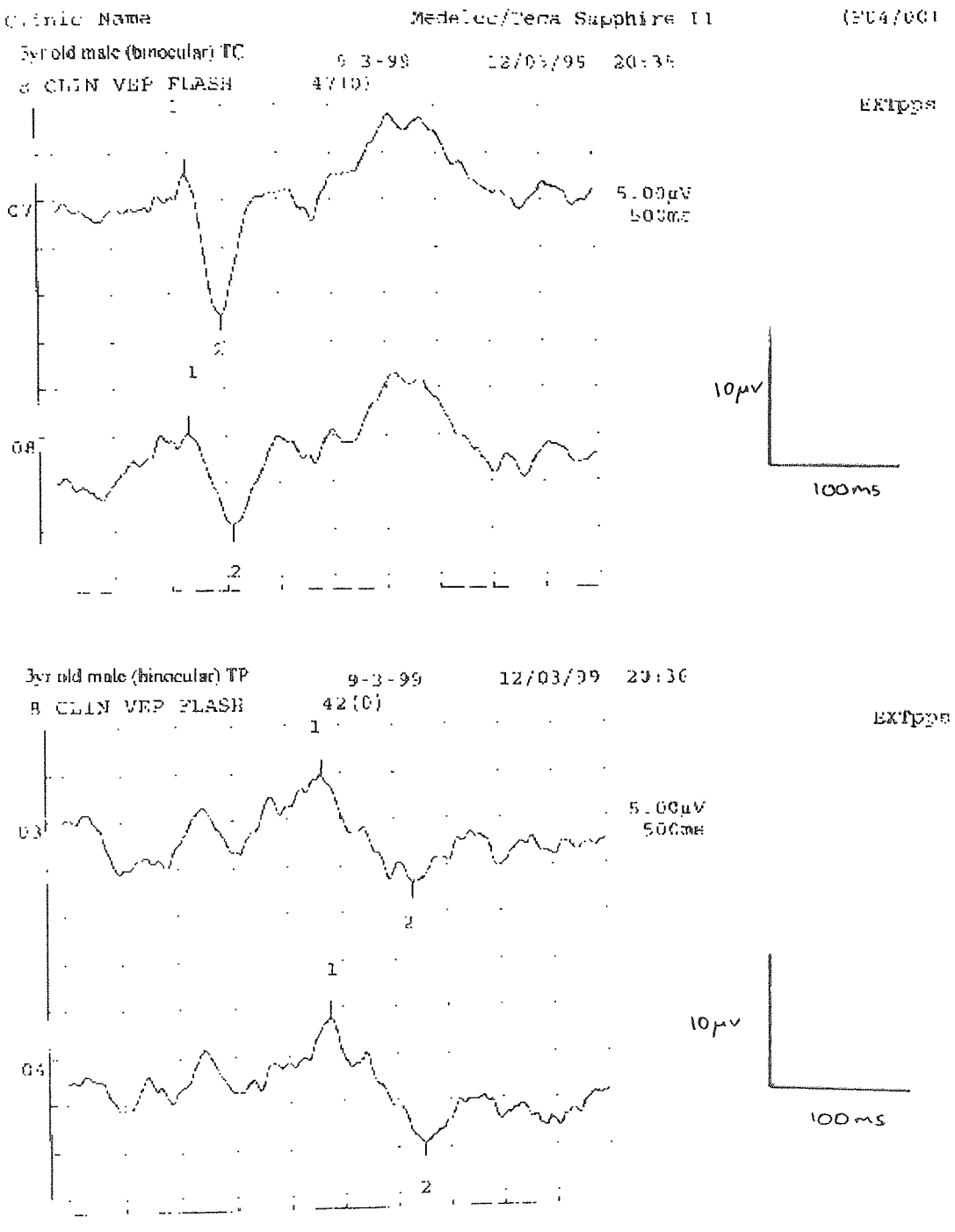


Figure 34 shows the binocular central P100 (above) and peripheral N135 (below) responses of a 3yr old healthy male

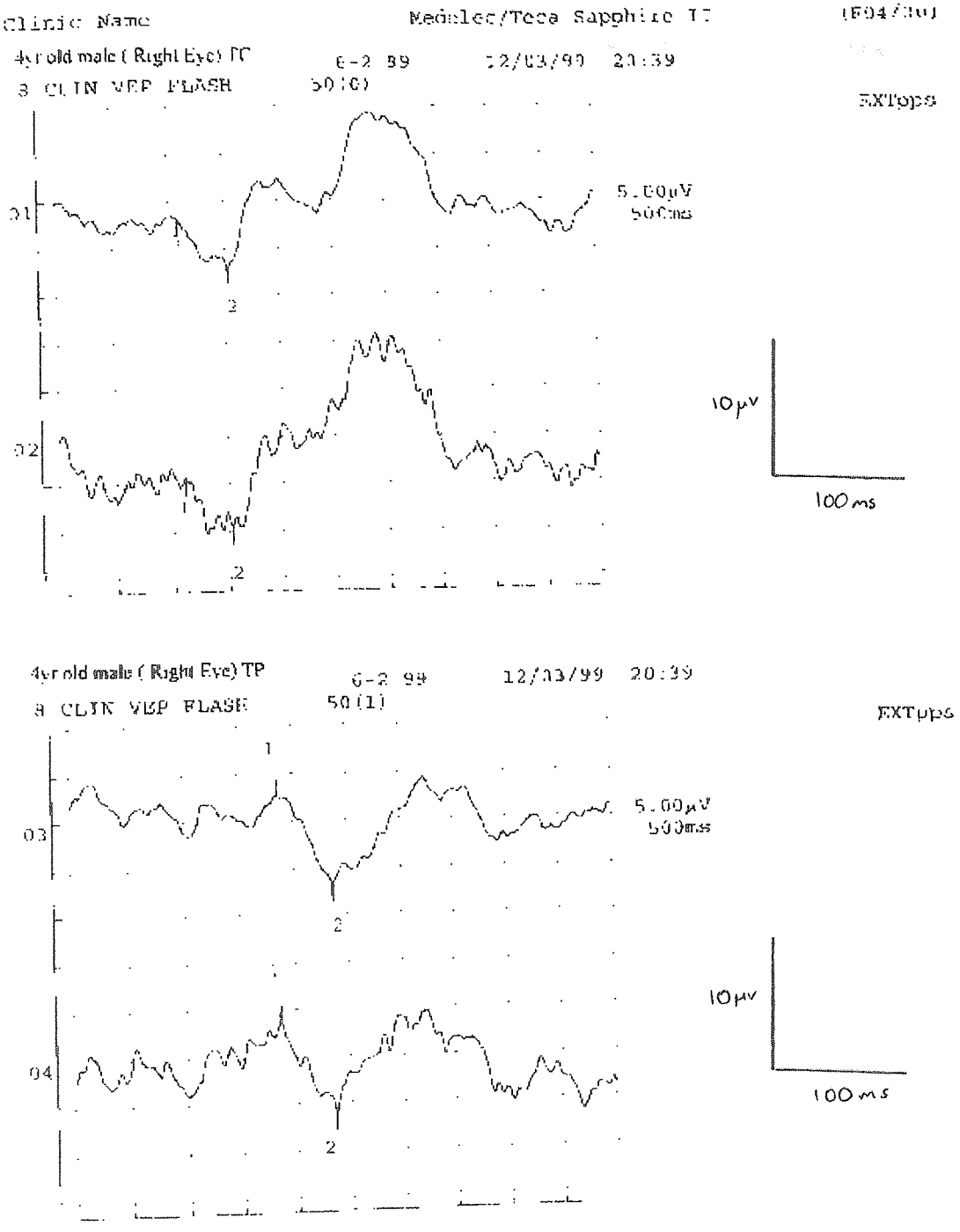


Figure 35 shows the central P100 (above) and peripheral N135 (below) responses of a 4yr old healthy male

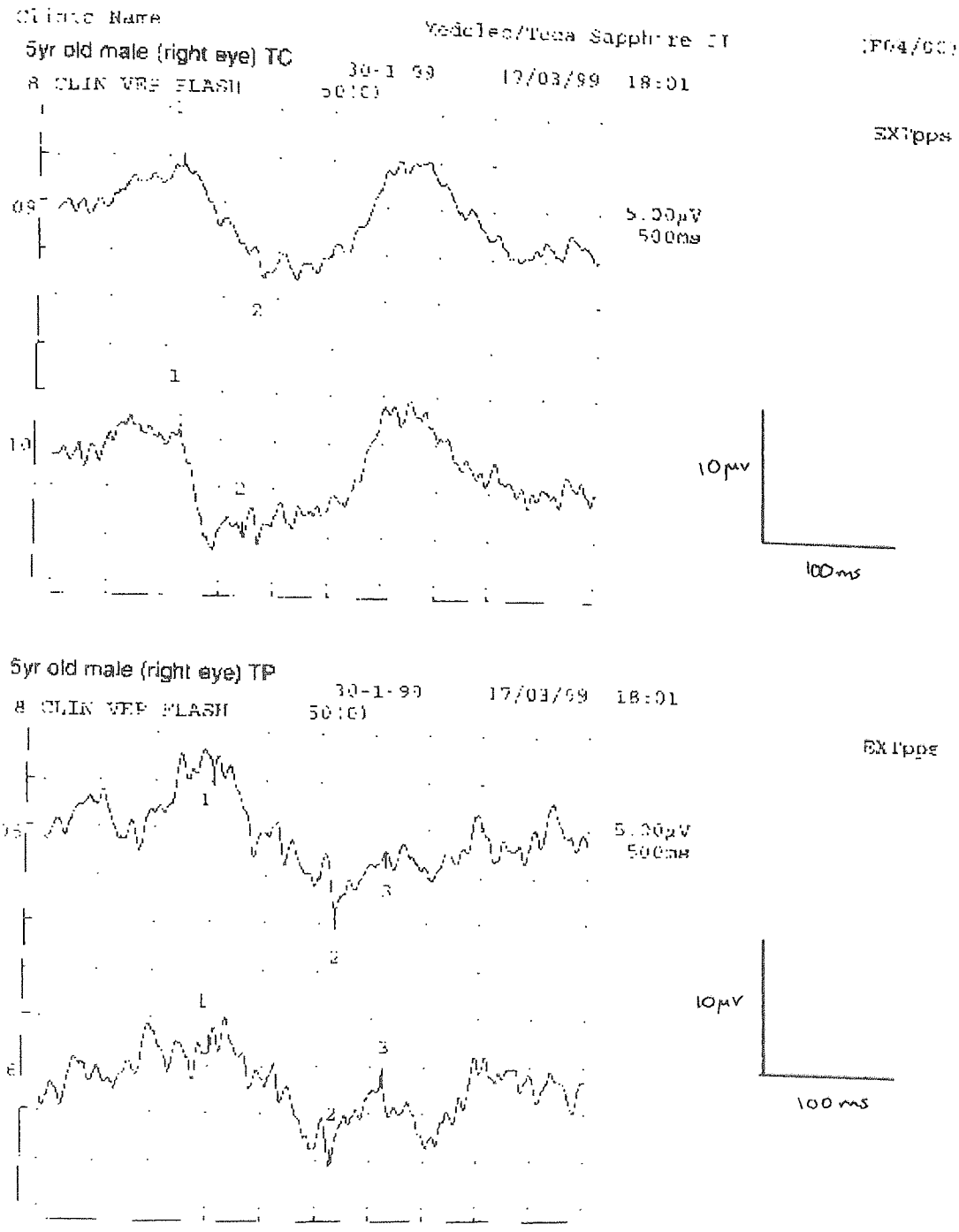


Figure 36 shows the central P100 (above) and peripheral N135 (below) responses of a 5yr old healthy male

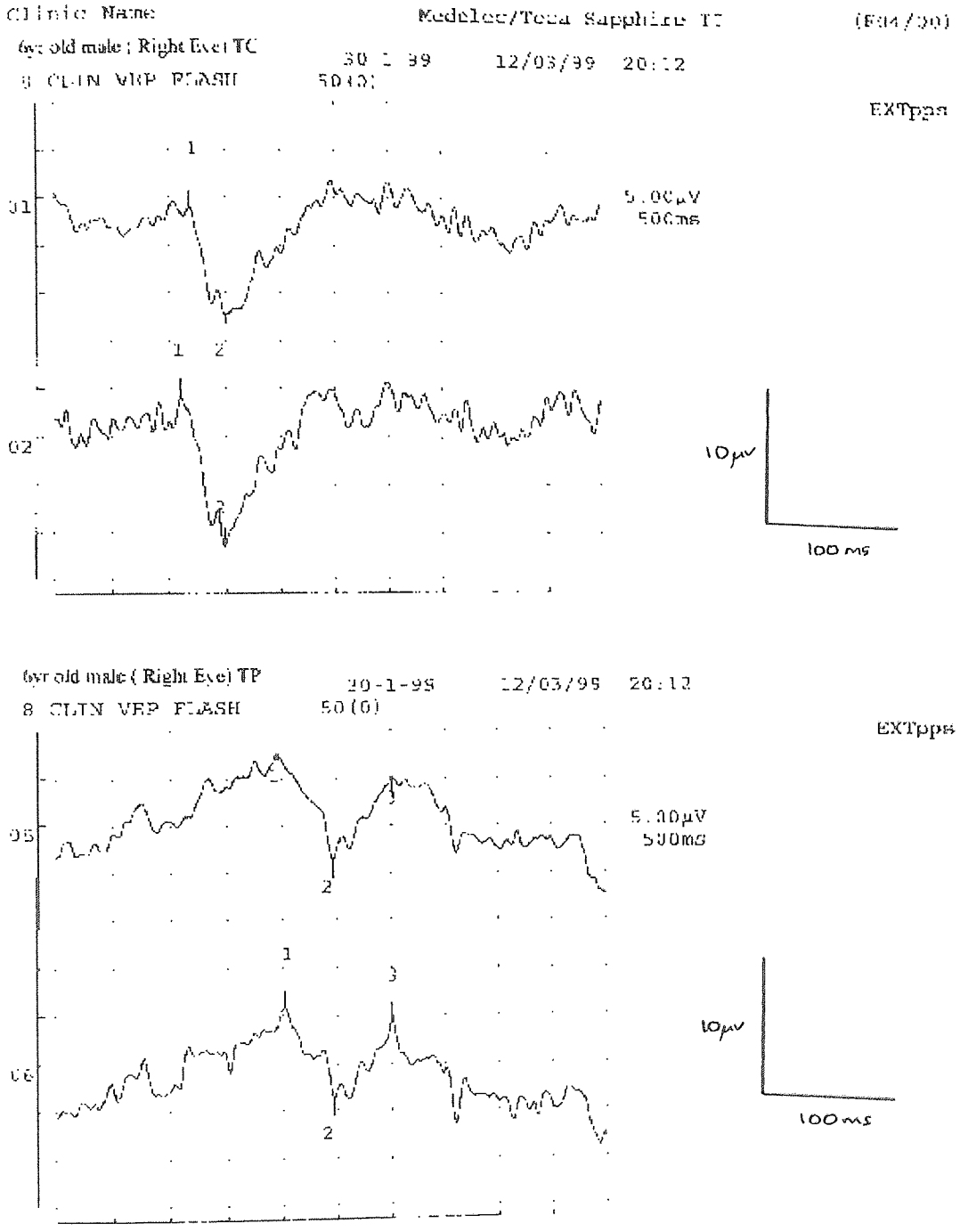


Figure 37 shows the central P100 (above) and peripheral N135 (below) responses of a 6yr old healthy male

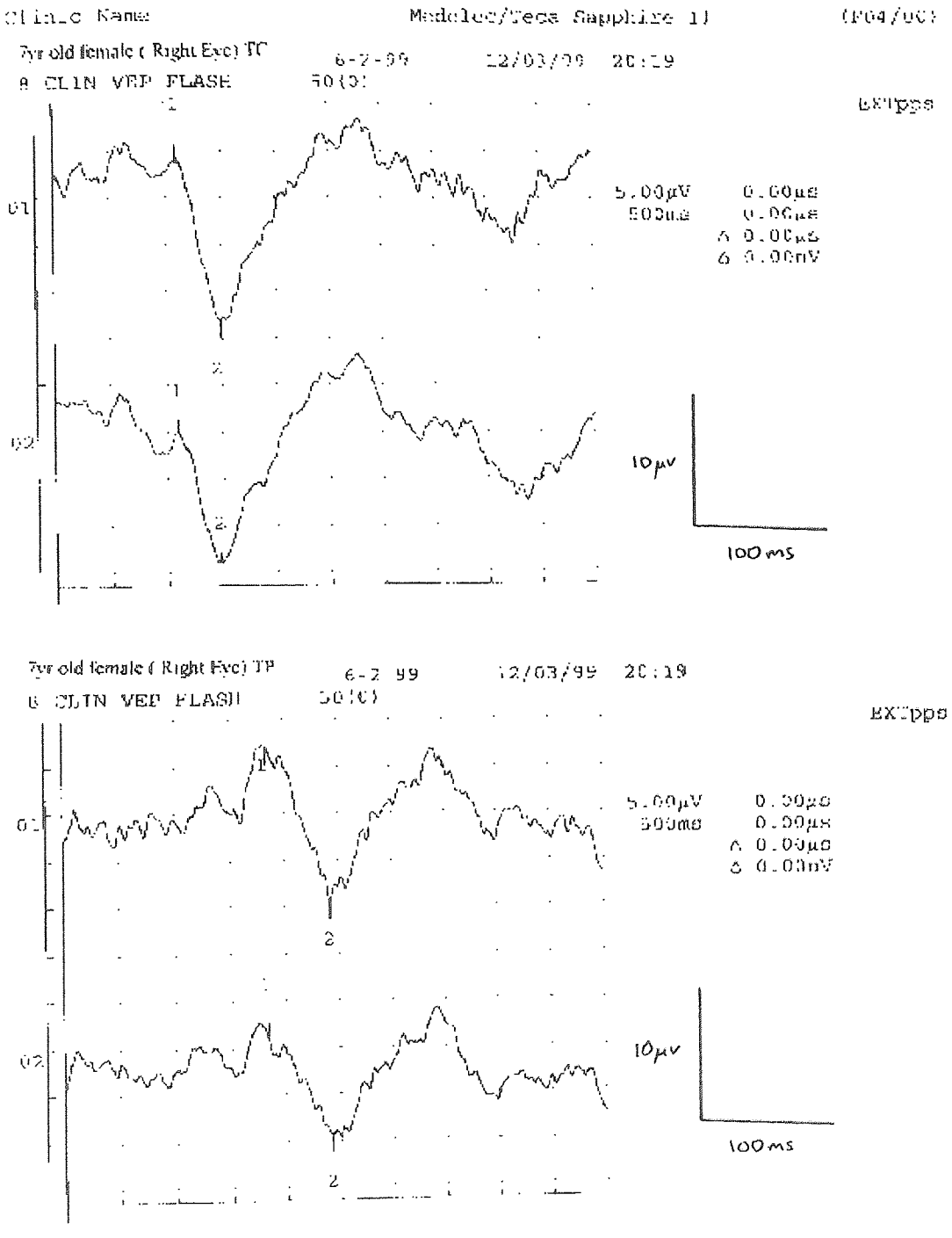


Figure 38 shows the central P100 (above) and peripheral N135 (below) responses of a 7yr old healthy female

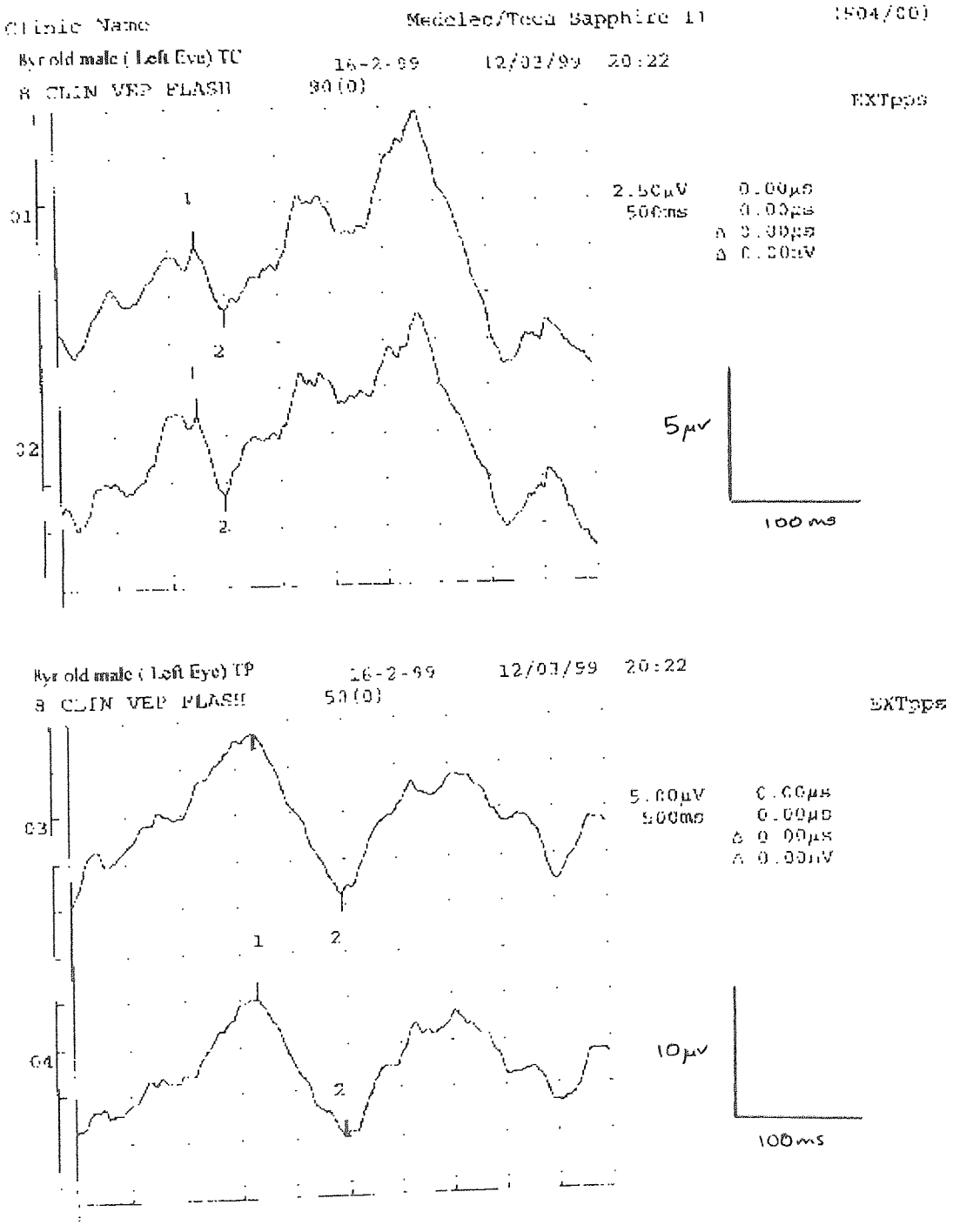


Figure 39 shows the central P100 (above) and peripheral N135 (below) responses of a 8yr old healthy male

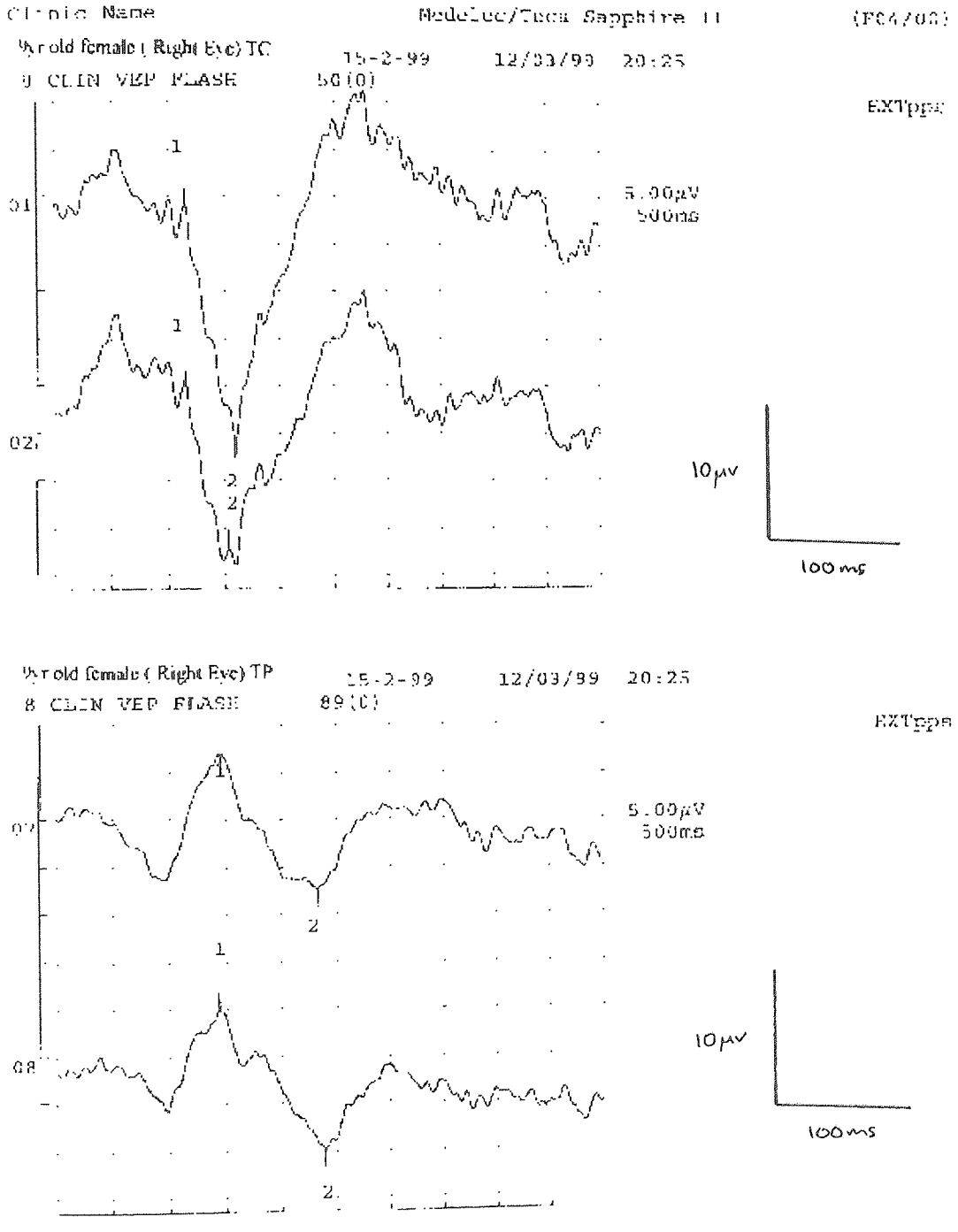


Figure 40 shows the central P100 (above) and peripheral N135 (below) responses of a 9yr old healthy female

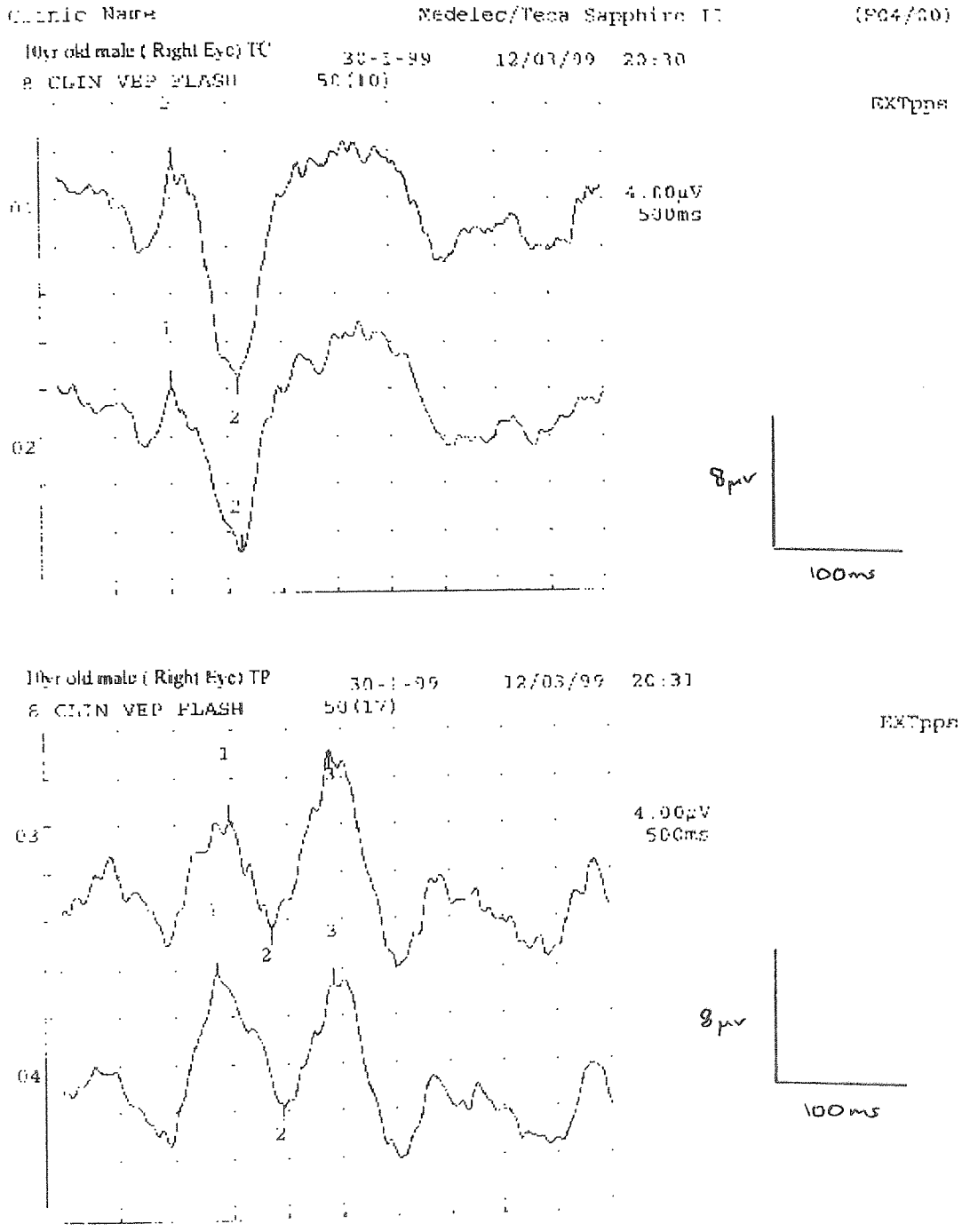


Figure 41shows the central P100 (above) and peripheral N135 (below) responses of a 10yr old healthy male

8.8.2 Central Responses

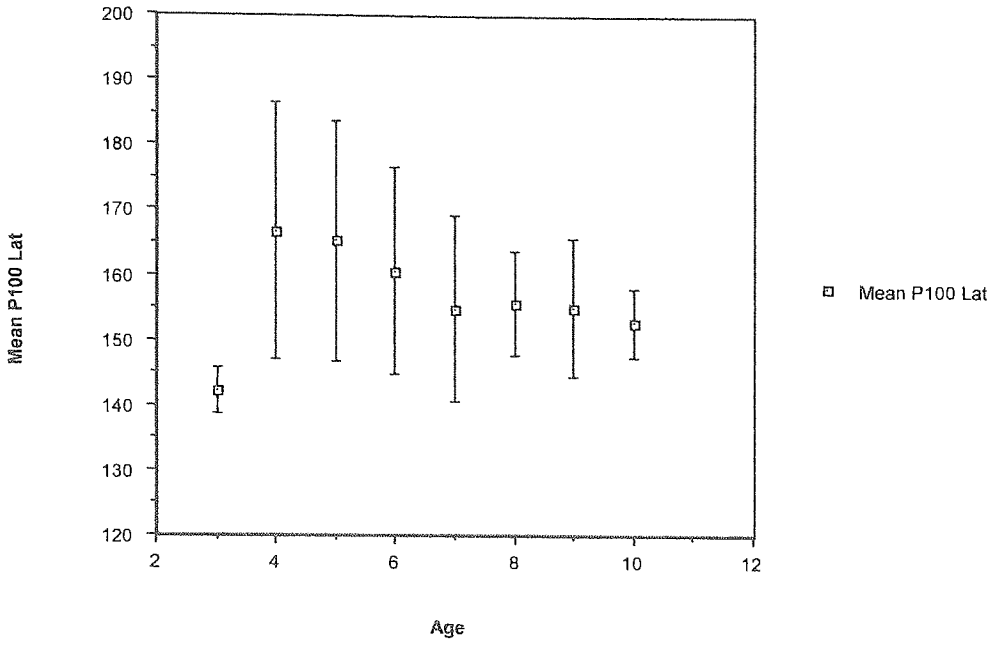
Latencies of the P100 component

The mean latency +/- 1SD of the P100 response for all 47 children was 157.92ms +/- 14.42ms. The binocular responses were found to have a shorter latency than those of the monocular responses. Overall the latency showed a clear tendency to decrease with an increase in age, the mean latency being 166.6 ms in the 4yr old group decreasing to 152.71 ms in the 10 yr old group. The mean latencies +/- 1SD for each age group can be found in table 31 and are presented graphically in figure 33. The regression line graphs of all the latencies of the central and peripheral responses can be found in figure 34.

Age	Mean P100 Latency	1SD P100	Mean N135 Latency	1SD N135	Nos. of Subjects	Binoc. Failures	Monoc. Failures
3.00	142.25	3.50	186.50	56.63	2.00	1	0
4.00	166.60	19.75	185.50	27.26	7.00	0	0
5.00	165.20	18.40	201.94	36.53	5.00	-	2
6.00	160.63	15.88	202.97	35.04	6.00	-	1
7.00	154.83	14.31	186.22	21.06	5.00	-	1
8.00	155.69	8.12	163.00	15.95	4.00	-	0
9.00	154.97	10.63	164.47	27.14	9.00	-	1
10.00	152.71	5.25	164.93	23.64	7.00	-	0

Table 31 shows the mean latency +/- 1SD of the P100 and N135 responses for each year age group from 3-10 yr. The number of subjects completed in each age group and the number of binocular or monocular failures can also be seen. A failure is characterised as not obtaining either a central or peripheral response in that subject.

From the central latency values of the healthy adult responses described in section 8.6 it can be seen that the values of the 10 year old children are only a little more prolonged. The characteristic delay of the central response compared with those of the traditional pattern VEP P100 component was probably associated with the small visual angle of 5 degrees. Yiannikas and Walsh (1983) demonstrated a significant prolongation of the P100 latency with 0-2 degree and 0-4 degree stimulation when compared to their full-field 32 degree P100 latency. The prolongation of the P100 latency recorded using the H-stimulus was probably increased further by the very small sizes of the central stimuli.



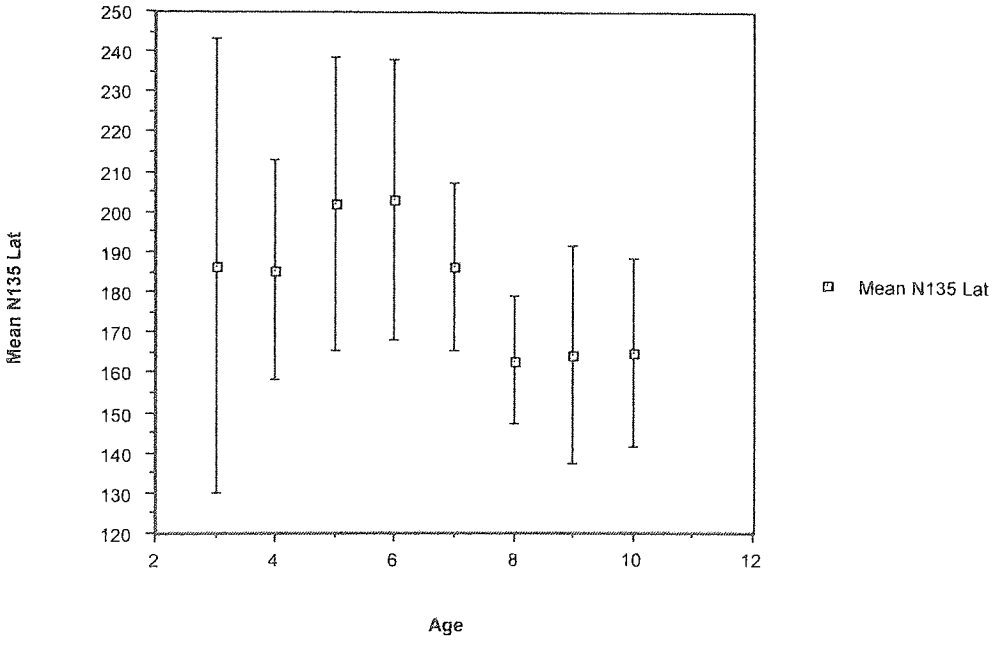
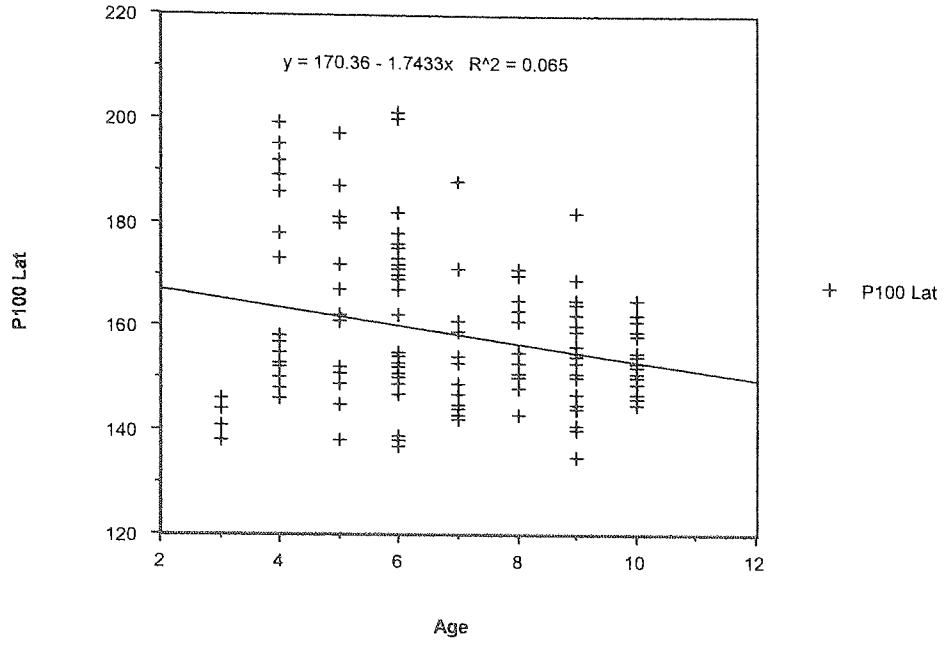


Figure 42 shows the graphical presentation of the mean P100 latency (ms) +/- 1SD above and mean N135 latency +/- 1SD for the H-stimulus responses for each year group of children from 3-10 yrs.



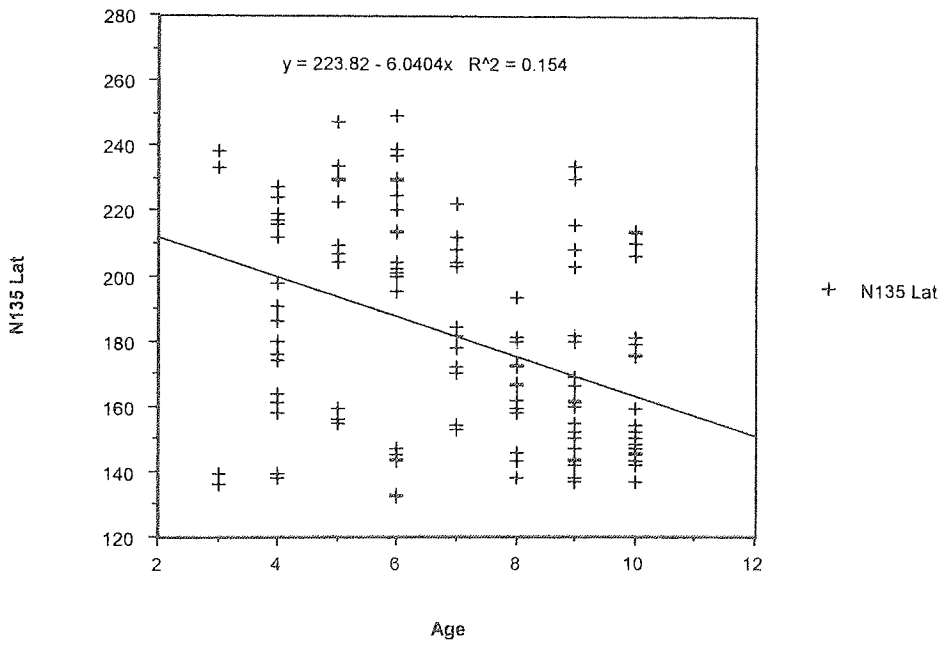


Figure 43 shows regression plots for the P100 latencies (ms) (above) and the N135 latencies (ms) (below) for the responses of all 47 children with age. The P100 latency can be seen to decrease with the increase in age. This decrease in latency with age is more marked with the N135 responses.

Amplitudes of the P100 component

The amplitudes of the central responses were very variable throughout all 47 children. The mean +/- 1SD P100 amplitude for each age group can be found in table 32. The mean amplitude +/- 1SD for all 47 children was 12.72 μv +/- 6.18. The amplitudes in the monocularly tested children (5 years and above) showed a trend to increase with age although this was not found to be significant. The low value in the 8 year old group was due to small responses of one subject with amplitudes ranging from 3.3 μv – 5.5 μv. Since an optician, prior to testing did not see the children, it may be that the subject had required corrected vision at a distance of 15cm which had not been previously detected. Before future testing near vision should be checked using vocational test cards for near vision.

Age	P100 Amplitude	1SD
3	8.69	3.79
4	15.12	9.33
5	11.87	4.47
6	11.19	4.04
7	12.52	4.84
8	9.18	4.79
9	14.60	7.18
10	13.66	5.75

Table 32. shows the mean amplitude (μv) +/- 1 SD for the P100 responses in each age group for the 47 children.

8.8.3 Peripheral Responses

Latencies of the N135 component

As with the central responses, the peripheral N135 responses were shorter in latency when stimulated binocularly rather than monocularly. The mean N135 latency +/- 1SD (ms) for each age group can be found in table 29. The mean latency for all 47 children was 180.53 ms +/- 32.57. The N135 responses showed greater variability than the P100 responses, which can be seen graphically in, figure 34. The latency of

the N135 response was increased when compared with the central P100 response, although this difference became less apparent with the increase in age of the subjects.

Appearance of the peripheral waveform

The peripheral waveforms were broader than the central responses and on 3 subjects showed a biphasic waveform. These findings support those of Meredith and Celesia (1982). When comparing pattern VEP responses obtained at 8 and 14 degrees eccentricity compared with those recorded at 0 degrees eccentricity, they found broader waveforms with polarity reversal in some subjects (the major component being negative). They also described a tendency towards a triphasic configuration.

Subject Compliance and latency

With the testing of young children and the subject being seated very close (15cm) to the stimulus, it was difficult to constantly observe whether the child was maintaining fixation. Two children (both aged 5 yr) were instructed to maintain fixation on one outer segment of the peripheral stimulus whilst peripheral responses were recorded. The response recorded to this had the P100 trough with a latency very close to that recorded from the central stimulus, these values can be found in table 33. Therefore, it was possible from the results to ascertain whether the child was being compliant and whether a repeat recording was necessary. A waveform showing the response obtained when fixating on the peripheral stimulus during peripheral stimulation can be seen in figure 36.

Subject	Central Latency	Watching Periphery	Peripheral Latency
Child 1 (O2)	167	184	277
Child 1 (O1)	167	184	276
Child 2 (O2)	151	141	262
Child 2 (O1)	152	141	266

Table 33 shows the latencies of the central and peripheral responses of two five year old males. The middle column shows the latency of the peripheral response obtained when the children were fixating on the peripheral response. The response showed a P100 trough at a similar latency to the central response.

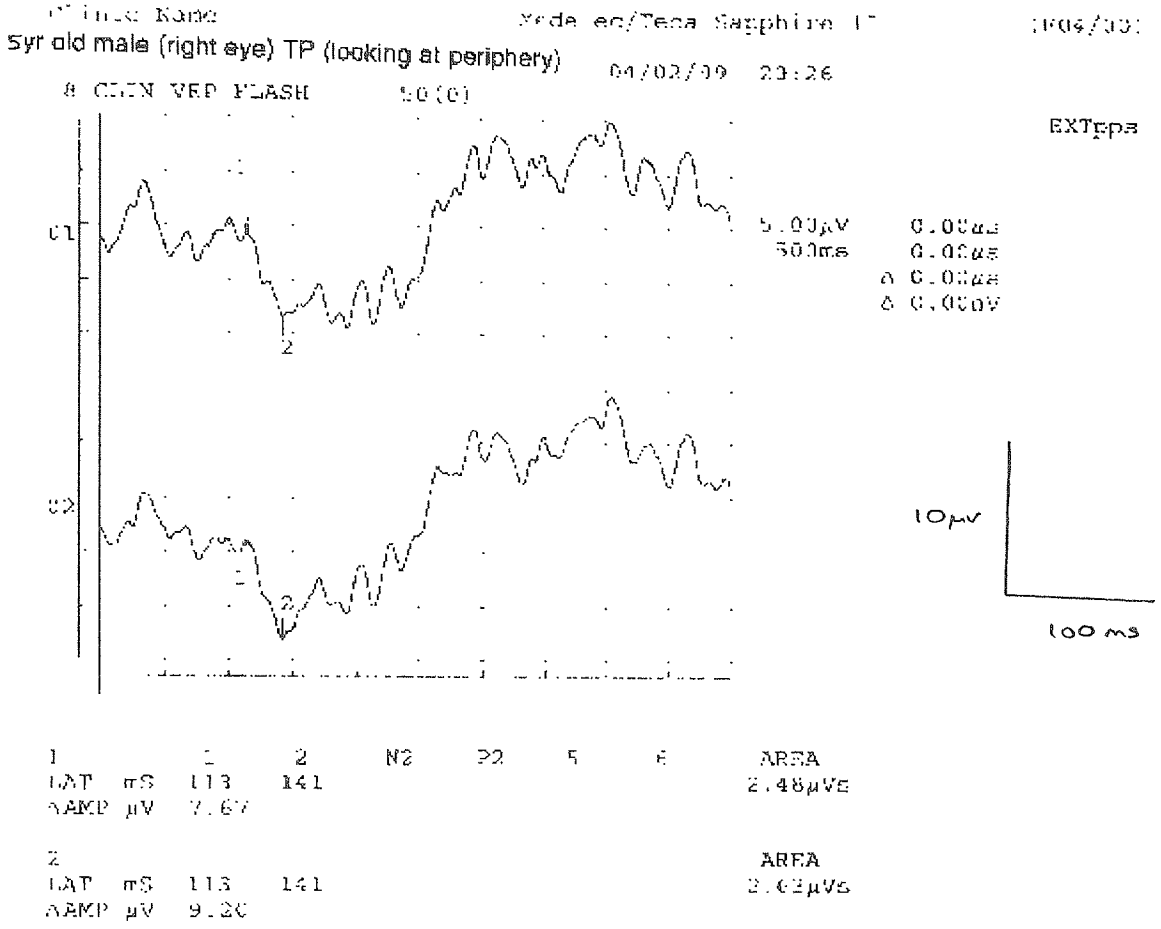


Figure 44 shows the same 5yr old male from figure 36 . This response was obtained from the peripheral trigger but with the subject fixating on the peripheral stimulus.

Amplitudes of the peripheral N135 response

The amplitudes of the peripheral response were very variable throughout the 47 children showing no trend to increase with an increase in age, as was seen with the central P100 amplitudes. The mean amplitude +/- 1SD of all 47 children was 11.05μv +/- 4.5. The amplitudes for each age group can be found in table 34.

Age	N135 amplitude	1SD
3	10.41	2.29
4	11.02	4.07
5	11.01	3.53
6	10.38	4.62
7	9.69	4.37
8	13.20	5.93
9	10.37	4.23
10	10.82	4.49

Table 34 shows the average amplitude (μv) +/- 1SD of the peripheral N135 response for each age group.

8.9 Overall findings and future aims

The pilot study results with the 3 healthy subjects and 4 vigabatrin patients with known visual field constriction described in 8.6, showed that a peripheral H-stimulus response could not be evoked when the severity of the loss reached more than 30 degrees. The peripheral visual field of patient SUSE showed some temporal sparing up to 35-40 degrees although that was not sufficient to evoke a response. This finding supported the simulation study described in 8.7 where the peripheral stimulus was constricted from 60 degrees to 35 degrees in 5 degree stages using a healthy subject. No response could be obtained with a 30-35 degree stimulus with the lower nasal quadrant occluded.

The H-stimulus was originally designed for detection of visual field constriction in children. The collection of normal child data described in 8.8 showed that children as young as three or four years could produce valid responses, although, the degree of visual angle would be slightly altered in these children since they were tested binocularly. With binocular testing the child was aligned centrally (the centre being

midway between the two eyes) therefore, the degree of visual angle affected would depend on half the interpupillary distance (which is small with this age group).

The latencies of the P100 and N135 responses could be seen to decrease with an increase in age and the responses showed an amplitude ratio of approximately 1:1.

Since it is not practical for all clinical units to invest in the equipment required to use the H-stimulus, a video version of the stimulus could be used if played on a large monitor or screen. A 28 inch television (the screen size 41.5 cm in height and 56 cm width) and with the subject seated at 15cm; the outer peripheral border would be 54 degrees in height and 62 degrees in width. Although the vertical visual angle is slightly decreased, a reasonable response should be evoked from the stimulus. The use of a screen may also reduce the variability in luminance and contrast of the stimulus experienced when the projector was used.

As yet there is no other way to test for peripheral visual loss associated with vigabatrin in children. Porro et al (1998) recently reported a new behavioural visual field test whereby a white ball is moved from the periphery of the vision towards the centre and the reaction of the child is monitored. Although they report success rates of 66% in infants and 100% in young children, the test does depend on the behaviour and co-operation of the child more so than with the H-stimulus.

CHAPTER 9 CONCLUSION

Vigabatrin has been successful in reducing the frequency of seizures in patients with epilepsy especially when used as an 'add-on' drug with patients with complex partial seizures. It acts by increasing the GABA levels (a major inhibitory neurotransmitter) in the brain.

In 1996 however, Eke et al reported visual field constriction, a low EOG Arden index and reduced oscillatory potentials of the ERG in patients and this was thought to be associated with vigabatrin.

Since many of the patients prescribed vigabatrin were often taking a combination of other antiepileptic drugs and were still suffering from seizures, it was necessary to try and establish whether the visual field constriction and abnormal visual electrophysiology was:

A) associated with a combination of drugs (carbamazepine usually being the first drug of choice to treat complex partial seizures);
B) in some way associated with the presence of epilepsy;
C) a reversible effect which reverted to normal on cessation of the drug.

The characteristic pattern of the visual field constriction showed a concentric visual field loss more extensively nasally with temporal sparing. The effect on the ERG and EOG also indicated retinal involvement of the effect of vigabatrin.

Since central visual acuity did not appear to be affected by vigabatrin and the field defect was in the periphery, patients did not tend to complain of visual impairment.

Initially in this study, three of the patients reported by Eke et al (1997), and another five patients who had been receiving vigabatrin (two of which were currently taking the drug) were referred to Aston for visual field testing and full visual electrophysiology. Both central 30-2 and peripheral 60/30-2 visual fields tests were completed and flash and pattern ERG's, EOG's flash and pattern VEP's and multifocal ERG's responses were tested. Different disease processes affect different cells of the retina and the effect of this is not always evenly distributed. The advantage of the multifocal ERG is that it records responses from the outer retinal layers with the distribution of the responses corresponding to the density of the cones

(Sutter and Tran, 1992). In this way, small localised lesions may show which would not be detected by the full field ERG.

With the eight referred patients, all flash and pattern VEP's and pattern ERG's were within normal limits previously established in the department. Before testing dilated ERG's, EOG's and VERIS, a database of normal values was collected using the Medelec Sapphire 4E and Ganzfeld stimulator and VERIS equipment. All eight patients showed a visual field constriction, although the degree of the involvement varied between the patients. There was some agreement between the visual fields and VERIS results in the severity of the defects, although the patient, who showed the most severe abnormalities in the VERIS response, had less severe visual field defects. This showed that vigabatrin may affect different mechanisms in the retina to different extents.

With the flash ERG, the latency of OP1 appeared abnormal binocularly in seven patients and monocularly in one. The amplitude of the 30Hz flicker response was abnormally low in all patients (only monocularly in two though).

Most EOG responses were normal, however, six out of the eight patients were no longer taking vigabatrin at the time of testing and Arden indexes have been shown to return to normal after cessation of the drug.

In order to assess the effect of vigabatrin in the visual system without the additional factors of other antiepileptic drugs or the presence of epilepsy, a double blind cross over placebo controlled study with healthy subjects either taking carbamazepine, vigabatrin or placebo over three ten day periods was undertaken. The drugs were titrated up to the maximum dose of 2g of vigabatrin and 800mg of carbamazepine over four days and then kept at maximum dose until the evening of day nine. After day ten, time was allowed for the drug to wash out of the system. Central and peripheral visual fields, EOG's and dilated ERG's were performed at half maximum dose (day two), the first day of maximum dose (day four) and maximum dose (day nine). Although the drop out rate was high in the study associated with nauseous side effects of the high dose of carbamazepine, eight subjects completed the carbamazepine cycle and eleven completed the vigabatrin and placebo cycles. The subjects acted as their own controls, the values obtained from baseline responses prior to taking any drug.

No visual field loss was seen over any of the cycles however, the photopic b-wave latency did significantly increase from baseline to days 2,4 & 9 in the vigabatrin cycle supporting the findings of Harding et al (1995) and Duckett et al (1998).
The EOG also showed a significant decrease in Arden index between baseline and day nine of the vigabatrin cycle. No significant changes were found during the carbamazepine or placebo cycles, and the EOG responses returned to normal after cessation of vigabatrin. The double blind study therefore supported the findings of Eke et al (1997) of a decreased Arden index and an increased photopic b-wave latency (Harding et al, 1995) associated with vigabatrin but in the absence of visual field loss. The oscillatory potentials which showed most abnormalities in the previous eight vigabatrin patients appear to be somehow more associated with visual field loss and are thought to be a separate response to the b-wave, arising from slightly different depths in the retina.

By 1998 many patients who had taken vigabatrin were having the drug withdrawn and the medical profession were more reserved about commencing patients on vigabatrin. Due to this, a longitudinal study following patients before vigabatrin and during treatment appeared unlikely. In order to investigate any association with epilepsy and other drug therapy combined with vigabatrin, two sets of patients were referred to Aston. Of the 22 patients, half were receiving antiepileptic drugs but had never taken vigabatrin and half (age matched, sex matched and seizure type matched) had taken vigabatrin for at least two years. All 22 patients underwent central and peripheral visual field tests and full visual electrophysiology. Seven of the eleven vigabatrin patients showed visual field defects, again varying in severity between the patients. With the VERIS responses, none of the non-vigabatrin group showed abnormal responses and the vigabatrin patients again showed abnormal VERIS plots differing in severity between patients in a similar manner to the previous eight patients although not correlated with the visual field abnormalities. The vigabatrin group of patients also showed abnormal responses to the 30Hz flicker ERG but also showed more prolonged photopic b-wave latencies when compared to the eight patient study.

Since the visual field constriction appeared not to be reversible after cessation of the drug and the findings of abnormal visual electrophysiology appeared directly associated with vigabatrin, consideration was turned to paediatric patients. With

children suffering from partial epilepsy and infantile spasms (West's syndrome), vigabatrin has been shown to be highly affective in reducing the frequency of episodes. Visual field testing and most visual electrophysiology requires good co-operation and concentration by the patient and would be too demanding for a child to undertake. It was therefore necessary to devise a stimulus that could achieve a reliable response in young children to assess whether vigabatrin was also causing visual defects in the paediatric vigabatrin patient population. A stimulus was designed to test the central and peripheral visual responses. It comprised of a black and white reversing dartboard stimulus pattern. A VEP response could be obtained monocularly from the central 5 degrees (radius) of the visual field. Surrounding this was a neutral background annulus and then a peripheral stimulus obtained a response from the 30-60 degrees of the visual field. The stimulus was optimised using three healthy adult subjects and then the responses of four of the vigabatrin patients with known visual field defects were collected. Co-operation could be assessed by the achievement of a good central P100 waveform and continued co-operation was observed by use of the ABBA design for collection of the central P100 and N135 responses. A patient not fixating at the centre of the stimulus, but looking at the peripheral stimulus during peripheral stimulation was also shown to produce a P100 type waveform indicating non co-operation. The patients with known visual field defects produced good central responses but only background EEG activity and noise on peripheral stimulation.

Co-operation was found to be good in children as young as three years old and normal responses were obtained from 47 children aged between three and ten years old.

Although this is a crude method of testing peripheral visual field loss compared to perimetry, the reliability of the results appears good in children and can form some assessment to the effect of vigabatrin on the visual field.

Vigabatrin which acts by blocking GABA transaminase (the enzyme that breaks down GABA) increases brain and retinal GABA levels. GABA is a neurotransmitter normally found in the retina and GABA-ergic transmission is found between horizontal cells, amacrine cells, bipolar cells and photoreceptors. An increase in GABA levels would therefore probably have an effect on retinal function and show a

change in retinal function tests. Vigabatrin has also shown to affect the EOG Arden index response on initial treatment indicating involvement of the retinal pigment epithelium. The cone responses of the VERIS and the 30Hz flicker ERG have also been shown to be affected by vigabatrin. The abnormal oscillatory potential responses of the ERG seem to be more evident with a marked visual field constriction, the latter currently thought to affect up to 40-50% of the adult vigabatrin patient population and this appears non reversible on cessation of the drug. Although doctors are more reluctant to continue vigabatrin treatment after these findings, the benefit of vigabatrin in seizure reduction especially in children must be weighed against the visual side effects. However, with the visual electrophysiological and visual field marker responses more clearly known patients can be more carefully monitored.

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APPENDIX

8 Patient data

List of publications

PHOTOPIC	Lat a	Lat b	Amp a-Amp b	30Hz Lat a	30Hz Lat b	30Hz Amp a-Ampb	Scot Lat a	Scot Lat b	Scot Amp a-Ampb
1-R	17.8	33	67	22.6	30.8	31	16	38.4	301
1-L	18	33.2	60	22.8	32.8	21	16.4	39.2	229
2-R	16.1	38.1	74	17.6	29.2	40.5	17.6	41.7	251
2-L	16.6	38.2	58.4	18	29.6	29.4	17.3	40.9	219
3-R	15.1	35.8	79	19.5	28.5	51.3	15.6	39.5	316
3-L	15.3	35.2	67	18.5	27.6	38.1	15.6	40.2	307
4-R	17.4	39.6	63.7	24.8	33	32.9	17.6	40.6	336
4-L	17	39.4	68.7	19.4	32.8	32.9	17.6	42.6	311
5-R	17	38.1	58.7	26.1	32	14.8	16.7	38.3	231
5-L	17.2	37.9	78.2	25.7	31.4	21.5	17.7	36.8	311
6-R	17.5	36	80.8	20.5	33.9	31.6	18	38.1	414
6-L	17	36.4	87.1	20.3	33.4	27.2	17.3	38.1	386
7-R	15.9	34	52.9	16.8	27.4	30.7	15.3	39	304
7-L	15.7	34.4	45.8	16.8	27	29.3	15.3	39	281
8-R	17.3	37.2	132	23.5	33.8	21.5	17.4	37.3	485
8-L	17	36.9	108	23.2	32.4	24.6	17.2	39	518
EOG	Arden Index (%)	Light Peak	Dark Trough	PERG56 Lat P50	PERG56 Lat N95	PERG56 Amp P50-N95	PERG28 Lat P50	PERG28 Lat N95	Amp P50-N95
1-R	327	429	131	53.6	96.8	3.81	53.6	88.8	3.21
1-L	333	380	114	52.8	96	3.3	53.6	85.6	2.88
2-R	218	827	378	52.8	88.8	7.72	52.8	96.8	7.32
2-L	231	734	317	54.4	93.6	6.36	56	99.2	4.48
3-R	274	874	319	48	96.8	2.94	52	96.8	4.32
3-L	261	795	305	50.4	92.8	2.91	50.4	98.4	3.12
4-R	249	449	180	53.6	84.6	6	53.6	91.2	3.04
4-L	260	393	151	52.8	84.8	7.68	54.4	96	5.48
5-R	192	844	439	49.6	88	4.86	54.4	88	3.72
5-L	179	854	476	49.6	85.6	4.92	52	91.2	3.51
6-R	216	605	280	51.2	89.6	6.48	53.6	91.2	4.38
6-L	186	583	314	52.8	94.4	4.38	54.4	92.8	3.9
7-R	195	588	302	50.4	96	3.4	49.6	98.4	2.52
7-L	192	495	258	50.4	94.4	3	50.4	96.8	2.2
8-R	183	598	327	51.2	95.2	5.08	52.8	93.6	2.48
8-L	166	556	334	53.6	93.6	5.36	54.4	94.4	2.36

Subject	FL4 VEPLat N2	FL4 VEPLat P2	Amp N2-P2	VEP 56Lat N75	VEP56Lat P100	Amp N75-P100	VEP28 Lat N75	VEP28 Lat P100	Amp N75-P100
1-R-O2	54	90	8.4	46	112	15.2	72	108	10.1
1-R-O1	52	98	11.4	46	104	15.8	74	104	8.5
1-L-O2	56	102	11.1	76	116	14	48	114	14.7
1-L-O1	56	106	12.3	64	116	14.6	48	112	15.9
2-R-O2	72	114	16.5	62	110	20.7	72	108	18.2
2-R-O1	74	116	19	68	108	21.1	74	108	16.7
2-L-O2	80	112	10.9	74	114	17.7	78	108	17.1
2-L-O1	80	118	8.3	72	112	16.5	78	108	20.1
3-R-O2	68	100	8.7	76	104	7.86	78	106	10.5
3-R-O1	68	100	9.6	76	106	10.5	80	106	13.1
3-L-O2	70	106	11.7	78	106	8	72	102	8.2
3-L-O1	68	108	14.9	78	108	9.8	78	104	10.4
4-R-O2	88	124	11.3	54	112	12	66	100	6.54
4-R-O1	90	124	12.3	46	112	11.4	72	98	5.7
4-L-O2	72	124	9.3	80	106	5.1	60	112	5.46
4-L-O1	62	126	11.4	68	104	6.42	60	116	6.72
5-R-O2	62	94	6.42	82	114	7.3	48	120	9.8
5-R-O1	64	92	4.62	94	112	5	48	120	6.7
5-L-O2	64	96	8.9	86	128	10.9	64	136	7
5-L-O1	64	86	4.9	92	126	7.6	68	118	3.8
6-R-O2	56	130	9.6	70	104	5.8	86	110	3.3
6-R-O1	54	130	11.9	78	104	5.7	82	108	5.64
6-L-O2	66	132	11.2	80	106	4.6	80	106	4.86
6-L-O1	66	134	12.7	72	106	7.26	80	106	8.1
7-R-O1	64	106	16.3	72	104	7.8	78	108	5.2
7-R-O2	64	106	14.5	74	102	6.7	76	108	4.6
7-L-O1	64	106	11.9	74	114	9.3	80	112	5.5
7-L-O2	64	102	12.8	74	114	8.9	82	112	5.1
8-R-O1	100	124	10.3	78	112	4.5	66	108	5.8
8-R-O2	100	124	12.1	84	110	3.1	64	108	7.4
8-L-O1	102	130	16.9	60	102	11.5	84	108	3.4
8-L-O2	102	128	17.9	60	104	15.6	84	106	4.4

Table 1 shows the visual electrophysiology values for ERG's, EOG's PERG's and flash and pattern VEP's for all the 8 patients. The values for the ERG oscillatory potentials can be found in table 2.

Patient	Lat a	Lat OP 1	amp OP1	Lat OP2	amp OP2
1-R	9.7	19.6	19	25.5	7.45
1-L	10.4	19.9	16	25.4	5.68
2-R	11.1	19.9	19	26.9	7.63
2-L	11	20.9	11.2	26.4	6.96
3-R	10.4	19.4	13	27.1	10
3-L	10.9	18.8	10	26.3	7
4-R	13	21	14.3	26.2	10.1
4-L	10.4	20.2	11.3	26.6	12.1
5-R	11.8	20.2	12.4	28.5	6.71
5-L	12.1	21.2	16.2	28.6	12.7
6-R	13.1	20.6	17.9	29.4	6.78
6-L	12.1	20.9	16.5	29.4	7.39
7-R	10.8	19.6	26.9	25.6	9.77
7-L	10.8	19.6	18.1	25.2	7.2
8-R	12.6	22.8	20.6	29	7.45
8-L	10.6	20.8	19.5	27.7	5.68

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