THE ROLE OF THE CORTICAL OCCIPITAL SPIKE IN PHOTOSENSITIVE EPILEPSY

RUTH MARY WEBB

Doctor of philosophy

ASTON UNIVERSITY

April 2001

ASTON UNIVERSITY

THE ROLE OF THE CORTICAL OCCIPITAL SPIKE IN PHOTOSENSITIVE EPILEPSY

RUTH MARY WEBB

Doctor of philosophy

2001

Chapters one to three are an introduction to photosensitive epilepsy, electroencephalography (EEG) and the magnocellular and parvocellular visual pathways.

Photoparoxysmal response (PPR) are strongly associated with photosensitive epilepsy. Chapters four to nine investigated whether occipital spikes were associated with PPR and hence with photosensitive epilepsy. The chapters investigated whether the response types showed similar dependence on stimulus characteristics using EEG. Chapters four and five found that occipital spikes and PPR showed different dependence on colour and luminance contrast. The differences were consistent with the magnocellular pathway mediating occipital spikes and the pavocellular pathway mediating PPR. The study in chapter eight found that monocular occlusion had a significantly greater effect on PPR than on occipital spikes, which is further evidence against an association between the two types of response. Chapters six and seven showed that occipital spikes and PPR had similar optimum spatial and temporal frequencies. Chapter nine showed that both response types could be generated via stimulation of the periphery of the retina. However, these three chapters are not strong evidence of an association, as the results do not contradict the theory that the responses are generated via different pathways. The magnocellular and pavocellular pathways have similar optimum temporal and spatial frequencies and both are present in the periphery.

In chapter ten, magnetoencephalography was used to estimate the source of activity underlying the components of the VEP and occipital spike. Changes in the amplitude and latency in the components of the normal VEP are associated with epilepsy. However, the source underlying the occipital spikes was not related to that underlying the components of the VEP so this is also removed as a source of evidence for an association between occipital spikes and photosensitive epilepsy.

Occipital spikes should therefore not be assumed to have a role in photosensitive epilepsy.

Keywords: Electroencephalography, Magnetoencephalography, Stimulus Characteristics, Visual Evoked Potential, Clinical significance.

Acknowledgements

The work described in the thesis was carried out by the author, with the following exceptions:

The data collection for experiment one, chapter four was carried out with the assistance of Janet Wilkie, an undergraduate student. In chapter ten, the data collection and analysis were carried out with the assistance of Arjan Hillebrand and Fiona Fylan.

Signed: Ruth Webb

I have received assistance and support from many other sources, without which this work could not have been completed.

My thanks to the Dr Hadwin Trust for Humane Research who provided the funding and to Professor GFA Harding for providing the means and opportunity for me to carry out this work. I would also like to thank Fiona Fylan for her constant academic assistance and emotional support over the last four years.

I learnt many skills during the course of this study and would like to thank Andrea Edson, both for her patience in training me in EEG and for her constant support in the work described in chapters four to nine. I would also like to thank Arjan Hillebrand, Gareth Barnes and the rest of the MEG team for introducing me to the field of MEG.

Many thanks also to Peter Liepins of King's College London for his assistance in printing the gratings used in experiment two, chapter six and to the Independent Television Commission for providing the stimulus tape used in experiment two, chapter five.

My final thanks must go to all the department, including to my fellow postgraduates, for their support and friendship, and of course to all the subjects who so willingly gave up their time to make this study possible.

Contents

Figures

Chapter One

Photosensitive epilepsy and electroencephalography

Epilepsy is a syndrome that is characterised by a tendency towards recurrent seizures. Sensory stimuli such as light, sound and touch can induce seizures in a small percentage of epileptic patients. This type of provocation is termed reflex epilepsy (Kasteleijn-Nolst Trenite, 1989). Photosensitive epilepsy is a form of reflex epilepsy in which the seizures are precipitated by intermittent visual stimuli.

Electroencephalography (EEG) is used to investigate epilepsy by recording the electrical activity of neurones within the cortex, via electrodes placed on the subject's scalp. The aim of this study is to investigate the relationship between waveforms recorded in the EEG of photosensitive subjects, during various forms of visual stimulation, and the diagnosis of epilepsy. This chapter will therefore begin with an introductory overview of the basics of EEG and the clinical features of photosensitivity. It will then continue into a discussion of the waveforms recorded during visual stimulation and their clinical significance.

1.1. The electroencephalograph

The EEG records the extracellular current flow that arises when a population of near vertical neurones depolarise. Whether a discharge is recorded is dependent on voltage of the discharge, the area of cortex involved and the location of the response. There is an increased likelihood of recording the activity if the

recording is for a long period of time and the source is in an accessible area of the brain. Standardised systems of electrode placement are used so that an estimation of the source of the discharge can be made and so that experimental conditions may be replicated. The standardised system used in this investigation was the 10-20 system, which is well described by Harding (1974), and an overview is given below.

1.1.1. Positioning the electrodes (the 10-20 system)

The 10-20 system is based on a number of basic principles. First, the positions of the electrodes are determined by measurements of the skull. This means that the measurements are roughly proportional to the skull size and shape. Second, the electrode positions are named after the underlying brain areas, so that the recording can be interpreted easily. Third, anatomical studies have been carried out to determine which areas of the cortex are likely to be found beneath each of the electrode positions in the average person. This allows the location of the source to be estimated.

The 10-20 system positions the electrodes via a series of measurements. A tape measure is first placed over the centre of the skull from front to back. The distance between the nasion (the dip at the top of the nose) and the inion (the lowest bump at the base of the skull) is then measured. One electrode is then positioned 10% of this distance above the nasion, and one 10% of the distance above the inion, along the line of measurement. A further three electrodes are then placed, again along the line of measurement, with 20% of the distance

between each. These five electrode points are named the Frontal pole (Fp), Frontal (F), Central (C), Parietal (P) and Occipital (O). The line of measurement is termed the midline. The distance between the pre-auricular points (depressions at the root of the cheekbones), passing through the central midline point (C), is then measured. The electrodes are positioned, along this line of measurement, in the same manner as the arrangement on the midline. The process is then repeated measuring between Fp and the occipital midline point, passing through the temporal electrodes (the temporal line). The remaining four electrodes are placed midway between the midline and temporal lines of electrodes in each quarter of the head.

Even numbers are used to indicate electrodes on the right hand side of the head, odd numbers to denote ones on the left hand side, and the letter z to indicate that the electrode lies on the midline.

1.1.2. Interpreting the recordings from the electrodes

The basic principle of EEG is that when one electrode becomes electronegative in relation to a second electrode there is an upward deflection of the recording. There are two main recording methods. The first is monopolar recording in which the potential difference is measured between an active electrode and a reference electrode. There is an upward deflection when the potential of the active electrode becomes electronegative relative to the reference. Ideally, the reference should be inactive.

The second recording type is bipolar recording in which the potential difference is recorded between a pair of active electrodes. If a negative potential develops under one electrode that is common to two recording channels, phase reversal of the potential is seen between the channels. However, if the negative potential arises midway between two electrodes there is no potential difference between them. Therefore, the channel connecting these electrodes will show no deflection and the adjacent channels will show phase reversal. These principles can be used to approximately localise the response to an area of the cortex.

There are many factors that may lead to artefacts appearing in the EEG. The potential across the eye, between the aqueous and vitreous humours, is about 1000 times greater than the potentials that are recorded in the EEG (Harding, 1974). The frontal electrodes are therefore affected by eye movements and central reference electrodes are preferable (Wright, 1985). If the electrode is placed too close to a blood vessel it will record pulse artefact. During recordings, patients should be relaxed to avoid high frequency electrical contamination from muscle tension, but must not become drowsy to avoid appearance of the alpha rhythm.

1.1.3. Basic waveforms in the EEG recording

There are four basic waveforms in the EEG. Alpha waves occur at 8-13 cycles per second (cps) in normal adults and are usually about 10 cps. In infants, alpha waves are 3-5 cps increasing to 6-8 cps at one year. Alpha is normally within the adult range by about 9 years of age. Alpha waves are higher in amplitude in the

parietal-occipital channels but may extend to temporal and central regions. They are most prevalent when the subject is relaxed with their eyes closed and should attenuate when the eyes are opened. Beta waves occur above 13 cps. The two most common frequency ranges are 14-16 cps and 18-25 cps. They are present in almost all EEG recordings and are normally low in amplitude, occurring in the anterior region. Theta waves occur between 4-8 cps and are common in young adults but rare in older people. They appear when the subject is drowsy, replacing the alpha rhythm. Theta waves are said to be abnormal if they are localised to one area and occurring in well-organised runs or bursts. Delta waves occur at less than 4 cps in the waking subject's EEG and at less than 2 cps when sleeping.

Two other waveforms may be observed. Lamda waves are triangular or saw-tooth waves that are about 200 msecs in duration. They occur in the occipital region when the subject looks at a pattern, especially in a well-lit room, and may be related to the scanning movement of the eyes. The Mu-rhythm is a comb-shaped wave that reflects the idling of the motor cortex and is blocked if the subject moves an arm or a leg.

Epileptiform discharges are associated with epilepsy, and are often spikes or sharp waves occurring as discrete events, clearly distinct from, and normally at a higher voltage than the background activity recorded. The patient may also be recorded while asleep, sleep deprived, during hyperventilation or during intermittent photic stimulation (Pedley, 1984). In general, epileptiform

discharges are highly correlated with epilepsy but their absence does not exclude the condition (Pedley, 1984).

1.1.4. The resting EEG of photosensitive subjects

Many subjects who have photosensitive epilepsy show normal resting EEG. In the 81 photosensitive subjects studied by Aziz et al (1989), the EEG was normal in 60% of cases. 18.8% had non-specific disrhythmias and 21% had spike and wave complexes in their resting EEG. In the large survey, of approximately 90% of all EEG performed on people with newly diagnosed seizures in Britain (Quirk et al, 1995(a)), 39% of the subjects had normal basic EEG. 9% of the subjects showed non-specific abnormalities, such as excessive slow wave activity, and 52% showed epileptiform activity in the basic EEG. However, the second study used a definition of photosensitivity that excluded all subjects except those with the most severe abnormalities. In Kasteleijn-Nolst Trenite (1989), the posterior dominant rhythm was defined as well organised if there was no intermingling of slow waves with the alpha frequencies. Photosensitive subjects had good organisation significantly less often than other epileptic subjects. It was suggested that the poor organisation of the alpha rhythm may be due to continuous activation via subclinical stimuli.

1.2. Clinical features of photosensitivity

1.2.1. Seizure types in photosensitive epilepsy

There are 12 main seizure types in epilepsy as described in Covanis et al (1982). These are listed below:

(1) Simple absence seizures: There is a cessation of activity with no motor component except very slight movement of the eyelids.

(2) Complex absence seizures: Consciousness is lost and activity may cease, be initiated or continue. Tonic clonic seizures may occur and automatisms are common.

(3) Myoclonic absence seizures: Rhythmic jerking is associated with each spike of the EEG discharge and tonic clonic seizures may occur.

(4) Myoclonic epilepsy of childhood or adolescence: Singular myoclonic jerks during childhood or adolescence.

(5) Myoclonic epilepsy with photosensitivity: Clinically as above but also have abnormal discharges to visual stimulation.

(6) Photosensitive epilepsy: All patients have abnormal responses to visual stimulation and seizures to environmental stimulation. The seizures are usually tonic clonic but may be absence, myoclonic or sometimes partial. No spontaneous seizures occur.

(7) Eyelid myoclonia and absence seizures: Eyelid myoclonia with absences and occasional tonic clonic seizures.

(8) Primary tonic clonic seizures: Subjects do not experience aura. Both the EEG and the clinical features are bilateral.

(9) Primary tonic clonic seizures with abnormality on visual stimulation: Clinically as above but subjects have abnormalities to visual stimulation and no spontaneous seizures.

(10) Secondary tonic clonic seizures: Subjects experience aura and show unilateral features (clinical or EEG) or neurological abnormality.

(11) Simple partial seizures: Characterised by focal abnormalities. Motor, or sometimes sensory, symptoms occur, often during the night.

(12) Complex partial seizures: Subjects experience complex auras and automatisms. Occur most frequently in the temporal lobe and tonic clonic seizures may occur.

The seizures in photosensitive epilepsy are predominantly generalised (Kasteleijn-Nolst Trenite, 1989). The most common type is tonic clonic but myoclonic and absence seizures also occur (Jeavons et al, 1985; Kasteleijn-Nolst Trenite, 1989; Harding, 1994(a)). Partial seizures may occur but are uncommon (Jeavons et al, 1985). When 81 photosensitive subjects were studied, 44.4% showed primary generalised tonic clonic seizures and 36.6% had secondary generalised seizures (Aziz et al, 1989). In the large survey, carried out on approximately 90% of all EEG performed on people with newly diagnosed seizures in Britain, the subjects showed four seizure types. 68% showed generalised, 11% showed absence seizures, 8% myoclonic and 2% showed partial seizures, (10% could not be classified) (Quirk et al, 1995(a)).

1.2.2. Classification of photosensitive subjects

Patients are frequently classified in research papers as those that have pure photosensitivity and those that have epilepsy with photosensitivity. The distinction should also be made between those patients with photosensitivity, defined by EEG abnormality to intermittent photic stimulation (IPS) and photosensitive epilepsy, defined by seizures to visual stimuli, as this may account for some of the contradictions found in the literature. Several classifications have been used in research. Most classification systems include categories of pure photosensitive epilepsy (with no spontaneous seizures), epilepsy with photosensitivity (with visually induced and spontaneous seizures) and a category for those subjects with sensitivity to visual stimulation in the clinic but no history of seizures. Other categories used include subjects with spontaneous seizures and sensitivity to IPS but no environmental visually induced seizures (Harding, 1994(b)). The subjects in this category may have had seizures due to visual stimulation that have not been documented. Additional categories may be added for seizures to the TV (Hess et al, 1974) or subjects showing myoclonic jerks, self induction or pattern sensitivity (Jeavons, 1985). About 40% of patients with photosensitivity are thought to have pure photosensitive epilepsy (Kasteleijn-Nolst Trenite, 1989). The subjects in this study were classified purely on the basis of the abnormalities in the EEG recorded during visual stimulation. This avoids the problems involved with obtaining accurate descriptions of seizure conditions. It also allows the inclusion of subjects with no history of seizures, many of who may have experienced seizures if they had not been diagnosed and medicated when young.

1.2.3. The relationship between pattern and photosensitivity

About half of photosensitive patients also show abnormalities to stimulation with high contrast patterns (Jeavons, 1982). Pattern sensitivity does occur without photosensitivity but the disorders are probably a continuum (Harding, 1994(a)).

In a study by Kasteleijn-Nolst Trenite (1989), a pattern of black and white stripes evoked abnormalities in 54% of the photosensitive subjects investigated, even though there was no movement component to the stimulus. 19% of the subjects that were sensitive to the patterns were not sensitive to photic stimulation with the eyes open, even though all pattern stimulation was carried out with the subject's eyes open. There was no difference in the sensitivity ranges to IPS depending on whether the subject was pattern sensitive (Kasteleijn-Nolst Trenite, 1989).

Brinciotti et al (1994) examined 67 subjects who had been referred on the basis of visually induced seizures. Patterns were presented on a monitor and the luminance contrast was reversed. 83.5% of the subjects were sensitive to intermittent photic stimulation, 67.2% to the reversing patterns. The subjects were classified as photo and pattern sensitive (51%), photosensitive only (33%) and pattern sensitive only (16%). The types of reflex seizure were not significantly different between the groups. Patients in the 'photosensitive only' group were significantly less likely to have abnormalities in the basic EEG and focal abnormalities were more common in the pattern sensitive group, though this difference was not significant. In all the categories the reported

environmental stimuli coincided well with the categories to which they had been placed from the lab stimulation. 87% of overall patients were sensitive to the TV which was the most common stimulus in all categories. In contrast to Kasteleijn-Nolst Trenite (1989), the photosensitive range was lower in subjects with photosensitivity only, than in those with pattern sensitivity. However, this may have been due to the differences in the methods of pattern stimulation used in the two studies, as the second type of pattern stimulation did involve a motion component.

Pattern and photosensitive epilepsy represent a continuum rather than two separate syndromes (Harding and Jeavons, 1994). It is therefore possible to investigate the stimulus characteristics of visual stimulation using pattern or photic stimulation or a combination of both methods. All the studies in this investigation used combinations of pattern and flicker stimulation to maximise the probability of evoking abnormal response.

1.3. Therapy

1.3.1. Non-drug therapy

Several methods of behavioural therapy are used to treat photosensitive epilepsy, particularly in subjects who show EEG abnormalities to visual stimulation but have yet to exhibit clinical symptoms. Three methods of conditioning therapy are used. Subjects are stimulated monocularly, with frequencies outside their sensitivity range, or with reduced amplitude of modulation to increase their

thresholds. Conditioning therapy is not considered effective (Hess et al, 1974; Jeavons, 1982). Habituation of the 50 Hz response has been suggested but no significant differences between repeated presentations have been found unless the trials were placed close together in the protocol (Topalkara et al, 1998). This suggests that the effects of habituation are both frequency specific and short lived, and therefore have little relevance to therapy.

Other behavioural therapy involves advice to patients, particularly in relation to watching television. The television should be viewed from a distance of more than 2 metres (Hess et al, 1974; Jeavons, 1982; Kasteleijn-Nolst Trenite, 1989; Binnie and Jeavons, 1992; Harding, 1994(b)) and smaller televisions are less provocative (Jeavons, 1982). The room should be well lit and a lamp placed on the top of the television set (Jeavons, 1982; Jeavons et al, 1977(b)). Subjects should try to avoid approaching the TV set but if necessary should cover one eye with the palm of their hand (Hess et al, 1974; Jeavons, 1982; Kasteleijn-Nolst Trenite, 1989; Binnie and Jeavons, 1992; Harding, 1994(a)). Monocular occlusion can also be used to protect from other stimuli and is discussed in more detail in chapter eight. Polarising screens and dark or polarising spectacles can also reduce the risk of seizure (Hess et al, 1974; Harding, 1980; Jeavons, 1982; Kasteleijn-Nolst Trenite, 1989; Jeavons et al, 1997(b)).

In this study, the exact parameters of the stimuli that provoke abnormalities are investigated. This can lead to improvements in the advice given to patients who wish to avoid provocative stimulation. It can also be used to improve the

regulation governing television images or other environmental stimuli with regards to what should be controlled or contain warnings.

1.3.2. Drug therapy

A good review of the current drug therapy in epilepsy is presented in Feely (1999) and the main points are summarised below.

There are five new drugs on the market that may have relevance to the future treatment of photosensitivity. Tigabine has only recently been licensed and its role has not yet been established. Topiramate is a very potent and very toxic drug, which can cause numerous psychological and cognitive changes, and is only used to treat very severe cases of epilepsy. Gapapentine is less effective, and less toxic, than other drugs and is mainly used in newly diagnosed cases. The effects of both Lamotrigine and Vigabatine are currently being investigated.

There are three main established drugs in the treatment of epilepsy. These are carbamazepine, sodium valporate and phenytoin. Caramazepine is used to treat both partial and generalised tonic clonic seizures. It is tolerated well in children and young adults when it is introduced gradually. The maximum dose is determined by monitoring symptoms, rather than drug concentrations, as shortly before the maximum tolerated dose the subject begins to experience transient double or blurred vision. Side effects include an allergic rash, which is common but not severe. There may also be interactions with drugs such as the

contraceptive pill, and carbamazepine has teratogenic effects including increased risks of spina bifida.

Phenytoin produces the most severe side effects of the three drugs and requires careful monitoring of drug concentrations, as it has complicated metabolic properties. It can be used to treat partial and generalised tonic clonic seizures but is now mainly used when other treatments are unsuccessful. Teratogenic effects include cardiac defects and cleft lip or palate.

Sodium valporate is the third main drug, which is used to treat the same seizure types as carbamazepine but is also the drug of choice for absences and myoclonic seizures. It has the advantage that it does not have to be introduced gradually. It also has teratogenic effects as it is implicated in spina bifida. There are also some problems with weight gain but it is the drug of choice in elderly patients. Sodium valporate is used frequently in the treatment of photosensitivity and is discussed in more detail in section 1.3.3 as several of the patients on the study were treated with it. Its effectiveness also represents a difference between the different types of abnormalities evoked by IPS.

1.3.3 Sodium valporate in the treatment of photosensitivity

In 1977(b), Jeavons et al investigated the effects of treatment with sodium valporate on patients with various forms of generalised epilepsy. 9 patients had typical absences, 33 absences with automatisms, 28 had tonic clonic seizures with or without photosensitivity and 72 had various myoclonic epilepsies. Seizures were controlled in 63% of all cases and a further 18% showed an

improvement of greater than 50%. In the 69 patients who showed 3 cps spike and wave discharges in their EEG, 81% were free from seizures. Sodium valporate is therefore a good choice of treatment for epilepsies associated with spike and wave discharges such as photosensitive epilepsy. Even higher levels of control were found in a later trial of 605 subjects (Covanis et al, 1982) with 80% of patients with absences, myoclonic jerks and primary tonic clonic seizures having complete control.

Sodium valporate is commonly used in the treatment of photosensitive epilepsy (Kasteleijn-Nolst Trenite, 1989; Binnie and Jeavons, 1992). Photosensitivity is markedly reduced or completely abolished in about 80% of patients (Harding, 1994(a); Harding, 1994(b)). The effects of drugs in photosensitivity are investigated via EEG recordings during IPS. Harding et al (1978) studied the effect of sodium valporate on the photosensitive range of 50 subjects. Photosensitivity was abolished in 54%, improved significantly in 24% and improved but not significantly in 22%. There was no difference in the effect depending on the subject's age, sex or whether the subject also had spontaneous seizures. There was, however, a significant effect of dosage. Significantly higher doses of sodium valporate were given to the abolished and significantly improved groups than were given to those who showed no significant improvement. The effects of dosage were investigated in more detail by Jeavons et al (1977(b)). 35 patients were given doses from 600 to 1400 mg daily. The response to intermittent photic stimulation was tested before the trial and at each dose level. Abnormal discharges disappeared from the basic EEG first, often at

doses of 1000 mg or less. At this dosage, 12 of the subjects showed no abnormality to IPS. At the maximum dose, 20 of the subjects showed no abnormality to IPS and a further 7 showed improvement by more then 80%. The main side effect of sodium valporate is weight gain (Harding et al, 1978; Covanis et al, 1982; Kasteleijn-Nolst Trenite, 1989). Indigestion, nausea and an increase in hair curliness have also been reported (Harding et al, 1978). 19% of the patients reported unpleasant side effects but these were only severe enough for the drug to be withdrawn in 6% of the cases.

Sodium valporate is most effective at normalising the photosensitive EEG but has no effect on the presence of occipital spikes in the EEG (Harding et al, 1978; Harding, 1994(b)). This may represent an important difference between occipital spikes and photoparoxysmal response and will be discussed in more detail later.

1.4. Genetics

A family history of photosensitivity, epilepsy, or photosensitive epilepsy is often present in photosensitive epilepsy but the inheritance pattern is still unknown. First degree relatives are at the greatest risk and the risk diminishes with increasing genetic distance (Kasteleijn-Nolst Trenite, 1989). Investigations into the genetics of photosensitivity are complicated by the fact that some subjects may grow out of their photosensitivity. Many family members who are not found to be photosensitive report that they didn't like flickering lights when they were young (Jeavons, 1982).

Inheritance may be complex. One study (Herrick et al, 1975) investigated 11 siblings, of which three had experienced seizures to televisions. Spike and wave discharges were recorded in the three children who had experienced the seizures and in one other. A further three siblings and the mother had occipital abnormalities. This illustrates that many types of abnormal response can occur in one family.

Estimates of the percentage of photosensitive subjects showing a family history of epilepsy are variable and include 8% (Jeavons, 1985), 10% (Harding, 1994(b)), 14% (Aziz et al, 1989), 21% (Kasteleijn-Nolst Trenite, 1989), 43% (Campanille et al, 1995), 45% (Brinciotti et al, 1994) and 51% (Harding et al, 1997). Harding (1994(b)) commented that there can be wide discrepancies between the reported family history of epilepsy (10%) and the percentage with relatives sensitive to intermittent photic stimulation (40%).

Several experimenters have avoided the difficulties involved in obtaining an accurate family history by investigating the first-degree relatives directly. In the first of these studies the incidence of EEG abnormalities, to intermittent photic stimulation, were compared in the siblings of photosensitive and non-photosensitive epileptics. EEG abnormalities to photostimulation were found in 23% of the siblings of the subjects with photosensitivity, compared to 11% in the siblings of the non-photosensitive epileptic group (Baier and Doose, 1992). Siblings of female patients were at a higher risk of manifesting spike and waves

than siblings of males. In a further study (Waltz et al, 1992), 135 photosensitives were investigated to examine whether there was any difference in the likelihood of abnormalities in the relatives, depending on whether the photosensitive had a history of seizures. 65 subjects had epilepsy and 70 had no history of seizures. There was no significant difference between the incidence of abnormalities to visual stimulation in the first-degree relatives of the two groups. The incidence of EEG abnormalities was 39% for those with epilepsy and 44% in those without, in the siblings. The incidence in the parents was lower than in the siblings, in both groups, but was also similar between the two groups at 15% and 18% respectively. Female relatives were significantly more likely to be affected (36%) than male (25%). This evidence supports studying photosensitive subjects together, regardless of their seizure history, as in this thesis.

A genetic component to pattern sensitivity has also been suggested, for example Brinciotti et al (1992). Some genetic component of pattern and photosensitivity is apparent but the exact symptoms, EEG abnormality and sensitivity do not appear to be inherited in a simple manner.

Establishing a genetic component to photosensitive epilepsy is important as it allows subjects who are at risk to be investigated for EEG signs of photosensitivity and then medicated or advised on behavioural therapy before seizures occur. Many of the subjects in this study had no history of seizures but were the first-degree relatives of subjects with photosensitivity. Although they have remained seizure free, they may have experienced seizures if they had they not been treated.

1.4.1. The Incidence of photosensitive epilepsy

Estimates of the prevalence of photosensitivity vary between 4-5% of the epileptic population (Aziz et al, 1989; Binnie and Jeavons, 1982; Harding, 1994(b)) up to 9% (Jeavons, 1982). Incidence is age dependent and is approximately 1 in 10,000 of the Western population (Harding, 1980), rising to 1 in 4,000 during the adolescent (Jeavons, 1982; Harding, 1980; Harding, 1994(b)). Lower estimates of incidence were found in a nation-wide study of approximately 90% of all EEG performed on people with newly diagnosed seizures (Quirk et al, 1995(a)), with incidence of 1.1 in 100,000 in the population and 5.7 in 100,000 in the age group 7-9 years. However, the definition of photosensitivity in this study was strict and the authors themselves stated that their estimates of incidence were likely to be conservative. A number of possible explanations were suggested for this. People experiencing minor clinical seizures may not be aware of them, people with a first seizure may not report it to the doctor, people may not be referred for or attend an EEG, and a single routine EEG may not reveal abnormalities even when the patient suffers from them. The relatively low incidence of photosensitivity within the epileptic population has implications for patient recruitment but also highlights the importance of establishing whether photosensitivity is present. Subjects should not be restricted to avoiding visual stimuli if their epilepsy is not evoked in this manner.

The prevalence of photosensitive epilepsy has been estimated in several other ethnic populations. The epileptic populations of India (Saleem et al, 1994) and

Africa (Danesi and Oni, 1983) have both been investigated. The prevalence of photosensitivity was found to be much lower, at 0.6% and 1.6% respectively, than the 5% estimated for Western populations. It was suggested, initially, that the high levels of sunlight in these areas were protective. However, the prevalence of photosensitivity in the Saudi and Yemini Arabs was comparable to estimates in the Western population at 7.3% (Obeid et al, 1991). These experimenters stimulated at higher frequencies but it seems likely that the lower prevalence in Africa and India is due to genetic factors rather than sunshine. Further evidence of this came from a study of the three main ethnic groups in Nambia (De Graaf, 1992). The main ethic groups in Nambia are black, people of mixed race and whites. Photosensitivity occurred in 0.4, 4.2 and 5.2% respectively. The prevalence in the white population is therefore similar to that found in white populations of other geographic areas. This presents further evidence that genetic, rather than environmental factors are involved, especially as the mixed race group showed an intermediate prevalence.

1.4.2. Age and photosensitivity

There is some debate in the published research as to whether the age of onset of photosensitivity is around puberty or earlier. Estimates of the mean age of onset vary between 8 years (Kasteleijn-Nolst Trenite, 1989; Campanille et al, 1995) and 14 years (Jeavons, 1982; Jeavons, 1985; Harding, 1994(b)). One group of experimenters found that two thirds of subjects had onset of symptoms before age 6 (Gerken, 1969). Some of this discrepancy may be explained by the fact that though photosensitivity is often detected at 12-14 years, clinical histories

indicate it may have been present for some years before it is recognised (Binnie and Jeavons, 1992). There is agreement that the age of onset of photosensitivity is early, with between 76% (Harding, 1994(b)), 80% (Jeavons, 1982) and 90% (Harding 1994(b)) of subjects having their first seizure before age 20.

There may also be some differences in the age of onset between males and females. Males have been found to have a higher mean age of onset (14.9 years) than females (11.8 years) (Aziz et al, 1989). These differences suggest that the hormonal changes in puberty are involved. The prevalence of photosensitivity is higher between 10 and 25 years (Kasteleijn-Nolst Trenite, 1989) than above or below these ages.

Photosensitivity often persists to at least 24 years of age and sometimes beyond (Harding, 1994(a)). Patients have been studied over several years to investigate how long photosensitivity persists (Harding et al, 1997). The mean duration of follow up was 14 years and 63% of the patients still showed signs of photosensitivity. Investigations of persistence may depend on the definition of photosensitivity. Generalised abnormalities decrease with age more than spikes which are localised to the occipital cortex (Waltz et al, 1992). This may illustrate a further difference between the two types of abnormalities, which are discussed in more detail in section 1.6.

1.4.3. The role of gender

Photosensitive epilepsy is more common in females than in males, with a ratio of approximately 2:1 (Gerken, 1969; Harding, 1980; Kasteleijn-Nolst Trenite, 1989; Jeavons, 1982; Jeavons, 1985; Binnie and Jeavons, 1992; Harding, 1994(a); Harding, 1994(b); Quirk et al, 1995). Females have also been shown to be sensitive to significantly wider ranges of stimulation frequencies (to have a greater photosensitive range) (Kasteleijn-Nolst Trenite, 1989). This predominance of women may be genetic or hormonal but the fact that it is independent of age suggests that genetic factors are more likely (Kasteleijn Nolst-Trenite et al, 1994).

1.5. Precipitating factors

1.5.1. Non-specific precipitants of seizures in photosensitive epilepsy

Several non-specific factors are thought to increase the probability of seizures occurring. These include fever, sleep deprivation, hyperventilation, drug or alcohol withdrawal and physical exercise (Kasteleijn-Nolst Trenite, 1989). The effects of emotion and levels of consciousness are less reproducible and may well be related to their influence on the state of arousal (Kasteleijn-Nolst Trenite, 1989). Menstruation and puberty can both alter the risk of seizures via hormones. The degree to which hormones alter seizures depends on seizure types, epileptic syndrome, sex and reproductive status (Gerkin, 1969).

1.5.2. Environmental visual precipitants

Numerous sources of flickering lights in the environment have been reported as precipitating seizures. These include sunlight interrupted by roadside trees or reflected from water, disco lights, faulty fluorescent lights and fairground or amusement arcade lights (Hess et al, 1974; Jeavons, 1982; Kasteleijn-Nolst Trenite, 1989). Seizures can also be provoked by high contrast patterns in the environment such as the metal stair tread of escalators, window blinds, striped materials and fluted glass or roof tiles (Jeavons, 1982; Kasteleijn-Nolst Trenite, 1989).

For many years the most common environmental precipitant of seizures has been the domestic television, which is thought to involve both pattern and flicker effects. This will be discussed in more detail below. Television is the most common precipitant in approximately 60% of cases (Kasteleijn-Nolst Trenite, 1989; Harding, 1994(b); Campanille et al, 1995) with shorter viewing distances, of under 1 metre, being a factor in 70% of cases. More recently (Quirk et al, 1995(a)), electronic screen games utilising TV monitors and computer packages have been found to be as common as broadcast TV and with increased usage this trend is likely to continue. Estimates of seizures to sunlight are between 36% (Campanille et al, 1995) and 56% (Kasteleijn-Nolst Trenite, 1989) and to artificial light 38% (Kasteleijn-Nolst Trenite, 1989). Seizures to environmental pattern are much less common and between 11% (Kasteleijn-Nolst Trenite, 1989) and 20% (Binnie and Jeavons, 1992).

There are several factors that could account for the role of the domestic television in photosensitivity. The 50 Hz flicker on television sets, in the UK, is created as the picture is scanned. As the screen is interlaced, a flicker frequency of half the speed may be resolved at close viewing distances. The 25 or 30 Hz (in countries with 60 Hz mains frequency) flicker, that occurs at close viewing distances, is more epileptogenic as it is closer to the optimal temporal frequency for abnormal activity and because the flicker is patterned (Wilkins et al, 1979(a)).

Sensitivity to 50 Hz IPS and the televisions at viewing distances of over 1 metre are significantly correlated, but no relationship has been found between patterned flash and viewing distance. This suggests that patients who are sensitive to 50 Hz television, at viewing distances over 1 m, are not simply 'more sensitive' with wider sensitivity range. If this was the case the sensitivity to TV would show a correlation with patterned flash as well as diffuse flash (Wilkins et al, 1979 (a)). This indicates that the 50 Hz sensitivity and sensitivity to the TV are more directly related than simply both being common in severe cases.

There are two possible explanations as to why increasing the viewing distance from the TV reduces the probability of abnormalities. First, it reduces the visual angle that the screen subtends, and second, it reduces the visual angle that the interlaced lines subtend. Televisions with large screens may be masked to provide a screen with the same visual angle but a larger line subtense. Comparisons can then be made between the large and small screen televisions to separate these two factors. Screen subtense appears to be more important in patients who are sensitive to conventional viewing distances of over 1.5 metres,

but the visual angle which the interlaced lines subtend appears to be the more important factor in patients that are only sensitive at short distances of less than 1 metre. The responses to small screen televisions have been found to be less than predicted from line subtense. However, if the screen viewing distance must be reduced to as short as 25 cm for it to be epileptogenic, then accommodation may be unable to retain the focus of the image, and the 25 Hz flicker may not be resolved (Wilkins et al, 1979 (a)).

The visibility of background flicker on television screens is thought to depend primarily on the luminance, the visual angle the screen subtends and the field repetition frequency. The direction in which the field is scanned to produce the image may also be involved. Flicker has been found to be more visible when the screen is scanned in a direction other than the normal top to bottom. These differences are significant at several different levels of picture luminance and could be illustrating a form of long term adaptation, which cannot be reversed by short term adaptation in the opposite direction. Although this finding should be replicated in countries with 60 Hz sets, or where no television is viewed, it could have implications for the generation of abnormal discharges (Corbette and White, 1976).

Photosensitive patients are often recommended to watch televisions in a room with high background illumination as this reduces the luminance contrast between the screen and the background illumination and should reduce the risk of seizures (Harding and Jeavons, 1994). At viewing distances of 1 m or more patients are more sensitive to television when the lights are turned off. However,

at distances of 1 m or less, more discharges are evoked when the lights are on. This could be due to increased resolution of the interlaced line as the contrast threshold is reduced with increased ambient lighting (Binnie et al, 1980).

Recently, television sets that have increased refresh rates of 100 Hz have become available and are thought to reduce the risk of seizures to TV. When identical patterns are presented on a 50 Hz and 100 Hz television, 92% of the patients show reduced or no sensitivity to the 100 Hz television (Fylan and Harding, 1997). There is also significantly less risk of abnormal discharges with TV watching and video playing on a 100 Hz screen (Ricci et al, 1998). However, there is still some risk involved while watching 100 Hz TV as 50 Hz flicker can be resolved at short viewing distances and the sequence of pictures itself may contain flicker or highly patterned sequences.

In 1981, a letter was published that described a case in which the arcade game astro-fighter had evoked a tonic-clonic seizure. The subject confirmed that it was a sequence of multicoloured flashes, at about 15 Hz, that had previously made him feel strange (Rushton, 1981). Other seizures to arcade games have since been reported and the subjects confirmed as photosensitive (Harding et al, 1994(a)) or as having focal abnormalities (Helgott and Meiser, 1983).

Surprisingly, a case has also been reported in response to a low luminance hand held game. This subject was found to be photosensitive, but was not sensitive to conventional pattern stimulation. However, at these luminance levels it appears likely that pattern sensitivity is a factor (Jeavons et al, 1981).

When video games are played using a domestic television as the monitor there is an increased risk of seizure as the video sequences are combined with the underlying flicker of the television screen. Numerous papers have described seizures to these types of games (Hart, 1990; Maeda et al, 1990; Allen and Morrow, 1994; Harding et al, 1994(a)). In all but one of the experimental groups (Allen and Morrow, 1994), photic stimulation and pattern testing were carried out. Only two cases were described in which the subjects were neither pattern or photosensitive during clinical testing. Both these cases were only tested for photosensitivity between 3 and 30 Hz, so they may have been sensitive to higher flash rates. However, alternative explanations for non-photosensitive video game seizures include cognitive and emotional factors.

A case study has described a subject who has seizures while playing checkers (Seigal et al, 1992). No EEG activation occurred during staring at the checkerboard or while manipulating the checker pieces. Several neuropsychological tests were administered and it was concluded that emotional factors such as emotion and frustration were not factors. However, EEG abnormalities were evoked when tasks required consequential or strategic thinking. The latency of abnormal responses evoked while playing games has been found to shorten when concentration increased and mental calculation has been found to elicit abnormality in a non-photosensitive video game epilepsy subject (Takahashi et al, 1995 (a)).

In a survey of most of the EEG departments in Britain, the annual incidence of first seizures triggered by playing electronic screen games was estimated to be

1.5/ 100,000 where the seizures could be related to photosensitive epilepsy. However, the number of patients for whom no causal relationship was found was no greater than that expected by the chance occurrence of two common events, the playing of video games and the incidence of epilepsy (Quirk et al, 1995(b)). It has also been noted that as EEG recorded at different times show differences in sensitivity, so the failure to find photo or pattern sensitivity may be due to the individual differences over time (Graf et al, 1994). It therefore appears that video game epilepsy and photosensitive epilepsy are closely related.

Further evidence for a connection between photosensitive epilepsy and video game epilepsy comes from the fact that there are several similarities between the two populations. These include the fact that the most common precipitant is television and that the mean age of onset is around puberty. The main difference between the populations is that for video game epilepsy the male/female ratio is estimated at 4.7:1, compared to a ratio of 1:1.7 for photosensitive epilepsy. However, a Sega marketing survey found that 82% of video game players are male. When this predominance of males is corrected for, the sex ratios between the populations are similar (Harding et al, 1994(a)).

It appears that although factors such as fatigue, excitement and decision making may play a role in video game epilepsy, photo and pattern sensitivity are also common. Provocative sequences include the appearance of patterns, such as black and white blocks, multicoloured or white flashing lights, rapid changes of scene and rolling or flickering patterns (Maeda et al, 1990; Graf et al, 1994).

1.5.3. Self induced photosensitivity

Photosensitive subjects have been reported exhibiting self-induction of their seizures. In one study, 37% of photosensitives showed self-induction during a 2 hour monitoring period though only 5% admitted to it (Kasteleijn-Nolst Trenite, 1989). Self-induction can be carried out via hand waving, eye blinking in sunlight or slow eye closure. The seizures induced are normally absence (Kasteleijn-Nolst Trenite, 1989).

Some patients who are sensitive to the TV exhibit compulsive attraction to it. Harding (1980) reported that 10% of his 500 patients were attracted to the TV. This is a form of self-induction but it is thought to be separate for a number of reasons. Self-induction is predominantly female but compulsive attraction is predominantly male. Subjects showing compulsive attraction are more likely to have spike and wave in the basic EEG and are less likely to have problems with their cognitive development than subjects with other forms of self-induction. Seizures are normally tonic clonic rather than absence (Jeavons, 1982).

Self-induction is hard to treat (Binnie and Jeavons, 1992) and may be less common than originally thought as blinking and hand waving may be a symptom of the seizure, rather than the stimulus which induces the seizure.

1.5.4. Stimulation recommendations in the clinical environment

There are some general recommendations for stimulation that increase the chances of detecting whether photosensitivity is present. A detailed description of which stimulus parameters are provocative is provided in chapters four to nine.

Intermittent photic stimulation should be varied between 1 and 60 Hz, with separate presentations of each frequency (Jeavons, 1982). Particular attention should be paid to stimulation at 25 Hz and 50 Hz, as they are relevant to television sensitivity (Jeavons, 1982). A grid should be placed over the photostimulator, to create a high contrast pattern over the area of illumination (Jeavons, 1982; Binnie and Jeavons, 1992; Harding, 1994(a); Harding, 1994(b)). Spectacles should be worn, if required, to ensure that the grid can be resolved (Jeavons, 1982). Fixation should be central (Jeavons, 1982; Binnie and Jeavons, 1992; Harding, 1994(a); Harding, 1994(b)) and stimulation should be binocular (Binnie and Jeavons, 1992) with the effects of monocular occlusion tested (Jeavons, 1982; Harding 1994(a)). The subjects should be tested for pattern sensitivity at spatial frequencies between 1-4 cpd. The luminance and contrast of the pattern should be high and a greater line to width ratio is more provocative. A temporal frequency modulation of 15-20 Hz is optimal, regardless of spatial frequency (Harding, 1994(b)).

1.6. Electroencephalographic responses to intermittent photic stimulation

The photosensitive range is a measure of the frequencies of intermittent photic stimulation that provoke abnormalities in the subject. It has been established every hour from 9.00 am-7.00 pm and the vast majority of patients showed consistent circadian rhythm of photosensitivity (Binnie et al, 1986).

The photosensitive range is also consistent over longer time periods. When the sensitivity range was established and the examination repeated 3 months later, the mean variation in the lower limit was only 2.75 flashes per second (fps) and the mean upper limit variation was only 9.43 fps (Harding, 1980). A larger sample of photosensitive subjects was examined over a period of 10 years. Only 19 out of the 167 patients showed any spontaneous remission (Harding et al, 1978). The lower limit of sensitivity varied by a maximum of 5.3 fps over 12 years, which is only twice the variation seen in the three month interval (Harding, 1980). Therefore, if the medication is kept constant the sensitivity range varies minimally over months or even years (Harding, 1994(b)). Sensitivity to diffuse intermittent photic stimulation and pattern sensitivity does not appear to show significant differences between the seasons (Kasteleijn-Nolst Trenite, 1989).

Responses to intermittent photic stimulation can broadly be classified as photic driving, photomyoclonic responses, occipital spikes and the photoparoxysmal response.

1.6.1. Photic driving

Photic driving is rhythmic activity, either at the stimulus frequency or at its multiples (harmonics) or subharmonics (submultiples). It is confined to the occipital and parieto-occipital areas and is especially common at flash rates of 8-20 fps (Kasteleijn-Nolst Trenite, 1989). The activity is normally symmetrical but the response may have a lower amplitude on one side (Jeavons, 1982).

Kasteleijn-Nolst Trenite (1989) recorded photic driving in 74% of the photosensitives studied and in 94% of control subjects. It is a normal physiological response that is time locked to the stimulus and thought to represent the visual evoked potential in the unaveraged EEG. The visual evoked potential will be discussed in more detail in chapter two.

1.6.2. Photomyoclonic response

The photomyoclonic response is recorded, in the EEG, as anterior spikes occurring at the same temporal frequency as the flash stimulation (Jeavons, 1982). The spikes are associated with rhythmic action potentials in the orbital and other facial muscles (Kasteleijn-Nolst Trenite, 1989). They occur only when the eyes are closed and are more common if the photostimulator is placed close to the eyes or intensity of stimulation is high (Kasteleijn-Nolst Trenite, 1989; Jeavons, 1982). Photomyoclonic responses are not thought to be indicative of photosensitive epilepsy (Hess et al, 1974; Jeavons, 1982; Kasteleijn-Nolst Trenite, 1989; Harding, 1994(a)).

1.6.3. Occipital spikes

Occipital spikes are confined to the occipital regions and are time locked to the stimulus. They have increased definition with increased flash rate and when a pattern is superimposed on the photostimulator. Monocular occlusion reduces their amplitude. The clinical significance of occipital spikes is debated and is one of the factors under investigation in this study.

The main component of occipital spikes is negative with small positive components immediately before and after (Panyiotopoulos et al, 1972). They show phase reversal at the occipital electrode and maximum amplitude at the same electrode during average reference recording (Panyiotopoulos et al, 1972). The initial positive wave has a latency of approximately 87.5 msec, which is constant within subjects regardless of the flash rate (Panyiotopoulos et al, 1972). Negative occipital spikes appear 0.2 to 3 seconds after stimulus onset. With increasing flash rate they tend to appear earlier but never appear after the first flash (Panyiotopoulos et al, 1972). The spikes increase in amplitude until 3-9 fps and at low flash rates (5-8 fps) normally show a progressive decline in amplitude. At high flash rates the spikes were more likely to terminate in photoparoxysmal response as described in the section below.

1.6.4. Photoparoxysmal response

Photoparoxysmal responses (PPR) are, broadly speaking, transient abnormalities provoked by intermittent photic stimulation or pattern stimulation. Several

different classifications are used to define the characteristics. Quirk et al (1995(a)) used four classifications of photoparoxysmal response. Type one were spikes with occipital rhythm. Type two were parieto-occipital spikes with biphasic slow wave. Type three were type two with spread to the frontal regions. Type four were generalised spike and wave or poly-spike and wave.

The type 1 classification is the occipital spike described in the previous section. Types 2 and 3 are also classified as degraded PPR and type 4 as the classic PPR. The classic PPR has a 3 cps slow wave component (Jeavons, 1982). The statistical association between PPR and photosensitive epilepsy is dependent on their type, as is discussed in the following section.

1.7. The clinical significance of EEG abnormalities to IPS

In 1975, Mahashwari and Jeavons investigated the clinical significance of occipital spikes. 45 patients were identified with occipital spikes to photic stimulation, normal basic EEG and no classic or degraded PPR. Only 2 out of the 45 had a history of photosensitive epilepsy, 22 had a history of epilepsy of another type and 21 had no history of seizures. The incidence of occipital spikes in the EEG of epileptic subjects was high but they are not good indicators of epilepsy, as 47% had no history of seizures.

Occipital spikes are considered normal responses to photic stimulation by numerous authors (Jeavons, 1982; Jeavons 1985; Kasteleijn-Nolst Trenite, 1989)

and it has been suggested that they simply represent augmented visual evoked potentials. However, occipital spikes can be distinguished from the driving response by the fact that they are of constant duration and latency regardless of the flash rate, they appear earlier after stimulus onset with increased flash rates and they increase in amplitude with longer periods of stimulation (Panayiotopoulous et al, 1970(a)). The relationship between occipital spikes and the VEP will be discussed in more detail in chapter two.

In 1969, Gerken investigated 195 photosensitive children and found that 168 suffered seizures, although only 4 could be associated with visual stimuli. No details of their definition of photosensitivity were included. PPR are found in about 2-3% of patients that are referred for EEG examination and are rarely found in the normal population unless they are relatives of people with epilepsy (Jeavons, 1982). They may represent a low convulsive threshold which is genetically determined but doesn't necessarily indicate the presence of clinical symptoms (Jeavons, 1982). Several papers have estimated the occurrence of epilepsy in patients showing PPR to be as high as 95% (Kasteleijn-Nolst Trenite, 1989; Binnie and Jeavons, 1992; Harding, 1994(b)). If a PPR is associated with myoclonic jerks there is an increased probability that the subject has epilepsy (Jeavons, 1985).

No significant difference has been found between the incidence of seizures in patients showing PPR that outlast the stimulus compared to those who show self limiting PPR (Jayakar and Chiappa, 1990). However, there are problems with this classification system. First, the slow wave component may continue without

the spikes after the stimulus stops and second, the abnormality may appear self-limiting if the stimulus is presented for longer.

Subjects with spontaneous epileptogenic abnormalities are more likely to experience seizures than those with PPR alone (Gilliam and Chiappa, 1995). There is also a significant association between the type of spontaneous abnormality and the seizure classification. If the spontaneous abnormality is localised then the subject is more likely to have partial seizures, and generalised spontaneous abnormalities are associated with generalised seizures.

Epileptiform discharges have been investigated in healthy children, who had completed questionnaires to determine that there was no past history of epilepsy (Okubo et al, 1994). 5% of the 1,057 children were found to have epileptiform discharges. Occurrence of positive past history of febrile convulsions was higher in those children with epileptiform discharges (18.9%) than those without (9%).

In 1987, Kasteleijn-Nolst Trenite studied 36 photosensitive subjects for clinical signs during intermittent photic stimulation. Of the 32 patients showing discharges lasting less than 3 seconds, 24 showed clinical features. If PPR lasted longer than 3 seconds the subject always suffered from clinical signs but discharges as short as 0.5-1.5 seconds could be accompanied by clinical symptoms. The clinical features observed were changes in consciousness, myoclonic jerks of any body part, eye opening, feelings such as dizziness, eye pain, crying, and queer feelings in the stomach. 44% of patients showed one clinical feature, 31% more than one. As only 25% of the patients reported

subjective sensations, 56% of patients therefore showed clinical signs without being aware of them. 39% complained of eye pain, which was also commonly reported to environmental stimuli. Only 25% of the 24 control subjects had symptoms of dizziness and headache and none had complaints about pain in the eyes. 9 out of 14 patients complaining of eye pain showed eyelid myoclonia, which may be related. When withdrawing antiepileptic medication it should be considered that patients may experience subtle seizures without being aware of them.

Generalised PPR are good indicators of epilepsy. However, the role of the occipital cortex and occipital spikes in photosensitivity is still unknown and is discussed in more detail in the following chapter.

Chapter Two

The role of the occipital cortex in photosensitive epilepsy

The role of the occipital cortex in photosensitive epilepsy is controversial and fundamental to the role of the cortical occipital spikes. Much of the work to investigate the role of specific areas of cortex has involved the use of animal models of photosensitivity, which are discussed at the beginning of this chapter. The relevance of these models to man and the use of the visual evoked potential to investigate the occipital cortex in man will then be described.

2.1. Animal models of photosensitive epilepsy

There are several ways in which photosensitive responses can be induced in animals. Focal excitability can be the result of lesions such as irritative scarring, tumour or experimental and accidental application of convulsive drugs. Generalised excitability can be induced via convulsant drugs or may be genetic. Acute foci may be created by the acute application of penicillin or by freezing with topical ethyl chloride (Naquet and Valin, 1998). Chronic irritative lesional foci may be created with alumina cream (Naquet and Valin, 1998). Systemic injections of penicillin can provoke spike and wave discharges at subliminal doses when combined with intermittent photic stimulation (Naquet and Valin, 1998)

Several differences may occur between human and animal models. The clinical symptoms are often not similar and the stimuli that provoke seizures may differ. Animals normally exhibit only one type of reflex, whereas humans often have a mixture, for example sensitivity to both auditory and visual stimuli. The EEG recordings may also be very different. Fepi chickens exhibit audiogenic and photosensitive epilepsy but no EEG abnormalities. Feline generalised penicillin-induced epilepsy (FGPE) is similar to that in humans as it shows generalised spike and wave discharges that are synchronous spike and wave at 2.5 Hz. However, though the onset of the discharge is cortical, the highest amplitude of activity is over the pre-rolandic area rather than the occipital cortex as recorded in man (Quesney, 1984).

The papio-papio baboon is considered a more natural model of photosensitive epilepsy as they have a genetic tendency towards photosensitivity. 60% of papio-papio show bilateral spikes or spike and wave in the frontal or central regions during EEG recordings of IPS and the activity spreads from here (Naquet et al, 1975). The photoconvulsive response is not time locked to the stimulus, either in frequency or termination, and is strongly associated with epilepsy (Meldrum and Wilkins, 1984). It has a strong genetic determinate as incidence is higher in inbred populations (Meldrum and Wilkins, 1984). Age and sex dependence are similar to man but baboons show maximum sensitivity at slightly higher frequencies of intermittent photic stimulation (Meldrum and Wilkins, 1984).

Naquet et al (1975) found three main sources of evidence for the involvement of the frontal cortex in the generation of the photosensitive response in papio-papio. First, the discharge remains dominant at the focus even after the response is generalised. Second, if a callosal section is accompanied by a frontal-rolandic cortical lesion, the EEG discharge only occurs in the unlesioned hemisphere and the clinical attack is contra-lateral. Third, when lesions are made to the occipital hemisphere, photic stimulation provokes an attack that originates occipitally but remains limited to the occipital regions and does not generalise. However, as ablation of the occipital lobe removes both the EEG and the clinical abnormalities, the frontal and occipital cortex are probably both involved. Anatomical connections between the occipital and frontal cortex have been found that are specific to the papio-papio and may represent a pathway via which the activity spreads. There is, however, evidence that the involvement of the frontal cortex is greater.

The spike of the spike and wave, recorded in the papio-papio, coincides in time with muscular activation, the slow wave with inactivation (Naquet et al, 1995). When the baboon is exposed to intermittent photic stimulation the action potentials in the frontal cortex gradually become shorter and the action potential frequency is increased to about 800 Hz (Menini and Silva-Barrat, 1998). At this stage EEG abnormalities can be recorded but are restricted to the frontal-rolandic area. The inactive period between the bursts is correlated with the slow-wave of the abnormality and a linear relationship exists between the number of action potentials in the burst and the amplitude of the spike in the EEG abnormality.

This hyperexcitability has only been recorded in the frontal regions, not in the occipital cortex, suggesting that the frontal cortex plays a greater role than the occipital cortex, in the generation of the seizure (Menini and Silva-Barrat, 1998)

Other investigations into the role of the occipital cortex have used GABA applications. Enhancing GABA mediated inhibition has been a major strategy in the search for novel antiepileptic drugs for many years (Meldrum, 1984). There are four strains of evidence that GABA is involved in photosensitivity, which are discussed in Meldrum and Wilkins, 1984. First, drugs that block postsynaptic inhibitory effects of GABA can facilitate the induction of PPR or seizures. Second, compounds that block the synthesis of GABA enhance photosensitivity in baboons and induce the syndrome in non-photosensitive animals, without modifying the clinical or neurophysiological features. Third, photosensitivity in man is increased during the withdrawal of barbiturates or alcohol, which are believed to be associated with a relative impairment of GABA mediated inhibition. Fourth, photosensitivity is improved in man and the baboon with medications that are known to enhance GABA mediated inhibition. Localised infusion of GABA to the frontal cortex of the photosensitive baboon has two effects: a powerful anticonvulsive effect on the generalised photosensitivity and spontaneous paroxysmal activity occurs after GABA withdrawal (Menini et al, 1988). This presents further evidence of the involvement of the frontal cortex in the abnormality.

In summary, there is minimal evidence for the involvement of the occipital cortex in the photosensitivity of the papio-papio baboon. There are many similarities between man and the baboon. They are both more likely to have spontaneous abnormalities when the eyes are closed and they are relaxed. Both have spike and wave activity without detectable lesions and often have normal basic EEG. Seizures are increased with stress and hyperventilation and show similar sex and age dependence. However, differences between man and baboon are that baboons are maximally sensitive at higher frequencies and that no occipital spikes or seizures occur in the baboon. It is therefore possible that there is a greater role of the occipital cortex in man.

2.2. The role of the occipital cortex in photosensitive epilepsy in man

Intermittent photic stimulation can induce focal seizure arising from the occipital lobe in man. Guerrini et al (1995) examined 10 patients, all of whom had reliable clinical electroclinical documentation of reflex occipital lobe epilepsy. Computer games, TV or both triggered the seizures. Symptoms consisted of a small bright or multicoloured spot, which sometimes became blindness or blurring. The seizures are associated with headaches and post-ictal vomiting. The aura and cephalic pain often lead to a misdiagnosis of migraine rather than occipital lobe epilepsy.

Occipital onset or maximum amplitude was found in 64% of photosensitive patients studied by Kasteleijn-Nolst Trenite (1989). Additional electrodes were used to record the spread of the discharge. In 26 patients the discharge spread from the occipital area, in 11 it began in the occipital area but remained confined. In the 26 patients with temporal onset, and the 5 with parietal onset, the discharge always spread to other regions. These results suggest that separate pathways may be involved in the spread of the evoked discharge. They also suggest that occipital activity may represent a separate syndrome from the generalised response and that the role of the occipital activity may be considerably more complex than it simply acting as a focus from which the generalised activity spreads.

In 1989, Takasaka et al used coherence and cross-phase-spectural analysis, which is based on Fast Fourier transform, to investigate the spread of discharges. This method has the advantage that it is possible to detect the direction of EEG transference, the extent of the relationship and very small time lags between the channels, which are not detectable by visual inspection. The discharge spreads from the occipital to the frontal regions only in those subjects whose discharges are predominantly in the occipital region. Once the discharge is generalised, the discharge recorded on the frontal channels precedes the occipital recordings, suggesting that the discharge may originate in the frontal cortex and then spread from there in a similar mechanism to that postulated for the papio-papio. This mechanism would also explain why occipital spike and wave does not always

spread. Most importantly it suggests that occipital spikes may not simply be the focus from which generalised discharges can spread.

2.2.1. The visual evoked potential

One method of investigating the occipital cortex in man is the visual evoked potential (VEP).

Visual evoked potentials are recorded between an electrode over the visual cortex and a reference electrode over a non-visual area during visual stimulation (Wright, 1985). They are of limited clinical use, unless averaged, as they are not often seen in the basic EEG (Harding, 1974). The principle of averaging relies on the assumption that the cortical response to the visual stimulus occurs at exactly the same time after each stimulus, each time it is presented. It therefore adds up in a cumulative response. Any random or unrelated activity is different every time so it gradually cancels out (Wright, 1985). Averaging allows the VEP to be clearly identified in all subjects but does not allow individual responses to be examined. There is also some debate as to whether the background EEG is truly independent of the timing of the stimulus (Harding, 1974). The visual evoked potential may be used to assess visual functioning in cases where patients are unable to give subjective responses, such as babies, patients who can't speak the language or the severely handicapped. It is also used when the patient's subjective responses cannot be relied on, such as in psychogenic blindness, suspected malingering and legal cases for compensation.

The distance between the recording electrodes must be keep constant, using a method such as the 10-20 system, as the recorded amplitude is in part a function of the distance between the electrodes (Harding, 1974). In clinical situations two or more channels may be used to sample the two halves of the visual cortex separately.

2.2.1.1. The basic form of the visual evoked potential

The visual evoked potential is normally displayed as a plot of amplitude against time. Flash stimulation, under 4 fps, evokes VEP in which the various components are normally similar between subjects. Broadly, it consists of a waveform with an initial negative component followed by a series of 6 fluctuations between negative and positive within 250 msec of the stimulus. Several different notations are used to name the components of the waveform but here it will be discussed in terms of an initial N_1 component, followed by P_1, then N_2 and so on until N_4. A diagram of the VEP is provided in Figure 2.1.

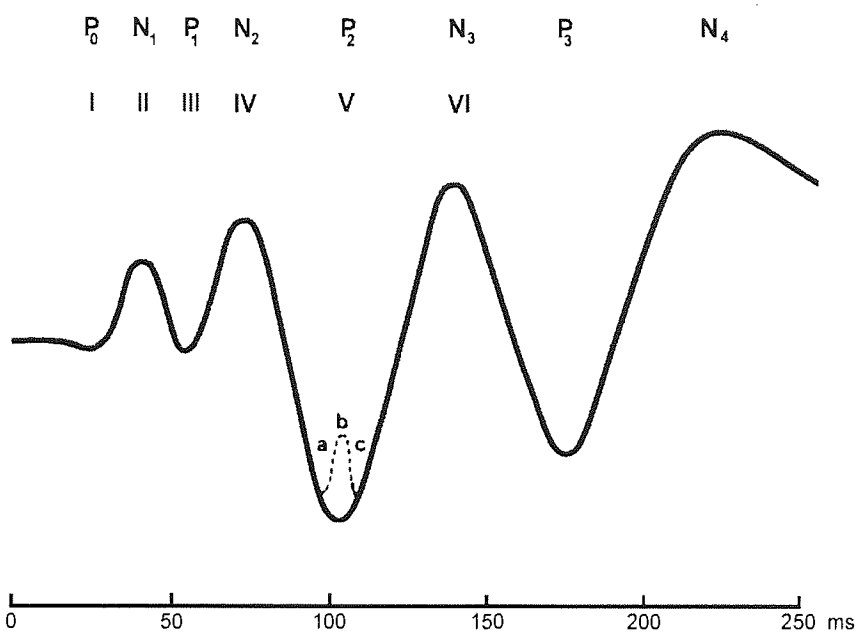


Figure 2.1. Idealised VEP recorded to low temporal frequency flash stimulation. From Harding and Jeavons (1994).

The primary components up to P_2, which occurs at approximately 100 msecs, are relatively invariant (Harding, 1974) and thought to arise from the primary visual cortex. After this the secondary components are influenced by stimulus variables and subject variables, such as subject motivation (Harding, 1974), and are thought to come from progressively higher stages of visual processing. The P_2 component at 100-120 msecs may represent the occipitally positive lamda waves seen in the EEG of subjects when they scan a patterned field (Harding, 1974). It is large in amplitude and may be triphasic with the peak interrupted by a small negative wave termed P_{2b}. In the triphasic P_2 the small positive peaks either side of the P_{2b} are termed P_{2a} and P_{2c}. This negative component is common

amongsubjects with photosensitivity and will be discussed in more detail later in the section on occipital spikes and the visual evoked potential.

Visual evoked potential may also be recorded during pattern stimulation. The methods involved require that the average illumination is kept constant throughout the stimulus cycle, so that no luminance response is evoked. There are two main methods. The first is the pattern onset response, in which the pattern abruptly appears and is then replaced by a blank field of equal luminance. The response consists of three components within 150 msecs of pattern presentation, followed by a small positive response to stimulus removal. The initial positive component, CI, and the offset response are thought to be responses to the transient change in contrast. The negative component, CII, and possibly the positive CIII are thought to represent the visual cortex response to the detail of the pattern, such as edges and angles. The pattern onset response is often used in research, as it is possible to vary all stimulus characteristics, but it is too variable for clinical diagnosis when the more reliable pattern reversal VEP is more often used. The pattern reversal VEP is a simple waveform. The main component is a positive response occurring approximately 100 msecs after each reversal, and therefore termed the P_{100}. As the contour response to the specific details of the stimulus is adapted in this method, the positive response is thought to be in response to the abrupt changes in contrast (Wright, 1985).

2.2.1.2. Factors affecting the components of the VEP

The intensity of flash stimulation can affect both the latency and the amplitude of the P_2 component but only around the threshold for VEP recording. The latency increases and amplitude decreases as the stimulus intensity is lowered (Harding, 1991). Pupil size has no significant effect on the latency or the amplitude of the flash evoked response (Harding, 1991).

Recording the VEP through the eyelid, when the eyes are closed, affects the VEP. Hobley and Harding (1988) examined the effect of eye closure on the visual evoked potential. Recording the flash VEP through a closed lid produced a significant increase in the latency of the P_2. There are numerous ways in which the eyelid could influence the components of the VEP so the various possibilities were investigated to see if they had similar effects to those of eye closure. Neutral density filters had no significant effect on latency, so the reduction in intensity during stimulation through the eyelids was unlikely to be responsible for the effects of eye closure. Performing a mental task had no significant effects on latency, with either the eyes open or closed. The P_2 latencies from the closed eyes, whilst performing a mental task, were still significantly later then those recorded from the open eyes, so the reduction in attention with the eyes closed is not responsible for the increased latency. The eyelid is not simply acting as a diffuser, as a diffuser placed over the photostimulator has no significant effect on latency. When the stimulation was with red light, the latency of the P_2

component was significantly later than those to white or green stimulation. The latencies to red light with the eye open were, in fact, similar to those recorded to white light with the eyes closed. There was no significant difference between them. The significant factor in the increase in P_2 latency on eye closure appears to be the eyelid acting as a red filter.

Increasing the temporal frequency of stimulation has the greatest effect on the components of the VEP. When the flash rate is increased above 3 Hz, the individual components are lost and it begins to resemble a sinusoidal response known as the steady state VEP. The steady state VEP is mainly used in the rapid assessment of visual acuity in children (Harding, 1991).

The effects of changing the stimulus parameters while recording the pattern reversal VEP have also been investigated. The size of the pattern stimulus and its position in the visual field affect the amplitude and lateralisation of the VEP (Harding, 1991). The effects of orientation on VEP, recorded to square-wave modulating gratings, have also been investigated (Skrandies, 1984). Vertical gratings produced VEP with the shortest latencies, followed by horizontal and oblique producing the longest latencies. All the differences between these orientations were significant and it was suggested that this is because less neurones are sensitive to oblique orientations.

The shortest component latencies were found for low spatial frequencies and the latencies increased with increasing spatial frequencies. The latencies for 9.2 cycles per degree (c/deg) were significantly longer than for 4.6 c/deg which in turn was significantly longer than the lower spatial frequencies of 1.5 and 2.3 c/deg in VEP recorded to square-wave modulating gratings (Skrandies, 1984).

The fact that altering the stimulus parameters can affect the components of the VEP is important in that it illustrates that the recording conditions must be kept constant if comparisons are to be made between two waveforms. They could also represent differences between the visual evoked potential and the occipital spike, which will be discussed in more detail in the experimental chapters.

2.2.1.3. Flash VEP in photosensitive epilepsy

If the VEP records the activity of the occipital cortex then it follows that the abnormalities in the VEP may indicate abnormalities in the activity of the visual cortex. There have been several investigations into the VEP in photosensitive subjects compared to that of other epileptic populations and to the normal population.

In 1969, Green et al studied the VEP in 16 photosensitive subjects and found no evidence of pathology. They did note, however, that in two patients an exceptionally large negative wave was recorded.

A later study (Lucking et al, 1970) investigated 42 patients with epilepsy and 30 controls. The patients had a history of either absences or tonic clonic seizures and only two were photosensitive. The intervariability of the VEP in the epileptic group was much greater but no consistent differences were found. No single component was especially prominent or deficient. The different types of seizure could not be discriminated by their VEP. There was, however, a tendency for the VEP of epileptics to be slightly smaller in amplitude, except for the two patients with photosensitivity who had abnormally large VEP. A further 7 photosensitives were studied by Lee et al (1980) and the amplitude of the VEP was again found to be generally higher in photosensitive subjects who were not being treated with anti-epileptic medication. In the subjects who were taking medication the VEP remained higher in amplitude than the 10 control subjects but the difference was not as pronounced as in the non-medicated group. The effects of medication will be discussed in more detail in section 2.2.1.5.

In 1969, Aoki found specific difference between the normal and the photosensitive VEP components. In this study the subjects were classified as posterior type (p-type), in which the discharge starts initially in the occipital area and spreads from there, and the anterior type (a-type) in which this discharge

starts simultaneously over all regions of the scalp or initially over the anterior region. The p-type VEP exhibited a number of significant differences from the control. The latencies of N_1, P_2, N_2, P_3 and P_4 were shorter and the N_1, N_2, P_3 and N_3 amplitudes were significantly greater in the photosensitive group than in the normal controls. The effect of the amplitude was greatest on P_3 and the effect of latency was greatest on N_3 and P_3. In the a-type VEP no significant differences were found in the latencies of the components but the amplitudes of P_2, N_2, P_3, N_3, P_4 were significantly greater in the photosensitive group. Differences between the photosensitive and normal VEP may therefore depend on classifying the electroencephalographic response more precisely.

2.2.1.4. The pattern reversal VEP in photosensitive epilepsy

Mervaala et al (1984) studied the pattern VEP in subjects with photosensitive epilepsy and found that the P_2 and N_3 latencies were prolonged, compared to the controls. Only about half the patients showed abnormal VEP. Fraught and Lee (1984) investigated the relationship between the clinical history of the subjects and abnormalities in the VEP. In subjects who had a history of seizures to environmental stimuli or to clinical IPS, the mean P_2 latency was significantly shorter than in the controls. No significant difference was found between the normal controls and the group who had abnormalities to IPS in the clinic, a history of spontaneous seizures but no history of seizures to visual stimulation. In the subjects who had a history of seizures to the television, the latency of the

P_2 was significantly shorter than in the other photosensitive groups, as well as the normals. There was a trend towards higher amplitude of the VEP in photosensitives but the difference was not significant.

The finding that subjects with photosensitive epilepsy had VEP with shorter latencies was contradicted a year later, in a study of 20 patients with generalised tonic clonic seizures and PPR in the EEG (Mervaala et al, 1985). The VEP of this group were found to have significantly longer latencies for the P_2 and N_3 components. However, this may be due to the improved methodology used and the fact that these patients were classified by EEG abnormality rather than clinical symptoms. The amplitude of the VEP was again found to be within normal limits.

In 1991, Donath investigated whether abnormalities in the VEP were related to the number of seizures the subject had. 72 patients were studied, with various types of epilepsy. The success of medication was divided into three groups. The first was compensated, in which the subject had 0-1 seizures per year; the second was sporadical with 2-5 seizures per year and the third was non-compensated, who had 6 or more seizures per year. The VEP was classified as abnormal if symmetrical or asymmetrical prolongations of the P_2 wave were found or if there were changes in the amplitude of the N_2 or P_2. The abnormal VEP findings were mainly in the non-compensated epileptic group (77%). 18.5% of the sporadical group showed abnormal VEP and only 4.4% of the compensated group showed

abnormalities. There were significantly higher numbers of abnormal VEP in the group with the greater frequency of epileptic seizures and a significantly greater number of normal VEP in cases with low frequency of epileptic seizures. This may, in part, explain the discrepancies in the literature, as little detail was given about the seizure frequencies of the subjects investigated. It also indicates that the abnormalities in the VEP, and hence the occipital cortex, are correlated with increased seizure frequency. This is strong support for the role of the occipital cortex in the generation of photosensitive seizures.

In 2000, Porciatti et al compared the amplitudes of the pattern reversal VEP in 11 subjects with photosensitive epilepsy and 12 control subjects. The stimulus was a black and white grating reversing at 4-10 Hz and 16-22 Hz. With reversal rates of 4-10 Hz the amplitude of the control subject VEP increased rapidly with increasing contrast and then saturated. At the same reversal rates the amplitude of the photosensitive VEP increased with increasing luminance contrast up to 100% contrast and showed no saturation. At the higher reversal rates (16-22 Hz) both the control and the photosensitive VEP showed similar increases in amplitude with increasing contrast and no saturation. The authors concluded that the contrast gain control of photosensitive subjects was impaired at low-medium temporal frequencies.

2.2.1.5. The effect of sodium valporate on the VEP

Herrick and Harding (1980) studied the flash visual evoked potential in 25 photosensitive subjects and found them to be significantly larger than in age and sex matched controls. 21 were recorded after control with sodium valporate. Treatment significantly decreased the amplitude of the P_2 though it remained significantly higher than in normals. 9 subjects were tested after the drug was withdrawn and the effects of the drug were still evident about one month after withdrawal. 8 of the patients studied by Fraught and Lee (1984) had poor seizure control and were treated with valporate. The latency of the P_2, which had previously been found to be significantly shorter than in normals, was increased in all 6 of the patients who improved with treatment by sodium valporate.

Sutherling et al (1980) repeated this finding that sodium valporate could normalise the abnormalities in the photosensitive VEP and decrease the overall response amplitude, but only in those patients with satisfactory control of clinical seizures. There was little change in the patients with poor control. The improvement of the VEP with valporate correlates better with clinical seizure control than with blood levels of the drug.

The above results suggest that sodium valporate acts to normalise the visual evoked potential rather than having specific effects. Harding et al (1985), who investigated the effects of sodium valporate on the VEP of 10 normal volunteers,

tested this theory. No significant differences were found in the latency or peak to peak amplitude of P_2 before or after treatment.

In summary, the abnormalities in the VEP of photosensitive subjects are associated with poor seizure control and are reduced when seizure control is improved. If the abnormalities in the VEP represent abnormal activity in the visual cortex then this finding is evidence for the role of the occipital cortex in photosensitive epilepsy.

2.3. Occipital spikes and the visual evoked potential

Eight of the patients studied by Hishikara et al (1967) showed occipital spikes in their visual evoked potentials. They found that the initial positive component of the spike corresponded to a positive component of the VEP and the negative spike to the latency of a negative component. The authors interpreted these findings as indicating that occipital spikes are simply unusually augmented components of the normal VEP and are similar to the abnormalities in the VEP that were discussed in the previous section.

Two years later, Broughton et al (1969) found that the small negative peak, which is sometimes recorded on the descending branch of P_2, was greater in amplitude in subjects with photosensitive epilepsy. In 4 out of 10 patients

studied by Panayiotopoulos et al (1970(a)), the latency of the negative occipital spike coincided with the latency of P_2 but only in one patient did it relate to the negative P_{2b} component. However, over half the patients seemed to have some relationship between the negative occipital spike and the positive P_2 wave of the VEP.

In 1972, Panayiotopoulos et al carried out a further investigation into occipital spikes. 38 patients with photosensitive epilepsy, 16 patients with epilepsy and abnormality to IPS and 18 normal subjects were studied. The latency of the negative spikes was about 106 msecs and the amplitude around 60-100 micro-volts. Occasionally the amplitude reached 150-200 microvolts. The second positive wave did not show constant latency. 33 out of the 38 photosensitive subjects showed occipital spikes preceding the PPR, as did 15 out of 16 of the patients with non-photosensitive epilepsy and abnormalities to IPS. No abnormality was evoked by IPS in the normal control group. 16 photosensitive subjects were examined in detail by Panayiotopoulous et al (1972). In 2 of the patients the occipital spikes seemed to relate to the negative wave of the triphasic P_2 and in one of these the component appeared to increase in amplitude with increasing flash rate gradually becoming the occipital spike (Figure 2.2).

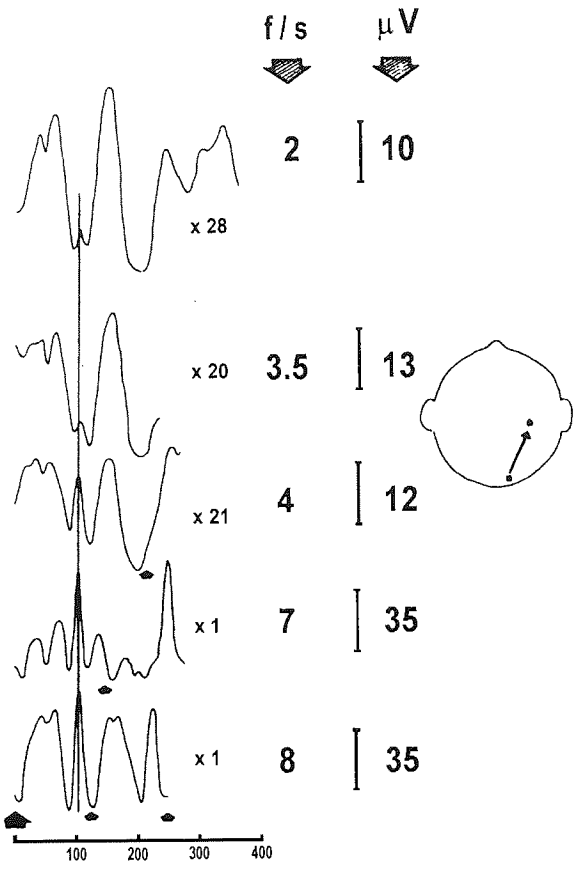


Figure 2.2. The development of an occipital spike from the P_{2b} component of the visual evoked potential. From Panaiotopoulos et al (1970(a)).

These results contradict Hishikawa et al (1967) for a number of possible reasons. Hishikawa et al stimulated with the eyes closed. The flash rates used were as high as 16 Hz so that the interval between flashes was shorter than the latency of the negative occipital spike. The latencies were compared to the mean for normal subjects rather than within the individual and as the range of latencies was wide the relationship between the occipital spike and the visual evoked potential may have been fortuitous.

There are three main observations that lead to the conclusion that the visual evoked potential and occipital spike are not related. First, there is no simple relationship between the components. Second, one patient was recorded on two separate occasions and showed occipital spikes only on one. This allowed direct comparisons to be made at the same flash rate and there was no relationship between the visual evoked potential and the occipital spike. Third, the visual evoked potential of normals did not show components comparable to those seen in photosensitives. This is investigated in chapter ten.

Sodium valporate has also been found to reduce the abnormalities in the VEP, so if occipital spikes were simply an augmented component then sodium valporate should also reduce them. The medication reduces seizures, PPR and abnormalities in the VEP but has no effect on occipital spikes. Even though the abnormalities in the VEP may indicate a role of the occipital cortex in the generation of seizure, occipital spikes may represent abnormal response unrelated to either the VEP or the PPR. One way to examine this is to use the specific characteristics of stimulation in an attempt to separate the responses into mediation via different visual pathways. These pathways will be discussed in more detail in the next chapter.

Chapter Three

The magnocellular and parvocellular systems

Two pathways are involved in the processing of visual information. Broadly speaking, the magnocellular pathway is involved in the processing of low spatial frequency, high temporal frequency, achromatic stimuli and is sensitive to low luminance contrast, saturating at low contrast. The parvocellular pathway is dominant in the processing of colour, high spatial frequencies and low temporal frequencies. It is less sensitive to luminance contrast, and shows a linear increase in activity as contrast is increased. The characteristics of the magnocellular and parvocellular pathways are discussed in more detail in each of the sections below.

Segregation of the pathways begins at the level of the retina, in the ganglion cells. The pathways are then thought to remain separate through the lateral geniculate nucleus (LGN), where they synapse in alternate layers. Much of the work discussed in this chapter involves recordings of the electrical activity of the retinal ganglion cells or from investigations of the function of the LGN to examine the differences between the pathways. The function of the LGN can be recorded in two ways. The electrical activity of the cells can be recorded directly or the visual function of the primate may be recorded after specific damage is made to the layers in which only one cell type synapse.

The differences between the response of the two cell types to changes in the stimulus parameters are discussed in the following sections, beginning with luminance contrast.

3.1. Luminance contrast

The magnocellular system responds at lower luminance contrasts than the parvocellular system. Magnocellular cells in the LGN of primates respond to contrast as low as 1% but similar parvocellular cells have higher contrast thresholds of above 12% (Hicks et al, 1983). Parvocellular ganglion cell activity in response to contrast modulations of 25% is weak, whereas magnocellular cells respond vigorously and the responses have opposite polarities depending on whether the cell is on or off centre (Kremers et al, 1993). Bernadete et al (1992) recorded parvocellular responses to contrasts as low as 4% but magnocellular cells had lower contrast thresholds of as low as 2%.

The magnocellular and parvocellular systems also show different contrast gains. Kaplan and Shapley (1986) recorded LGN cells. The magnitude of the response was plotted against the contrast of the stimulus and the slope of the graph used as a measure of the contrast gain of the recorded cell. In the magnocellular cells, the response increased rapidly with increasing contrast and saturated at about 8%, whereas in parvocellular cells the response increased gradually with increasing contrast and did not saturate at the highest contrast used (64%). The contrast gain of cells in the magnocellular layer was about ten times higher than

that of cells in the parvocellular layer. These differences could not be accounted for in terms of spatial frequency, as the optimum of the given cell used, or the drift rate, which was optimum for parvocellular cells and less than optimum for magnocellular (4 Hz). When coloured stimuli were used the parvocellular gains increased but remained much lower than those for the magnocellular cells.

The contrast needed to evoke 50% of the maximum response in LGN cells has also been used as a measure of contrast gain, as it avoids the effects of variable maximum firing rate. The magnocellular cells were found to reach 50% of their maximum rate at 3.5 times the background luminance and parvocellular cells at 5-10 times the background luminance. Magnocellular LGN cells therefore have much higher sensitivity to contrast (Hubel and Livingstone, 1990).

Retinal ganglion cells also show different contrast gains. Magnocellular cells show saturation at low luminance contrast but parvocellular cells did not (Yeh et al, 1995). Primate parvocellular ganglion cell responses have been shown to be linear up to about 50% luminance contrast, showing very little saturation between 50% and 100%. In comparison, magnocellular cells saturate at approximately 20% luminance contrast (Lee et al, 1994). The contrast gain of the magnocellular cells is always about 8 times that of the parvocellular cells whatever the temporal frequency of the stimulus (Lee et al, 1994). The linear response of parvocellular ganglion cells may represent a doubling in response impulses per second when contrast is doubled (Bernadette and Kaplan, 1997).

The magnocellular and parvocellular pathways can therefore be separated by their contrast threshold and contrast gain. The magnocellular pathway has lower contrast thresholds and higher contrast gain than the parvocellular.

3.2. Colour contrast

Approximately 90% of the parvocellular cells in the LGN layers are colour opponent (Livingstone and Hubel, 1988). The remaining 10% were originally thought to be a broadband classification of parvocellular cells. However, this has recently been disputed and it is now thought that the original lack of colour sensitivity may have been due to low lighting conditions during the classification. Under photic conditions cells show greater spectral sensitivity (Lee, 1996). Magnocellular cells were thought to sum cone input, losing the spectral sensitivity and therefore responding only to changes in luminance contrast (Livingstone and Hubel, 1988).

Parvocellular cells respond vigorously to colour and are likely to be the main pathway via which colour information is processed. In parvocellular LGN cells a wavelength can always be found which evokes a large sustained response. In magnocellular cells vigorous responses are similar over the whole spectrum. Parvocellular cells respond more strongly to coloured gratings than to those that vary only in luminance and respond differently to isoluminant gratings depending on their colour. Magnocellular cells respond scarcely to isoluminance or not at all (Hicks et al, 1983). Parvocellular ganglion cells show large sustained responses to chromatic modulation of red and green LED, which

reverse in phase depending on whether the cell is an on or off centre type (Kremers et al, 1993).

Behavioural studies in primates have also shown that the parvocellular pathway is dominant in colour processing. Primates can be trained to make saccades to one of eight stimuli, presented in a ring, which is different from the others. Ibotenic acid lesions can then be made, selectively, to either the magnocellular or the parvocellular layers of the LGN. These lesions are made so that they only affect a small area of the visual field. A comparison can then be made between the percentage of correct trials in the area of the visual field that is affected by the lesion, and the rest of the visual field. This ability of the animals to make saccades to a target stimulus, which was red, green or blue among yellow stimuli, has been investigated (Schiller et al, 1990). The ability was devastated in the area of the visual field affected by the parvocellular lesion but was unaffected in the area of the magnocellular lesion. In another behavioural study monkeys were trained to push buttons to say whether a red/green isoluminant grating was horizontal or vertical. Again, ibotenic lesions were made to the magnocellular or parvocellular layer of the LGN. With the parvocellular lesion there was a 4-fold loss in chromatic sensitivity but the magnocellular lesion had no effect (Merigan et al, 1991(a)). The sensitivity to colour that was still present after the lesion was attributed to the small lesion size.

More recent experimental work has found evidence that magnocellular cells, while much less sensitive to chromatic contrast, may still respond to isoluminant stimuli. Magnocellular ganglion cells have been recorded in response to

chromatic stimuli. The responses are weak and variable but there is often an increase in firing at the stimulus onset. No systematic differences have been noted between on- and off-centre cells (Kremers et al, 1993). When magnocellular cells were recorded in response to isoluminant red and green chromatic modulation, they were found to respond at twice the stimulation frequency. This effect was seen in both on- and off-centre cells, especially when the modulation frequency was under 20 Hz, and has been termed the frequency doubling effect (Yeh et al, 1995).

A novel apparent motion stimulus was designed in the form of a heterochromatic sign wave that reverses while moving. This results in an effect in which apparent movement in one direction has borders that are defined by signed chromatic contrast, i.e. the border is red on one side and green on the other, and there is apparent motion in the opposite direction that has borders defined by unsigned chromatic contrast, i.e. the border always differs in colour from one side to the other but the difference in colour is not consistent along its length. Human subjects viewed this stimulus while the luminance contrast was varied. The closer the stimulus was to isoluminance the more likely the subjects were to report motion in the unsigned direction. Achromatic stimuli with low luminance contrast were not detected in the unsigned direction so this must therefore be a colour rather than a low luminance effect (Dobkins and Albright, 1993). It has previously been noted that the quality of perceived motion is reduced at isoluminance but that some motion is still perceived. This is surprising as the magnocellular pathway is thought to be responsible for perceiving motion and it is supposed to be silenced at isoluminance. It appears that directionally sensitive

magnocellular cells may respond to motion which is defined by colour, even if they don't respond to colour per se.

In a later paper, directionally sensitive cortical neurones were recorded to the novel apparent motion stimulus and the preferred direction of motion determined. Again, at isoluminance or low luminance contrast, the preference is for the unsigned direction. The signed direction is also involved at high luminance contrast (Dobkins and Albright, 1994).

There are two theories as to how this could occur. The first is the use of unsigned chromatic contrast. In this theory chromatic differences define boundaries early in the visual system and motion neurones have access to the boundaries which are defined by the colour, even though information about the colours themselves is not available, i.e. the sign of the chromatic contrast is lost. The second theory is that of signed chromatic contrast in which the object colour per se determines motion correspondence. Response to signed cues are always greater than those to unsigned cues but in the environment signed and unsigned cues would normally occur in unison.

The frequency doubling effect supports the unsigned hypothesis as this effect occurs regardless of the polarity of the change. Recordings from on centre magnocellular cells have shown that, when non-isoluminant red-green stimuli are passed through the visual field, the firing rate increases when the brighter of the two colours enters the receptive field. However, when the red and the green have equal luminance many magnocellular cells respond with equal magnitude to each

chromatic change regardless of the direction of change (Dobkins and Albright, 1994). This leads to the frequency doubling effect.

The frequency doubling effect may be responsible for the ability to see motion that is only defined by luminance contrast. A second explanation is that the exact null point for magnocellular cells varies within the population and therefore the population as a whole is never truly silent. A third possibility is remains of the signed hypothesis where parvocellular cells project to the motion areas, carrying information about colour per se.

In spite of the recent findings, it is still thought that the majority of colour processing occurs via the parvocellular pathway and that the magnocellular can only respond in certain conditions and with much less differentiation of the detail of the stimulus. Responses that are generated via the parvocellular pathway should therefore be generated in response to colour contrast. Magnocellular responses would be expected to be absent or minimal in response to stimuli that vary only in colour contrast.

3.3. Spatial frequency

There are two different types of ganglion cells in the human retina, midget and parasol, that form two distinct clusters of size (Dacey and Peterson, 1992). When horseradish peroxidase is injected into the LGN it marks the anatomy of the cells that project to each layer. The parvocellular layers receive projections from type B cells, which have small cell bodies and the smallest dendritic fields.

The magnocellular layers receive projections from cells with large cell bodies and medium sized dendritic fields (Leventhal et al, 1981). These differences in the receptive fields of the magnocellular and parvocellular cells were thought to lead to large differences between the spatial frequencies that the different pathways were sensitive to. However, recent findings suggest that this might not be the case.

Recordings from LGN cells have found that the ability of parvocellular cells to resolve gratings is dependent on the cell type and on the colour of the grating. More surprisingly, the ability of magnocellular cells to resolve gratings was comparable to parvocellular cells (Hicks et al, 1983). It was suggested that the higher contrast sensitivity of the magnocellular cells may account for their ability to respond to fine gratings even though the receptive field is large. The dependence of parvocellular cells on colour also makes it hard to determine the ability of parvocellular cells to resolve fine gratings. Kaplan and Shapley (1986) recorded from retinal ganglion cells three year later and their results supported the theory that the higher contrast gain of the magnocellular cells is sufficient to account for the similar resolution of the cells, even though they have larger receptive fields.

Behavioural methods have also been used to investigate spatial frequency processing but the results are a little less conclusive than those from the physiological studies. One study (Merigan and Maunsell, 1990) recorded forced choice discriminations by monkeys after a lesion to the magnocellular layer of the LGN. The results showed that contrast sensitivity to very low spatial

frequencies and high temporal frequencies are dependent on the integrity of the magnocellular pathway but high contrast flicker and low temporal flicker are not. This suggests that there is a large overlap in the spatial sensitivity range with each pathway being more involved at one of the extremes.

A second study, in the same year (Schiller et al, 1990), contained two behavioural investigations into spatial frequency, both recording saccades to one of eight stimuli that was different. The contrast of one of eight checkerboards was varied and contrast sensitivity found to be reduced at all spatial frequencies in primates with parvocellular lesion. The deficit was worse at higher spatial frequencies and was very severe at 4.15 c/deg. The region of the visual field affected by magnocellular lesions showed very little difference in contrast sensitivity to that of the unaffected regions of the visual field. This indicates that the parvocellular cells are essential to the extremes of contrast sensitivity. However, it does not indicate that magnocellular cells do not respond to high frequencies, just that they do not respond to the same extent as parvocellular do. The second study investigated pattern discrimination where saccades were designated correct if they were to the target that had a different spatial frequency. Large deficits in this task were found with the parvocellular lesion but not with magnocellular (Schiller at al, 1990). However, this deficit could be due to the cognitive decision process involved and does not just indicate the ability to recognise the stimuli.

A study carried out a year later investigated acuity by making very small ibotenic acid lesions to the magnocellular or parvocellular pathway at a given

eccentricity. Monkeys were trained to press the right or left button, depending on whether the grating was horizontal or vertical for a given eccentricity. The highest spatial frequency that could be resolved was established at each eccentricity, before and after the lesions. Before the lesion acuity decreased with eccentricity but after the parvocellular lesion there was a dramatic decrease in acuity, which was restricted to the eccentricity affected. Magnocellular lesions had no effect on the maximum spatial frequency that could be resolved (Merigan et al, 1991(a)). This indicates that the parvocellular pathway mediates the upper limits of the spatial frequency range. However, the parvocellular pathway may also mediate the limits of contrast sensitivity at low spatial frequencies. There is a 4-fold decrease in the contrast sensitivity to static gratings of 2 cpd with parvocellular lesions but no difference was found with the magnocellular lesion. However, this result may have been affected by using a stationary rather than a moving stimulus and indeed, contrast sensitivity to the grating modulated at 10 Hz (1cpd), was reduced by 2-3 fold, with either a magnocellular or a parvocellular lesion. The parvocellular pathway may mediate detection at low temporal and high spatial frequencies, but the magnocellular pathway plays an increasingly important role in detection as temporal frequency is raised and spatial frequency is lowered.

3.4. Temporal frequency

The previous section discussed how magnocellular cells were traditionally thought to respond to low spatial and high temporal frequencies and that it is now thought that there is a large overlap in the spatio-temporal characteristics

(Merigan and Maunsell, 1993). However, there is still evidence that the magnocellular pathway is dominant over the parvocellular in detecting movement. Selective ibotenic acid lesions can be made to the layers of the LGN and monkeys trained to make saccades to one of eight LED that is flickering. There appears to be no deficit in this task, in the area of the visual field affected by parvocellular lesion but there were large deficits in the area which represents the magnocellular lesion (Schiller et al, 1990). Detection of gratings which vary in spatial and temporal frequency has been investigated in monkeys with ibotenic acid lesions, by training them to push buttons to indicate whether the grating has appeared on the left or the right. Parvocellular lesions lead to a 4 fold decrease in sensitivity to a 1cpd static grating but the magnocellular lesion have no effect. When a modulation grating was used (2 cpd) a 2-3-fold loss in sensitivity was found with either a magnocellular or a parvocellular lesion (Merigan et al, 1991(a)). This suggests two points: first, that the magnocellular pathway is only involved in low spatial frequency detection if temporal frequency is high; second, that the parvocellular pathway is also involved in the detection of moving stimuli. Primates with ibotenic acid lesions to the magnocellular layers have been trained to press buttons to indicate the presence of gratings drifting at 1, 5, and 20 Hz. There is little loss of contrast sensitivity to the drifting grating at 1 Hz, large deficits when it is drifting at 5 Hz and profound deficits when it is drifting at 20 Hz (Merigan et al, 1991(b)).

The effects of contrast on movement perception have also been investigated using forced choice discrimination by monkeys, after ibotenic acid lesions of the LGN layers. Flicker thresholds were measured at three contrast levels before and

after lesions to the magnocellular pathway. It was found that there was a decrease in the modulation sensitivity rather than a reduction of temporal resolution per se. If the contrast of the modulation was high the magnocellular lesion had little effect. High contrast flicker may well be mediated by either pathway (Merigan and Maunsell, 1990). Behavioural experiments recording saccades to stimuli that are different have revealed similar effects. Random dot arrays can be designed so that the task is either detecting an area that is moving or discrimination of an area that has different rate or direction of movement. The parvocellular lesions have no effect but the magnocellular produce strong deficits, which are worse at low contrast but still apparent at high contrast. It appears that though the parvocellular system is not necessary for this task, it can compensate slightly in the absence of the magnocellular system, but only if the modulation contrast is high (Schiller et al, 1990).

Speed and direction discrimination are also mediated via the magnocellular pathway but again the parvocellular pathway may be able to compensate at high contrast. In primates, with ibotenic acid lesions to the magnocellular pathways, making forced choice discriminations, the speed threshold was reduced markedly at 20% contrast, somewhat at 40% contrast but there was no change at 80% (Merigan et al, 1991(b)). The magnocellular pathway appears to affect visibility of moving stimuli, particularly when they have low spatial frequency. However, at high contrasts deficits in the magnocellular pathway have no effect on the ability to detect speed or direction. The parvocellular pathway can detect speed and direction but visibility is poor for some spatio-temporal stimuli.

The optimal drift frequencies have also been established in both pathways. LGN cells have been recorded in primates in response to sine wave gratings. Both parvocellular and magnocellular cells respond maximally at drift rates of 10-20 Hz. Parvocellular cells respond at temporal frequencies lower than 1 Hz, magnocellular cells do not. The phasic nature of magnocellular cells would predict that they would not respond well to sinusoidal modulation of luminance over the receptive field if the temporal modulation was low (Hicks et al, 1983).

Investigations into the effects of overall retinal illumination have shown there is no segregation of the magnocellular and parvocellular pathways by optimal temporal frequency at high retinal illumination. For both the magnocellular and the parvocellular pathway the optimum decreases as retinal illumination decreases. The frequency at which the peak of the curve occurs does not separate the pathways, but magnocellular cells are always more responsive at their maximum than parvocellular at theirs (Purpura et al, 1990). Measurements of LGN cells have also shown that the response curves to varying temporal frequency are similar in shape between the pathways and in both the optimum spatial frequency is approximately 20 Hz (Kremers et al, 1997). High contrast flicker may well be mediated by either pathway as both are optimal at 10-20 Hz and extend well above 40 Hz (Merigan and Maunsell, 1990).

Investigations of the human visual system have shown similar results to those from animal investigations. People can resolve brightness alterations at much faster rates than isoluminant colour alterations suggesting that the parvocellular pathway colour processing has a lower maximum temporal frequency than the

magnocellular. Movement perception is impaired at isoluminance and if the spatial frequency is high (parvocellular function) but not if luminance contrast is low (magnocellular function) (Livingstone and Hubel, 1988). When luminance is modulated in time, sensitivity is maximal at approximately 10 Hz. In comparison, chromatic modulation sensitivity is maximal at frequencies lower than 5 Hz (Valberg and Lee, 1992).

Psychophysical stimuli have been developed which are uniform fields that are modulated only in time. This allows the effects of temporal frequency to be investigated without the effects of spatial frequency. Contrast discrimination is measured by the incremental threshold, the smallest increment in contrast required to differentiate one stimulus (pedestal plus incremental contrast) from another (pedestal contrast only). At high temporal frequencies contrast discrimination approximately follows Weber's law. At low temporal frequencies it approximately follows the square root law. Neural stimulation of magnocellular and parvocellular cells produces two distinct incremental threshold functions which are similar to psychophysical results at the highest and lowest temporal frequencies respectively (Chen et al, 1996). However, overall the magnocellular pathway is still dominant in motion perception.
Further investigations have used stimuli that differ from the background in three ways, in colour only or in low or high levels of luminance contrast. Presentation of flashing distracters in one part of the visual field impairs identification of the temporal structure of a simultaneously presented stimulus elsewhere in the visual field. A single flash may be perceived as a flickering double flash if that is the temporal structure of the distracter. Isoluminant distracters were always

ineffective and the low contrast target was never distractible. One explanation for this is that the low contrast stimulus is unaffected as the magnocellular pathway processes it and the colour ineffective as it doesn't stimulate the magnocellular pathway. The magnocellular pathway can therefore influence the perception of temporal structure encoded by parvocellular but not vice versa. This is further evidence that the magnocellular pathway is dominant over the parvocellular in motion processing (Leonards and Singer, 1997).

In summary, the magnocellular pathway is dominant over the parvocellular pathway in the perception of movement and extends over a greater range of frequencies and contrast modulations. However, the optimum temporal frequencies are similar between the pathways.

3.5. Monocular stimulation

The LGN has six layers, four dorsal small cell layers in which the parvocellular cell synapse and two ventral large cell layers in which the magnocellular cells synapse. Each eye projects to alternate layers to synapse in only two of the parvocellular layers and only one of the magnocellular (Livingstone and Hubel, 1988). As the information from each eye is still segregated at this level the effects of the integrated inputs cannot be investigated. However, there is some evidence that the parvocellular pathway mediates binocular processes, such as stereopsis (depth vision). This remains highly controversial but some of the evidence is discussed below.

Monkeys with ibotenic acid lesions were trained to make saccades to one of eight stimuli that was different from the others. Two experimental conditions were examined. The first was a random dot stereogram, which could be organised so that either one area only appeared to be sunken or raised or that one out of the eight stimuli had a greater depth disparity than the others. The second experimental condition was a low spatial frequency stereogram. In the first condition parvocellular lesions produced large deficits, especially with small depth disparities (6.6 mins). At large disparities, stereopsis was poor but above chance, so the magnocellular pathway is probably involved to some extent, even though the magnocellular lesion had no effect itself. The sensitivity to the low spatial frequency stereogram was also unaffected by the magnocellular lesion. This indicates that even at low spatial frequencies, the parvocellular pathway mediates stereopsis. In summary, it appears that the parvocellular system is essential for high frequency stereopsis. The magnocellular pathway can compensate slightly at low spatial frequencies but is not necessary at any spatial frequency (Schiller et al, 1990). A second paper using the same methods confirmed the results that stereopsis was only affected by lesions to the parvocellular pathway and then only at high spatial frequencies and small disparities (Schiller et al, 1991).

Further evidence for the parvocellular processing in stereopsis can be found in investigations using isoluminant stimuli. Perception of depth in random dot stereograms, defined only by colour, is dependent on information about the direction of colour contrast, not just on the presence of chromatic borders. As chromatic information is at least as important as luminance information, the

parvocellular pathway must be involved (Schiller et al, 1992). However, if the disparities are large, depth can be perceived down to luminance contrasts as low as 10% suggesting that the magnocellular pathway is also involved (Li and Guo, 1995).

Response generated via the parvocellular pathway would therefore be expected to be decrease in monocular occlusion to an equal or possibly greater extent than those generated via the magnocellular pathway.

3.6. Eccentricity

Magnocellular and parvocellular cells have different anatomy, which varies with eccentricity across the retina. Injections of horseradish peroxidase into LGN cells have shown that the cells that project to the parvocellular cell layers have small cell bodies and the smallest dendritic fields. Cells that project to the magnocellular layers have large cell bodies and medium sized dendritic fields (Dacey and Peterson, 1992). The population size of the two cell types is also different. Parvocellular cells are estimated to be about 8-10 times more numerous than magnocellular cells (Valberg and Lee, 1992).

Human parvocellular ganglion cells and magnocellular ganglion cells form two distinct clusters of size that both decrease in size with decreasing distance from the fovea. Parvocellular cells show a greater decrease in field size than magnocellular cells so that the ratio decreases from approximately 10:1 at 3 degrees eccentricity to about 3:1 at 50 degrees eccentricity (Dacey and Peterson,

1992). Receptive field sizes and sensitivities can be calculated from the contrast sensitivity functions of cell, using the Difference of Gaussians method (DOG). Acuity is related to receptive field centre size whereas peak sensitivity is thought to be related to both surround and centre size. With a low surround size / centre size ratio the cell is relatively low pass. As the ratio increases the roll off becomes progressively less until the cell becomes narrow band pass when the ratio is greater than one (i.e. the surround is larger than the centre). In one paper (Irvin et al, 1993) both parvocellular and magnocellular centre sizes were found to increase with increased retinal eccentricity. Parvocellular surround size was also found to increase as a function of eccentricity and hence the ratio of centre to surround size remains relatively constant. In magnocellular cells, however, the surround size is independent of eccentricity so as centre size increases the average surround size / centre size ratio increases as a function of eccentricity, which would lead to the cell becoming more low pass. However, a second paper (Croner and Kaplan, 1995) which used the same methods found no systematic variation in the ratio across the retina.

In summary, although the relative numbers of magnocellular cells increase with increasing eccentricity, the pathways show similar characteristics between central and peripheral regions.

The following chapters investigate the effects of various stimulus parameters on the probability of occipital spikes and PPR. The findings are then compared to the characteristics of the two pathways to examine which responses are generated

by each pathway and whether the occipital spikes and PPR are generated by the same pathway.

Chapter Four

The role of luminance contrast in photosensitive epilepsy

Abnormal discharges have been investigated in dark-adapted subjects. The duration of the abnormal discharge increases when luminance is increased (Chatrian et al, 1970). The luminance contrast of a pattern is the difference between the highest and lowest luminance.

Early investigations into the effects of luminance contrast on the probability of evoking abnormal responses used patterns printed onto transparencies and the luminance of the background behind them was reduced to decrease the contrast. Using this method, Chatrian et al (1970) found that the lower the luminance contrast the less epileptogenic the pattern became. This relationship may not, however, be linear, as the probability of a PPR in some individuals increases rapidly with increasing contrast up to 30%, when it saturates. Although group data may appear to have a linear relationship with contrast, this may mask non-linear effects of individuals (Wilkins, 1995). Paroxysmal activity is elicited at lower contrasts if the visual angle, which the pattern subtends, is increased, suggesting that there is an additive effect between the firing rate of the neurones and the number of cells stimulated (Wilkins et al, 1980).

Soso et al (1980 (a)) studied two subjects. They found that when very low-contrast patterns were presented, the activation was occipital and appeared to spread anteriorly as contrast increased. This suggests that discharges localised to the occipital cortex (such as occipital spikes) may be produced at lower contrasts than generalised PPR. This result is interesting as it indicates that the two responses may have different dependence on contrast and therefore that clinical protocols that are designed for detecting one type of response are not necessarily ideal for detecting the other.

In chapter three the literature relating to the effects of varying luminance contrast on the response characteristics of the two visual pathways was discussed. As the two pathways can show different response characteristics it would be interesting to see how their responses compared to those of the two types of abnormal response to see if any comparisons can be made. If different pathways generate the two response types then the assumption that they are related is not valid.

Two studies were carried out. The first was a pilot study: to investigate whether any differences in the contrast thresholds of the two responses could be established. The second study investigated differences in contrast gain in more detail.

4.1. Experiment one

4.1.1. Method

4.1.1.1. Participants

Participants were excluded from this study if the abnormalities recorded were too inconsistent to record a contrast threshold. Nine participants, three male and six female, were consistent and were investigated in this study, selected from the Aston University clinical neurophysiology database. The participants were selected on the basis that they had previously shown clear PPR or OS to the clinical pattern stimulation protocol. The participants ranged from 17-35 years of age and the mean participant age was 27 years. The basic record was within normal limits for eight participants and for the two participants where abnormality was seen in the basic EEG recording, the spontaneous abnormality was sufficiently different in distribution to that evoked by stimulation, that the experimenter could confidently distinguish between them. All but one of the participants had a history of seizures. The other was diagnosed as photosensitive after his sister began to experience photosensitive seizures. Six of the participants were taking anti-epileptic medication. Four were taking sodium valporate, one carmamzepine and one lamotrigine.

4.1.1.2. Stimulus

The patterns were generated by an SC Electronics T22 gratings generator and displayed on a Philips television with a 50 Hz frame rate and a mean luminance 190 cd/m^2. The television was viewed from a distance of 1.5 metres and subtended 18 degrees horizontal by 14 degrees vertical of the subjects' visual

angle. The luminance of the stimulus was measured via a Minolta LS-110 spot photometer from a distance of 1.5 metres. Contrast was calculated using the equation below.

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

Where Lmax is the maximum luminance of the stimulus and Lmin is the minimum luminance of the stimulus.

4.1.1.3. Procedure

The participants viewed the stimulus from a distance of 1.5 metres and were instructed to fixate on a central point. The Aston University clinical pattern testing protocol was carried out to establish the most provocative pattern stimulation. Vertical square-wave gratings, reversing at 1 Hz, were presented for 10 seconds, 5 with the eyes open and 5 with the eyes closed. The spatial frequencies of the gratings were 0.5 cpd, 2 cpd, 3 cpd and 6 cpd. If at any time during any of the stimulation procedures a generalised abnormal response was recorded the pattern was removed from the screen and the participant rested for a period of at least 10 seconds. Sine-wave stationary gratings, with the same spatial frequencies, were then presented. The grating that provoked the most consistent, high amplitude response was then used for the contrast testing protocol. During the contrast testing procedure, the test grating was presented for 10 seconds, 5 seconds with the eyes open and 5 seconds with the eyes closed. If an abnormal response was recorded then the contrast of the grating was reduced in each presentation until the response was no longer present. The contrast was

increased to ensure that the response was still present, and decreased below the threshold value to ensure the response was absent, a number of times until a consistent threshold had been recorded.

4.1.2. Results

Of the 8 participants, 5 participants showed PPR only and 2 showed occipital spikes only in responses to the pattern stimulation. The remaining participants was tested twice during removal of medication and showed only occipital spikes in one session and only PPR in the other.

The results were examined to investigate whether there were any differences between the groups other response type. An independent samples t-test was carried out on the participant's ages and Fisher's exact probability tests on the other variables. There was no significant difference between the group showing PPR and those showing occipital spikes with respect to age (t=0.397; p=0.702)(95%CI=-8.83-12.49), sex (p=0.548), whether the participants were taking anti-epileptic medication (p=0.548), whether the participants had a history of seizures (p=0.400) or whether the resting EEG that was recorded was within normal limits (p=0.167). There was a high probability of abnormal response in both participants groups when the stimulus was high in contrast and a low probability when the contrast was low. Occipital spikes were recorded in response to lower contrasts than PPR. The lowest contrast at which the abnormality was consistently evoked was recorded as the contrast threshold for

each participant. The mean contrast threshold for the participants showing occipital spikes (23.2%) was lower than that for PPR (36.8%), as is illustrated in Figure 4.1.

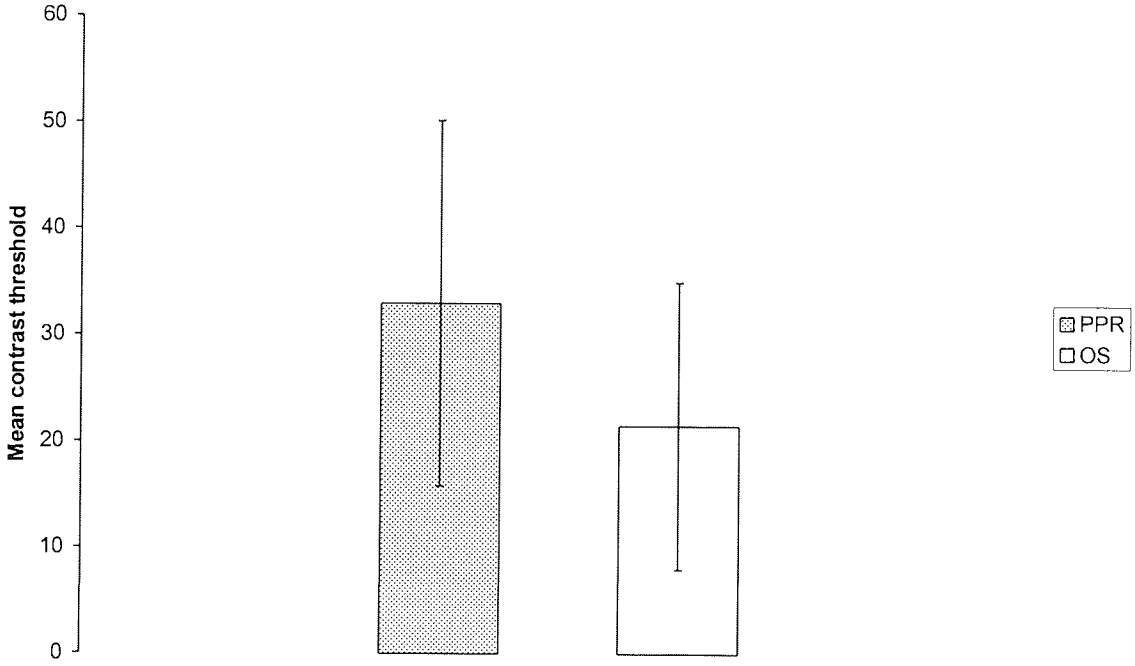


Figure 4.1. The difference in luminance contrast thresholds for photoparoxysmal response and occipital spikes in experiment one. Mean thresholds and standard deviation are illustrated.

As the data was a mixture of a between subjects and a within subjects design, no further analysis was carried out. However, the study quickly gave an indication that the response characteristics of the two abnormalities to luminance contrast were not similar. The data was plotted to examine if there were any differences in the two populations' response to contrast over the whole range of contrasts. The

number of participants showing each response type at each contrast value was calculated and is shown in Figure 4.2.

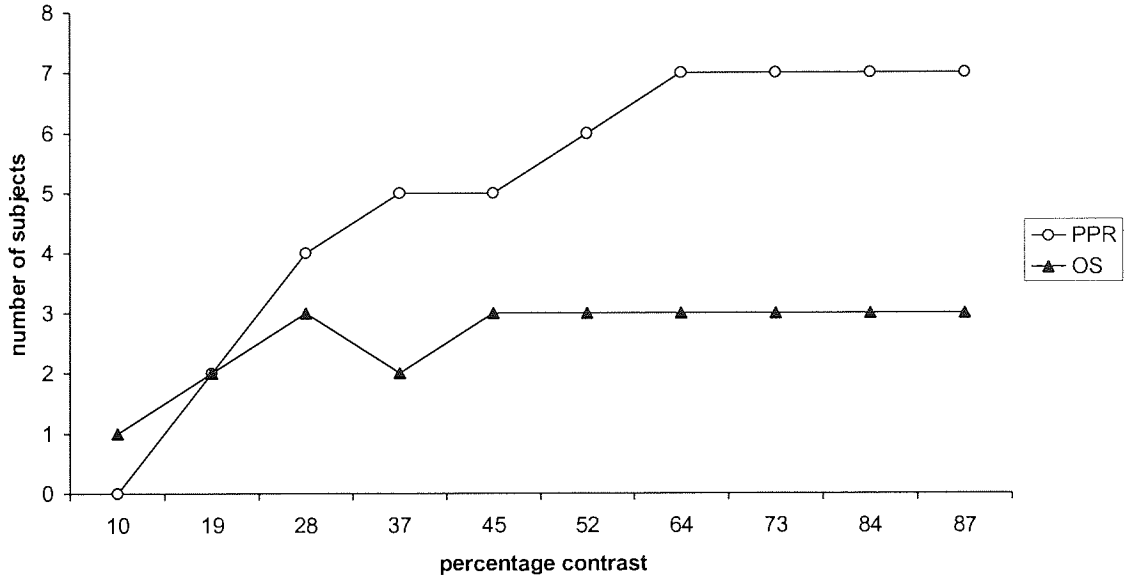


Figure 4.2. The number of subjects showing photoparoxysmal response or occipital spikes to a given percentage contrast in experiment one

This graph suggests that the relationship between contrast and the proportion of participants showing PPR responses is linear whereas the probability of occipital spikes saturates at relatively low contrast levels of approximately 30%.

4.2. Experiment two

The results from experiment one showed that occipital spikes and PPR show difference relationships with luminance contrast, as occipital spikes have lower contrast thresholds and saturate at lower contrasts. A second study was therefore carried out, with more rigorous control over the experimental conditions. There are a number of problems with the experimental design of the previous study, which are addressed in experiment two. First, the experiment was a mixture of a between subjects and a within subjects design and therefore no statistical analysis was possible. Second, the method of experiment one was designed to find contrast thresholds rather than examine the responses over a range of contrasts. Experiment two was designed to investigate the whole range by randomising the presentation of several different contrast levels. This had two advantages: the reduction of order effects from fatigue and standardisation of the stimulus, so that it varied in luminance contrast within subjects, but not in spatial frequency or in luminance modulation type (i.e. sine-wave or square-wave) between the subjects.

4.2.1. Method

4.2.1.1. Participants

15 participants, 5 male and 10 female, were investigated in this study. The age range of the participants was between 8 and 45 years and the mean participants age was 29 years. The basic record was within normal limits for 13 participants,

and for the two participants where abnormality was seen in the basic EEG recording, the spontaneous abnormality was sufficiently different in distribution to that evoked by stimulation that the experimenter could confidently distinguish between them. All but two of the participants had a history of seizures. In the two participants with no history of seizures both were photosensitive and one was the brother, one the daughter of patients with photosensitive epilepsy within the unit. All participants were selected on the basis that they showed classic occipital spikes or PPR but not both and that the abnormalities evoked were consistent over the time required for the test period. A response was classified as consistent if the change in amplitude and time of onset was no more than 20%. The responses must have a similar form and there must be no change in the areas of the cortex from which the response is recorded. Twelve of the participants were taking anti-epileptic medication. Ten were taking sodium valporate, two carbamazepine. The remaining three subjects were not taking anti-epileptic medication.

4.2.1.2. Stimulus

The patterns were generated by an SC Electronics T22 gratings generator and displayed on a Philips television with a 50 Hz frame rate and a mean luminance 190 cd/m^2. The television was viewed from a distance of 1.5 metres and subtended 18 degrees horizontal by 14 degrees vertical of the subjects' visual angle. The luminance of the stimulus was measured via a Minolta LS-110 spot photometer from a distance of 1.5 metres. Contrast was calculated using the equation below.

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

Where Lmax is the maximum luminance of the stimulus and Lmin is the minimum luminance.

The stimulus was standardised as 3 pd square reversing wave, for all subjects.

4.2.1.3. Procedure

The participants viewed the stimulus, as in experiment one, and were asked to fixate on a central point. The stimulus was again presented for 10 seconds, 5 with the eyes open and 5 with them closed. The contrast of the stimulus was varied in the following sequence: 5, 20, 50, 15, 30, 70,10, 60, 40, 80%. The sequence allowed the contrast to be presented in a pseudo-random manner while allowing rapid changes at the stimulus generator. In half the participants the sequence was presented in the reverse order. The clinical contrast (87%) was presented before and after the test sequence as a second control to ensure that the response was still present at the end of the testing. If at any time during the testing a fully generalised response was recorded the stimulus was immediately removed and the participants rested for at least 10 seconds.

4.2.2. Results

Five of the participants showed occipital spikes is response to the stimulation and 10 showed PPR. The results were examined to investigate whether there were any differences between the groups other response type. An independent samples t-test was carried out on the participant's ages and Fisher's exact probability tests

on the other variables. There was no significant difference between the group showing PPR and those showing occipital spikes with respect to age (t=0.597; p=0.561) (95%CI=-7.60-13.40), sex (p=0.434), whether the participants were taking anti-epileptic medication (p=0.264), whether the participants had a history of seizures (p=0.571) or whether the resting EEG that was recorded was within normal limits (p=0.571). The probability of both PPR and OS was high at high contrast and low at low contrast. The mean thresholds for each group were calculated as in experiment one and are plotted in Figure 4.3. Again, the mean contrast threshold for the participants showing occipital spikes (16.0%) was lower than that for participants showing PPR (42.0%)

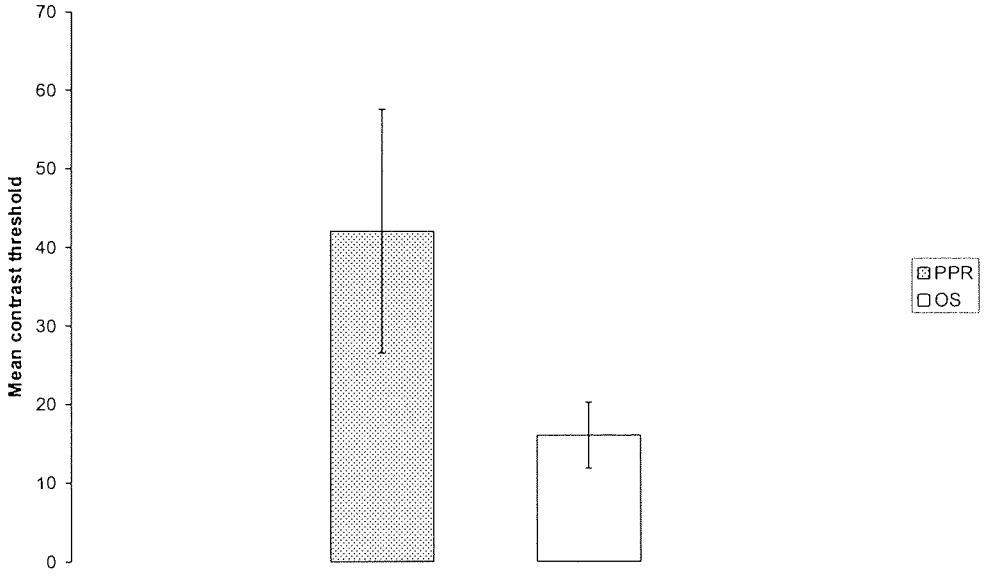


Figure 4.3. The difference in luminance contrast thresholds for photoparoxysmal response and occipital spikes in experiment two. Mean and standard deviation are illustrated.

From the graph it can be seen that the contrast thresholds for the PPR group are on average higher than those for the occipital spike group. This difference was found to be significant ($t = -4.96$, $p < 0.00$). The data was then plotted to examine if there were any differences in the response characteristics over the whole range of contrasts. The number of participants sensitive to each contrast was plotted and is shown in Figure 4.4.

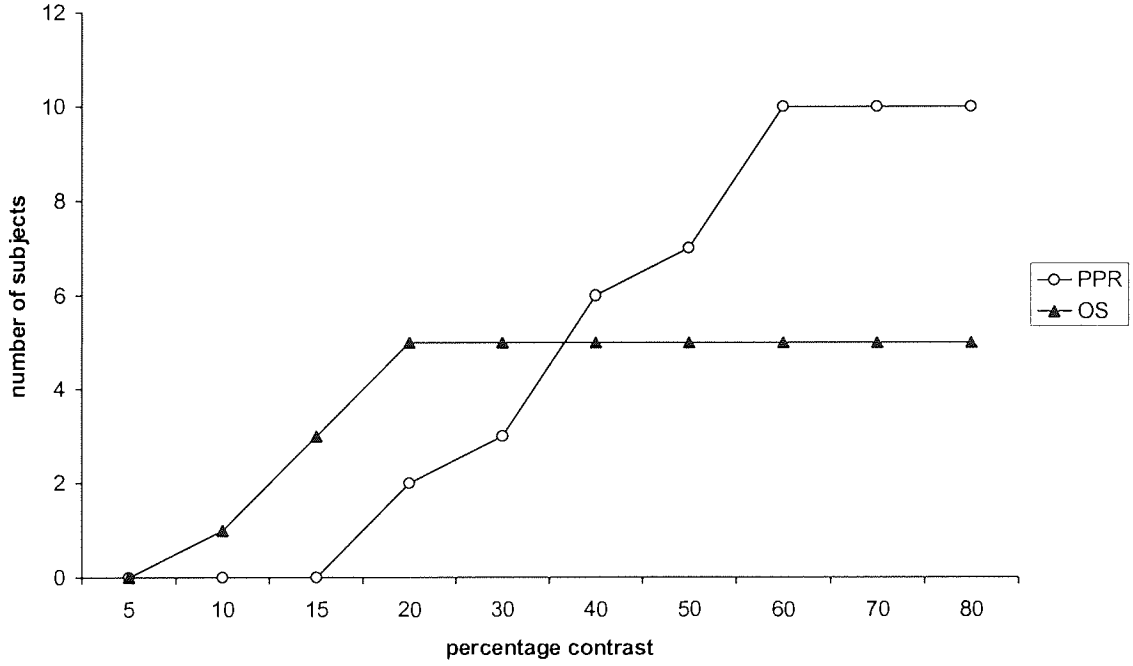


Figure 4.4. The number of subjects showing photoparoxsmal response or occipital spikes to a given percentage contrast in experiment two.

This graph confirms the previous result that the relationship between contrast and the proportion of participants showing PPR responses is linear, up to

approximately 60% contrast, whereas the probability of occipital spikes saturates at relatively low levels, approximately 20% contrast.

4.3. Discussion

The results of the two experiments show two main features. First, the mean contrast threshold for occipital spikes was lower than that for PPR. This result appears to quantify the observation of Soso et al (1980(a)) that occipital abnormalities are produced by low contrast patterns and that the discharge appears to spread forward at high contrast. However, this apparent spread may be an illusion created by the different contrast properties of two separate responses.

The second feature of the results is that the probability of provoking occipital spikes saturates at low contrast values (20%), while the probability of a PPR appears to increase linearly with increasing contrast up to high levels (60%), as was mentioned in the introduction.

Wilkins (1995) found that, in group data, the relationship between PPR and contrast may appear linear but found that in some individuals the probability increased rapidly to 30% and then saturated. It may therefore be that the relationship between PPR and contrast is not in fact linear but that individual

differences in the contrast saturation point are masked when the data from several subjects is combined. However, this does not explain the differences found between the contrast thresholds.

A second explanation for both the decreased threshold and the lower saturation point is the effects of medication on PPR and OS. As mentioned earlier, one of the differences between occipital spikes and PPR is the action of the anti-epileptic drug sodium valporate, which has been found to be very effective at reducing PPR but to have little or no effect on occipital spikes. 10 out of the 15 participants in experiment two were medicated with sodium valporate and the increased sensitivity to contrast in the occipital spike group could therefore be a result of less effective control by the medication.

A third explanation for the differences in the response characteristics of the two abnormal responses is that they are mediated via different pathways. The literature relating to the luminance contrast response characteristics was described in chapter three. Magnocellular cells respond to much lower contrast than parvocellular cells. The fact that occipital spikes are still provoked at very low contrasts may therefore indicate that they are mediated by the magnocellular system. The contrasts discussed in chapter three are much lower than those in the experimental results but they are the thresholds at which a response can be recorded from the cell. The experimental results represent a higher contrast value

at which the system becomes active above a higher threshold to produce an abnormal response.

A second characteristic of the contrast response is the rate at which they increase with increasing contrast; the contrast gain of the response. If the response increases rapidly with increasing contrast above threshold then it will reach the threshold for abnormality at lower contrasts. Both the ganglion cells and the LGN cells of the magnocellular pathway have been shown to have much greater contrast gain than those of the parvocellular cells. This could explain both the lower contrast threshold for occipital spikes and the differences in the saturation points.

Both occipital spikes and the magnocellular pathway show rapid increases with increased luminance contrast but which saturate at low values. The response characteristics of the PPR, however, mimic the characteristics of the parvocellular system, showing a linear increase with increasing contrast and very little saturation of the response.

The linear response characteristics of the PPR may be due to the variability between the subjects. However, this cannot account for the differences in the contrast threshold, which may be due to occipital spikes being mediated by the magnocellular pathway, which has lower thresholds to contrast and higher contrast gain. Alternatively, we cannot, at present, rule out the explanation that

the effect is due to the fact that the occipital spikes are relatively less affected by medicating with sodium valporate, compared to PPR.

Clinically, the most important finding is that in order to detect PPR the contrast of patterns must be kept high and that the higher the contrast of the patterns shown on the television the higher the risk of evoking PPR and hence seizures. Contrast levels should therefore be specified in ITC television guidelines. However, occipital spikes are still evoked at low contrast and those individuals who experience unpleasant subjective sensations while they are recorded should avoid even low contrast stimuli. All individuals with occipital spikes should be cautious, as we have not yet discounted the possibility that occipital spikes represent a focus from which seizure activity may spread.

In conclusion, the response characteristics of OS are similar to those of the magnocellular pathway and those of PPR to the parvocellular pathway. However, there are several other explanations for the difference in the response characteristics of the two responses, which cannot at this point be discounted.

Chapter Five

The role of colour contrast in photosensitive epilepsy

The effect of colour on the probability of generating abnormal responses has been investigated. Much of this work centres on examining whether specific wavelengths, or colours, of light are more provocative than white light and whether stimulation with isoluminant grating, varying only in colour contrast, can produce abnormal responses.

Many of the earlier studies investigating the effects of colour on the response to IPS failed to compensate for the changes in luminance that occur when filters are placed in front of the photostimulator. When luminance changes were compensated for, some authors found that red stimulation was significantly more provocative then white (Carterette and Symmes, 1952; Takahasi and Tsukahara, 1976). Other author's findings were contradictory. Harding and Jeavons (1994) found that the range of sensitivity was not consistently increased when red light was used to stimulate. Green light was also found to produce sensitivity ranges that were the most similar to those in response to stimulation with white light. The sensitivity ranges produced by stimulation with blue light are significantly lower than those with white light (Harding and Jeavons, 1994).

The above contradiction was, in part, explained by the recognition that the different authors used different wavelengths of red filters. Information about the colour properties of the environment is transmitted via inhibitory and excitatory receptive fields. Red and green light stimulate opponent cells in excitatory or inhibitory arrangements. The visual system of the eye contains three cone types, sensitive to long, medium and short wavelengths of light. Low wavelength light is in the blue spectrum, middle wavelength light is in the green and long wavelength light is in the red spectrum, though there is overlap between the regions (Figure 5.1). However, very long wavelength light stimulates only the red cones and not the blue or green.

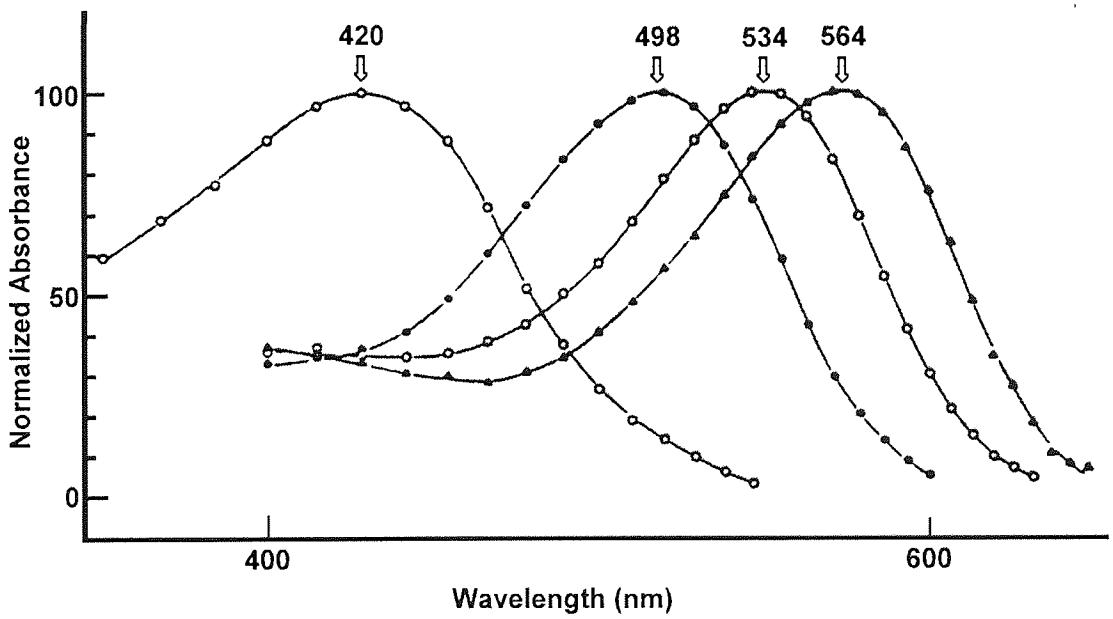


Figure 5.1. The mean absorbance spectra of the outer segments of the four classes of human photoreceptors, rods and the three cone types. From Bowmaker and Dartnall (1980).

Takahashi and Tsukahara (1976) used a deep red filter (long wavelength light) that stimulated the red cones with very little stimulation of the other cone types in the retina. Hence, they may have avoided inhibitory effects.

The effects of stimulating one cone type without its opponent colour were investigated using a technique known as silent substitution, where the intensities of red and green light are altered so that flicker is only detectable by one cone type (Binnie et al, 1984). A stimulus is presented which alternates between the two colours and stimulates both cone types. The light can be adjusted by a deutranope, with reduced sensitivity to green wavelengths of light, until they no longer perceive flicker. In a subject with normal colour vision only the green cones will be stimulated by this flicker, as the red cones will be equally stimulated by the red and green light, resulting in an impression of steady illumination. A combination that only stimulates the red cones can also be achieved via adjustment by a protonope, with reduced sensitivity to red wavelengths of light. Under these conditions both the red and green light are significantly more provocative than the white light. This suggests that it is not the wavelength of light itself that is more provocative than white light, but simply that when only one type of cone is stimulated the probability of abnormal responses increases. Hence, red filters should not be used in routine EEG photic stimulation because this will not render the stimulus more provocative and will simply reduce the intensity of stimulation.

In 1995(b), Takahasi et al found that, in subjects with normal colour vision, the only wavelengths essential for epileptogenesis were 600-720 nm, which are the wavelengths that stimulate red cones only. However, if a photosensitive subject has deutronomaly (reduced sensitivity to green) they are sensitive to shorter wavelengths than trichromat subjects and show responses to 550-700 nm (Takahasi et al, 1995 (b)). This result is further evidence that single-cone stimulation is very provocative, as the shorter wavelengths would not have antagonism in a subject with reduced sensitivity of the green cones.

In contrast to the previous results, good correlation between the wavelength of light used to stimulate and the severity of responses has been reported (West and Penisten, 1996) suggesting that the wavelength itself may influence epileptogenicity. However, this study used a single subject and the EEG data showed no correlation with wavelength. The correlation was, in fact, found between the subject's own subjective rating of the intensity of his absence seizures and the wavelength of the light. As the subject was aware that red light was expected to be more epileptogenic, this paper does not provide strong evidence against the single cone stimulation theory.

Yellow and orange gratings have been found to be significantly less epileptogenic than black, red, green or blue (Chatrian et al, 1970). However, as the authors stated, the differences due to wavelength and those that were due to differences in luminance were not separated in this study. In two studies which stimulated

photosensitive subjects with isoluminant red/green gratings, patients were not sensitive to patterns which varied only in colour contrast and not in brightness (Wilkins et al, 1975 (a); Wilkins et al, 1979(b)). Again, this indicates that colour is not epileptogenic if the opponent colour is present.

A dramatic illustration of how stimulating single cone groups may provoke seizures occurred in Japan recently, when 685 Japanese children and adults had seizures to the pocket monsters cartoon. On studying the tape it appeared that the provocative sequence might be a sequence of red and blue flashes alternating at 12 cycles per second. The effect of this sequence on photosensitive subjects is investigated in the first experiment in this chapter.

5.1. Experiment one

5.1.1. Method

5.1.1.1. Participants

Eight participants were investigated in this study, two male and six female, selected from the Aston University clinical neurophysiology database. The age range of the participants was between 11 and 37 years and the mean age was 27 years. The basic record was within normal limits for all participants. All but three of the participants had a history of seizures, the others being diagnosed as photosensitive after being tested when family members were identified as having

photosensitive epilepsy. Six of the participants were taking sodium valporate. The remaining two were not taking any anti-epileptic medication.

5.1.1.2. Stimulus

The stimulus was a sequence of the cartoon that had provoked the seizures in Japan. The sequence consisted of a series of reversals between red and blue frames alternating at 12 cycles per second. The luminance modulation was between the red frames, which have a luminance of 45.6 cd/m^2, and the blue, which have a higher luminance at 70.2 cd/m^2. Spectral analysis showed that the red frames have two sharp peaks at 625 and 704 nm and that the blue frames have a single peak at 452 nm. In the second condition the colour contrast was removed and the luminance modulation was equal to that in the colour condition. This was termed the luminance only condition. The sequence was presented on the 50 Hz television set which was described in detail in chapter 4.

5.1.1.3. Procedure

The participants viewed the television from a distance of 1.5 metres and the sequence was presented in an ABBA design between the luminance only and the coloured condition. The stimulus was removed immediately if any of the participants produced a fully generalised response. The response were noted and the results analysed using the McNemar test of change.

5.1.2. Results

Seven out of the eight participants showed PPR or degraded PPR to the chromatic stimulus and none to the luminance only condition. None of the eight

participants showed occipital spikes to either the chromatic or the luminance only conditions. The results showed that the chromatic condition was significantly more likely ($p=0.0156$) to provoke abnormalities than the monochromatic condition, even though the small participants numbers make the test stricter.

5.1.3. Discussion

When the stimulus was coloured it was significantly more provocative than the luminance only condition, even though the luminance modulation between the frames was the same in the two conditions. This indicates that the provocative nature of the stimulus must, at least in part, be due to the wavelength alternation between the frames.

As mentioned earlier, the blue frames of the cartoon sequence are maximal at 452 nm. Low wavelength light is in the blue spectrum, middle wavelength light is in the green and long wavelength is in the red spectrum over the visible spectrum. Red and green light stimulates opponent cells in excitatory or inhibitory arrangements. Very long wavelength light stimulates only the red cones and not the blue or the green. The wavelength of the blue frames stimulates all three cone types and therefore activates both excitatory and inhibitory mechanisms simultaneously. Long wavelength red light, such as that admitted by the red frames, stimulates only the red or long wavelength cones. This results in excitatory input to the visual cortex without the corresponding inhibitory input

and could be an explanation as to why the response in the cortex was great enough to reach the threshold for generating abnormal response.

A second experiment was carried out to investigate which features of the sequence are epileptogenic, the luminance contrast combined with the colour or the colour contrast alone.

5.2. Experiment two

In experiment one the effects of luminance modulation and chromatic modulation could not be fully separated. The engineering department of the Independent Television Commission recorded a sequence onto videotape. This sequence contained isoluminant alternations between blue and red or green and red frames at 12 cycles per second. This stimulus allows two factors to be examined. First, whether chromatic modulations can provoke abnormality in the absence of luminance modulation and second whether the main factor is the presence of the long wavelength red per se or its presence in the absence of its opponent green wavelength.

5.2.1. Method

5.2.1.1. Participants

Eight participants, three male and five female, were investigated in this study, selected from the Aston University clinical neurophysiology database. The age range of the participants was 7-35 years and the mean participant age was 21 years. The basic record was within normal limits for six participants and for the two participants where abnormality was seen in the basic EEG recording the spontaneous abnormality was sufficiently different in distribution to that evoked by stimulation that the experimenter could confidently distinguish between them. All but one of the participants had a history of seizures; the other was identified as photosensitive after his sister began to experience visually induced seizures. Four of the participants were taking sodium valporate, three were taking lamotrigine and the last was not taking any anti-epileptic medication.

5.2.1.2. Stimulus

The video contained two sequences, red/blue alternations and red/green alternations between each frame at 12 cps. Each sequence was 10 seconds long. This was shown on a broadcast quality monitor to remove the effects of the background flicker on the television screen. The luminance of each frame was approximately 45 cd/m^2 so there was minimal luminance modulation between the frames.

5.2.1.3. Procedure

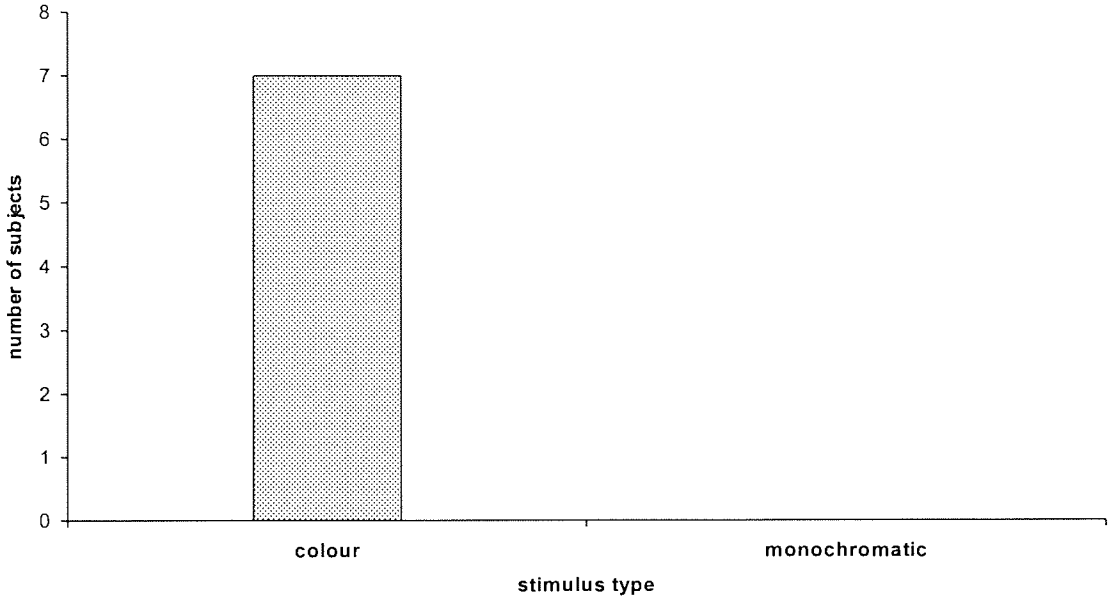
Each participants viewed the stimulus from a distance of 1.5 metres and was asked to fixate on central point. Between the presentations the participant's eyes

were covered with a plain white piece of paper and they were immediately re-covered if a fully generalised response was recorded. If no abnormality was recorded the viewing distance was decreased to 1 metre. The red/green sequence was shown first, followed by red/blue, then red/blue repeated then finally red/green was presented again. The responses were noted and the results analysed using the McNemar test of change.

5.2.2. Results.

Only one participant showed a PPR to the stimulus and then only in the red/blue condition. No occipital spikes were provoked by the stimulus and no response were evoked by the red/green stimulus. This time the results showed no significant difference between the conditions ($p=1.00$). Although the test is strict with small participants numbers, this result still indicates that the colour stimulus was less provocative without the accompanying luminance changes and underlying flicker as the difference between the conditions in experiment one is significant. The results from both experiments are illustrated in Figure 5.2.

(A)



(B)

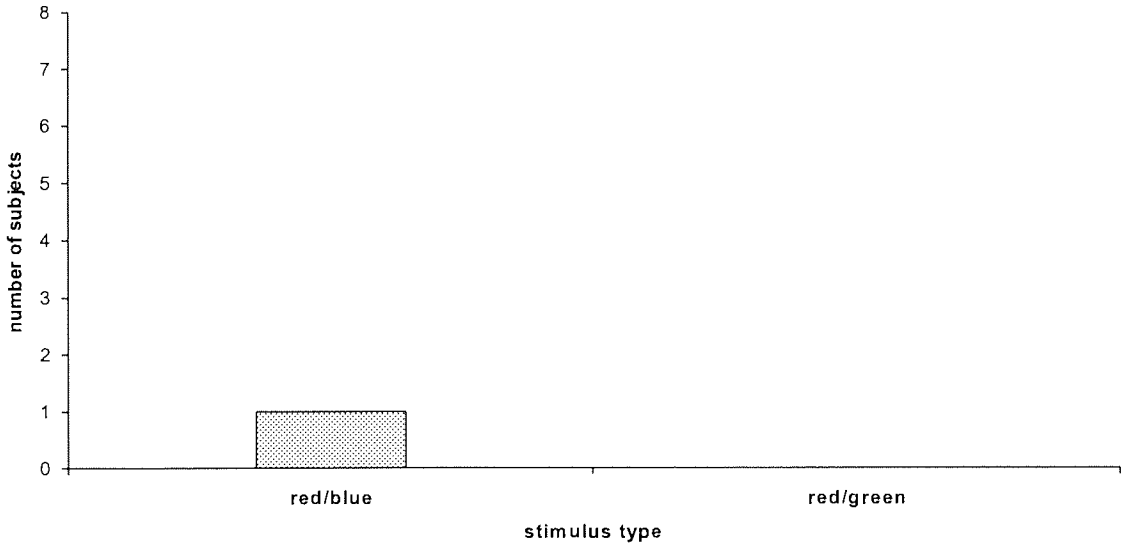


Figure 5.2. **The number of subjects showing abnormal response to the different stimulation types in experiment one, luminance and colour combined (A) and experiment two, colour only (B).**

5.3. Discussion

There are two main findings in this chapter. First, the experiments provide further evidence that colour may play an active role in the generation of epileptogenic response. The conditions under which colour is epileptogenic are when colour are presented in such a way that only one cone type is stimulated, as there is no stimulation of the inhibitory opponent colour. In the second study, a PPR was produced, which indicates that changes in colour contrast can still be provocative, even in the absence of luminance contrast. This could have consequences for ITC guidelines, which will be discussed later in this chapter.

Second, the results suggest that the different types of provocative stimulus characteristics may be combined to provoke an abnormal response and that even non-provocative stimuli may combine to potentiate another stimulus. This finding is similar to that found for the spatial frequency of gratings. Comparisons have been made between when a 5 c/deg grating is presented with or without the presence of a 15 c/deg grating superimposed. Although a grating of 15 c/deg is not epileptogenic in its own right, it can enhance the epileptogenicity of a 5 c/deg grating (Soso et al, 1980(b)). However, this experiment showed potentiation between two separate stimulus characteristics.

The results of experiment one showed that the stimulus that varied in colour and luminance was more provocative than the one that varied in luminance alone. This suggests that the parvocellular pathway mediates the response as its cells respond vigorously to colour. However, in chapter three recent discoveries that magnocellular cells do respond to motion which is defined by colour were described. The magnocellular pathway cannot therefore be discounted as the mediator of the response. The frequency doubling effect may be sufficient, when combined with the luminance modulation, to provoke the responses that were observed. The result that only one response was elicited in the second experiment, when the stimulus was isoluminant, also initially suggests that the low levels of luminance modulation were an important factor and therefore that the response is more likely to be magnocellular than parvocellular. However, there has been much controversy in recent work about the usefulness of isoluminant stimuli in isolating responses mediated by the parvocellular system.

Red and green stimuli may be varied in luminance to establish the null point at which no response is recorded for magnocellular and parvocellular LGN cells. Magnocellular cells have been recorded which respond at isoluminance and therefore cannot be summing the medium and long wavelength cone inputs in a linear manner. If magnocellular cells still respond at isoluminance then isoluminant stimuli are not effective at isolating parvocellular pathway function. Behavioural studies, where monkeys make saccades to one of eight stimuli that are different, have also been studied using isoluminant stimuli. Stimuli differing in motion characteristics, which are thought to be mediated via the magnocellular

pathway, are still recognised at rates better than chance. Chromatic contrast must therefore be used at isoluminance, though to a lesser extent than luminance contrast. Stimuli that differ in texture cues, which are thought to be mediated by the parvocellular pathway, are reduced to the same extent as motion. This suggests that the functioning of the parvocellular pathway is also reduced at isoluminance (Logothetis et al, 1990). In another behavioural study, using similar stimuli, ibotenic acid lesions were made to the magnocellular or parvocellular layers of the LGN. The use of isoluminant stimuli produces similar deficits in animals with either lesion and in animals with intact LGN, suggesting that both the magnocellular and parvocellular pathways are compromised at isoluminance. Experiments using isoluminant, achromatic and non-isoluminant chromatic stimuli have revealed that combined colour and luminance are easier to detect that either modulation alone (Gur and Akri, 1992). Mathematically the probability of detecting combined luminance and colour was far greater that if it was simply the summed activation of the magnocellular and parvocellular pathways. Processing of colour and luminance do not appear to be independent, especially as the reaction times to combined luminance and colour modulation were shorter than those to either. There must be an interaction, as if processing were parallel the reaction times would be the same as luminance or colour, whichever was faster. When the effect of colour on luminance contrast sensitivity function was investigated it was found that colour contrast that cannot be detected can boost luminance contrast detection (Gur and Akri, 1992).

This literature provides support for the finding that the visual system can combine colour and luminance to create a larger response. This could explain why the colour in the cartoon sequence was more provocative than the luminance only condition even though the colour alone in experiment two was not as provocative as the cartoon sequence. It also provides support for the theory that PPR are generated by the parvocellular system as the colour combined with the luminance in the cartoon sequence would stimulate the parvocellular pathway more optimally than the isoluminant stimulus in experiment two.

However, though the isoluminant stimuli in experiment two was not as provocative as the cartoon sequence it did provoke a PPR in one subject. This may mean that the ITC guidelines should be altered to include restrictions on rapid alterations between non-opponent colours. These sequences may be provocative if they are isoluminant but are likely to be highly provocative if they are combined with even low levels of contrast modulation.

Chapter Six

The role of spatial frequency in photosensitive epilepsy

Spatial frequency is a measure of how many times a pattern repeats within a degree of the visual field, or more simply, how fine the detail of the pattern appears. It is a function of the actual size of the pattern elements and the distance between them and the subjects' eyes. The visual angle subtended by the lines in a pattern is important in determining how epileptogenic that pattern will be. The optimum spatial frequency lies between 1 and 4 c/deg (Wilkins et al, 1979 (b)).

Pattern sensitive subjects have been presented with patterns that varied in spatial frequency between 1 and 10 c/deg and the degree of abnormality provoked by each was plotted as a percentage of the maximum abnormality provoked. The values at which the discharge counts were 50% of maximal were separated by just over one octave regardless of whether the stimulation was with sine- or square-wave gratings. The visual system is thought to process spatial frequency in channels that have similar characteristics, suggesting that pattern sensitivity is a disorder involving one or a few adjacent spatial frequency channels (Soso et al, 1980 (a and b)).

The spatial characteristics of patterns placed over photostimulation lamps have also been investigated. The inspiration for this work came from the observation

that the Kaiser photostimulator appeared to be more effective at evoking abnormal responses than the Grass photostimulator. The Kaiser stimulator subtends only a slightly larger visual angle (28°) than the Grass (24.5°) and the intensities are similar between the two lamps. The main difference between the stimulators is the presence of a protective metal grid, which produces a square grid pattern over the stimulation area. When patterns were added to the Grass stimulator, small squares, subtending about 22' of the visual angle, appear most provocative, suggesting that patterned flash of this type is more provocative than diffuse. 1 mm horizontal and vertical lines were also more effective than diffuse flash. 3 mm by 3 mm squares surrounded by 3 mm lines, over the photostimulator, were not effective in provoking abnormalities and this may be due to the reduction in luminance (Jeavons et al, 1972 (a)). When checkerboard patterns are placed over the lamp there is no consistent increase in sensitivity across patient groups, but this again could be due to the reduction in luminance (Engel, 1974).

Flickering dot stimulation, when a pattern of black circles on a transparent background is placed over the lamp, has been used to examine the effects of spatial frequency in patterns placed over photostimulators. The results suggest that the optimum spatial frequency of a pattern placed over flash is between 1.5 and 2.1 c/deg (Takahasi and Tsukahara, 1998). This supports the result that the 22' space in the pattern is effective, as 2.1 c/deg corresponds to 23' of the visual

angle. However, in this type of stimulation only the spatial frequency of the dots may be calculated and there is no way of quantifying the spaces between the dots.

The first experiment described in this chapter investigates several different parameters of patterns placed over a photostimulator and was designed to establish which should be used clinically. The second experiment is a more detailed investigation intending to investigate the optimum spatial frequency of patterns placed over a photostimulator. In chapter four it was noted that the optimum pattern stimulation frequency was often of lower spatial frequency for the occipital spike subjects than for the PPR subjects. The results of the second study in this chapter will quantify this observation, which will then be discussed in relation to the visual physiology.

6.1. Experiment one

6.1.1. Method

6.1.1.1. Participants

Six participants were investigated in this study, two male and four female, selected from the Aston University clinical neurophysiology database. The age range of the participants was from 9–33 years and mean age of the participants was 23 years. All but two of the participants had a history of seizures. The remaining two participants were found to be photosensitive after routine testing, as their mothers had previously been diagnosed as photosensitive. The basic record was within normal limits for four participants and for the two participants

where abnormality was seen in the basic EEG recording the spontaneous abnormality was sufficiently different in distribution to that evoked by stimulation that the experimenter could confidently distinguish between them. Three of the participants were taking sodium valporate, one was taking lamotrigine and carbamazepine combined therapy, and the remaining two were not taking anti-epileptic medication.

6.1.1.2. Stimulus

The grids were drawn using the Corel Draw graphics program and printed onto acetates. The acetates were then displayed in front of a Grass photostimulator and viewed at a distance of 30 cm, at which they subtended 24.5 degrees of the visual angle. Grid one had the same parameters as the most provocative grid in the study by Jeavons et al, 1972(a) (0.3 mm line thickness, 2 mm square space with a mark to space ratio of 1:6.6). In grids 2 through 5 the square space was kept the same size and the mark to space ratio was varied by increasing the line thickness. Grids 2-5 therefore had mark to space ratios of 1:5, 1:4, 1:2.8 and 1:2 respectively. In grids 6 through 9 the line thickness was calculated so it matched grids 2-5, while the square space between the line was increased to ensure the mark to space ratio was the same as that used in Jeavons et al (1972(a)), 1:1.6. Grids 2-5 therefore varied in line thickness and mark to space ratio while grids 6-9 varied in the size of the space and in the number of lines on the grid.

6.1.1.3. Procedure

The participants viewed the photostimulator and were asked to fixate on the central spot. The clinical photostimulation protocol was then carried out. The

stimulation frequency was increased in steps from 1 Hz until an abnormality was evoked. The stimulation was then decreased from 60 Hz until the upper limit of the range was established. The stimulation frequency was then decreased further in steps of 5 Hz to establish whether the response was still present. The optimum frequency of stimulation was established and used as a test stimulus for the experimental protocol. In the experimental protocol the grids were placed in front of the photostimulator in random order. Stimulation was for 10 seconds, 5 with the eyes open and 5 with the eyes closed. The clinical grid was presented before and after the sequence of test grids to ensure the response was still present. The grid was examined before each presentation to ensure that the lines appeared vertical and horizontal to avoid the oblique effect (Long and Tuck, 1991). If at any time during the procedure a fully generalised response was recorded the stimulus was removed and the participant rested for at least 10 seconds.

6.1.2. Results

Two of the participants showed occipital spikes in response to the stimulation and four showed PPR. The results were examined to investigate whether there were any differences between the groups other response type. An independent samples t-test was carried out on the participant's ages and Fisher's exact probability tests on the other variables. There are no significant differences between the participants showing PPR and those showing occipital spikes with respect to age ($t=0.73$; $p=0.948$) (95%CI=-44.15-45.65), sex ($p=0.400$), whether the participants were taking anti-epileptic medication ($p=0.800$), whether the

participants had a history of seizures (p=0.600) or whether the resting EEG recorded were within normal limits (p=0.600).

The abnormal responses recorded during the test protocol were examined and a rank allocated to the severity of each. Severity was determined by a combination of amplitude of response, degree of spiking, speed of onset and apparent self-limiting nature. The most severe response was assigned the highest rank. The median rank for each grid was calculated separately for the PPR and the occipital spike group and is illustrated in Figure 6.1.

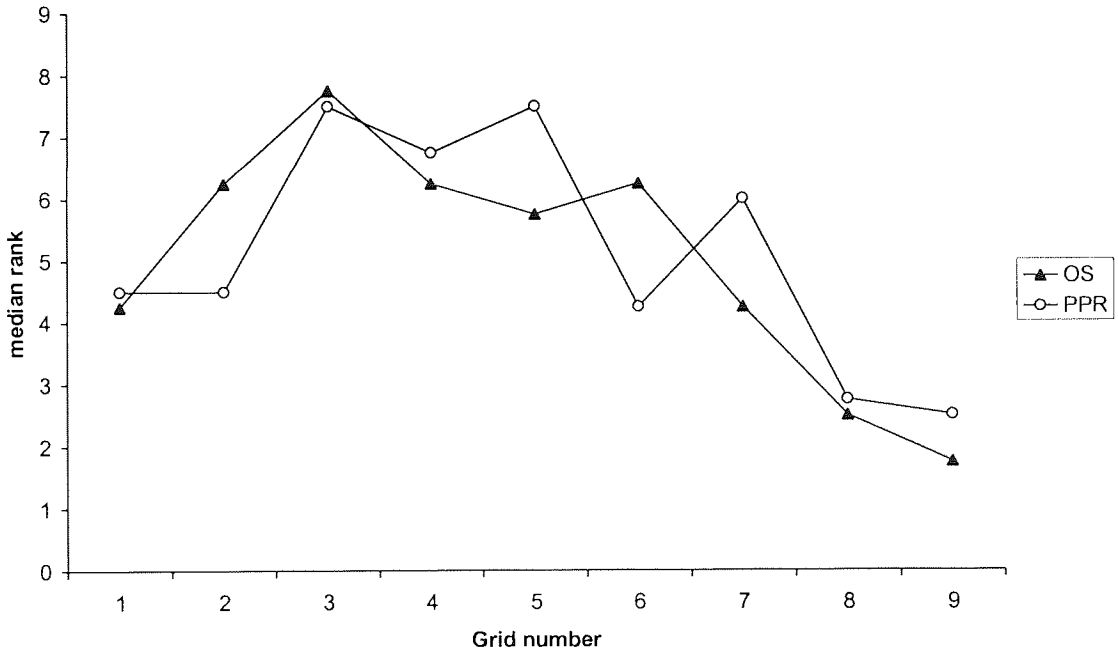


Figure 6.1. The median rank assigned to the degree of abnormality evoked by each grid in the subjects showing PPR and those showing occipital spikes.

Both the response types were maximal during stimulation with grids 2-5, in which the size of the square space between the lines was constant. There does not appear to be a different pattern of responses depending on whether the response is a PPR or an occipital spike. A two related samples sign test was carried out and there was no significant difference (p=0.5078) between the median ranks for the occipital spike and PPR groups.

The data was then plotted to see if it revealed which stimulus parameters, that varied between the grids, merited further investigation. The data for all the subjects was plotted together, as there was no significant difference between the categories, in order to increase subject numbers.

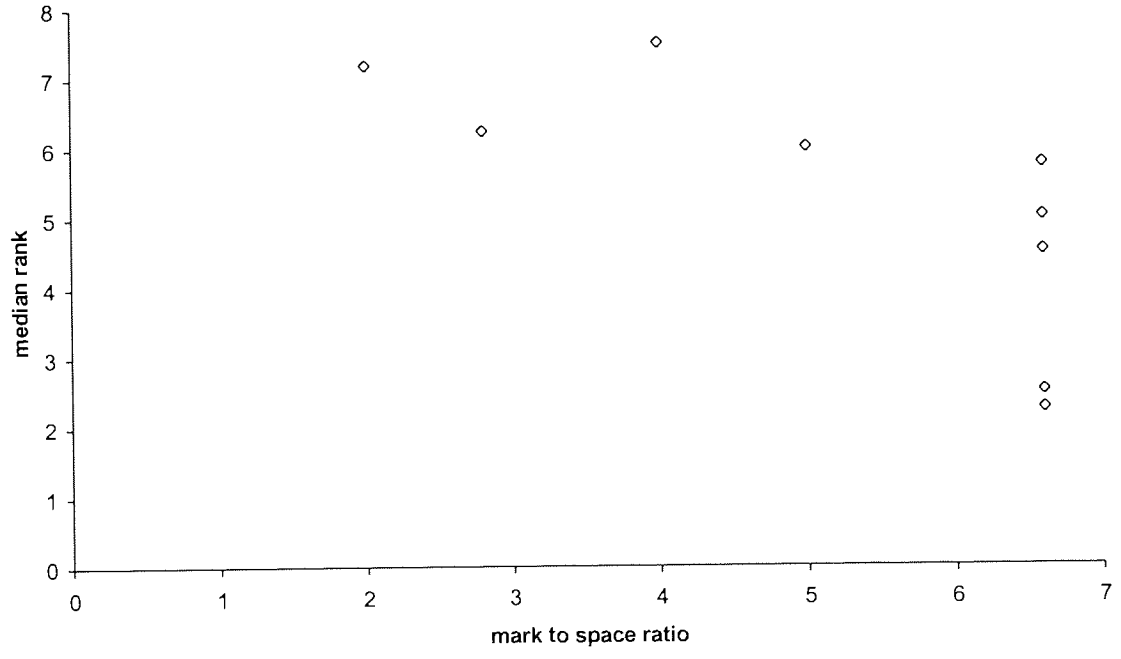


Figure 6.2. The relationship between the median rank assigned to the abnormality and the mark to space ratio of the grid provoking it.

On initial inspection the severity of response appears to decrease with increasing mark to space ratio and the Kendal correlation coefficient was significant (p=0.011), indicating a negative correlation between mark to space ratio and median rank of response. However, this may be due to the large data set at 1:6.6. There appears to be little relationship between 1:1 and 1:5 and the spread of the data at 1:6 mark to space ratio does not indicate a strong relationship.

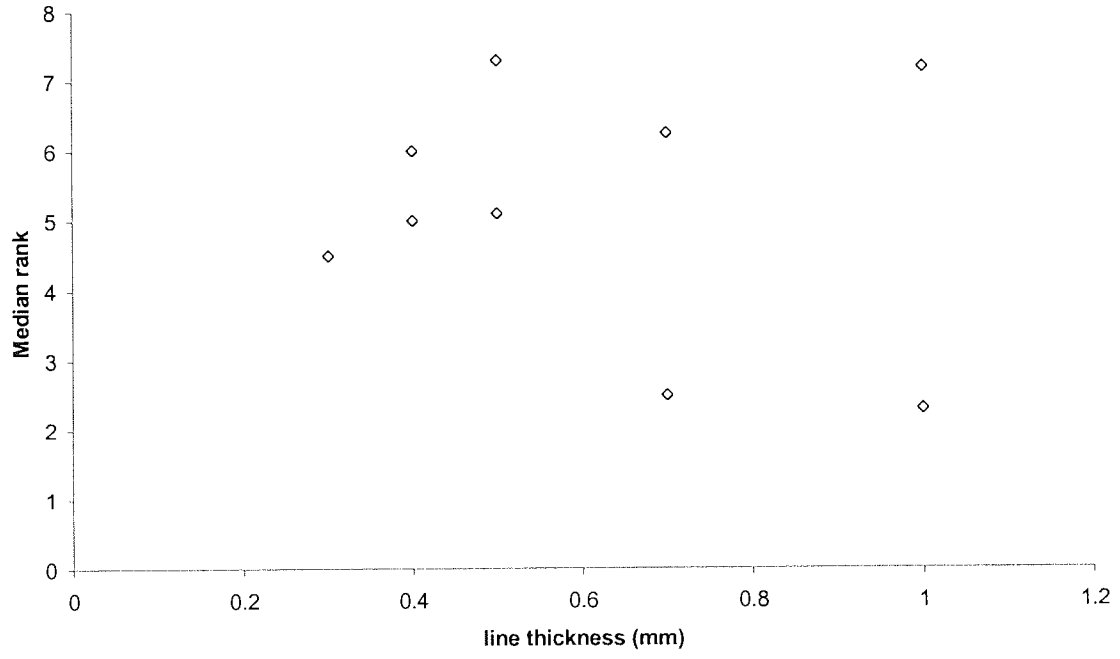


Figure 6.3. The relationship between the median rank assigned to the abnormality and the line thickness of the grid provoking it.

There does not appear to be a consistent relationship between line thickness and the median rank of severity and the Kendall correlation coefficient was not significant (p=0.831).

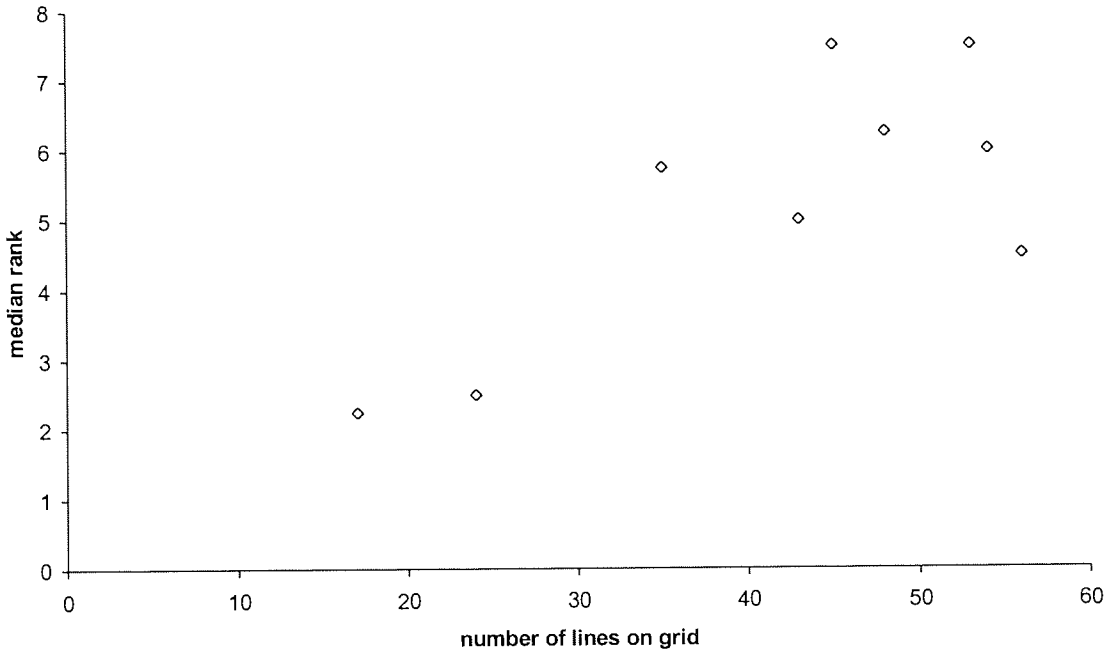


Figure 6.4. The relationship between the median rank assigned to the abnormality and the number of lines on the grid that provoked it.

The median rank of severity appears to increase with increasing number of lines on the grid. The Kendall correlation coefficient was not significant ($p=0.173$) but this may have been due to the uneven distribution of the data along the x-axis. This relates well to the finding that median rank decreased rapidly between grids 5-9 as the number of lines also decreased.

6.2. Experiment two

In experiment one the effects of spatial frequency and mark to space ratio could not be separated and the effects of luminance were not controlled. However,

there does seem to be an effect of the number of lines, so the effects of spatial frequency were examined in more detail in experiment two. This is also of interest as it will allow the effects of patterns placed in front of the photostimulator to be compared to the literature which investigated spatial frequency in pure pattern stimulation.

6.2.1. Method

6.2.1.1. Participants

Eight Participants were investigated in this study, three males and five females, selected from the Aston University clinical neurophysiology database. The age range of the participants was 7-29 years and the mean age was 21 years. All but one of the participants had a history of seizures and the other was found to be photosensitive after testing as his sister began to experience photosensitive seizures. The basic record was within normal limits for five participants and for the three where abnormality was seen in the basic EEG recording the spontaneous abnormality was sufficiently different in distribution to that evoked by stimulation that the experimenter could confidently distinguish between them. Four of the participants were taking sodium valporate, three were taking lamotrigine and one was not taking anti-epileptic medication.

6.2.1.2. Stimulus

The gratings were drawn using Corel Draw and printed on to acetates. The viewing distance was increased to allow higher spatial frequencies to be printed accurately. At 40 cm the Grass photostimulator subtended 18.7 degrees of the

visual angle. The gratings consisted of vertical lines with a mark to space ratio of 1:4. This was chosen to allow maximum luminance without decreasing the line thickness to a degree where printing would become inaccurate. As the mark to space ratio was constant then so therefore the luminance was constant and this was confirmed using a spot photometer. Seven grids of vertical lines were tested, with spatial frequencies of 2, 4, 6, 8, 10, 12 and 14 cpd.

6.2.1.3. Procedure

The most provocative photic stimulation frequency was established by the clinical protocol described in experiment one and used as the experimental stimulus. The gratings were presented in random order and the clinical grid presented before and after the experimental grids to ensure that the response was still present. Presentation was for 10 seconds, 5 with the eyes open and 5 with the eyes closed. If at any time during the procedure a fully generalised response was recorded the stimulus was removed and the participant rested for at least 10 seconds.

6.2.2. Results

Four of the participants showed occipital spikes in response to the grids and four showed PPR. The results were examined to investigate whether there were any differences between the groups other response type. An independent samples t-test was carried out on the participant's ages and Fisher's exact probability tests on the other variables. There were no significant differences between the participants showing PPR and those showing occipital spikes with respect to age

(t=1.232; p=0.264) (95%CI=-8.13-24.63), sex (p=0.500), whether the participants were taking anti-epileptic medication (p=0.500), whether the participants had a history of seizures (p=0.500) or whether the resting EEG recorded were within normal limits (p=0.500).

The maximum amplitude of the response, on any channel, was taken as a measure of the severity of the response and was analysed separately for the subjects showing occipital spikes and those showing PPR. The mean maximum amplitudes for each group are shown in Figure 6.5.

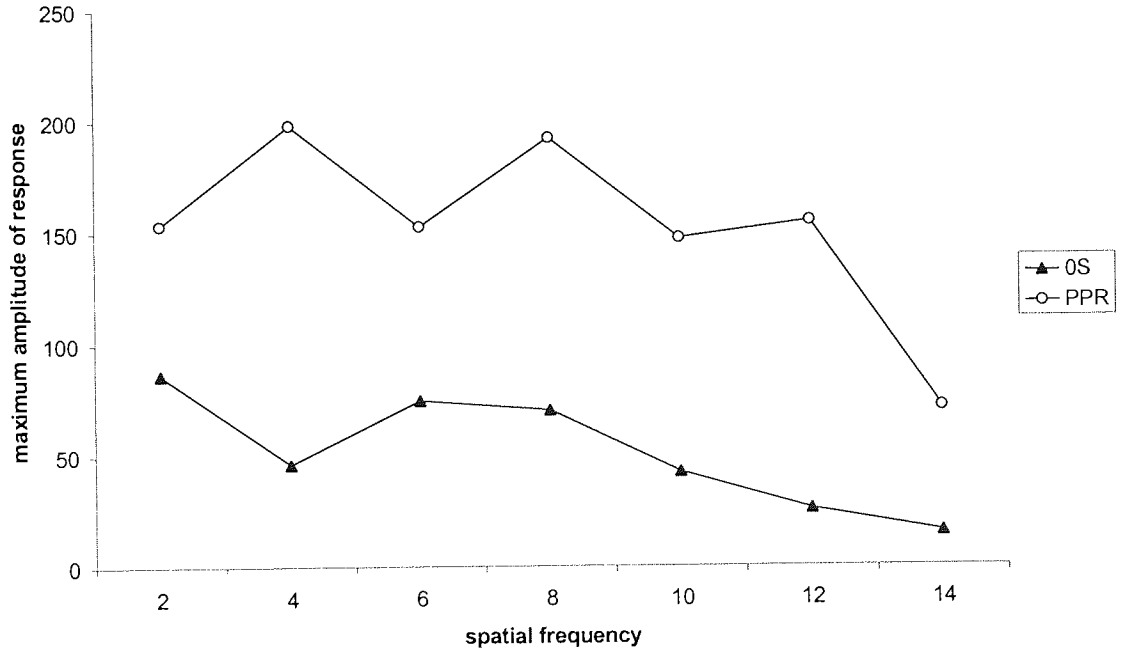


Figure 6.5. The mean maximum amplitude of the abnormality provoked by each spatial frequency grid for occipital spikes and PPR.

The occipital spikes were always lower in amplitude than the PPR. Both responses were maximal at the lower spatial frequencies and decreased gradually with increased spatial frequency. A mixed ANOVA was carried out on SPSS and there was no significant effect of spatial frequency. As this may have been due to the large between participants variability the data for each participant was normalised to the maximum response obtained from that participant. The normalised data is shown in Figure 6.6.

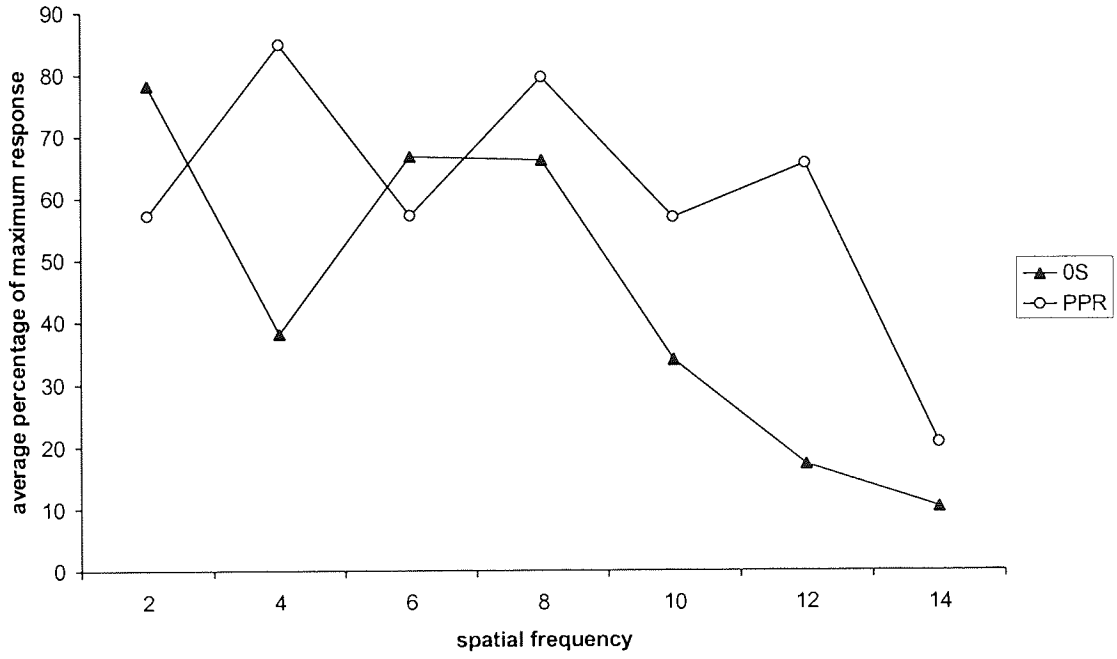


Figure 6.6. The mean maximum amplitude, normalised to the subjects' own maximum amplitude, of the abnormality provoked by each spatial frequency.

The decrease in maximum amplitude above 8 cpd can be seen more clearly in Figure 6.6 and occurs in both PPR and occipital spikes. No clear pattern

emerged between 2-8 cpd for either response. A second mixed ANOVA was performed. Whether the response was an occipital spike or a PPR did not significantly alter the amplitudes to spatial frequencies as the amplitudes were normalised ($p=0.252$). Spatial frequency had a significant main effect ($p=0.013$) and paired sampled t-tests were carried out to examine where the differences occurred. The 14 cpd grating was significantly less provocative than 2 cpd ($p=0.004$), 4 cpd ($p=0.022$), 6 cpd ($p=0.013$), 8 cpd ($p=0.009$) and 10 cpd ($p=0.026$). There are no other significant differences between the gratings.

6.3. Discussion

The main finding in experiment one of this chapter was that grids which have a space of 2 mm squared, at 30 cm viewing distance, are the most likely to provoke both occipital spikes and PPR. The mark to space ratios may be varied between 1:2 and 1:5 without having an effect on the probability of an abnormal response. This information is of use to other EEG departments who are beginning to use grids over their photostimulators to increase the detection of photosensitivity.

The main finding of experiment two of this chapter was that there is no significant difference between the spatial frequency characteristics of occipital spikes and PPR. However, both categories of response are significantly less likely to be provoked by high spatial frequencies of 14 cpd. This is consistent with the results of Wilkins et al (1979(b)), who found that the optimum spatial

frequency of stimulation was low and with Soso et al (1980(b)), who found that 15 cpd gratings were not provocative.

At first these results appear to support the idea that the same pathway mediates the response. However, as discussed in chapter three, the spatial frequency characteristics of the two pathways are now thought to be quite similar.

An important distinction in these studies is between acuity, which is the highest spatial frequency that can be resolved, and optimum spatial frequency, which is the spatial frequency that provokes the greatest response. Receptive field centre size is an excellent predictor of the high frequency cut off, but acuity and peak contrast sensitivity vary independently (Irvin et al, 1993). If receptive field size does not affect the maximum contrast sensitivity, then one would not expect the pathways to show different patterns of response to spatial frequency. Acuity is dependent on the parvocellular pathway but the optimum spatial frequencies of the pathways are probably more similar. It is the optimal spatial frequency that is relevant to the present investigation. The contrast sensitivity of the magnocellular pathway is not equal to that of the parvocellular but appears maximal at similar spatial frequencies. The experimental results, which show no difference in the optimum spatial frequency, therefore do not contradict the theory that the magnocellular pathway mediates occipital spikes and the parvocellular pathway mediates PPR.

Though this result does not indicate that OS and PPR are generated via the same mechanism or are related, it does have interesting clinical applications. Clinical protocols designed for the detection of PPR may also be used to detect occipital spikes with regards to spatial frequency, unlike colour or luminance contrast characteristics. The finding that spatial frequencies above 14 cpd are not effective indicates that very fine patterns in the environment need not be avoided or controlled by TV guidelines. It is also useful with regards to the design of clinical protocols. It is important to ensure that a sufficient range of patterns are tested to ensure that pattern sensitivity is identified but protocol can become so long that fatigue becomes a dominant factor. Testing sensitivity within the lower range of spatial frequencies, under 8 cpd, should be sufficient to test for the presence of any pattern sensitivity. The use of different spatial frequencies of grid placed over the photostimulator may also represent another method of pattern stimulation as an alternative to display on television, monitors or the presentation of patterned cards. It is also further evidence for pattern and photosensitivity representing the same syndrome as the spatial frequency dependence was similar when grids were placed over the photostimulator and when grating patterns are displayed on a monitor.

Chapter Seven

The role of temporal frequency in photosensitive epilepsy

Photosensitive abnormalities are evoked by intermittent photic stimulation and reversing patterns. This indicates that movement is an important stimulus characteristic.

The most epileptogenic frequencies in man are between 15 and 20 flashes per second (fps) (Jeavons et al, 1966). Individuals may have maximum sensitivity to frequencies outside this range, but the majority of patients are sensitive to these frequencies. Approximately 50% of photosensitive subjects are still sensitive to 50 fps but it is rare for a patient to be sensitive to 60 fps (Harding and Jeavons, 1994).

Movement is also a factor in sensitivity to pattern stimulation. It has been estimated that only 30% of photosensitive patients are sensitive to stationary patterns (Darby et al, 1980). After images of epileptogenic patterns do not provoke abnormalities (Wilkins et al, 1980). This could be due to the low levels of illumination but it suggests that patterns must be moving to evoke abnormalities, even by as little as that caused by tremor eye movements.

When patterns are rotated at approximately 15 reversals per minute there is a marked decrease in epileptic activity (Chatrian et al, 1970). However, if the pattern is vibrating, 64% of photosensitive patients are sensitive, which is a 2-fold increase compared to the number that are sensitive to the stationary patterns. The optimum frequency of pattern oscillation, which is movement of the pattern back and forth, from left to right, is between 15 and 20 Hz (Binnie et al, 1985). Drifting gratings are less effective than oscillating or phase reversing suggesting that the neurones in the eye must activate in synchrony to provoke an abnormal response.

It has been noted, during routine clinical observations within the department, that at the lower temporal frequencies of IPS, occipital spikes are more frequently evoked than PPR. Occipital spikes are also more frequently observed to stationary patterns than PPR. As this may illustrate a difference between the two response types a controlled study was carried out.

7.1. Method

7.1.1. Participants

22 patients, 8 male and 14 female, were investigated in this study selected from the Aston University clinical neurophysiology database. The age range of the patients was 9-55 years and the mean age was 22 years. The basic record was within normal limits for nine patients and for the remaining patients, where abnormality was seen in the basic EEG recording, the spontaneous discharge was

sufficiently different in distribution to that evoked by stimulation that the experimenter could confidently distinguish between them. All but one of the patients had a history of seizures, the other being diagnosed as photosensitive after his sister began to experience visually induced seizures. Eight of the patients were taking sodium valporate, two were taking carbamazepine, three were taking lamotrigine and one was taking a combination of carbamazepine and lamotrigine. The remaining eight patients were not taking any anti-epileptic medication.

7.1.2. Stimulus

The stimulus was a Grass photostimulator, viewed from a distance of 30 cm, at which it subtended 24.5 degrees of the visual angle. The stimulus was covered by a grid, which produced a pattern of small squares of the areas of illumination.

7.1.3. Procedure

In order to increase patient numbers, this study was retrospective of patients who had previously had clinical EEG examinations within the department. The patients were asked to fixate on the stimulus and viewed it for 10 seconds, 5 seconds with the eyes open and 5 with the eyes closed. The frequency of stimulation was varied between 1 Hz and 60 Hz, following the protocol described in chapter six, experiment one. The author recorded the frequencies that provoked an abnormal response and the abnormality was classified as occipital spikes or PPR.

7.2. Results

Eleven patients showed PPR in response to photic stimulation and 11 showed occipital spikes. The results were examined to investigate whether there were any differences between the groups other response type. An independent samples t-test was carried out on the patient's ages and Fisher's exact probability tests on the other variables. There were no significant differences between the patients showing PPR and those showing occipital spikes with respect to sex ($p=0.330$), whether the patient was taking anti-epileptic medication ($p=0.670$), whether the patients had a history of seizures ($p=0.238$) or whether the resting EEG recorded was within normal limits ($p=0.335$). The mean age of the patients who had occipital spikes was significantly higher than that for the patients showing PPR ($t=2.206$; $p=0.039$) (95%CI=0.49-17.69). The upper limit, lower limit and mid-point of the sensitivity range of the patient were then calculated. The frequencies which evoked an abnormal response in the patient were listed in numerical order. The mid-point was then taken as the value that was central on this list.

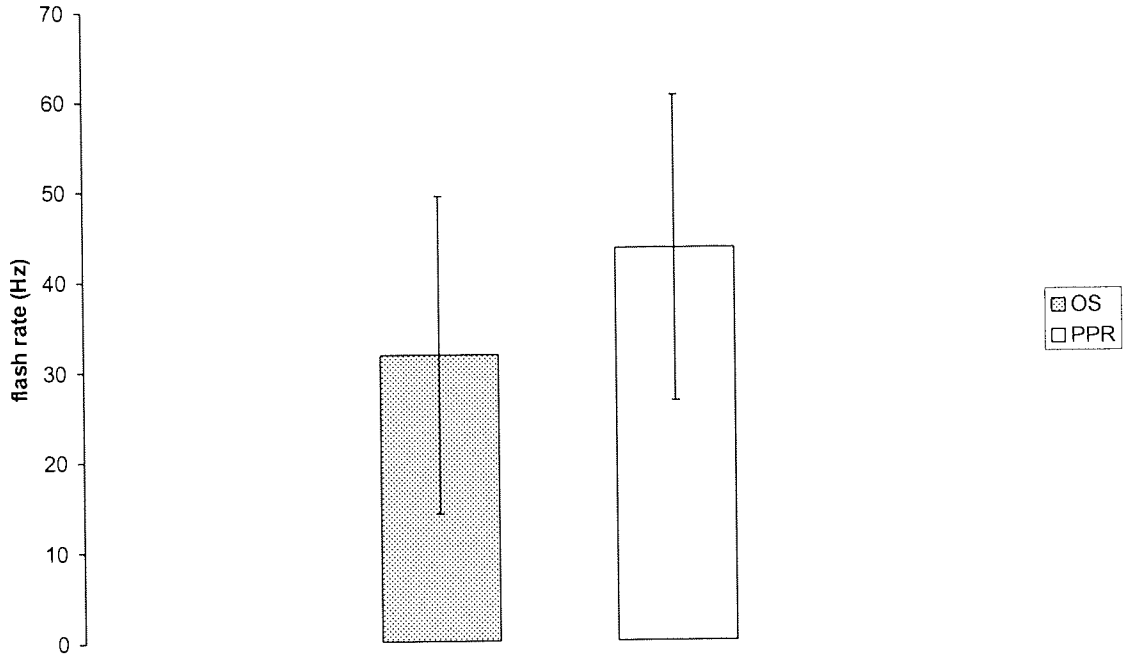


Figure 7.1. The differences in the upper - limit of the sensitivity range for subjects showing occipital spikes and photoparoxysmal response. Mean upper limits and standard deviations are illustrated.

The upper limit for PPR (43.5 Hz) was higher than that for occipital spikes (31.7 Hz) and the standard deviation was high in both groups.

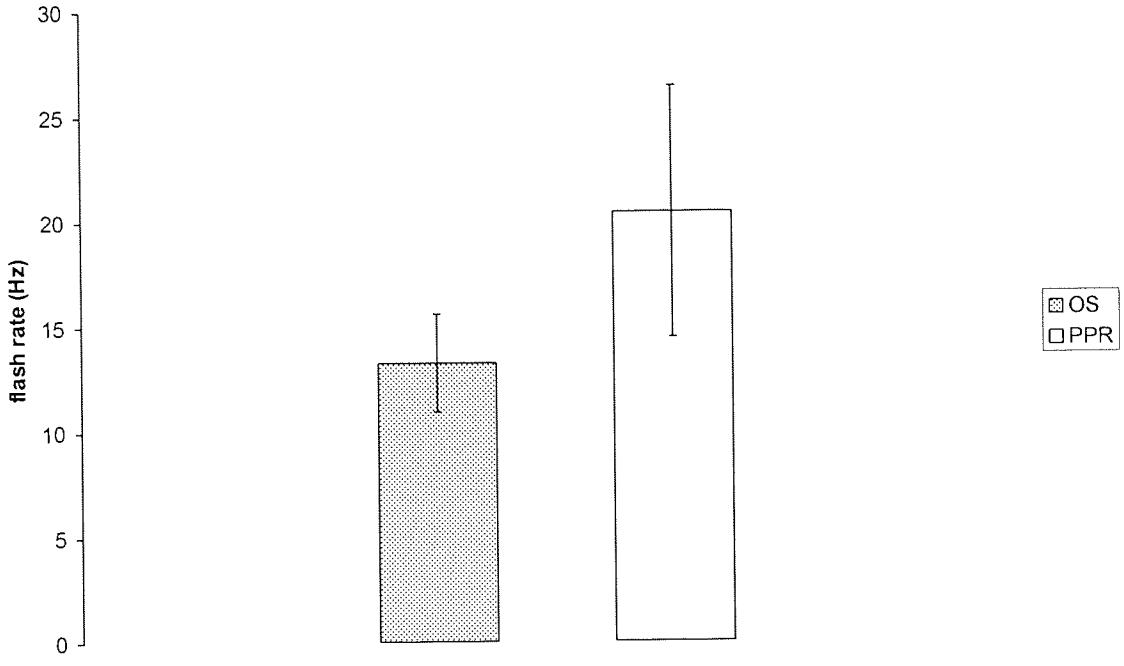


Figure 7.2. The differences in the mid-point of the sensitivity range for subjects showing occipital spikes and photoparoxysmal response. Mean mid-point and standard deviations are illustrated.

The mid-point of the range for the PPR group (20.5 Hz) was higher than that for occipital spikes (13.3 Hz) and the standard deviation of both groups was smaller than that for the upper limit.

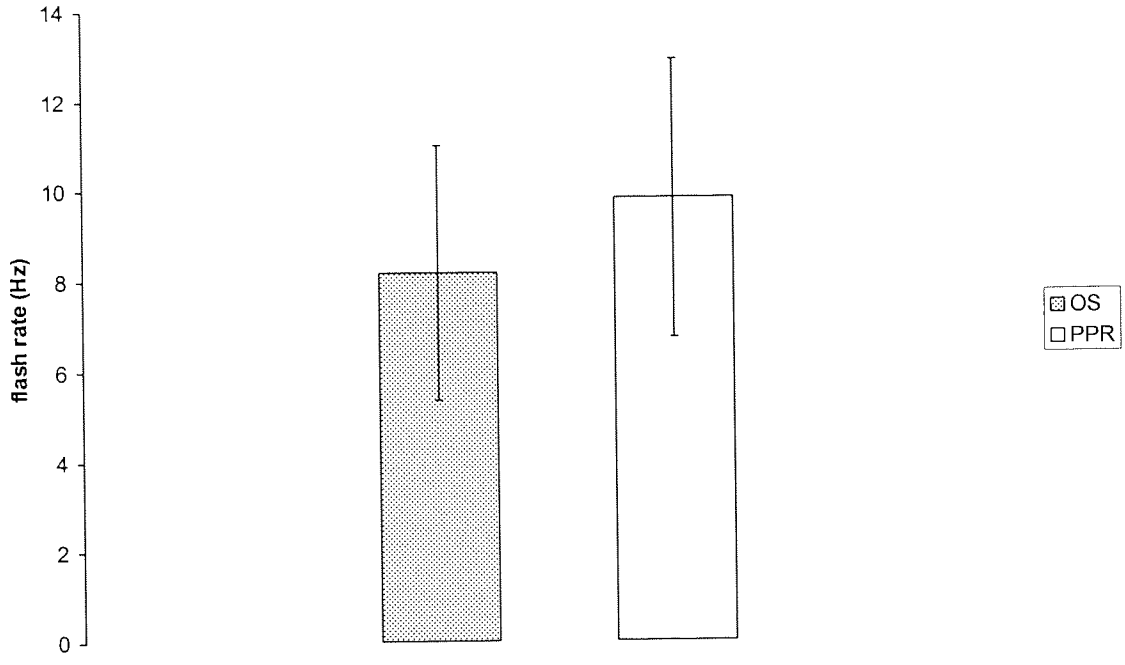


Figure 7.3. The differences in the lower limit of the sensitivity range for subjects showing occipital spikes and photoparoxysmal response. Mean lower limit and standard deviation are illustrated.

The lower limit for the PPR group (9.82 Hz) was higher than for the occipital spike group (8.18 Hz) but the difference was smaller than that for the mid-point or the upper limit.

A mixed ANOVA was performed on SPSS. Category has a significant main effect ($p=0.023$) so whether the response is PPR or occipital spikes influences at least one measure of the sensitive range. Independent sample t-tests were carried out and the mid-point of the sensitivity range for PPR patients was significantly

higher than the mid-point for occipital spikes (p=0.003). There was no significant difference between the upper limits (p=0125) or the lower limits (p=0.210) of the two groups.

7.3. Discussion

In this study the mean age of the patients in the occipital spike group was significantly higher than in the PPR group. This is consistent with the results of Waltz et al (1992) who found that generalised abnormalities decrease with age more than spikes localised to the occipital cortex. A simple explanation for this is that the younger patients have more generalised abnormalities as they have not achieved the same level of control with medication as adult patients, who have had years of investigation into the suitability of different anti-epileptic medication and dosage levels. However, as the groups differ in age, as well as in the type of abnormality they show, age cannot be discounted as a factor in any differences in the temporal frequency characteristics between the groups.

The main finding in this study was that the mid-point of the sensitivity range was significantly higher in patients showing PPR than in those showing OS in response to intermittent photic stimulation. The mid-point of the range should be considered a good measure of the patient's sensitivity, as it was common for the patients to be sensitive to a single low or high frequency. The mid-point for the PPR group confirms the data of Jeavons et al (1966) that the most provocative

frequencies are 15-20 Hz. It is also consistent with the work of Binnie et al (1979) that the patterns oscillating at 15-20 Hz are the most epileptogenic, as this work investigated patients showing PPR, although these authors used the probability of provoking response as a measure of epileptogenicity. The mid-point of the sensitivity range for patients showing occipital spikes falls slightly below the optimum range for PPR, which confirms the clinical observation that at lower temporal frequencies occipital spikes are more common than PPR.

The finding that occipital spikes are generated at lower temporal frequencies than PPR is not consistent with the parallel processing theories discussed in the previous chapter, as the magnocellular pathway is thought to respond to higher temporal frequencies than the parvocellular. However, the distinction should again be made between the high frequency cut off, which is dependent on the magnocellular pathway, and the optimum temporal frequencies, which are thought to be similar in both pathways. It appears that, though the magnocellular pathway is dominant in motion processing, either pathway may mediate it if the stimulus has high retinal illumination and luminance contrast, as was the case in this study. Therefore, the result that the temporal characteristics of the pathways are similar does not, in fact, contradict the theory that the responses are mediated via the two different pathways. It may be that the lower mid-point frequency for occipital spikes simply illustrates that it requires greater integration of the stimulus over time to reach the threshold for evoking a PPR.

Both the upper and lower limits of the photosensitive range were similar between the two types of response. This was initially surprising, as it appears to support the theory that they are generated via the same pathway. However, the point should be made again that the threshold for generating the abnormal response is not the same as that over which a response can be recorded from the cell. The photosensitive range therefore measures the frequencies that produce an optimum response in the cell that is high enough to reach the threshold for abnormalities, rather than the measuring extremes of the sensitivity range at which any response could be recorded from the cell. If the two response types are mediated via different pathways then any measure of the photosensitive range would be expected to be similar, as they all represent optimum stimulation frequencies rather than the limits of the cell ability to respond. The photosensitive range may also appear similar simply if the individual variation in photosensitive range was greater within the groups than between them.

The results of this chapter have implications for the design of clinical protocols for IPS as they illustrate the importance of testing the full range of frequencies, regardless of the abnormalities previously found, and that advice regarding the frequencies which the patients should avoid should be tailored to the individual. Patient age cannot be discounted as a factor in the differences between the groups in this chapter but the results may provide evidence that the responses are generated via different mechanisms. There is a significant difference between the frequency dependence of the two types of response, which suggests they are not

related even though these differences are not consistent with the magnocellular and parvocellular theories postulated in chapters four and five.

Chapter Eight

The effects of monocular occlusion in photosensitive epilepsy

Monocular occlusion is known to reduce the sensitivity range in many photosensitive patients and may abolish sensitivity to IPS and pattern stimulation. However, in the patients where some sensitivity remains the most provocative frequency is not altered when one eye is covered (Harding and Jeavons, 1994). A patient who was wearing a 24-hour EEG monitor wore spectacles that occluded the pattern vision in one eye, and the number of spikes recorded in a 2-day period was reduced by 80%, compared to a 2-day period not wearing the spectacles. The spectacles remained effective therapy over a nine-week period (Wilkins et al, 1975 (b)).

There are three possible explanations as to why monocular stimulation reduces sensitivity in many patients. The first explanation is that, when only one eye is stimulated, the total number of retinal ganglion cells available to be stimulated is reduced to half. The second explanation is that cells higher up the visual system, which only respond when they receive integrated input from both eyes, are involved in the generation of the response and therefore binocular stimulation per se is required to generate abnormal responses. The third explanation is that both the reduction in the number of cells that are stimulated and the elimination of binocular cell stimulation combine to reduce sensitivity when one eye is covered.

There is some evidence that binocular cells are involved. IPS has been presented alternately to one eye and then the other, or to just one eye. Under these conditions, the frequency of flicker, measured at one eye, at which the patient was maximally sensitive, differs between monocular and alternate eye stimulation (Wilkins et al, 1980). This suggests that some binocular input must have integrated the input from the two eyes. However, as the optimum frequency for monocular stimulation is not half that for alternate eye stimulation, the interaction is only partial suggesting that the third explanation may be the most complete (Wilkins et al, 1979 (b)).

Binocular patterns that can not be fused have also been used to investigate whether binocular cells are involved in the generation of abnormal responses or whether the effects of monocular stimulation are, at least in part, due to the fact that the number of cells that are stimulated is reduced. Binocular presentations that can not be fused are significantly less epileptogenic than those that can be fused (Wilkins et al, 1975(a) and 1979 (b)).

It appears that PPR are generated via binocular cells, at least in part, but there is little information on whether occipital spikes are affected by monocular stimulation in the same manner as PPR. A retrospective study of the patient population of Aston University was therefore carried out to compare the number of PPR responses affected by monocular occlusion with the number of occipital spike responses that were affected.

8.1. Experiment one

8.1.1. Method

8.1.1.1. Participants

54 patients, 18 male and 36 female, were investigated in this study, selected from the Aston University clinical neurophysiology database. The age range of the patients was 8-54 years and the mean age was 24 years. The basic record was within normal limits for 33 of the patients and for the remaining patients where abnormality was seen in the basic EEG recording the spontaneous abnormality was sufficiently different in distribution to that evoked by stimulation. All but three of the patients had a history of seizures. In the remaining three patients, two had mothers with photosensitive epilepsy and one had a sister with visually induced epilepsy. Eighteen of the patients were taking sodium valporate, four were taking carbamazepine and eight were taking lamotrigine. A further four patients were taking combined therapy, two were taking sodium valporate and lamotrigine, one was taking carbamazepine and lamotrigine and one was taking carbamazepine, lamotrigine and vigabatrin. The remaining 20 patients were not taking anti-epileptic medication.

8.1.1.2. Stimulus

The stimulus was a Grass photostimulator viewed from a distance of 30 cm, at which it subtended 24.5 degrees of the visual angle. The stimulus was covered by a grid, which created a pattern of squares, subtending 22', over the illumination.

8.1.1.3. Procedure

This study was a retrospective investigation of patients who had previously had clinical EEG examinations within the department, in order that a larger number of patients could be investigated. The patients were asked to fixate on the stimulus and viewed it for 10 seconds, 5 with the eyes open and 5 with the eyes closed. The frequency of stimulation was varied between 1 Hz and 60 Hz in the clinical protocol described in experiment one, chapter six. The most provocative frequency was established and was used as the experimental frequency. The patient was then requested to cover one eye with the palm of their hand. Hand position was examined to ensure that no light entered the eye and that the finger position was not interfering with the recording electrodes. The patient then viewed the experimental frequency for 10 seconds, 5 with the eyes open and 5 with them closed. The experimental protocol then was repeated with the other eye viewing. The experimental stimulus was then presented again with binocular viewing to check that the response was still present. Between each presentation in the experimental testing the patient was given a brief rest until they stated that the vision in the eye that had been covered had returned to normal. If at any time during the testing a fully generalised response was evoked then the stimulus was immediately removed and the patient rested for at least 10 seconds.

The author then inspected the trace and the effects of monocular occlusion were classified. The results were classified as response abolished or retained. The response was classified as retained if a clear response remained, even if it was

reduced in comparison to the response recorded in the binocular condition. If the effect was different between the eyes it was classified as retained.

8.1.2. Results

39 patients showed PPR in response to intermittent photic stimulation and 15 showed occipital spikes. The results were examined to investigate whether there were any differences between the groups other response type. An independent samples t-test was carried out on the patient's ages and Fisher's exact probability tests on the other variables. There were no significant differences between the patients showing PPR and those showing occipital spikes with respect to sex ($p=0.215$), whether the patients were taking anti-epileptic medication($p=0.509$), whether the patients had a history of seizures ($p=0.632$) or whether the resting EEG recorded were within normal limits ($p=0.110$). The mean age of the patients showing occipital spikes was significantly higher than that for patients showing PPR ($t=2.671$; $p=0.010$) (95%CI=2.00-14.08). The effects of monocular occlusion on the two response types are illustrated in Figure 8.1.

Chi squared tests were carried out on the SPSS computer package. Occipital spikes were significantly more likely to be retained, even if they are reduced, than PPR ($p=0.002$).

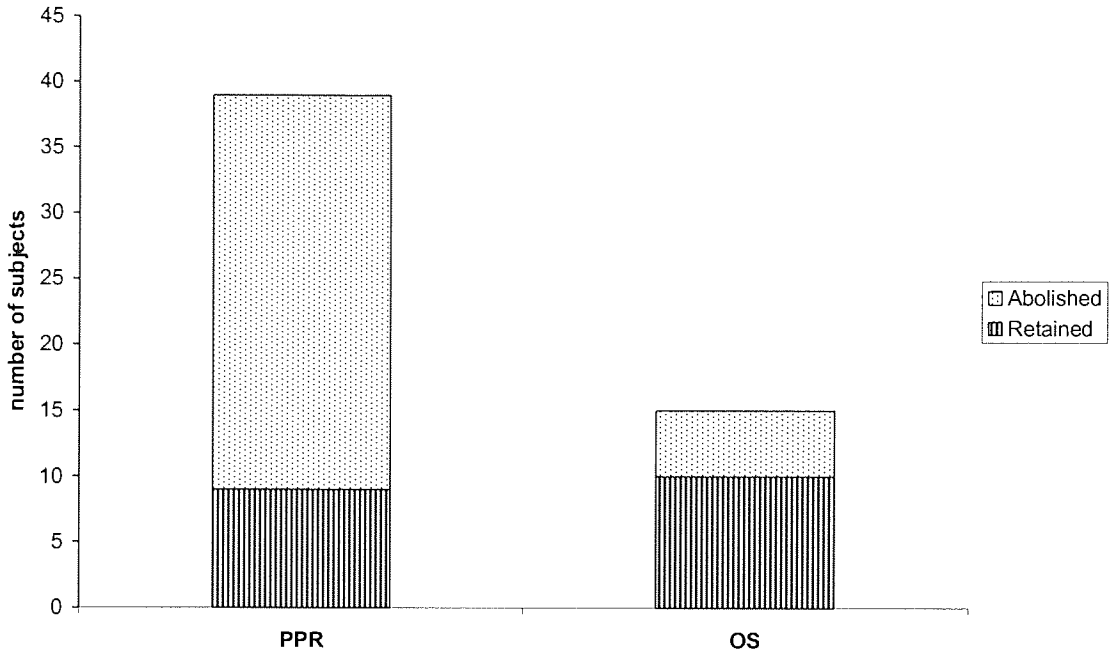


Figure 8.1. The effects of monocular occlusion on occipital spikes and photoparoxysmal response evoked by intermittent photic stimulation.

8.2. Experiment two

The results of experiment one suggest that monocular occlusion has a greater effect on PPR than on occipital spikes which are recorded during IPS. In experiment two the effects of monocular occlusion on response recorded during pattern stimulation were investigated.

8.2.1. Method

8.2.1.1. Participants

42 patients, 13 male and 29 female, were investigated in the study selected from the Aston University clinical neurophysiology database. The age range of the patients was from 9-47 years and the mean age was 25 years. The basic record was within normal limits for 25 of the patients and for the remaining patients where abnormality was seen in the basic EEG recording the spontaneous abnormality was sufficiently different in distribution to that evoked by stimulation that the experimenter could confidently distinguish between them. All but three of the patients had a history of seizures. In the remaining three, two had photosensitive mothers and one had a sister with photosensitive epilepsy. Seventeen of the patients were taking sodium valporate, nine were taking lamotrigine and one was taking combined therapy of lamotrigine and carbamazipine. The other 15 patients were not taking any anti-epileptic medication.

8.2.1.2. Stimulus

The patterns were generated by an SC Electronics T22 grating generator and displayed on a Philips television with 50 Hz frame rate and a mean luminance of 190 cd/m^2. The television was viewed from a distance of 1.5 metres and subtended 18 degrees horizontal by 14 degrees vertical of the subject's visual angle.

8.2.1.3. Procedure

This study was again retrospective of patients who had previously had clinical EEG examinations within the department. The patient was asked to fixate on the stimulus and viewed it for 10 seconds, 5 seconds with the eyes open and 5 seconds with the eyes closed. The patients viewed square and sine wave vertical gratings, which were either stationary or reversing at 1 Hz, and had spatial frequencies of 0.5, 2, 3 and 6 cpd. The most provocative stimulus was established and used as the experimental stimulus. The monocular occlusion protocol, described in experiment one of this chapter, was carried out and the response were classified as before.

8.2.2. Results

29 patients showed PPR in response to the pattern stimulation and 13 showed occipital spikes. The results were examined to investigate whether there were any differences between the groups other response type. An independent samples t-test was carried out on the patient's ages and Fisher's exact probability tests on the other variables. There were no significant differences between the patients showing PPR and those showing occipital spikes with respect to sex ($p=0.187$), whether the patients were taking anti-epileptic medication ($p=0.273$), whether the patients had a history of seizures ($p=0.138$) or whether the resting EEG recorded were within normal limits ($p=0.483$). The mean age of the patients showing occipital spikes was significantly higher than that for patients showing PPR

(t=2.507; p=0.016) (95%CI= 1.49-13.91). The effects of monocular occlusion are illustrated separately for the two response types in Figure 8.2.

There was no significant difference in the effects of monocular occlusion depending on whether the response was occipital spikes or PPR (p=0.06).

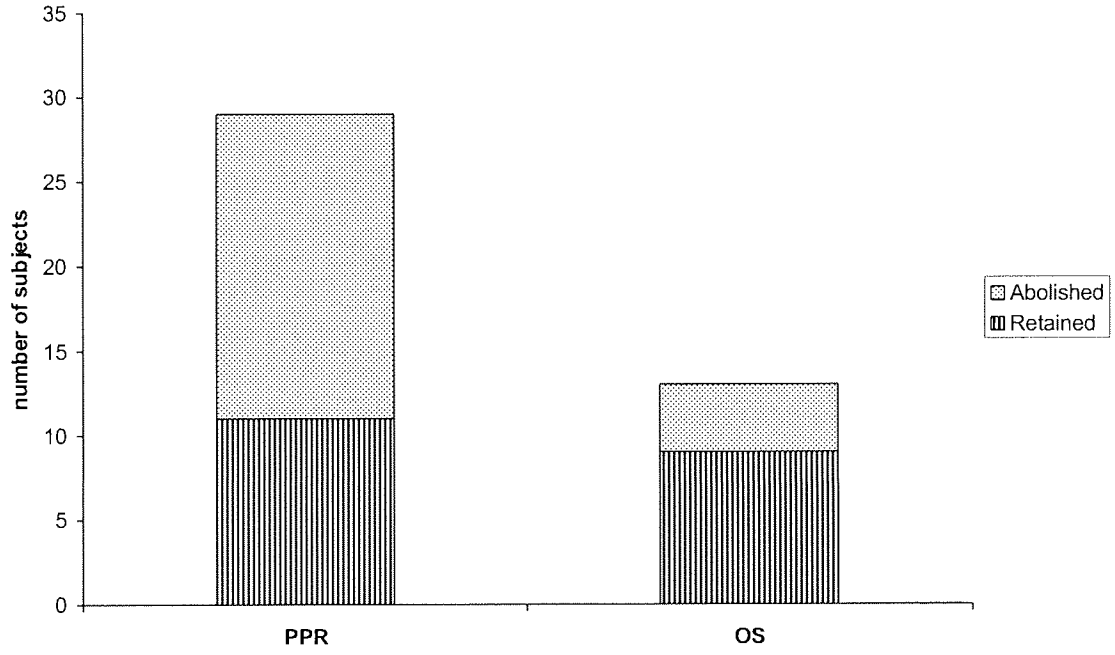


Figure 8.2. The effects of monocular occlusion on occipital spikes and photoparoxysmal response evoked by pattern stimulation.

8.3. Discussion

The age of the occipital spike group was found to be significantly higher than that of the PPR group. Possible explanations for this are discussed in chapter eight.

There are three main findings in this study. First is that both occipital spikes and PPR are significantly reduced by monocular occlusion. The finding that both occipital spikes and PPR are reduced by monocular occlusion supports the previous research that found that monocular occlusion reduced the effects of flash and that patterns that can't be fused are not epileptogenic. In the case of PPR this means that there is likely to be an involvement of binocular cells as the effects of monocular stimulation can not be compensated by increasing stimulus size or intensity or by performing alternate eye stimulation (Harding and Jeavons, 1994). However, the second finding in this study was that occipital spikes are significantly less affected by monocular occlusion. It is therefore possible that, in occipital spikes, the effects of monocular occlusion are due only to the reduction in the number of cells stimulated, without additional binocular effects or with less binocular cell involvement.

Cells that only respond to integrated input from both eyes are present in the cortex. However, it is now thought that there is no direct mapping between the subcortical and cortical pathways (Merigan and Maunsell, 1993; Nealey and Maunsell, 1994). It is therefore difficult to relate these results to segregation of the responses into the magnocellular and parvocellular pathways. However, there is some evidence that the magnocellular pathway is at least involved with binocular processes to a lesser degree than the parvocellular pathway, which is discussed in chapter three. This could account for the reduced effects of monocular occlusion on occipital spikes.

The involvement of the magnocellular and parvocellular pathways in binocular processing remains controversial. However, if binocular cells are involved in the generation of PPR and not occipital spikes then this is evidence against the two response types being related even if the data cannot be explained in terms of the magnocellular and parvocellular theories postulated in chapters four and five. It should be remembered, though, that as the mean age of the groups is significantly different this cannot be excluded as a factor in any differences found between the groups.

The third main finding in this chapter is that the differences between the categories only occur when the responses are recorded to IPS not to pattern. This could reflect the smaller number of patients in experiment two but could also illustrate a difference between pattern sensitivity and photosensitivity that merits further investigation.

Monocular occlusion is the most effective behavioural therapy for photosensitive epilepsy. Therefore the most important clinical finding is that monocular occlusion has variable effects both within response types and to a greater extent between response types. It is therefore important that the effects of monocular occlusion are investigated in the individual, especially as it is not as likely to be protective in subjects showing occipital spikes.

Chapter Nine

The role of the peripheral retina in photosensitive epilepsy

Investigations into the stimulus parameters that influence photosensitivity in papio-papio baboons have found that when the surface area of the stimulus is increased or the distance of stimulation is decreased, the paroxysmal activity induced is associated with more clinical symptoms, is more frequent, and the latency of the response is shorter (Serbanescu et al, 1973). When the distance between the eyes and the photostimulator is decreased, the number of spikes induced in human photosensitive subjects also increases (Plaster et al, 1979). However, varying the distance of stimulation alters a number of possible factors, mainly both the visual angle the stimulus subtends and the luminance reaching the subject's eyes. Though luminance is a factor in the probability of evoking abnormal responses, it has been noted that luminance averaged over time can be as little as 20 cd/m^2, with a modulation of 40% to provoke abnormalities (Wilkins, 1995). The visual angle, which the stimulus subtends, affects the probability of abnormal activity but it remains controversial as to whether the important factor is the total visual angle the stimulus subtends or whether only the central region of the visual field is involved in the production of paroxysmal responses.

When a photosensitive subject shifts their gaze to the edge of a photostimulator, abnormal responses to intermittent photic stimulation and photic driving are both

inhibited. Moving a photostimulator laterally as little as 30 degrees from the line of forward gaze also inhibits the generation of abnormal response. This reduction in epileptogenicity is greater than that found with monocular stimulation and can not be compensated for by an increase in intensity by eight times or by using two photostimulators, placed on either side of the subjects gaze, to lessen the effect of obstruction by the nose (Jeavons et al, 1972(b)). This result suggests that the periphery of the retina is not involved in the generation of epileptic discharges and therefore that visibility factors and convulsive properties are not always the same. Flicker is more visible in the periphery of the eye but is not as provocative in that region. However, subsequent authors (Takahasi, 1987; Takahasi and Tsukahara, 1998) have found evidence to suggest that the periphery of the visual field is involved in the generation of abnormal response. They used flickering dot stimulation, which is a pattern of black dots on a transparent background placed over the photostimulator. Flicking dot stimulation of the periphery was found to be more effective than stimulation of the central region. Sensitivity to red flicker was restricted to the central region but this is unsurprising, as the periphery of the retina is mainly rods which are not wavelength specific (Takahasi, 1987; Takahashi and Tsukahara, 1998). Stimulation of the periphery was especially effective if the spatial frequency of the dot pattern is low (0.5 c/deg) (Takahasi and Tsukahara, 1998).

The majority of research investigating the area of stimulation needed to provoke abnormal discharges uses pattern stimulation, rather than IPS, in order to avoid the effects of light dispersion. The probability of paroxysmal activity varies with

pattern size but the threshold at which an abnormal response is generated varies greatly between patients. When the probability of an abnormal response to a 2 cpd grating was plotted against the estimated number of cells stimulated the slope decreased as the threshold increased. However, rather than suggesting a different relationship between the number of cells stimulated and the probability of an abnormal response in the periphery, this result may simply reflect the number of cells in the periphery that are available to be stimulated by patterns of 2 cpd (Wilkins et al, 1979 (b)). The radius of a pattern must be doubled to increase the probability of an abnormal response from near zero to almost one (Wilkins et al, 1980).

The number of cells stimulated by a pattern does not increase uniformly with pattern radius, so sectors of pattern can be used to investigate the effects of pattern area. These sectors stretch from the centre to the periphery and can split the area into 2 or 4, to investigate distribution effects. The probability of abnormal activity increases as a linear function of pattern area. This suggests that the probability of paroxysmal activity is a function of the number of cells stimulated regardless of whether they are widely distributed over the cortex (Wilkins et al, 1980). Annuli covering 5-20 degrees of the visual field have also been used to investigate the effects of distribution. They are not effective in producing paroxysmal responses while a central region of the same area is (Chatrian et al, 1970). The effects of cortical magnification may be compensated by converting the area of pattern into a value of Q, which is an estimate of the number of cells that would be stimulated by the area at the given eccentricity.

Good correlation is found between the probability of PPR for discs and annuli with the same value of Q, but not for those with the same area. These results again suggest it is the number, rather than type of cell, that is important (Wilkins et al, 1980).

The effects of peripheral and central stimulation were investigated in the following study to confirm whether PPR are elicited by peripheral stimulation and to investigate if occipital spikes show similar characteristics.

9.1. Method

9.1.1. Participants

Six participants, two males and four females, were investigated in this study, selected from the Aston University clinical neurophysiology database. The age range of the participants was 7 to 29 years and the mean participant age was 20 years. The basic record was within normal limits for 5 of the participants and in the remaining participant where abnormality was seen in the basic EEG recording the abnormality was sufficiently different in distribution to that evoked by stimulation that the experimenter could confidently distinguish between them. All but one of the participant had a history of seizures and the other was found to be photosensitive after his sister began to experience visually induced seizures. Three of the participants were taking sodium valporate, two were taking lamotrigine and the remaining participant was not taking any anti-epileptic medication.

9.1.2. Stimulus

The patterns were generated by an SC Electronics T22 gratings generator and displayed on a Philips television with a 50 Hz frame rate and a mean luminance of 190 cd/m^2. The television was viewed from distance of 1.5 meters at which it subtends 18 degrees horizontal by 14 degrees vertical of the participant's visual angle when viewed full field. Cardboard screens were designed to fit over the television and reveal a circular central region or a peripheral ring around it. The areas of the central region and peripheral ring were calculated so that the number of cells stimulated by each area was equal, taking account of the effects of cortical magnification. The number of cells stimulated was estimated as the value of Q in the equation below, where K is the eccentricity

$$Q = 100 [1 - \exp (-0.0574 K)]$$

9.1.3. Procedure

The participants were asked to fixate on a central point and the stimuli were presented for 10 seconds, 5 with the eyes open and 5 with the eyes closed. The participants first viewed the television full field and square-wave gratings with spatial frequencies of 0.5, 3 and 6 cpd were presented to establish the spatial frequencies that provoked abnormal response in each participants. The first cardboard screen was then attached to the television so that the central region was visible and the peripheral ring was covered. The participants were then presented with square-wave gratings of 3, 0.5 and 6 cpd. Stimulation was again for 10 seconds, 5 seconds with the eyes open and 5 with them closed. The central region was then covered and the peripheral ring, calculated to have the

same value of Q, was revealed. Square-wave gratings of 3, 0.5 and 6 cpd were presented in the peripheral ring. To test for order effects the gratings were presented in the peripheral region again, followed by presentation in the central region.

9.2. Results

Three of the participants showed PPR to the pattern stimulation and three showed occipital spikes. The maximum amplitudes provoked by the 3 cpd grating in the central and peripheral conditions are shown in Figure 9.1 for the participants showing PPR and in Figure 9.2 for the participants showing occipital spikes.

There does not appear to be any difference in maximum amplitude of the response depending on whether stimulation is peripheral or central for either occipital spikes or PPR. Matched paired t-tests revealed that there was no significant difference between the maximum amplitudes depending on whether stimulation was peripheral or central ($p=0.639$) for either type of abnormality.

The number of participants showing abnormalities to stimulation with 0.5 cpd and 6 cpd square-wave gratings in the central and peripheral regions is shown in Figure 9.3A for the participants showing PPR, and in Figure 9.3B for the participants showing occipital spikes.

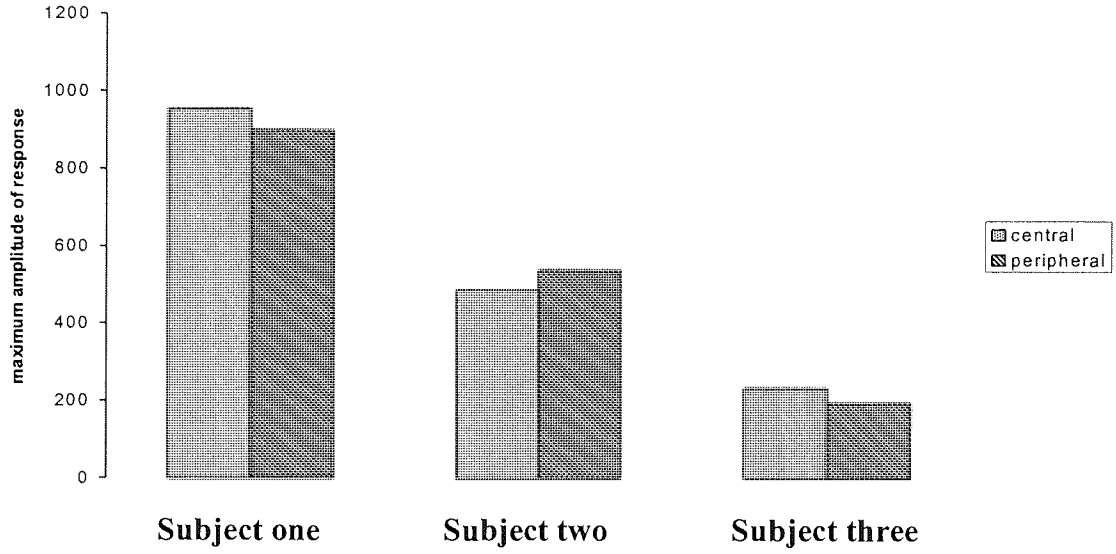


Figure 9.1. **The maximum amplitude of photoparoxysmal response in response to central and peripheral stimulation with a 3 cpd square-wave grating.**

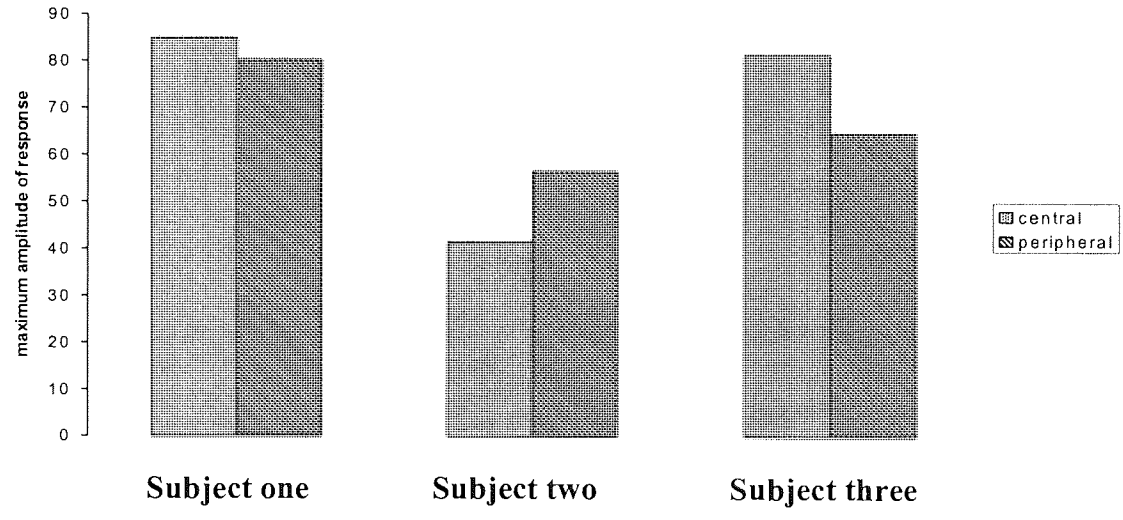
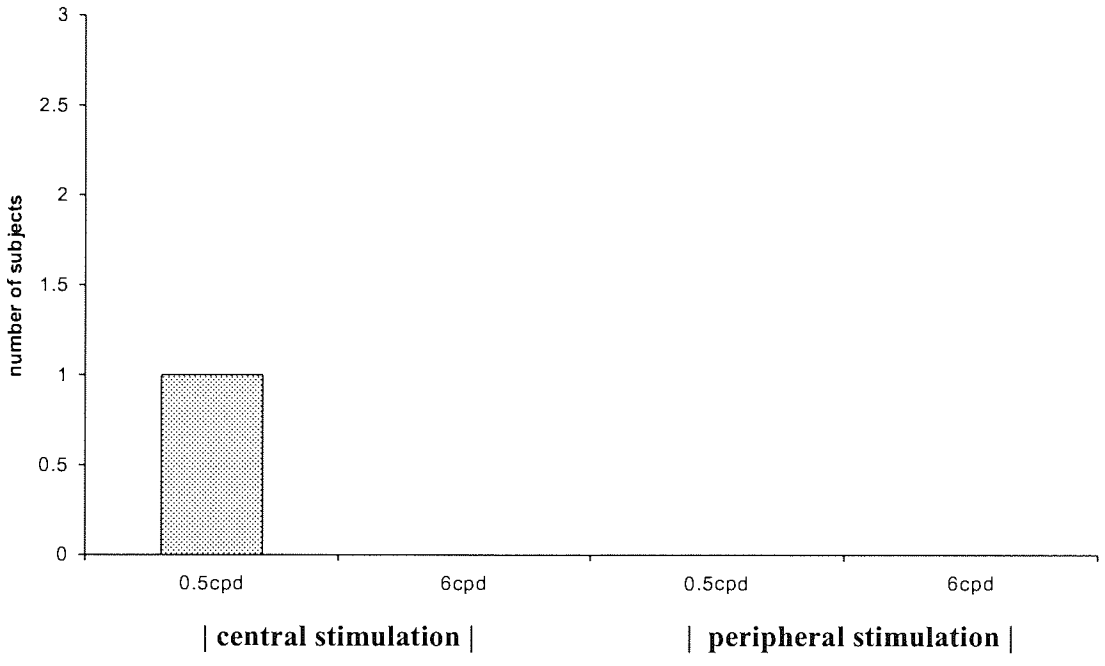


Figure 9.2. **The maximum amplitude of occipital spikes in response to central and peripheral stimulation with a 3 cpd square-wave grating**

(A)



(B)

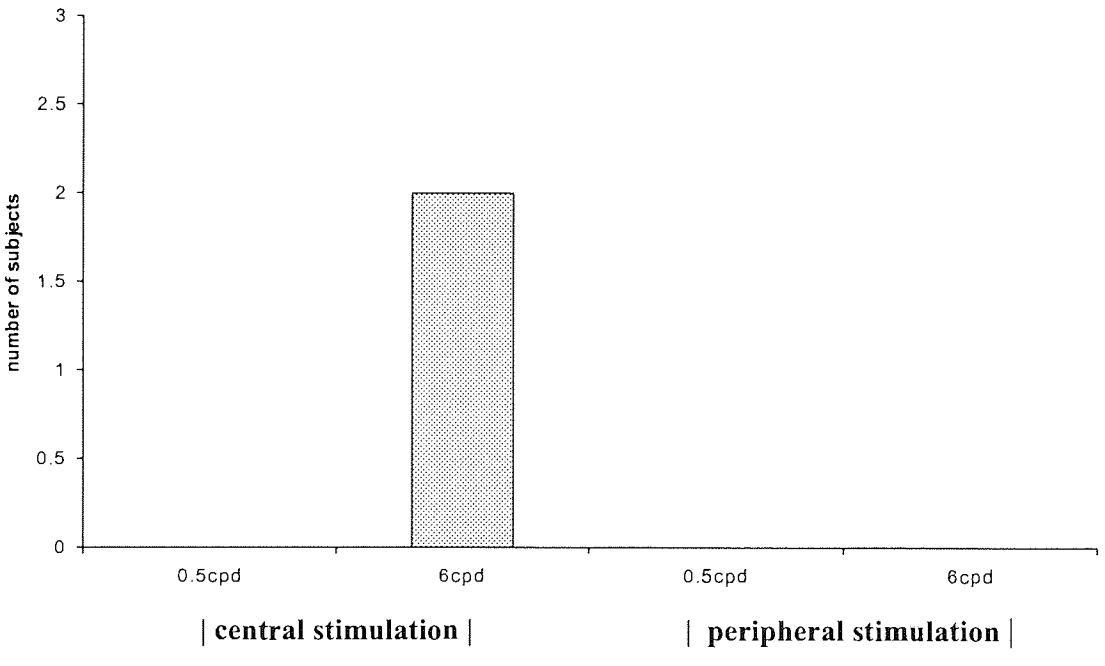


Figure 9.3. **Number of subjects showing photoparoxysmal response (A) and occipital spikes (B) in response to stimulation with 0.5 cpd and 6 cpd square-wave gratings in the central and peripheral visual field.**

There is a decrease in sensitivity to 6 cpd in the participants with occipital spikes when the peripheral region is stimulated compared to the central region but few other trends can be observed as the participants were not sensitive to 0.5 cpd in either central or peripheral stimulation.

9.3. Discussion

The main finding in this study is that both PPR and occipital spikes can be evoked by peripheral stimulation if the areas are calculated to compensate for the effects of cortical magnification. The result that PPR are produced by peripheral stimulation supports the previous literature and it appears that occipital spikes also show this characteristic.

A second finding is that the spatial frequency differences between the central and peripheral stimulation were not as large as expected. However, the decrease in sensitivity to 6 cpd in the periphery may represent a shift in the contrast sensitivity curve to lower spatial frequencies. The contrast sensitivity functions have been measured at varying eccentricities. With increasing eccentricity the curve shows both lower maximum sensitivity and a shift in the curve to lower spatial frequencies. This peripheral contrast sensitivity is thought to be due to the reduced cortical projection area (Rovamo et al, 1978).

The relationship between the magnocellular and parvocellular pathways and eccentricity was discussed in chapter three. Overall, it appears that, though the relative numbers of magnocellular cells increase with increasing eccentricity, there can be no segregation of the pathways by this method. Hence, the finding that both occipital spikes and PPR can be evoked by the periphery does not contradict the theory that each pathway mediates one of the responses as both pathways are present in the peripheral retina. Spatial frequency effects may interfere but should not be relevant here as the contrast was high and additional spatial frequencies were examined. However, the results of this experiment suggest that it is the number of cells stimulated rather than the cell type that is important.

Clinically, this result illustrates two main findings. The first is that protocols for clinical stimulation can be designed to only stimulate the periphery, if the situation arose in which it was more convenient for the patient, and both occipital spikes and PPR could be provoked. Second, ITC guidelines for the control of television broadcasts should adjust their recommendations to include the periphery of the viewing screen, especially if the area is large.

Chapter Ten

The relationship between occipital spikes and the photosensitive VEP

There are two main theories that lead to the assumption that occipital spikes are associated with photosensitive epilepsy. The first is that occipital spikes represent a focus from which the generalised response spreads, as they are frequently observed preceding the PPR (Harding and Jeavons, 1994; Panyiotopoulos et al, 1972). The studies in chapters four to nine investigated this assumption by examining whether occipital spikes and PPR showed similar response characteristics to various stimuli. No evidence was found for an association between the two response types and hence between occipital spikes and photosensitive epilepsy. The second assumption is that occipital spikes simply represent augmented components of the normal VEP. The differences between the amplitude and latency of the components of the photosensitive VEP and those in the normal VEP are reduced with medication and associated with poor seizure control (Fraught and Lee, 1984; Sutherling et al, 1980). Hence, if occipital spikes are simply augmented components that are present in the normal VEP then they are associated with photosensitive epilepsy regardless of whether they are associated with PPR. It is this assumption that is investigated in this chapter.

The literature investigating the relationship between occipital spikes and the VEP is discussed in chapter two. These investigations involved comparing the latencies of occipital spikes with the latencies of the normal components of the

VEP. One study (Hishikara et al, 1967) found that the latency of the initial positive component of the occipital spike corresponded to that of a positive component of the VEP and the negative spike to the latency of a negative component. However, three later studies found that the large negative component of the occipital spike did not coincide with the latency of any negative component of the VEP. In some subjects the negative spike coincided with the latency of the main positive component which occurred at approximately 100 msecs (Broughton et al, 1969; Panayiotopoulos et al, 1970(a) and 1972). In two cases the negative occipital spike appeared to interrupt the descending branch of the P_2 component and was thought to be associated with the P_{2b} component (Figure 10.1).

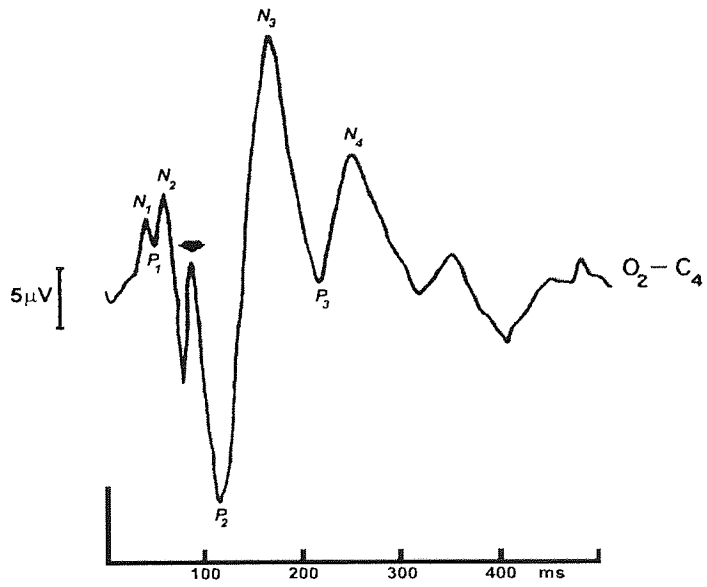


Figure 10.1. The VEP of patient with negative occipital spike (arrow) on the descending phase of the P_2 component. From Harding and Dimitrakoudi (1977).

These later studies do not support the assumption that occipital spikes are augmented components of the normal VEP. However, in all four studies, the latencies of the occipital spike could only be compared to the average latencies of the VEP components in the normal population. The variation in the latencies of the VEP components between subjects is large, even in the normal population, and the latencies of the components in the photosensitive population may show even greater variation.

An alternative method of investigating the components of the VEP is to estimate the electrically active region of the brain that is the source of the measured potential. This allows the components in a photosensitive VEP to be directly related to those in a normal VEP, by examining whether the sources underlying the components in a normal subject correspond to those underlying occipital spikes.

EEG measures the potential difference at the scalp. This is created by the electrically active source and by the extracellular currents that flow from the source to the scalp. EEG is therefore affected by any differences in electrical conductivity that occur in the path of the extracellular currents between the source and the scalp. The large differences in conductivity between the skull and surrounding tissue have the effect of spreading the potential patterns. This means that any estimate of the source that is based on these patterns is inaccurate, unless the precise value of the conductivity value is known. Magnetoencephalography (MEG) has previously been used in several studies to localise the source of the components of the VEP in the normal population (for

example: Armstong et al, 1991; Harding et al, 1991; Harding et al, 1992; Degg et al, 1992; Harding et al, 1994(b); Fylan et al, 1995). MEG measures the magnetic field that is created by the summed intracellular currents of many neurones. The magnetic field created by these electrical currents is not affected by changes in electrical conductivity within the head and therefore the spatial accuracy of MEG is theoretically better than that of EEG. Cohen et al (1990) contradicted this theory, but the methodology of the investigation has been criticised as favouring EEG. No difference in spatial resolution was found between MEG and EEG. However, twice the number of recordings were averaged for EEG and 10 of the 12 implanted sources were radial and were therefore not measured by MEG (Hamalainen et al, 1993). MEG had much better spatial resolution than EEG for the two tangential sources.

The magnetic fields measured by EEG are much smaller than those in an urban environment so measurements take place inside a magnetically shielded room. The fields are measured using Super Conducting Quantum Interference Devices or SQUIDS. The SQUIDS are contained in liquid helium, as they require very low temperatures to function. Gradiometers are used to decrease the influence of external noise sources, as they are more sensitive to fields produced by nearby sources than to those produced by distant sources.

A number of assumptions are made to localise the active sources within the brain that underlie the recorded magnetic fields. First, each source is modelled as a single equivalent dipole. A dipole is an abstract concept defined by current times length where length is infinitely small. It describes the source in terms of its

position within the head, its orientation and its strength. Second, the head is modelled as a single sphere that represents the inner boundary of the skull. In the occipital area, it is possible to approximate the circumference of the head well with this model.

An optimisation algorithm is then used to modify the parameters of the source model in order to achieve a good fit between the measured data and that predicted by the source model. The output is the source with the optimum parameters and a measure of the goodness of fit of the reconstruction.

A more detailed review of MEG is provided in Hamalainen et al (1993).

10.1. Methods

10.1.1. Participants

Three participants were investigated in this study selected from the Aston University clinical neurophysiology database and the neurophysiology units staff. Two of the participants were photosensitive. The first was a 25 year old male with no history of seizures but a history of large amplitude occipital spikes in response to both IPS and pattern stimulation. The second participant was his 26 year old sister who had a history of both visually induced seizures and occipital spikes in response to IPS and pattern stimulation. Both the photosensitive participants were taking sodium valporate and in both participants the resting EEG record was within normal limits. The third participants was a 34 year old female with no history of abnormalities to IPS or pattern stimulation and no history or family history of seizures.

10.1.2. Stimulus and recording system

The stimulus was a square-wave grating with a spatial frequency of 1 cpd reversing at 2 Hz. The stimulus was generated using the Neuroscan Stimulation Program (STIM) and displayed on a monitor with a 70 Hz refresh rate placed outside the magnetically shielded room. The monitor was viewed though a hole in the magnetically shielded room from a distance of 190 cm, at which it subtended 8.6 by 6.5 degrees of the visual angle.

The recordings were made with a 151 Channel, Omega whole-head MEG system (CTF Systems Inc). A synthetic third order gradiometer configuration was used and the sampling frequency was 1250 Hz. Three coils were used to determine the location of the head with respect to the sensors.

10.1.3. Proceedure

The participant sat in a comfortable upright position, with three head localisation coils attached to a velcro band that was wrapped around the head. An inflatable head cuff was placed around the head to minimise head movements. The subject's head was then positioned within the helmet shaped dewer containing the recording channels. The stimulus was viewed until 100 presentations had been recorded. The recording was then examined and any periods affected by eye movements or other sources of noise were removed. Time periods of 100 msecs before the stimulus and 300 msecs after the stimulus were averaged and the period before each stimulus was used to make the dc-correction. The data was filtered using 60 Hz and 50 Hz comb filters. After leaving the magnetically

shielded room the participants rested their teeth in a dental impression and their head shape was digitally recorded.

10.2. Results

The averaged magnetic visual evoked response for all three participants were then overlaid so that the response could be compared. This is illustrated in Figure 10.2.

A clear visual evoked response can be seen between 50 and 150 msecs in all three participants. The initial component occurred just before 100 msecs and had a shorter latency in the participants with photosensitive epilepsy (74 msec and 75 msec) than in the control subject (88 msecs). Another component of the opposite polarity is also present in all three participants between 120 and 130 msecs. There does not appear to be any difference in the latency of this component between the photosensitive participants and the control participant. A third component was visible only in the evoked potential of the photosensitive subjects. This component was the same polarity as the initial component and occurred at approximately 108 msecs. It is clearest on the channels overlying the left occipital cortex, ML033, ML032, ML022 and ML012. On these channels the third component interrupts the downward deflection between the other two components. This component is not visible in the magnetic visual evoked response of the control participant and represents the main component of the occipital spike.

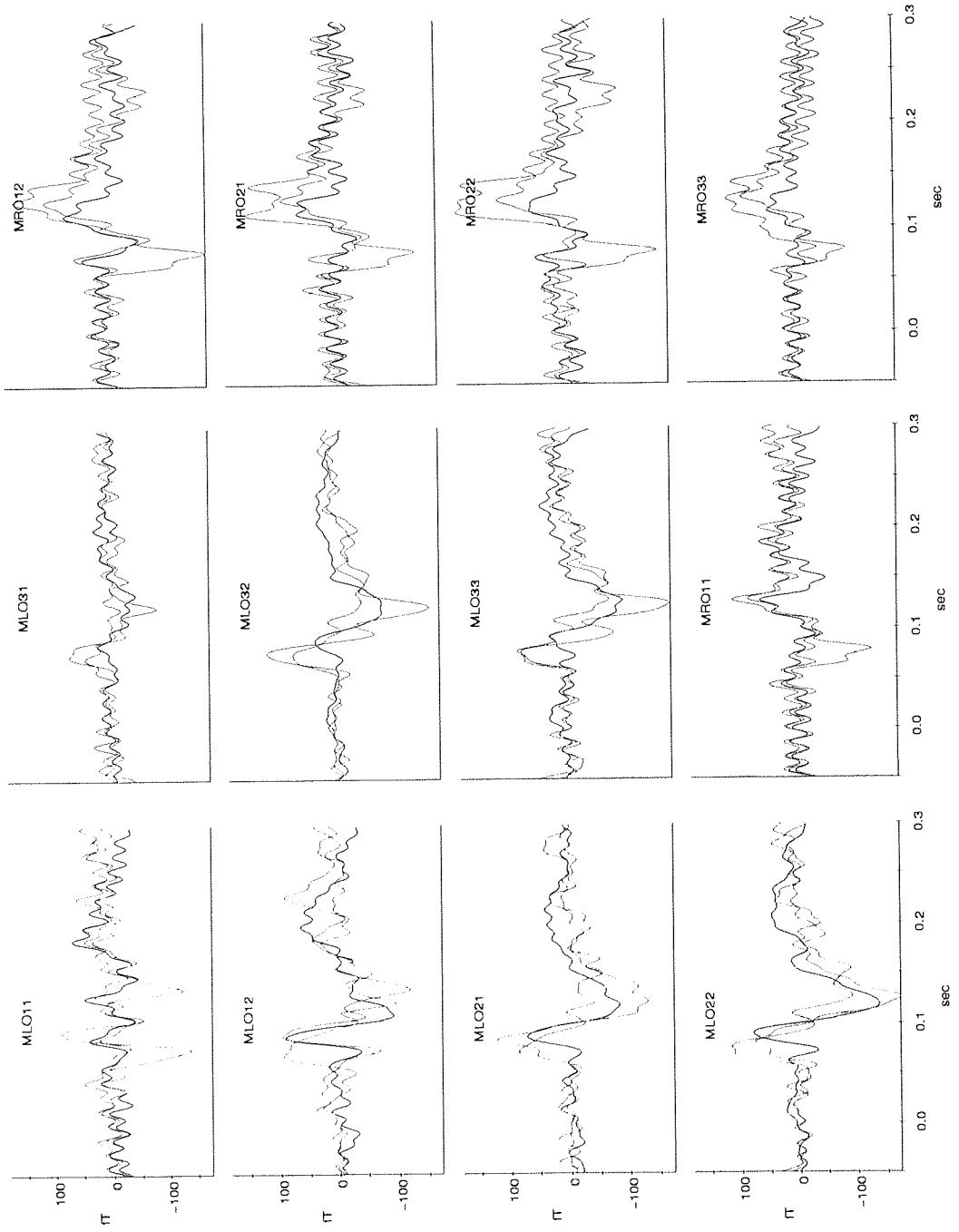


Figure 10.2. **The averaged magnetic evoked visual response recorded on selected occipital channels for all three subjects. The subjects illustrated in blue and red are photosensitive. The control subject is illustrated in black.**

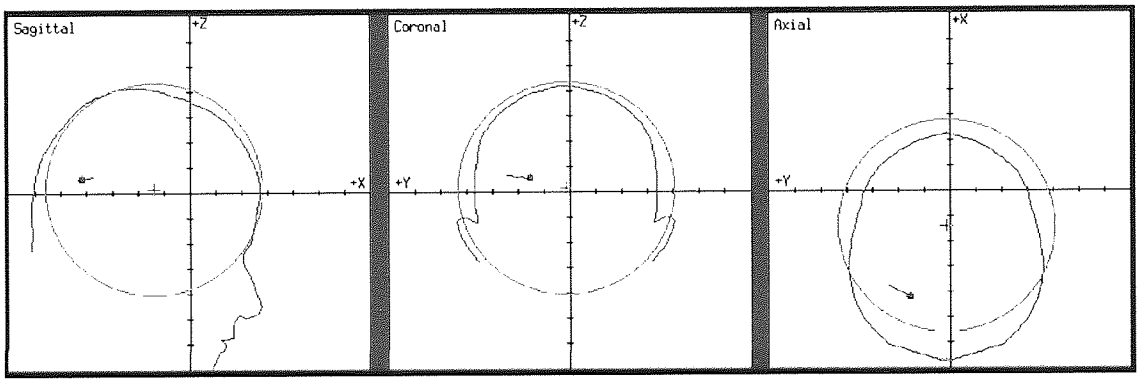
The active source, within the brain, underlying each component was then estimated. The magnetic field, which would be created by a given dipole, is compared to the recorded magnetic field. The dipole for which the difference between the computed and measured field is smallest, in the reduced chi-squared sense, is displayed on a schematic of the head, viewed from the top, the left and the back. A spherical estimate of the inside of the head is also displayed. The origin and radius of this sphere are calculated from the digitised head shape of the individual. The reduced chi-squared value gives a measure of how well the dipole or dipoles represent the underlying magnetic field. Monte Carlo analysis was carried out in order to test the stability of the solution with respect to the noise in the data. Random noise was added to the signals and source localisation was performed for each new noise realisation. The output is a 95% confidence volume for the best fitted dipole.

The initial dipole fit was estimated at the latency of the peak of each component with a single current dipole. The latency range was altered until a small chi-squared value was found and then the Monte Carlo volume was calculated. The source was then estimated with two current dipoles to examine whether this fit was more stable than the estimate with a single current dipole.

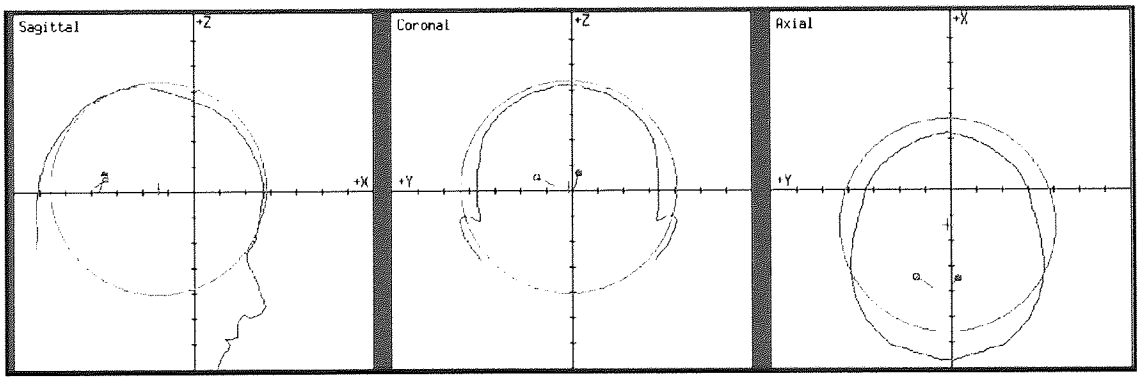
The dipole fits for the main components in one photosensitive participant and the control subject are shown in Figure 10.3. In the photosensitive participant a single current dipole was fitted at 74 msecs with a Monte Carlo volume of 0.251 cm^3 (Figure 10.3A). Two current dipoles were fitted to the component of opposite polarity over the latency range 122-126 msecs. The two Monte Carlo

volumes were 2.94 cm^3 and 0.566 cm^3 (Figure 10.3B). Similar results were found for the control participant. A single current dipole was fitted at 88 msecs with a Monte Carlo volume of 6.2 cm^3 (Figure 10.3C). Two current dipoles were fitted to the component with opposite polarity at 116-121 msecs. The two Monte Carlo volumes were 3.4 cm^3 and 0.8 cm^3 (Figure 10.3D).

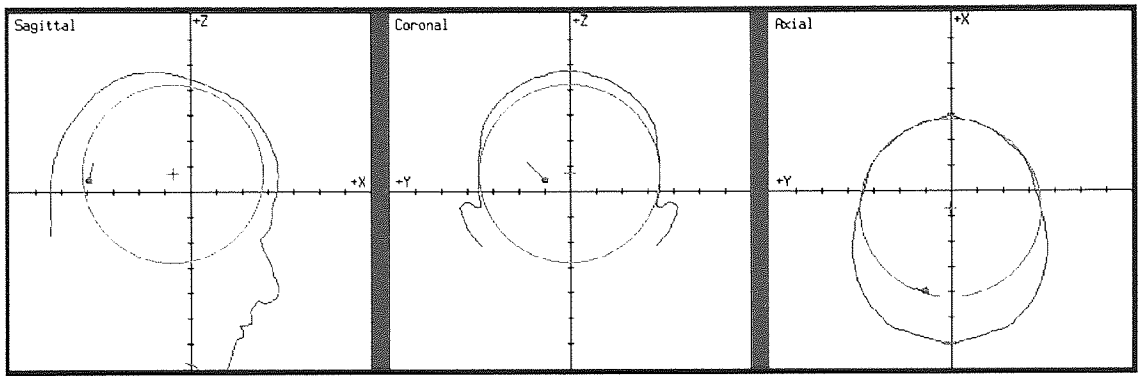
(A)



(B)



(C)



(D)

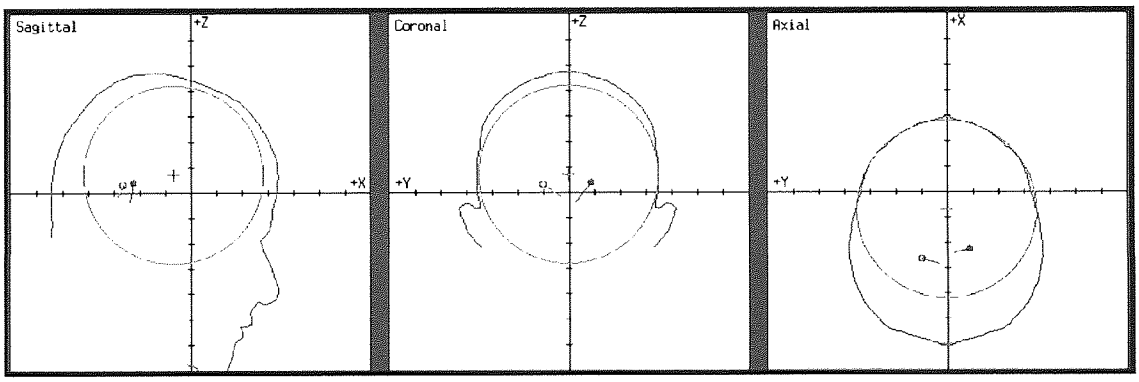
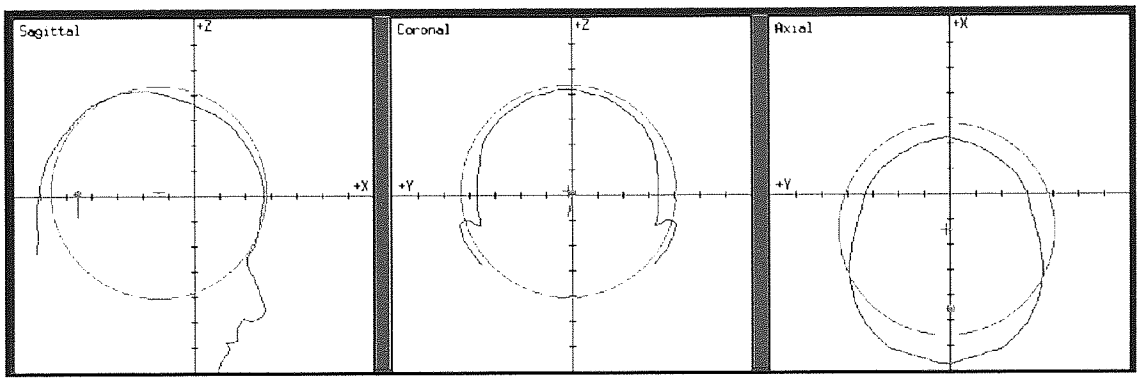


Figure 10.3. Diagrams of the dipole fits for the two components of the magnetic visual evoked response in a photosensitive subject (A+B) and a control subject (C+D). The dark blue line indicates the schematic outline of the head, the pale blue line indicates the spherical model of the head and the blue and pink circles within the sphere indicate the position of the dipole estimates.

The dipole fits for the occipital spikes that were only recorded in the photosensitive subjects are shown in Figure 10.4. In the first photosensitive subject, who was illustrated in the previous figure, a single current dipole was fitted at a latency of 109 msecs with a Monte Carlo volume of 0.420 cm^3 (Figure

10.4A). In the second photosensitive participant a single current dipole was fitted over the latency range 106-110 msecs with a Monte Carlo volume of 8.14 cm^3 (Figure 10.4B).

(A)



(B)

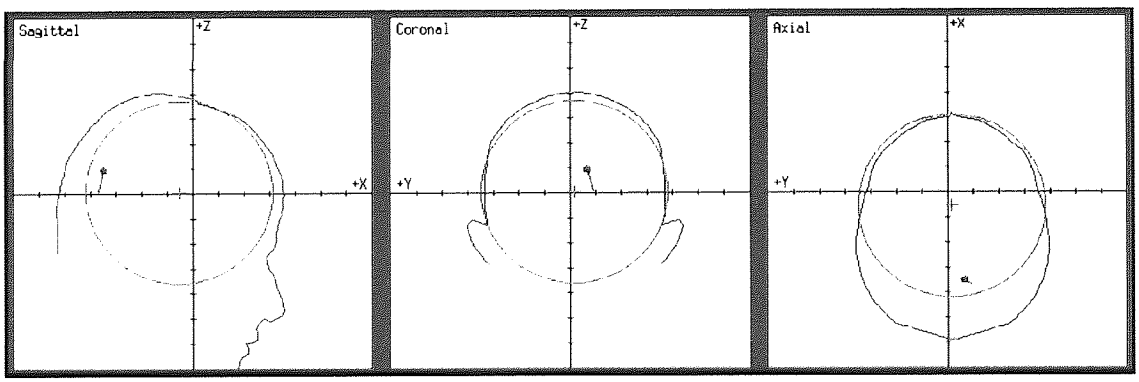


Figure 10.4. Diagrams of the dipole fits for the occipital spikes recorded in the magnetic visual evoked response of the two photosensitive subjects. The dark blue line indicates the schematic outline of the head, the pale blue line indicates the spherical model of the head and the blue and pink circles within the sphere indicate the position of the dipole estimates.

There is no evidence in Figure 10.3 and 10.4 that occipital spikes are generated via the same source as the component of the same polarity that proceeds them. From the coronal and axial view the source of the occipital spike appears to be on the right side of the head and the source of the main positive component on the left

10.3. Discussion

The results of this experiment illustrate two major findings. The averaged data from the occipital channels of the MEG (displayed in Figure 10.2) supports the finding that the P_2 of the photosensitive VEP is decreased in latency in photosensitive subjects (Faught and Lee, 1984). However, the small participant numbers meant that this was simply an observation and no statistical analysis could be carried out. They also illustrate that the additional component, that interrupts the P_2, is a separate component that is not present in the normal VEP. This component is thought to be related to the occipital spike when the stimulus frequency is increased (Panyiotopolous et al, 1972) (Figure 2.2).

The components appeared to be separate, so dipole estimates of the source were made to examine whether the electrical generators of the components were located in the same area of the brain. The dipole estimates of each of the component generators indicated that the source of the occipital spikes was not related to those of either of the main components that were recorded in the control subject. This is further evidence that the occipital spike is not simply an augmented component of the VEP.

The differences between the latency of the components in the normal and in the photosensitive VEP are associated with photosensitive epilepsy as they are more common in subjects with poor seizure control and are reduced when the seizures are controlled by medication. If the subject is medicated and still has poor seizure control then the abnormalities in the VEP remain (Sutherling et al,1980; Faught and Lee, 1984). It could therefore be argued that if the occipital spikes simply illustrate an augmentation and change in latency of the normal components then they too are related to photosensitive epilepsy. However, if, as this experiment suggests, occipital spikes represent an addition component then this argument is removed as a source of evidence that occipital spikes are involved in photosensitive epilepsy.

Chapter Eleven

Summary and conclusions

The main aim of this thesis was to investigate the role of cortical occipital spikes in photosensitive epilepsy. There are two sources of evidence that have lead to the assumption that occipital spikes are associated with photosensitive epilepsy. The first source of evidence is that PPR are associated with photosensitive epilepsy and occipital spikes are often observed preceding PPR. This has lead to the theory that occipital spikes represent a focus from which PPR spread and are therefore also associated with photosensitive epilepsy. The second assumption is that occipital spikes simply represent a change in the amplitude and latency of the normal components of the VEP. Differences between the amplitude and latency of the components of the normal and photosensitive VEP have been recorded and are associated with poor seizure control. Therefore, if occipital spikes were changes in the normal components of the VEP then they would be associated with photosensitive epilepsy even if they are not associated with PPR.

The theory that occipital spikes represent a focus for PPR was investigated in chapters four to nine by examining whether occipital spikes and PPR showed similar dependence on stimulus characteristics. The results were also compared to visual physiology literature to investigate whether the responses are generated via different pathways. If the responses are generated via different pathways then this would provide further evidence against an association between the response types.

The studies investigating the effects of luminance contrast were described in chapter four. The probability of PPR showed a linear increase with increasing luminance contrast and showed little saturation. The probability of occipital spikes increased rapidly with increasing luminance contrast and saturated at approximately 20% contrast. The contrast thresholds for occipital spikes were also significantly lower than for PPR. The linear increase in the group data for PPR may be explained in terms of individual differences in contrast thresholds but this does not explain the finding that the contrast thresholds for occipital spikes were significantly lower than those for PPR. The finding that occipital spikes and PPR show different dependence on luminance contrast is evidence against them acting as a focus for the generalised response and therefore against an association between the occipital spikes and PPR. The differences in contrast thresholds and contrast gain are also consistent with the contrast dependence of the magnocellular and parvocellular pathways. Occipital spikes showed similar contrast dependence to the magnocellular pathway and PPR similar to that of the parvocellular pathway.

In chapter five two studies were described which investigated whether colour contrast was involved in the production of occipital spikes and PPR. Occipital spikes were not provoked by changes in colour contrast even when they were combined with low levels of luminance contrast. PPR were provoked by isoluminant alterations in colour contrast but only when the opponent colour was not present. Alterations between non-opponent colours were also found to combine with luminance contrast to increase the probability of provoking a PPR. As occipital spikes and PPR show different dependence on colour contrast these

findings provide further evidence against an association between the response types and hence between occipital spikes and photosensitive epilepsy. The results are also consistent with the parallel processing theory postulated in chapter four, as the parvocellular pathway is dominant over the magnocellular in colour processing. This presents further evidence against an association between occipital spikes and PPR.

The spatial and temporal frequency characteristics of occipital spikes and PPR were investigated in the studies described in chapters six and seven. Occipital spikes and PPR were found to have similar optimum spatial and temporal frequencies, which may be evidence of an association between the two response types. However, this is not strong evidence of an association as different pathways may still generate the response. The magnocellular and parvocellular pathways show similar optimum spatial and temporal frequencies and differ only in the limits of the range over which the cells respond.

Monocular occlusion reduces the probability of abnormal response in many photosensitive subjects. Chapter eight described studies which compared the effects of monocular occlusion in subjects showing occipital spikes and PPR. Though both responses were reduced by monocular occlusion, the effects were significantly greater for PPR than for occipital spikes. Again, as monocular occlusion has different effects depending on the response type this is evidence against an association between occipital spikes and PPR.

In chapter nine the effects of peripheral and central stimulation were investigated. Both occipital spikes and PPR can be generated via central or peripheral stimulation if the area of the stimulus is adjusted to account for the effects of cortical magnification. However, again, this is not strong evidence for an association between the response types as both the parvocellular and magnocellular pathways are present in the periphery of the retina.

Chapters four to nine showed little evidence of an association between occipital spikes and PPR and no evidence against the theory that they are generated via different visual pathways. It is therefore unlikely that occipital spikes represent a focus from which PPR spread and hence this assumption can be removed as a source of evidence supporting the theory that occipital spikes have a role in photosensitive epilepsy.

The second source of evidence supporting the theory, that occipital spikes have a role in photosensitive epilepsy, is independent of an association between occipital spikes and PPR. This was investigated in the study described in chapter ten. The magnetic visual evoked response of the photosensitive subjects showed a separate additional component to those recorded in the control. The estimated dipole fits suggested that this occipital spike had a different underlying source from the components which were present in the control magnetic visual evoked response. This finding removes the assumption that occipital spikes represent changes in the amplitude and latency of the components of the normal VEP, as a source of evidence for occipital spikes having a role in photosensitive epilepsy.

In addition to the main finding of the study there were a number of interesting clinical findings in this thesis.

The investigation into the effects of luminance contrast showed that occipital spikes are provoked at lower contrast than PPR. In order to ensure that PPR are detected the contrast of pattern stimulation must therefore be high. This finding may also illustrate a way of detecting occipital spikes, while reducing the risk of provoking PPR by reducing the contrast, allowing occipital spikes to be investigated with a lower risk of provoking seizures.

The finding that colour may play a role in provoking abnormal response is important clinically as it was previously thought that isoluminant alterations of colour contrast did not provoke abnormal response. However, this is not the case if the alterations are between non-opponent colours. This suggests that Independent Television Commission guidelines should be expanded to include controls on rapid changes between non-opponent colours, especially if they are combined with even low levels of luminance contrast.

Chapters six and seven described studies which investigated the optimum spatial and temporal frequencies for detecting PPR and occipital spikes. This information could be used to improve the design of clinical protocols as, while it is important to detect any photosensitive response in the subject, it is also important to keep the testing period to a minimum to avoid the effects of fatigue.

Monocular occlusion is the main method of behavioural therapy in photosensitive epilepsy. The results of the studies described in chapter eight illustrate that the effects are variable even within the group showing PPR, and in some subjects monocular occlusion had no affect on the response. It is therefore important that the effects of monocular occlusion are investigated in the individual before they are advised that it is protective.

In conclusion, the finding of this study should lead to improvements in the design of clinical IPS and pattern stimulation protocols and in Independent Television Commission guidelines, which protect viewers from the risk of seizures. The role of the magnocellular and parvocellular pathways in the generation of the responses was not fully established but merits further investigation once the findings of the visual physiology are more precisely defined. The main finding of the study is that is serves to illustrate that, while occipital spikes should not be dismissed when they are recorded in the EEG of individuals, it should not be assumed that they play a role in photosensitive epilepsy.

References

Allen, A., Morrow, JI.

'Sonic, Tonic, Clonic' three cases of video game epilepsy

The Ulster Medical Journal 1994; 63: 99-102

Aoki, Y.

A clinical-electroencephalographic study on photosensitive epilepsy, with special reference to visual evoked potential

Folia Psychiatrica et Neurologica Japonica 1969; 23: 103-119

Armstrong, RA., Slaven, A., Harding, GFA.

Visual evoked magnetic fields to flash and pattern in 100 normal subjects

Vision Research 1991; 3: 1859-1864

Aziz, H., Francis, P., Ali, SM., Hasan, Z.

Epilepsy and photosensitivity

Journal of the Pakistan Medical Association 1989; 39: 212-214

Baier, WK., Doose, H.

Interdependence of different genetic EEG patterns in siblings of epileptic patients

Electroencephalography and Clinical Neurophysiology 1987; 66: 483-488

Baseler, HA., Sutter, EE.

M and P components of the VEP and their visual field distribution

Vision Research 1997; 37: 675-690

Benardette, EA., Kaplan, E.

The receptive field of the primate P retinal ganglion cell, I: Linear dynamics

Visual Neuroscience 1997; 14: 169-185

Benardette, EA., Kaplan, E., Knight, BW.

Contrast gain control in the primate retina: P cells are not X-like, some M cells are

Visual Neuroscience 1992; 8: 483-486

Binnie, CD., Wilkins, AJ., Darby, CE.

Pattern sensitivity: The role of movement

Proceedings of the Second European Congress of Electroencephalography and Clinical Neurophysiology 1979: 650-655

Binnie, CD., Darby, CE., De Korte, RA., Veldhuizen, R., Wilkins, AJ.

EEG sensitivity to television: effects of ambient lighting

Electroencephalography and Clinical Neurophysiology 1980; 50: 329-331

Binnie, CD., Estevez, O., Kasteleijn-Nolst Trenite, DGA., Peters, A.

Colour and photosensitive epilepsy

Electroencephalography and Clinical Neurophysiology 1984; 58: 387-391

Binnie, CD., Findlay, J., Wilkins, AJ.

Mechanisms of epileptogenesis in photosensitive epilepsy implied by the effects of moving patterns

Electroencephalography and Clinical Neurophysiology 1985; 61: 1-6

Binnie, CD., Kasteleijn-Nolst Trenite, DGA., De Korte, R.

Photosensitivity as a model for acute antiepileptic drug studies

Electroencephalography and Clinical Neurophysiology 1986; 63: 35-41

Binnie, CD., Jeavons, PM.

Photosensitive epilepsies

In: J. Roger, M. Bureau, Ch. Dravet, FE. Dreifuss, A. Perret and P.Wolf (1992). Epileptic syndromes in infancy, childhood and adolescence. John Libbey and Company Ltd: 299-305

Bowmaker, JK., Dartnall, HJA.

Visual pigments of rods and cones in the human retina

Journal of Physiology 1980; 298: 501-511

Brigell, M., Strafella, A., Parmeggiani, L., Demarco, P.J., Celesia, G.G.

The effects of luminance and chromatic background flicker on the human visual evoked potential

Visual Neuroscience 1996; 13: 265-275

Brinciotti, M., Trasatti, G., Pelliccia, A., Matricardi, M.

Pattern-sensitive epilepsy: Genetic aspects in two families

Epilepsia 1992; 33: 88-92

Brincotti, M., Matricardi, M., Pelliccia, A., Trasatti, G.

Pattern sensitivity and photosensitivity in epileptic children with visually induced seizures

Epilepsia 1994; 35: 842-849

Broughton, R., Meier-Ewert, KH., Ebe, M.

Evoked visual, somato-sensory and retinal potentials in photosensitive epilepsy

Electroencephalography and Clinical Neurophysiology 1969; 27: 373-386

Campanille, V., Corral, S,. Gori, H., Grippo, J.

Photosensitive epilepsy

Epilepsia 1995; 36 (suppl. 3): S197

Carterette, EC., Symmes, D.

Colour as an experimental variable in photic stimulation

Electroencephalography and Clinical Neurophysiology 1952; 4: 289-296

Chatrian, GE., Lettich, E., Miller, LH., Green, JR.

Pattern sensitive epilepsy; Part one: An electrographic study of its mechanisms

Epilepsia 1970; 11: 125-149

Chen, Y., Bedell, HE., Frishman, LJ.

Temporal-contrast discrimination and its neural correlates

Perception 1996; 25: 505-522

Cohen, D., Cuffin, BN., Yunokuchi, K., Maniewski, R., Purcell, C., Cosgrove, GR., Ives, J., Kennedy, JG., Schomer, DL.

MEG versus EEG localisation test using implanted sources in the human brain

Annals of Neurology 1990; 28: 811-817

Corbett, JM., White, TA.

Visibility of flicker in television pictures

Nature 1976; 261: 689-690

Covanis, A., Gupta, AK., Jeavons, PM.

Sodium valporate: Monotherapy and polytherapy

Epilepsia 1982; 23: 693-720

Croner, L.J., Kaplan, E.

Receptive fields of P and M ganglion cells across the primate retina

Vision Research 1995; 35: 7-24

Dacey, DM., Petersen, MR.

Dendritic field size and morphology of midget and parasol ganglion cells of the human retina

Proceedings of the National Academy of Science USA 1992; 89: 9666-9670

Danesi, MA., Oni, K.

Photosensitive epilepsy and photoconvulsive responses to photic stimulation in Africans

Epilepsia 1983; 24: 455-458

Darby, CE., Wilkins, AJ., Binnie, CD., deKorte, R.

Routine testing for pattern sensitivity

Journal of Electrophysiological Technology 1980; 6: 202-210

Declerk, AC., Oei, LT., Arnoldussen, W., te Dorsthorst, M.

Alterations in transient visual-evoked potentials induced by clonazepam and sodium valporate

Neuropsychobiology 1985; 14: 39-41

Degg, C., Slaven, A., Armstrong, RA.

Topographic mapping and source localisation of the pattern onset visual evoked magnetic response

Brain Topography 1992; 5: 11-16

De Graaf, AS.

Prevalence of photoparoxysmal response in the electroencephalograms in the three main ethnic groups of Namibia

Clinical Neurology and Neurosurgery 1992; 94 (Suppl): S67-S69

Dobkins, KR., Albright, TD.

What happens if it changes colour when it moves?: Psychophysical experiments on the nature of chromatic input to motion detectors

Vision Research 1993; 33: 1019-1036

Dobkins, KR., Albright, TD.

What happens if it changes colour when it moves?: The nature of chromatic input to macaque visual area MT

The Journal of Neuroscience 1994; 14: 4854-4870

Donath, V.

Pattern reversal VEP in epilepsy (A prognostic tool?)

Homeostasis in Health and Disease 1991; 33: 34-38

Engel, J.

Selective photoconvulsive responses to intermittent diffuse and patterned photic stimulation

Electroencephalography and Clinical Neurophysiology 1974; 37: 283-292

Fraught, E., Lee, EE.

Pattern-reversal visual evoked potentials in photosensitive epilepsy

Electroencephalography and Clinical Neurophysiology 1984; 59: 125-133

Feely, M.

Drug treatment of epilepsy

British Medical Journal 1999; 318: 106-109

Fylan, F., Holliday, IE., Singh, KD., Anderson, SJ., Harding, GFA.

Evoked magnetic response to chromatic and luminance patterns differ in area V1 in human

Investigative Opthalmology and Visual Science 1995; 36: S1053

Fylan, F., Harding, GFA.

The effect of television frame rate on EEG abnormalities in photosensitive and pattern sensitive epilepsy

Epilepsia 1997; 38: 1124-1131

Gerken, H.

Clinical observations on photosensitive epilepsy

Electroencephalography and Clinical Neurophysiology; 27: 683

Gilliam, FG., Chiappa, KH.

Significance of spontaneous epileptiform abnormalities associated with a photoparoxysmal response

Neurology 1995; 45: 453-456

Graf, WD., Chatrian, G., Glass, ST., Knauss, TA.

Video game related seizures: A report on 10 patients and a review of the literature

Pediatrics 1994; 93: 551-556

Green, JB.

Photosensitive epilepsy: The electroretinogram and visually evoked response

Archives of Neurology 1969; 20: 191-198

Guerrini, R., Dravet, C., Genton, P., Bureau, M., Bonanni, P., Ferrari, AR., Roger, J.

Idiopathic photosensitive occipital lobe epilepsy

Epilepsia 1995; 36: 883-891

Gur, M., Akri, V.

Isoluminant stimuli may not expose the full contribution of colour to visual functioning: Spatial contrast sensitivity measurements indicate interaction between colour and luminance processing

Visual Research 1992; 32: 1253-1262

Hamalainen, M., Hari, R., Ilmoniemi, RJ., Knuutil, J., Lounamaa, OV.

Magnetoencephalography-theory, instrumentation and applications to non-invasive studies of the working human brain

Reviews of Modern Physics 1993; 65: 413-495

Harding, GFA.

The visual evoked response

In: MJ. Roper-Hall et al (1974). Advances in ophthalmology 28. Kager-Basel: 2-28.

Harding, GFA.

Photosensitive epilepsy

In: DJ. Osborne, MM. Gruneberg, JR. Eiser (1980). Research in psychology and medicine. Academic Press, London.

Harding, GFA.

Technical issues in visual evoked cortical potential recording

In: JR. Heckenlively, GB. Arden, (eds), E. Arachi-Usami, GFA. Harding, SE.Nilsson, RG. Weleber (Assoc eds) (1991). Principles and practice of clinical electrophysiology of vision: Part X: Visual evoked cortical potentials. Mosby Year Book Inc. St. Louis, USA: 435-437.

Harding, GFA.

Photosensitive epilepsy: comment article

Neurology 1994(a); 10: 3-7

Harding, GFA.

Photosensitivity: a vestigial echo? The first Grey Walter lecture

International Journal of Physiology 1994(b); 16: 273-279

Harding, GFA., Dimitrakoudi, M.

The visual evoked potential in photosensitive epilepsy

In: JE. Desmedt (Ed). Visual evoked potentials in man: New developments

Oxford. Clarendon Press. pp 75-87.

Harding, GFA., Herrick, CE., Jeavons, PM.

A controlled study of the effect of sodium valporate on photosensitive epilepsy and its prognosis

Epilepsia 1978; 19: 555-565

Harding, GFA., Alford, CE., Powell, TE.

The effect of sodium valporate on sleep, reaction times and visual evoked potential in normal subjects

Epilepsia 1985; 26: 597-601

Harding, GFA., Janday, B., Armstrong, RA.

Topographic mapping and source localisation of the pattern reversal visual evoked magnetic response

Brain Topography 1991; 4: 47-55

Harding, GFA., Armstrong, RA., Janday, B.

Visual evoked electrical and magnetic response to half-field stimulation using pattern reversal stimulation

Ophthalmic and Physiological Optics 1992; 12:171-174

Harding, GFA., Jeavons, PM.

Photosensitive epilepsy.

MCO. Bax, PA. Davis, M. Pountney, P. Chappelle (Eds). London: Mac Keith Press. (1994).

Harding, GFA., Jeavons, PM., Edson AS.

Video material and epilepsy

Epilepsia 1994(a); 35: 1208-1216

Harding, GFA., Degg, C., Anderson, SJ., Holliday, I., Fylan, F., Barnes, G., Bedford, J.

Topographic mapping of the pattern onset evoked magnetic response to stimulation of different portions of the visual field

International Journal of Psychophysiology 1994(b); 16: 174-183

Harding, GFA., Edson, A., Jeavons, PM.

Persistence of photosensitivity

Epilepsia 1997; 38: 663-669

Hart, EJ.

Nintendo epilepsy

The New England Journal of Medicine 1990; 322: 1473

Harter, MR., White, CT.

Evoked cortical responses to checkerboard patterns: effect of check-size as a function of visual acuity

Electroencephalography and Clinical Neurophysiology 1970; 28: 48-54

Helgott, PC., Meiser, J.
Seizures apparently triggered by video games
Journal of the American Medical Association 1983; 250: 1273

Herrick, CE., Jeavons, PM., Harding, GFA.
Study of a photosensitive family
Electroencephalography and Clinical Neurophysiology 1975; 39: 438-430

Herrick, CE., Harding, GFA.
The effect of sodium valporate on the photosensitive VEP
In: C. Barber. Evoked Potentials. MTP Press, Lancaster: 539-547, 1980

Hess, RF., Harding, GFA., Drasdo, N.
Seizures induced by flickering light
American Journal of Optometry and Physiological Optics 1974; 51: 517-529

Hishikawa, Y., Yamamoto, J., Furuya, E., Yamada Y., Miyazaki, K., Kaneko, Z.
Photosensitive epilepsy: relationships between visual evoked responses and the epileptiform discharges induced by intermittent photo stimulation
Electroencephalography and Clinical Neurophysiology 1967; 23: 320-334

Hicks, TP., Lee, BB., Vidyasagar, TR.
The responses of cells in macaque lateral geniculate nucleus to sinusoidal gratings
Journal of Physiology 1983; 337: 183-200

Hobley, AJ., Harding, GFA.
The effect of eye closure on the flash visually evoked response
Clinical Vision Science 1988; 3: 273-278

Hubel, DH., Livingstone, MS.
Colour and contrast sensitivity in the lateral geniculate body and primary visual cortex of the macaque monkey
The Journal of Neuroscience 1990; 10: 2223-2237

Irvin, GE., Casagrande, VA., Norton, TT.

Centre / surround relationships of magnocellular, parvocellular, and koniocellular relay cells in primate geniculate nucleus

Visual Neuroscience 1993; 10: 363-373

Jayakar, P., Chiappa, KH.

Clinical correlation's of photoparoxysmal responses

Electroencephalography and Clinical Neurophysiology 1990; 75: 251-254

Jeavons, PM.

Photosensitive epilepsy

In: J. Laidlaw, A. Richens (1982). A textbook of epilepsy. Churchill Livingstone, Edinburgh: 195-211

Jeavons, PM.

Photosensitive epilepsies

In: J. Roger, C. Dravat, M. Bureau, FE. Dreifuss, P. Wolf (1985). Epileptic syndromes in infancy, childhood and adolescence. John Libbey Eurotext Ltd: 232-236

Jeavons, PM., Harding, G., Bower, BD.

Intermittent photic stimulation in photosensitive epilepsy

Electroencephalography and Clinical Neurophysiology 1966; 21: 308

Jeavons, PM., Harding, GFA., Panayiotopoulos, CP., Drasdo, N.

The effect of geometric patterns combined with intermittent photic stimulation in photosensitive epilepsy

Electroencephalography and Clinical Neurophysiology 1972(a); 3: 221-224

Jeavons, PM., Harding, GFA., Panayiotopoulos, C.

The effect of lateral gaze and lateral illumination on photoconvulsive responses to intermittent photic stimulation

Electroencephalography and Clinical Neurophysiology 1972(b); 33: 445-448

Jeavons, PM., Clark, JE., Maheshwari, MC.

Treatment of generalised epilepsies of childhood and adolescence with sodium valporate ('epilim')

Developmental Medicine and Child Neurology 1977(a); 19: 9-25

Jeavons, PM., Herrick, CE., Maheshwari, MC., Harding, GF.

Therapy and prophylaxis in photosensitive epilepsy

In: J. Majowski 1977(b) Post-traumatic epilepsy and pharmacological prophylaxia. Warsaw: 238-240

Jeavons, PM., Barton, ME., Bishop, A.

Seizures and hand-held space invaders

The Lancet 1981; Oct 3: 758

Kaplan, E., Shapley, RM.

The primate retina contains two types of ganglion cells, with high and low contrast sensitivity

Proceedings of the National Academy of Science 1986; 83: 2755-2757

Kasteleijn-Nolst Trenite, DGA.

Photosensitivity in epilepsy-Electrophysiological and clinical correlates

Acta Neurologica Scandinavica, Supplementum 1989; 80 (suppl.125): 3-149

Kasteleijn-Nolst Trenite, DGA.

Video-game epilepsy

Lancet 1994; 344: 1102-1103

Kasteleijn-Nolst Trenite, DGA., Binnie, CD., Meinardi, H.

Photosensitive patients: Symptoms and signs during intermittent photic stimulation and their relation to seizures in daily life

Journal of Neurology, Neurosurgery and Psychiatry, 1987; Vol 50: 1546-1549

Kasteleijn-Nolst Trenite, DGA., van Emde Boas, W., Binnie, CD.

Photosensitivity - a human 'model' of epilepsy

In: A. Malafosse, P. Genton, E. Hirst, C. Marescaux, D. Brogin, R. Bernasconi (1994). Idiopathic generalised epilepsies: clinical, experimental and genetic aspects. John Libbey and Company Ltd. London: 297-303

Kremers, J., Lee, BB., Pokorny, J., Smith, VC.

Responses of macaque ganglion cells and human observers to compound periodic waveforms

Vision Research 1993; 33: 1997-2011

Kremers, J., Weiss, S., Zrenner, E.

Temporal properties of marmoset lateral geniculate cells

Vision Research 1997; 37: 2649-2660

Kubova, Z., Kuba, M., Spekreijse, H., Blakemore, C.

Contrast dependence of motion onset and pattern reversal evoked potentials

Vision Research 1995; 35: 197-205

Lee, BB.

Receptive field structure in the primate retina

Vision Research 1996; 36: 631-644

Lee, SI., Messenheimer, JA., Wilkinson, EC., Brinkley, JJ., Johnson, RN.

Visual evoked potentials to stimulus trains: normative data and application to photosensitive seizures

Electroencephalography and Clinical Neurophysiology 1980; 48: 387-394

Lee, BB., Pokorny, J., Smith, VC., Kremers, J.

Responses to pulses and sinusoids in macaque ganglion cells

Vision Research 1994; 34: 3081-3096

Leonards, U., Singer, W.

Selective temporal interactions between processing streams with differential sensitivity for colour and luminance contrast

Vision Research 1997; 37: 1129-1140

Leventhal, AG., Rodieck, RW., Dreher, B.

Retinal ganglion cell classes in the old world monkey: Morphology and central projections

Science 1981; 213: 1139-1142

Livingstone, M., Hubel, D.

Segregation of form, colour, movement, and depth: Anatomy, physiology, and perception

Science 1988; 240: 740-749

Logothetis, NK., Schiller, PH., Charles, ER., Hurlbert, AC.

Perceptual deficits and the activity of the colour-opponent and broad-band pathways at isoluminance

Science 1990; 247: 214-217

Long, GM., Tuck, JP.

Comparison of contrast sensitivity functions across three orientations: implications for theory and testing

Perception, 1991; 20: 373-380

Lucking, CH., Creutzfeldt, OD., Heinemann, U.

Visual evoked potentials of patient with epilepsy and of a control group

Electroencephalography and Clinical Neurophysiology 1970; 29: 557-566

Li, CY., Guno, K.

Measurements of geometric illusions, illusory contours and stereo-depth at luminance and colour contrast

Vision Research 1995; 35: 1713-1720

Maeda, Y., Kurokawa, T., Sakamoto, K., Kitamoto, I., Ueda, K., Tashima, S.

Electroclinical study of video game epilepsy

Developmental Medicine and Child Neurology 1990; 32: 493-500

Maheshwari, MC., Jeavons, PM.

The clinical significance of occipital spikes as a sole response to intermittent photic stimulation

Electroencephalography and Clinical Neurophysiology 1975; 39: 93-95

Meldrum, B.

Gaberergic agents as anticonvulsants in baboons with photosensitive epilepsy

Neuroscience Letters 1984; 47: 345-349

Meldrum, BS., Wilkins, AJ.

Photosensitive epilepsy in man and the baboon: Integration of pharmacological and psychophysical evidence

In: PA. Schwartzkron, HV. Wheal. (1994). Electrophysiology of epilepsy. Academic Press. London.

Menini, C., Brailowsky, S., Silva-Barrat, C., Riche, D., Naquet, R.

Cortical GABAeric control of photosensitivity in baboons

Epilepsia 1988; 29: 216

Menini, C., Silva-Barrat, C.

The photosensitive epilepsy of the baboon - A model of the generalised reflex epilepsy

In: BG. Zifkin, A. Beaumanoir, AJ. Rowan (1998) Advances in Neurology, Vol 75: Reflex Epilepsies and reflex seizures. Lippincott-Raven Publishers, Philadelphia.

Merigan, WH., Maunsell, JHR.

Macaque vision after magnocellular lateral geniculate lesions

Visual Neuroscience 1990; 5: 347-352

Merigan, WH., Katz, LM., Maunsell, JHR.

The effects of parvocellular lateral geniculate lesions on the acuity and contrast sensitivity of macaque monkeys

The Journal of Neuroscience 1991(a); 11: 994-1001

Merigan, WH., Byrne, CE., Maunsell, JHR

Does primate motion perception depend on the magnocellular pathway?

The Journal of Neuroscience 1991(b); 11: 3422-3429

Merigan, WH., Maunsell, JHR.

How parallel are the primate visual pathways?

Annual Review of Neuroscience 1993; 16: 369-402

Mervaala, E., Penttila, M., Keranen, T., Partanen, J., Riekkinen, P.

Pattern-VEP and SEP study in photosensitive and partial epilepsy

Acta Neurologica Scandinavica 1984; 70: 245

Mervaala, E., Kerenen, T., Penttile, M., Partanen, JV., Riekkinen, P.

Pattern-reversal VEP and cortical SEP latency prolongations in epilepsy

Epilepsia 1985; 26: 441-445

Nealey, TA., Maunsell, JHR.

Magnocellular and parvocellular contributions to the responses of neurones in macaque striate cortex

The Journal of Neuroscience 1994; 14: 2069-2079

Naquet, R., Catier, J., Menini, C.

Neurophysiology of photically induced epilepsy in Papio papio

In: BS. Meldrum and CD. Marsden (1975) Advances in neurology Vol 10. Raven Press, New York: 107-118

Naquet, R., Silva-Barret, C., Menini, C.

Reflex epilepsy in the papio-papio baboon, particularly photosensitive epilepsy

The Italian Journal of Neurological Sciences 1995; 16: 119-125

Naquet, RG., Valin, A.

Experimental model of reflex epilepsy

In: BS. Meldrum and CD. Marsden (1998). Advances in neurology Vol 75: Reflex epilepsies and reflex seizures. Lippincott-Raven Publishers, Philadelphia.

Obeid, T., Daif, AK., Waheed, G., Yaqub, WB., Panayiotopoulos, CP., Tahan, AR., Shamena, A.

Photosensitive epilepsies and photoconvulsive responses in Arabs

Epilepsia 1991; 32: 77-81

Okubo, Y., Matsuura, M., Asai, T., Asai, K., Kato, M., Kojima, T., Toru, M.

Epileptiform EEG discharges in healthy children: prevalence, emotional and behavioural correlates and genetic influences

Epilepsia 1994; 35: 832-841

Panayiotopoulos, CP., Jeavons, PM., Harding, GFA.

Relation of occipital spikes evoked by intermittent photic stimulation to visual evoked responses in photosensitive epilepsy

Nature1970(a); 228: 566-567,

Panayiotopoulos, CP., Jeavons, PM., Harding, GFA.

Occipital spikes during photic stimulation and their relation to visual evoked responses in photosensitive epilepsy

Electroencephalography and Clinical Neurophysiology 1970(b); 29: 327

Panayiotopoulos, CP., Jeavons, PM., Harding, GFA.

Occipital spikes and their relation to visual evoked responses in epilepsy, with particular reference to photosensitive epilepsy

Electroencephalography and Clinical Neurophysiology 1972; 32: 179-190

Pedley, TA.

Epilepsy and the human electroencephalogram

In: PA. Schwartzkron, HV. Wheal. (1984). Electrophysiology of epilepsy. Academic Press. London.

Plaster, GA., Lodge, KJ., Mulvaney, DE.

Effect of distance of photostimulation on a photosensitive epileptic subject

Psychological Reports 1979; 45: 271-274

Porciatti, V., Bonanni, P., Fiorentini, A., Guerrini, R.

Lack of cortical contrast gain control in human photosensitive epilepsy

Nature Neuroscience 2000; 3: 259-263

Purpura, K., Tranchina, D., Kaplan, E., Shapley, RM.

Light adaption in the primate retina: Analysis of changes in gain and dynamics of monkey retinal ganglion cells

Visual Neuroscience 1990; 4: 75-93

Quesney, LF.

Pathophysiology of generalised photosensitive epilepsy in the cat

Epilepsia 1984; 25: 61-69

Quirk, JA., Fish, DR., Smith, SJM., Sander, JWAS., Shorvon, SD., Allen, PJ.

Incidence of photosensitive epilepsy: a prospective national study

Electroencephalography and Clinical Neurophysiology 1995(a); 95: 260-267

Quirk, JA., Fish, DR., Smith, SJM., Sander, JWAS., Shorvon, SD., Allen, PJ.

First seizures associated with playing electronic screen games: A community-based study in Great Britain

Annals of Neurology 1995(b); 37: 733-737

Ricci, S., Vigevano, F., Manfredi, M., Kasteleijn-Nolst Trenite, DGA.

Epilepsy provoked by television and video games: Safety of 100-Hz screen

Neurology 1998; 50: 790-793

Rovamo, J., Virsu, V., Nasanen, R.

Cortical magnification factor predicts the photic contrast sensitivity of peripheral vision

Nature 1978; 271: 54-56

Rushton, DN.

Space invader epilepsy

The Lancet 1981; Feb 28: 501

Saleem, SM., Thomas, M., Jain, S., Mahashwari, MC.

Incidence of photosensitive epilepsy in unselected Indian population

Acta Neurologica Scandinavica 1994; 89: 5-8

Schiller, PH., Logothetis, NK., Charles, ER.

Role of the colour-opponent and broad-band channels in vision

Visual Neuroscience 1990; 5: 321-346

Schiller, PH., Logothetis, NK., Charles, ER.

Parallel pathways in the visual system: Their role in perception at isoluminance

Neuropsychologia 1991; 29: 433-441

Serbanescu, T., Naquet, R., Menini, C.

Various physical parameters which influence photosensitive epilepsy in the papio-papio

Brain Research 1973; 52: 145-158

Siegal, M., Kurzrok, N., Barr, WB., Rowan, AJ.

Game-playing epilepsy

Epilepsia 1992; 33: 93-97

Soso, MJ., Lettich, E., Belgum, JH.

Pattern-sensitive epilepsy, 1: A demonstration of spatial frequency selective epileptic response to gratings

Epilepsia 1980(a); 21: 301-312

Soso, MJ., Lettich, E., Belgum, JH.

Responses to stripe width changes and to complex gratings of patient with pattern sensitive epilepsy

Electroencephalography and Clinical Neurophysiology 1980(b); 48: 998-101

Skrandies, W.

Scalp potential fields evoked by grating stimuli: effects of spatial frequency and orientation

Electroencephalography and Clinical Neurophysiology 1984; 58: 325-332

Stuart, GW., Edwards, M., Cook, ML.

Colour inputs to random dot stereopsis

Perception 1992; 21: 717-729

Sutherling, WW.,Wilkinson, EC., Brinkley, JM., Sackellares, JC., Johnson, RN., Lee, SI.

Sodium valporate-induced changes of the VEP tp paired stimuli in photosensitive epilepsy

Electroencephalography and Clinical Neurophysiology 1980; 50: 168P

Takahashi, T.

Central visual field stimulation by epileptogenic visual stimuli in patients with photosensitive epilepsy

Electroencephalography and Clinical Neurophysiology 1987; 66: 94P

Takahashi, T., Tsukahara, Y.

Influence on colour on the photoconvulsive response

Electroencephalography and Clinical Neurophysiology 1976; 41: 124-136

Takasaka, Y., Takamatsu, K., Nakagawara, M.

Anterior-posterior relationships of EEG in photosensitive subjects: coherence and cross-phase spectral analysis

The Japanese Journal of Psychiatry and Neurology 1989; 43: 651-663

Takahashi, Y., Shigematsu, H., Kubota, H., Inoue, Y., Fujiwara, T., Yagi, K., Seino, M.

Non-photosensitive video game induced partial seizures

Epilepsia 1995(a); 36: 837-841

Takahashi, Y., Fujiwara, T., Yagi, K., Seino, M.

Wavelength specificity of photoparoxysmal response in idiopathic generalized epilepsy

Epilepsia 1995(b); 36: 1084-1088

Takahashi, T., Tsukahara, Y.

Photoparoxysmal response elicited by flickering dot pattern stimulation and its optimal spatial frequency of provocation

Electroencephalography and Clinical Neurophysiology 1998; 106: 40-43

Thompson, DA., Drasdo, N.

Colour, contrast and the visual evoked potential

Ophthalmic and Physiological Optics 1992; 12: 225-228

Tobimatsu, S., Tomoda, H., Kata, M.

Parvocellular and magnocellular contributions to visual evoked potentials in humans: stimulation with chromatic and achromatic gratings and apparent motion

Journal of the Neurological Sciences 1995; 134: 73-82

Topalkora, K., Alarcon, G., Binnie, CD.

Effects of flash frequency and repetition of intermittent photic stimulation on photoparoxysmal responses

Seizure 1998; 7: 249-255

Tumus, V., Sakamoto, AC.

Comparison of the mechanisms of latency shift in pattern reversal visual evoked potential induced by blurring and contrast reduction

Electroencephalography and Clinical Neurophysiology 1997; 104: 96-100

Valberg, A., Lee, BB.

Main cell systems in primate visual pathways

Current Opinion in Opthalmology 1992; 3: 813-823

Waltz, S., Christen, HJ., Doose, H.

The different patterns of the photoparoxysmal response - A genetic study

Electroencephalography and Clinical Neurophysiology 1992; 83: 138-145

West, RW., Penisten, DK.

The effect of colour on light induced seizures: A case report

Optometry and Vision Science 1996; 73: 109-113

Wilkins, A

Visual stress.

T. Shallice, J.L. McGough, N.J. Mackintosh, E. Tulving, L. Weiskrantz (Eds). Oxford: Oxford University Press. (1995).

Wilkins, A., Andermann, F., Ives, J.

Stripes, complex cells and seizures

Brain 1975(a); 98: 365-380

Wilkins, A., Andermann, F., Ives, J.

Stripes, complex cells and seizures

Electroencephalography and Clinical Neurophysiology 1975(b); 39: 428

Wilkins, AJ., Darby, CE., Binnie, CD., Stefansson, SB., Jeavons, PM., Harding, GFA.

Television epilepsy – the role of pattern

Electroencephalography and Clinical Neurophysiology 1979(a); 47: 163-171,

Wilkins, AJ., Darby, CE., Binnie, CD.

Neurophysiological aspects of pattern-sensitive epilepsy

Brain 1979(b); 102: 1-25

Wilkins, AJ., Binnie, CD., Darby, CE.

Visually-induced seizures

Progress in Neurobiology 1980; 15: 85-117

Wright, C.

Electrical signals from the visual system: How can we use them?

The Opthalmic Optician 1984: 542-545

Wright, CE.

Introduction to the visual evoked potential (VEP) – basic techniques, and theories on normal flash and pattern waveforms

Optometry Today 1985; 25: 415-418

Yeh, T., Lee, BB., Kremers, J.

Temporal response of ganglion cells of the macaque retina to cone specific modulation

Journal of the Optical Society of America A 1995; 12: 456-464

Appendix one

Further details of patient recruitment

Abbreviations used in appendices two and three

A general clinical history for each patient is detailed in appendix two. Clinical and EEG details at the time of the experimental protocol or data extraction are detailed in appendix three. Drug doses are given in all tables but not blood levels as Aston University does not have the facilities for routinely performing this procedure. The investigations in the thesis were conducted between 1996 and 1999.

The participants and patients in all the studies were selected by examining the past EEG in the Aston University clinical neurophysiology database. The number of EEG available for each individual is detailed in the tables in appendix two. A standard departmental EEG includes at least 20 minutes of resting EEG, 2 minutes of hyperventilation, 2 minutes recovery from hyperventilation and full photo and pattern testing. Individuals were identified as previously showing classic PPR or occipital spikes and either normal resting EEG or spontaneous abnormalities that could easily be distinguished from the induced response. Spontaneous abnormalities that were distinguishable include focal abnormalities and spike and wave that only occurred in concurrence with visible absences (in the case of retrospective studies only). For the experimental studies subjects with few clinical symptoms were given priority, as these were more likely to take part. Possible participants for 4, 5, 6 and 9 were contacted to request their participation.

The abbreviations used in the appendix are detailed in the table below.

Cbz	Carbamazipine
LTG	Lamotrigine
SV	Sodium valporate
Phy	Phenytoin
Vig	Vigabatrine
Photo/sen	Photosensitive
Enviro	Environmental
meds	Medication
JME	Juvenile myoclonic epilepsy
WNL	Within normal limits
N/A	Not applicable
NAD	No abnormality detected
fps	Flashes per second
cps	Cycles per second
cpd	Cycles per degree
OS	Occipital spikes
PPR	Photoparoxysmal response
dPPR	Degraded Photoparoxysmal response

Appendix two

General clinical history of participants

	Subject 1	Subject 2	Subject 3	Subject 4	Subject 5
Reason for referral	Dizziness and seizures to computers	Compulsive attraction + previous diagnosis of photo/sen	Suspected photo/sen epilepsy	Suspected photo/sen	Discomfort to enviro flicker with seizure
Diagnosis	Pattern sensitive partial complex seizures	JME	Generalised epilepsy with photo/sen	None recorded	JME with photo/sen
Aura	Perceived flickering of screens	None recorded	None recorded	None recorded	None recorded
Seizures	Numerous partial complex	15 –20 times / day. Tonic clonic and absences	40-50 tonic clonic and absences	8 tonic clonic	1 tonic clonic
Sensitivity in enviro	Seizures to computers	Seizures to TV and changes in illumination	Seizures to TV	All seizures to TV	Discomfort in enviro flicker
Medication history (dose in mg / day)	1993 Cbz 400mg+SV 800mg 1994 1000mg SV 1995 LTG 75mg + 1000mg SV 1996 LTG 100mg and 1500mg SV	1993 1000mg SV 1995 75mgLTG	400mg SV	2000mg-2500mg SV	1995-1997 250mg Phy 1997-300mg LTG + 200mg Phy
Protocols performed	Ch 8, exp1	Ch 7, Ch 8, exp 1+2	Ch 7, Ch 8, exp 1	Ch 4, exp 2 Ch 5, exp 1 Ch 8, exp 1+2	Ch 8, exp 1
Number of EEG	6	7	1	13	3

	Subject 6	Subject 7	Subject 8	Subject 9	Subject 10
Reason for referral	Suspected photo/sen, sister had seizure to TV	LTG research project	Mother has photo/sen epilepsy	LTG research project	Mother and sister have photo/sen epilepsy
Diagnosis	None recorded	Primary generalised epilepsy	None recorded	Secondary generalised epilepsy	None recorded
Aura	None recorded	Not present	N/A	Present but symptoms unknown	N/A
Seizures	Numerous tonic clonic	8 tonic clonic	NONE	Numerous tonic clonic	NONE
Sensitivity in enviro	Several seizures to TV	One seizure to TV	None recorded	Seizures to computers	Dislikes sunlight though trees
Medication history (dose in mg / day)	3000mg SV subject overweight	10mg LTG	NONE	25mg LTG does not tolerate SV	1000mg SV
Protocols performed	Ch 4, exp 2 Ch 8, exp 1+2	Ch 8, exp 1+2	Ch 4, exp 2 Ch 6, exp1 Ch 8, exp 2	Ch 7 Ch 8, exp 1+2	Ch 6, exp 1 Ch 8, exp 1+2
Number of EEG	8	5	1	1	4

	Subject 11	Subject 12	Subject 13	Subject 14	Subject 15
Reason for referral	LTG research project	Seizure to TV	Sister has photo/sen epilpsy	Suspected photo/sen	Seizure to flicker
Diagnosis	None recorded	None recorded	None recorded	None recorded	None recorded
Aura	None recorded	Floating feeling	N/A	None recorded	Headache and neck pain
Seizures	1 tonic clonic	3 tonic clonic	NONE	1 tonic clonic and numerous simple partial	2 tonic clonic
Sensitivity in enviro	Seizure to video game on TV	2 seizures to TV	Dislikes enviro flicker and pattern	None recorded	At least one seizure to flicker
Medication history (dose in mg / day)	1998-2000 5mg-50mg LTG	1983-2000 600mg-1000mg SV	1982-1988 none 1989-2000 500mg-700mg SV	NONE	NONE
Protocols performed	Ch 8, exp2	Ch 4, exp 1+2 Ch 5, exp 1+2 Ch 6, exp2 Ch 8, exp 1+2 Ch 9	Ch 4, exp 1+2 Ch 5, exp 1+2 Ch 6, exp 2 Ch 7 Ch 8, exp 1 Ch 9	Ch 8, exp2	Ch 7 Ch 8, exp 1
Number of EEG	2	20	19	1	1

	Subject 16	Subject 17	Subject 18	Subject 19	Subject 20
Reason for referral	Tonic clonic to video game	Compulsive attraction and seizures to TV	LTG research project	Suspected photo/sen	Father has photo/sen epilepsy
Diagnosis	None recorded	None recorded	Primary generalised epilepsy	None recorded	None recorded
Aura	Swirling colour in head	None recorded	Not present	Not present	N/A
Seizures	One tonic clonic	10 tonic clonic	2 tonic clonic+ myoclonic jerks and eyelid myoclonic with absences	Numerous tonic clonic and absences	NONE
Sensitivity in enviro	Seizure to video game	Seizures to TV and compulsive attraction	Seizure to TV and disco lights	None recorded	None recorded
Medication history (dose in mg / day)	None	1989-2000 1000mg SV except 1990+1993 no meds for pregnancy	Until 2000 700mg SV 2000 200mg LTG	Until1998 none 1998 LTG introduced	NONE
Protocols performed	Ch 7, Ch 8, exp 1+2	Ch 4, exp 2 Ch 5, exp 1 Ch 7, Ch 8, exp 1	Ch 8, 1+2	Ch 4, exp2 Ch 5, exp2 Ch 6, exp 1+2 Ch 8, exp 1+2	Ch 5, exp1
Number of EEG	1	13	5	12	8

	Subject 21	Subject 22	Subject 23	Subject 24	Subject 25
Reason for referral	LTG research project	Second opinion on photo/sen seizures	Seizures to sunlight	Suspected photo/sen	LTG research project
Diagnosis	None recorded	Photo/sen epilepsy	None recorded	None recorded	Primary generalised epilepsy
Aura	None recorded	Subjective sensations to patterns	Strange sensation in head	None recorded	Not present
Seizures	Numerous tonic clonic	8 tonic clonic	50 tonic clonic	8 tonic clonic	Numerous, type unknown
Sensitivity in enviro	Seizures to TV	All seizures to flashing lights	Seizures to sunlight and pattern stimulation in EEG	All seizures to TV	None recorded
Medication history (dose in mg / day)	1000mg SV and 200mg LTG	1000mg SV	1977-1999 400mg-1500mg SV	1200mg SV	1000mg SV
Protocols performed	Ch 8, exp 1+2	Ch 8, exp 2	Ch 8, exp 2	Ch 4, exp 2 Ch 5, exp 2 Ch 6, exp 2 Ch 7, Ch 8, exp 1+2 Ch 9	Ch 8, exp 2
Number of EEG	3	6	12	12	25

	Subject 26	Subject 27	Subject 28	Subject 29	Subject30
Reason for referral	Tonic clonic seizure to video game	Check for safety as fireman	Photo/sen seizure and suspected absences	Twin sister had absences	Suspected absences
Diagnosis	Photo/sen epilpsy	None recorded	None recorded	None recorded	None recorded
Aura	Nausea	Not present	None recorded	None recorded	None recorded
Seizures	1 tonic clonic	4-5 episodes of loss of conscious-ness	14 tonic clonic and absences	4 episodes with myoclonic jerks	9 tonic clonic and absences
Sensitivity in enviro	Seizure to video game	All seizure to TV or video game	All seizures to TV, video or sunlight	Discomfort to video games	Seizures to TV
Medication history (dose in mg / day)	NONE	NONE	1997-1999 400mg-800mg SV as growing	400mg SV removed as not tolerated	800mg SV then combined with 200mg Cbz
Protocols performed	Ch 7, Ch 8, exp 1+2	Ch 8, exp 1+2	Ch 5, exp 2 Ch 6, exp 2 Ch 8, exp 1+2	Ch 4, exp 1 Ch 8, exp 2	Ch 4, exp 1+2
Number of EEG	1	1	3	18	18

	Subject 31	Subject 32	Subject 33	Subject 34	Subject 35
Reason for referral	Suspected photo/sen	Episodes to computers and TV	Subjective sensations to sunlight	Has aura of flashing lights	Suspected photo/sen
Diagnosis	Rolandic epilepsy with photo/sen	Photo/sen epilepsy with pattern sensitivity	None recorded	Simple complex and partial seizures	None recorded
Aura	None recorded	None recorded	None recorded	Flashing lights and replays of scenes	None recorded
Seizures	20 tonic clonic with numerous leg jerks	6 episodes of loss of consciousness	10 tonic clonic and numerous absences	70 complex and numerous simple	8 tonic clonic
Sensitivity in enviro	1 seizure to sunlight though trees, 2 seizures to computers	All episodes to computers or TV	Subjective sensations to sunlight and flashes on the TV	Seizures to computers	Seizures to TV
Medication history (dose in mg / day)	-1995 1400mg SV 1995 400mg LTG	1994 1000mg SV 1995 1500mg SV	-1995 250mg SV 1995 combined with 25mg LTG	1995 300mg Cbz + 2000mg Vig 1996 600mg Cbz, + 2000mg Vig + 300mg LTG	1981-1985 1000mg SV 1986-1999 1500mg SV
Protocols performed	Ch 8, exp 2	Ch 7, Ch 8, exp1	Ch 8, exp 1	Ch 8, exp 1	Ch 4, exp 2 Ch 8, exp 1+2
Number of EEG	7	3	2	2	16

	Subject 36	Subject 37	Subject 38	Subject 39	Subject 40
Reason for referral	LTG research project	Seizures to computer game	Seizures to TV	Suspected photo/sen	Legal case
Diagnosis	JME	None recorded	None recorded	None recorded	Temporal lobe epilepsy with photo/sen
Aura	None recorded	NONE	None recorded	None recorded	None recorded
Seizures	1 tonic clonic and numerous absences	2 tonic clonic	2 tonic clonic	4 tonic clonic	Numerous focal seizures with automatism
Sensitivity in enviro	None recorded	1 seizure to video game	1 seizure to TV and 1 to sunlight	None recorded	None recorded
Medication history (dose in mg / day)	-1995 1000mg SV 1995-1999 5mg-300mg LTG	NONE	1982-1996 2000mg-1000mg SV	1983-1989 1500mg SV 1989-1999 700mg SV	400mg Cbz
Protocols performed	Ch 4, exp 1 Ch 5, exp 2 Ch 6, exp 2 Ch 7, Ch 8, exp 1+2 Ch 9	Ch 8, exp 1	Ch 4, exp1 Ch 8, exp 1+2	Ch 8, exp 2	Ch 4, exp 2
Number of EEG	4	1	11	17	1

	Subject 41	Subject 42	Subject 43	Subject 44	Subject 45
Reason for referral	Seizure to TV	LTG research project	Change in medication for pregnancy	Seizures to flickering light	Seizure to TV
Diagnosis	None recorded	None recorded	JME	None recorded	None recorded
Aura	None recorded	Some jerking before tonic clonic	None recorded	Floating feeling	None recorded
Seizures	6 tonic clonic	1 tonic clonic	Numerous tonic clonic	10 tonic clonic and numerous myoclonic jerks	1 tonic clonic and numerous myoclonic jerks
Sensitivity in enviro	Seizure to TV	Possible absences to TV	None recorded	All seizures to flickering light	Tonic clonic to TV
Medication history (dose in mg / day)	1500mg SV	NONE	600mg Cbz	1983-1989 1000mg SV 1989-1994 500mg SV 1994 none	1000mg SV
Protocols performed	Ch 4, exp 1+2 Ch 5, exp 1 Ch 8, exp 2	Ch 7, Ch 8, exp 1	Ch 7	Ch 4, exp 1 Ch 7 Ch 8, exp 1+2	Ch 7, Ch 8, exp 1+2
Number of EEG	17	2	1	15	14

	Subject 46	Subject 47	Subject 48	Subject 49	Subject 50
Reason for referral	Suspected photo/sen	Considering change in meds	Seizure to TV	Not controlled by meds	Seizure to computer
Diagnosis	None recorded	JME	None recorded	None recorded	None recorded
Aura	None recorded	None recorded	Strange feeling in head	None recorded	None recorded
Seizures	10 tonic clonic	Numerous tonic clonic, absences and myoclonic jerks	50 tonic clonic	4 tonic clonic and suspected absences	1 tonic clonic
Sensitivity in enviro	None recorded	None recorded	Seizures to TV and computers	Possible seizure to striped shirt	Seizure to computer
Medication history (dose in mg / day)	1000mg SV	1000mg SV	1981-1995 1500mg SV 1096-1999 2000mg SV	25mg LTG	None
Protocols performed	Ch 5, exp1 Ch 7, Ch 8, exp 1	Ch 8, exp1	Ch 8, exp2	Ch 8, exp 1+2	Ch 8, exp 2
Number of EEG	14	8	15	1	1

	Subject 51	Subject 52	Subject 53	Subject 54	Subject 55
Reason for referral	Episodes to computer games	Familiy history of photo/sen epilepsy	LTG research project	LTG research project	Second opinion requested
Diagnosis	None recorded	None recorded	None recorded	Primary generalised epilepsy	None recorded
Aura	None recorded	None recorded	None recorded	Not present	Strange feeling in head
Seizures	3 episodes of altered conscious-ness (15-20 mins)	4 tonic clonic	3 tonic clonic	Numerous tonic clonic and suspected absences	Numerous occipital lobe focal seizures
Sensitivity in enviro	Episodes to computer games	All seizure to TV	None recorded	None recorded	Seizures associated with TV
Medication history (dose in mg / day)	NONE	-1988 none 1998 1000mg SV	-1988 none 1998-2000 100mg-2000mg LTG	10mg LTG	NONE
Protocols performed	Ch 7, Ch 8, exp1	Ch 4, exp 2 Ch 8, exp 1+2	Ch 8, 1+2	Ch 8, exp 1+2	Ch 8, exp1
Number of EEG	1	3	3	1	2

	Subject 56	Subject 57	Subject 58	Subject 59	Subject 60
Reason for referral	Second opinion requested	Mother has photo/sen epilepsy	Suspected photo/sen epilepsy	LTG research project	Second opinion for career options
Diagnosis	Photo/sen epilepsy and myoclonic jerks	None recorded	None recorded	None recorded	None recorded
Aura	None recorded	Nausea	None recorded	None recorded	None recorded
Seizures	Numerous absences with myoclonic jerks	2 tonic clonic	4-6 seizure type unknown	Numerous tonic clonic and absences	History of seizures type unknown
Sensitivity in enviro	Dislikes enviro flicker and pattern	1 seizure to TV	Seizure to black and white TV	Seizures to TV	Seizures to computers
Medication history (dose in mg / day)	1982-1999 1200mg SV except 1996-1997 when no meds for pregnancy	NONE	1982-1984 1500mg SV 1984-1992 1000mg SV 1992-1995 500mg SV 1995 none	SV not tolerated Cbz and LTG combined: dose unknown	Unknown
Protocols performed	Ch 6, exp 1 Ch 8, exp 2	Ch 5, exp 2 Ch 6, exp 2 Ch 8, exp 1+2 Ch 9	Ch 4, exp 1	Ch 6, exp 1 Ch 7 Ch 8, exp 1+2	Ch 7, Ch 8, exp 1
Number of EEG	20	2	19	1	1

	Subject 61	Subject 62	Subject 63	Subject 64	Subject 65
Reason for referral	Suspected photo/sen epilepsy	Ambulatory monitoring	Sister has photo/sen epilepsy	LTG research project	Photo/sen mother and maternal aunt and uncle
Diagnosis	None recorded	None recorded	None recorded	JME	None recorded
Aura	None recorded	None recorded	N/A	None recorded	N/A
Seizures	Numerous primary tonic clonic, myoclonic jerks and absences	Numerous absences	NONE	Numerous tonic clonic and suspected absences	NONE
Sensitivity in enviro	None recorded	Dislikes disco lights	Dislikes enviro flicker and pattern	None recorded	Feels dizzy in disco lights
Medication history (dose in mg / day)	Cbz then 600mg SV	NONE	NONE	Cbz No other details known	NONE
Protocols performed	Ch 7, Ch 8, 1+2	Ch 7, Ch 8, exp 1+2	Ch 8, exp2	Ch 8, exp1	Ch 5, exp1 Ch 8, exp1
Number of EEG	1	1	16	2	3

	Subject 66	Subject 67	Subject 68	Subject 69	Subject 70
Reason for referral	LTG research project	Suspected photo/sen with JME	Comparison with sister with JME	Suspected photo/sen epilepsy	LTG research project
Diagnosis	None recorded	JME	JME	JME	JME with photo/sen
Aura	None recorded	Sees flashing lights	None recorded	Coloured, flickering lights	None recorded
Seizures	1 tonic clonic and suspected absences	10 tonic clonic and daily absences with myoclonic jerks	Numerous tonic clonic, myoclonic jerks and absences	3 tonic clonic and myoclonic jerks with absences	3 tonic clonic
Sensitivity in enviro	None recorded	Seizures to TV	Discomfort to envio flicker and pattern	Myoclonic jerks to computer games	All seizures to computer games
Medication history (dose in mg / day)	NONE	-1995 800mg Cbz 1996 LTG mono-therapy	200mg LTG	-1996 200mg Cbz 1996 400 LTG	-1999 none then LTG introduced
Protocols performed	Ch 8, exp 1	Ch 8, exp 1+2	Ch7, Ch 8, exp1	Ch 8, exp1	Ch 5, exp2 Ch 6, exp 2 Chap 8, exp 1+2 Ch 9
Number of EEG	3	1	1	2	5

	Subject 71	Subject 72	Subject 73	Subject74
Reason for referral	Absences in clubs	Removal of meds during pregnancy	Suspected absences	LTG research project
Diagnosis	None recorded	None recorded	None recorded	JME
Aura	None recorded	None recorded	None recorded	None recorded
Seizures	6 tonic clonic and suspected absences	Numerous tonic clonic	Numerous absences	Numerous tonic clonic and suspected absences
Sensitivity in enviro	Suspected absences in clubs	Seizures mainly to TV	Absences to TV	None recorded
Medication history (dose in mg / day)	NONE	Previously taking SV. Stopped 4 months before referral	1980 1000mg SV 1982 1200mg SV 1989-1999 1500mg SV	Cbz No other details known
Protocols performed	Ch 8, exp1	Ch 8, exp1	Ch 4, exp 2 Chap 6, exp1	Ch 8, exp 1
Number of EEG	1	1	15	2

Appendix three

Clinical and EEG details at time of investigation

Chapter 4 Experiment 1	Subject 12	Subject 13	Subject 30	Subject 36
Age at time of exam	24 years	22 years	21 years	16 years
Medication at time of exam	1000mg SV	700mg SV	200mg Cbz	300 mg LTG
Number of seizure to date	2	NONE	5	Numerous
Time since last seizure	11 years	N/A	2 months	Not known
Resting EEG	WNL	WNL	WNL	Eyelid myoclonia
Clinical response to hyper-ventilation	None recorded	None recorded	None recorded	None recorded
EEG during hyper-ventilation	WNL Increased theta	WNL Increased theta	WNL Some increased delta and theta	Induced sharp theta activity
Clinical to visual stimulation	None recorded	None recorded	None recorded	None recorded
Photo/sen range	8-20+60fps OS 50+25fps PPR	8-50fps OS	40-50fps dPPR	10-50fps PPR
Pattern sensitive range	2-6cpd OS	2-6cpd OS	1.5-3cpd PPR	0.5-6cpd PPR

Chapter 4 Experiment 1	Subject 38	Subject 41	Subject 44	Subject 57
Age at time of exam	35 years	32 years	36 years	33 years
Medication at time of exam	500mg SV	1500mg SV	NONE	NONE
Number of seizure to date	2	6	10	4-6
Time since last seizure	15 years	4 years	13 years	10 years
Resting EEG	Generalised bursts of theta activity	WNL	WNL Some sharpened theta	WNL
Clinical response to hyper-ventilation	None recorded	None recorded	None recorded	None recorded
EEG during hyper-ventilation	Increased abnormality	No change	No change	No change
Clinical to visual stimulation	None recorded	None recorded	None recorded	None recorded
Photo/sen range	8-18+50fps PPR	NAD	8-12+ 50-60fps OS	45-50fps OS
Pattern sensitive range	0.5-6cpd PPR	2-6cpd PPR	2-3cpd OS	0.5-3.5cpd OS

Chapter 4 Experiment 1	Subject 57
Age at time of exam	33 years
Medication at time of exam	NONE
Number of seizure to date	4-6
Time since last seizure	10 years
Resting EEG	WNL
Clinical response to hyper-ventilation	None recorded
EEG during hyper-ventilation	WNL Some increased alpha
Clinical to visual stimulation	None recorded
Photo/sen range	40-50fps OS
Pattern sensitive range	2-4cpd OS

Chapter 4 Experiment 2	Subject 4	Subject 6	Subject 8	Subject 12
Age at time of exam	37 years	37 years	8 years	24 years
Medication at time of exam	2500mg SV	300mg SV	None	1000mg SV
Number of seizure to date	8	Numerous	None	2
Time since last seizure	25 years	3 years	N/A	12 years
Resting EEG	WNL	WNL	WNL Some theta	WNL
Clinical response to hyper-ventilation	None recorded	None recorded	None recorded	Not performed
EEG during hyper-ventilation	No change	No change	WNL Some increase in theta	Not performed
Clinical to visual stimulation	None recorded	None recorded	None recorded	None recorded
Photo/sen range	16-18fps PPR	10-20fps PPR	8-18+50fps dPPR	Not performed
Pattern sensitive range	2-3cpd PPR	2-6cpd dPPR	2-3cpd PPR	2-6cpd PPR

Chapter 4 Experiment 2	Subject 13	Subject 17	Subject 19	Subject 24
Age at time of exam	23 years	32 years	33 years	28 years
Medication at time of exam	700mg SV	1000mg SV	None for 10 years	1200mg SV
Number of seizure to date	NONE	10	Numerous	8
Time since last seizure	N/A	6 years	15 years	7 years
Resting EEG	WNL	WNL	WNL	WNL
Clinical response to hyper-ventilation	None recorded	None recorded	None recorded	None recorded
EEG during hyper-ventilation	WNL Increased slow	No change	WNL Increased theta in central and frontal regions	No change
Clinical to visual stimulation	None recorded	Subjective sensation to pattern	None recorded	None recorded
Photo/sen range	6-18+50fps OS	8-12+50fps OS	6-18fps PPR	8-50fps OS
Pattern sensitive range	2-6cpd OS	0.5-3cpd OS	2-3cpd PPR	2-6cpd OS

Chapter 4 Experiment 2	Subject 29	Subject 30	Subject 35	Subject 40
Age at time of exam	23 years	23 years	34 years	27 years
Medication at time of exam	NONE	200mg Cbz	1500mg SV	400mg Cbz
Number of seizure to date	4	5	8	Numerous
Time since last seizure	5 years	1 year	22 years	2 months
Resting EEG	WNL	WNL	WNL	Focal slow in left temporal
Clinical response to hyper-ventilation	None recorded	None recorded	None recorded	None recorded
EEG during hyper-ventilation	WNL Some increased alpha	WNL Some increased theta	WNL Some slowing of alpha	Increased abnormality
Clinical to visual stimulation	None recorded	None recorded	None recorded	None recorded
Photo/sen range	40-50fps dPPR	40-50fps DPPR	40-55fps OS	20-25fps PPR
Pattern sensitive range	2+6cpd dPPR	2-6cpd dPPR	2-6cpd OS	2-6cpd PPR

Chapter 4 Experiment 2	Subject 41	Subject 52	Subject 73
Age at time of exam	34 years	45 years	31 years
Medication at time of exam	1500mg SV	1000mg SV	1500mg SV
Number of seizure to date	6	4	Numerous
Time since last seizure	6 years	3 months	15 years
Resting EEG	WNL	Sharpened theta	WNL
Clinical response to hyper-ventilation	None recorded	None recorded	None recorded
EEG during hyper-ventilation	No change	No change	No change
Clinical to visual stimulation	None recorded	None recorded	None recorded
Photo/sen range	NAD	16-45fps OS	18-45fps dPPR
Pattern sensitive range	2-3cpd PPR	1-5cpd OS	2-6cpd dPPR

Chapter 5 Experiment 1	Subject 4	Subject 12	Subject 13	Subject 17
Age at time of exam	37 years	24 years	23 years	32 years
Medication at time of exam	2500mg SV	1000mg SV	700mg SV	1000mg SV
Number of seizure to date	8	2	NONE	10
Time since last seizure	25 years	12 years	N/A	6 years
Resting EEG	WNL	WNL	WNL	WNL
Clinical response to hyper-ventilation	None recorded	None recorded	None recorded	None recorded
EEG during hyper-ventilation	No change	Not performed	WNL Increased slow	No change
Clinical to visual stimulation	None recorded	None recorded	None recorded	Subjective sensations to pattern
Photo/sen range	16-18fps PPR	Not performed	6-18+50fps OS	8-12+50fps OS
Pattern sensitive range	2-3cpd PPR	2-6cpd PPR	2-6cpd OS	0.5-3cpd OS

Chapter 5 Experiment 1	Subject 20	Subject 41	Subject 46	Subject 65
Age at time of exam	24 years	34 years	32 years	11 years
Medication at time of exam	NONE	1500mg SV	1000mg SV	NONE
Number of seizure to date	NONE	6	10	NONE
Time since last seizure	N/A	28 years	13 years	N/A
Resting EEG	WNL	WNL	WNL	WNL
Clinical response to hyper-ventilation	None recorded	None recorded	None recorded	None recorded
EEG during hyper-ventilation	No change	No change	No change	WNL Some increased slow
Clinical to visual stimulation	None recorded	None recorded	None recorded	None recorded
Photo/sen range	18+40-50fps dPPR	NAD	NAD	10-40fps OS
Pattern sensitive range	2-3cpd dPPR	2-3cpd PPR	NAD	2-6cpd OS

Chapter 5 Experiment 2	Subject 12	Subject 13	Subject 19	Subject 24
Age at time of exam	27 years	24 years	35 years	29 years
Medication at time of exam	1000mg SV	700mg SV	50mg SV	1200mg SV
Number of seizure to date	3	NONE	numerous	8
Time since last seizure	15 months	N/A	1 years	8 years
Resting EEG	WNL Minimal alpha	WNL	Spontaneous focal spike and wave	WNL
Clinical response to hyper-ventilation	None recorded	None recorded	None recorded	None recorded
EEG during hyper-ventilation	No change	WNL Increased alpha	No change	No change
Clinical to visual stimulation	None recorded	None recorded	None recorded	None recorded
Photo/sen range	6-18+40fps OS	6-25+ 40-50fps OS	8-50fps PPR	8-10+20fps OS 12-50fps dPPR
Pattern sensitive range	2-6cpd OS	2-6cpd OS	2-6cpd PPR	2-6cpd PPR

Chapter 5 Experiment 2	Subject 28	Subject 36	Subject 57	Subject 70
Age at time of exam	10 years	19 years	7 years	14 years
Medication at time of exam	800mg SV	300mg LTG	NONE	100mg LTG
Number of seizure to date	14	numerous	2	3
Time since last seizure	3 years	8 months	2 weeks	Unknown
Resting EEG	WNL	Eyelid myoclonia	WNL	Non-specific abnormalities
Clinical response to hyper-ventilation	None recorded	None recorded	None recorded	None recorded
EEG during hyper-ventilation	No change	No change	WNL Some increased theta	No change
Clinical to visual stimulation	None recorded	None recorded	None recorded	None recorded
Photo/sen range	35-40fps PPR	8-60fps OS 10-50fps PPR	8-16+ 40-50fps PPR	8-16+ 40-50fps PPR
Pattern sensitive range	3cpd dPPR	0.5-6cpd PPR	unknown	2-6 PPR

Chapter 6 Experiment 1	Subject 8	Subject 10	Subject 19	Subject 55
Age at time of exam	8 years	15 years	33 years	32 years
Medication at time of exam	None	1000mg SV	None for 10 years	1200mg SV started 15 weeks previous
Number of seizure to date	NONE	NONE	Numerous	Numerous
Time since last seizure	N/A	N/A	15 years	12 years
Resting EEG	WNL Some theta	WNL occasional sharp waves in temporal region	WNL	WNL
Clinical response to hyper-ventilation	None recorded	Not performed	None recorded	None recorded
EEG during hyper-ventilation	WNL Some increase in theta	Not performed	WNL Increased theta in central and frontal regions	Little change
Clinical to visual stimulation	None recorded	NAD	None recorded	None recorded
Photo/sen range	8-18+50fps dPPR	8fps PPR	6-18fps PPR	12fps OS
Pattern sensitive range	2-3cpd PPR	2cpd PPR	2-3cpd PPR	2-6cpd OS

Chapter 6 Experiment 1	Subject 59	Subject 73
Age at time of exam	18 years	31 years
Medication at time of exam	400mg Cbz 400mg LTG	1500mg SV
Number of seizure to date	Numerous	Numerous
Time since last seizure	Unknown	15 years
Resting EEG	Single spikes in right rolandic region	WNL
Clinical response to hyper-ventilation	None recorded	None recorded
EEG during hyper-ventilation	Increased abnormality	No change
Clinical to visual stimulation	Whole body jerk at 12fps	None recorded
Photo/sen range	10-60fps PPR	18-45fps dPPR
Pattern sensitive range	2-6cpd PPR	2-6cpd dPPR

Chapter 6 Experiment 2	Subject 12	Subject 13	Subject 19	Subject 24
Age at time of exam	27 years	24 years	35 years	29 years
Medication at time of exam	1000mg SV	700mg SV	50mg SV	1200mg SV
Number of seizure to date	3	NONE	Numerous	8
Time since last seizure	15 months	N/A	1 year	8 years
Resting EEG	WNL Minimal alpha	WNL	Spontaneous focal spike and wave	WNL
Clinical response to hyper-ventilation	None recorded	None recorded	None recorded	None recorded
EEG during hyper-ventilation	No change	WNL Increase alpha	No change	No change
Clinical to visual stimulation	None recorded	None recorded	None recorded	None recorded
Photo/sen range	6-18+40fps OS	6-25+ 40-50fps OS	8+50fps PPR	8-10+20fps OS 12-50fps dPPR
Pattern sensitive range	2-6cpd OS	2-6cpd OS	2-6cpd PPR	2-6cpd PPR

Chapter 6 Experiment 2	Subject 28	Subject 36	Subject 57	Subject 70
Age at time of exam	10 years	19 years	7 years	14 years
Medication at time of exam	800mg SV	300mg LTG	NONE	100mg LTG
Number of seizure to date	14	Numerous	2	3
Time since last seizure	3 years	8 months	2 weeks	Unknown
Resting EEG	WNL	Eyelid myoclonic	WNL	Non-specific abnormalities
Clinical response to hyper-ventilation	None recorded	None recorded	None recorded	None recorded
EEG during hyper-ventilation	No change	No change	WNL Some increased theta	No change
Clinical to visual stimulation	None recorded	None recorded	None recorded	None recorded
Photo/sen range	35-40fps PPR	8+60fps OS 10-50fps PPR	8-16+ 40-60fps PPR	8-16+ 40-50fps PPR
Pattern sensitive range	3cpd dPPR	0.5-6cpd PPR	unknown	2-6cpd PPR

Chapter 7	Subject 2	Subject 3	Subject 9	Subject 13
Age at time of exam	13	26	29	22
Medication at time of exam	60mg SV	400mg SV	100mg LTG	700mg SV
Number of seizure to date	Numerous	45-50	Numerous	NONE
Time since last seizure	Continuing	Continuing	unknown	N/A
Resting EEG	Focal abnormality in parietal mid post temporal region	WNL	WNL Some sharp theta	WNL
Clinical response to hyper-ventilation	None recorded	None recorded	None recorded	None recorded
EEG during hyper-ventilation	Occasional slow waves in temporal regions and enhances focal abnormality	Generalised bursts of 3-6cps with slow recovery	WNL Increased alpha	WNL Increased theta
Clinical to visual stimulation	None recorded	None recorded	None recorded	None recorded
Photo/sen range	9-24+ 41-57fps PPR	7-9+ 20-60fps PPR	11-20+ 45-50fps OS	8-50fps OS
Pattern sensitive range	None performed	0.53-5cpd PPR	0.5-6cpd OS	2-6cpd OS

Chapter 7	Subject 15	Subject 16	Subject 17	Subject 24
Age at time of exam	54 years	13 years	32 years	26 years
Medication at time of exam	NONE	NONE	1000mg SV	1200mg SV
Number of seizure to date	2	1	10	8
Time since last seizure	6 months	1 year	6 years	5 years
Resting EEG	WNL	Abnormal sharp and slow in temporal and occipital regions	WNL	OS after eye closure only
Clinical response to hyper-ventilation	None recorded	None recorded	None recorded	None recorded
EEG during hyper-ventilation	No change	Increase in slow focus	No change	WNL
Clinical to visual stimulation	Subjective sensations	None recorded	Subjective sensations to pattern	None recorded
Photo/sen range	9-13fps OS	5-20fps OS	8-12+50fps OS	7-20fps OS
Pattern sensitive range	NAD	1-6cpd OS	0.5-3cpd OS	OS Frequencies unknown

Chapter 7	Subject 26	Subject 32	Subject 36	Subject 42
Age at time of exam	9 years	15 years	16 years	14 years
Medication at time of exam	NONE	1000mg SV	300mg LTG	NONE
Number of seizure to date	1	4	Numerous	1
Time since last seizure	4 month	6 months	Not known	1 month
Resting EEG	WNL	mid-temporal 3cps spike and wave	Eyelid myoclonia	Focal temporal abnormality
Clinical response to hyper-ventilation	None recorded	None recorded	None recorded	None recorded
EEG during hyper-ventilation	WNL Little change	Increase slow	Induced sharp theta activity	Increased slow but no increase in abnormality
Clinical to visual stimulation	None recorded	Whole body jerks	None recorded	None recorded
Photo/sen range	7-60fps PPR	11-17+ 40-50fps PPR	10-50fps PPR	7-20fps PPR
Pattern sensitive range	1-6cpd PPR	0.25-6cpd PPR	0.5-6cpd PPR	Minimal abnormality

Chapter 7	Subject 43	Subject 44	Subject 45	Subject 46
Age at time of exam	25 years	36 years	34 years	29 years
Medication at time of exam	600mg Cbz	NONE	NONE	1000mg SV
Number of seizure to date	Numerous	10	1	10
Time since last seizure	Continuing	13 years	12 years	10 years
Resting EEG	WNL	WNL Some sharpened theta	WNL Some theta	WNL
Clinical response to hyper-ventilation	Unresponsive during spike and wave	None recorded	None recorded	None recorded
EEG during hyper-ventilation	Induced spike and wave	No change	WNL increased theta	No change
Clinical to visual stimulation	None recorded	None recorded	None recorded	None recorded
Photo/sen range	11-14 fps OS	8-12+ 50-60fps OS	9-20fps PPR	13-15fps OS
Pattern sensitive range	NAD	2-3cpd OS	2-6cpd PPR	NAD

Chapter 7	Subject 51	Subject 59	Subject 60	Subject 61
Age at time of exam	10 years	18 years	18 years	17 years
Medication at time of exam	NONE	400mg Cbz 400mg LTG	1250mg SV 400mg Cbz	600mg SV
Number of seizure to date	3	Numerous	Unknown	Numerous
Time since last seizure	1 month	Unknown	Unknown	1 week
Resting EEG	WNL	Single spikes in right rolandic region	WNL	Spike and wave associated with absence
Clinical response to hyper-ventilation	None recorded	None recorded	None recorded	None recorded
EEG during hyper-ventilation	Little change Some increased theta	Increased abnormality	No change	No change
Clinical to visual stimulation	None recorded	Whole body jerk at 12fps	None recorded	None recorded
Photo/sen range	6-18+ 45-50fps PPR	10-60fps PPR	13-47fps PPR	7-17fps OS
Pattern sensitive range	Unknown	2-3cpd	Unknown	OS Frequencies unknown

Chapter 7	Subject 62	Subject 68
Age at time of exam	17 years	22 years
Medication at time of exam	NONE	200mg LTG
Number of seizure to date	20	Numerous
Time since last seizure	Continuing	Continuing
Resting EEG	WNL	WNL
Clinical response to hyper-ventilation	None recorded	None recorded
EEG during hyper-ventilation	WNL Some increased theta	WNL Increased alpha
Clinical to visual stimulation	None recorded	None recorded
Photo/sen range	5-20+50fps OS	13-17fps PPR
Pattern sensitive range	2.5-3.5cpd OS	PPR Frequencies unknown

Chapter 8 Experiment 1	Subject 1	Subject 2	Subject 3	Subject 4
Age at time of exam	13 years	16 years	26 years	35 years
Medication at time of exam	1500mg SV 25mg LTG	75mg LTG	400mg SV	2500mg SV
Number of seizure to date	Numerous	Numerous	45-50	8
Time since last seizure	Continues to have episodes every 2 weeks	Continuing	Continuing	23 years
Resting EEG	WNL	WNL	WNL	WNL
Clinical response to hyper-ventilation	None recorded	None recorded	None recorded	None recorded
EEG during hyper-ventilation	WNL Some theta Rapid recovery	WNL Occasional ragged complexes in temporal regions, rapid recovery	Generalised bursts of 3-6cps activity, Slow recovery	No change
Clinical to visual stimulation	None recorded	None recorded	None recorded	None recorded
Photo/sen range	45-50fps PPR	13+45-60fps PPR	7-9+ 20-60fps PPR	9-11fps PPR
Pattern sensitive range	1.25-5cpd PPR	2.5cpd PPR	0.53-5cpd PPR	2-3cpd PPR

Chapter 8 Experiment 1	Subject 5	Subject 6	Subject 7	Subject 9
Age at time of exam	24 years	37 years	11 years	29 years
Medication at time of exam	200mg Phy 300mg LTG	300mg SV	10mg LTG	100mg LTG
Number of seizure to date	1	Numerous	8	Numerous
Time since last seizure	2 years	3 years	3 weeks	Unknown
Resting EEG	WNL	WNL	Suppression of normal background activity on left	WNL Some sharp theta
Clinical response to hyper-ventilation	None recorded	None recorded	None recorded	None recorded
EEG during hyper-ventilation	WNL	No change	Increased abnormal sharp theta in anterior region	WNL Increased alpha
Clinical to visual stimulation	None recorded	None recorded	None recorded	None recorded
Photo/sen range	7-8fps OS 13fps PPR	10-20fps PPR	40-50fps PPR	11-20+ 45-50fps OS
Pattern sensitive range	NAD	2-6cpd dPPR	2-3cpd PPR	1.5-6cpd OS

Chapter 8 Experiment 1	Subject 10	Subject 12	Subject 13	Subject 15
Age at time of exam	17 years	23 years	21 years	54 years
Medication at time of exam	1000mg SV	1000mg SV	700mg SV	NONE
Number of seizure to date	NONE	2	NONE	2
Time since last seizure	N/A	10 years	N/A	6 months
Resting EEG	WNL	WNL	WNL	WNL
Clinical response to hyper-ventilation	None recorded	None recorded	None recorded	None recorded
EEG during hyper-ventilation	Induces slow rhythms of 6-7cpd	WNL Some increased slow	WNL Some increased slow	No change
Clinical to visual stimulation	Twitch of the arms at 40fps	None recorded	None recorded	Subjective sensations
Photo/sen range	6-50fps PPR	5-17fps OS	5-55fps OS	9-13fps OS
Pattern sensitive range	2-6cpd PPR	OS Frequencies unknown	2-6cpd OS	NAD

Chapter 8 Experiment 1	Subject 16	Subject 17	Subject 18	Subject 19
Age at time of exam	13 years	30 years	17 years	34 years
Medication at time of exam	NONE	1000mg SV	700mg SV	NONE
Number of seizure to date	1	10	2	Numerous
Time since last seizure	1 year	5 years	2 years	16 years
Resting EEG	Abnormal sharp and slow in temporal and occipital	WNL	Spontaneous frontal spike and wave	Abnormal sharp theta
Clinical response to hyper-ventilation	None recorded	None recorded	None recorded	None recorded
EEG during hyper-ventilation	Increase in slow focus	No change	Increased abnormal discharge	No change
Clinical to visual stimulation	None recorded	Subjective sensations to pattern	None recorded	None recorded
Photo/sen range	5-20fps OS	7-20+ 45-55fps OS	16-30fps PPR	10-25fps PPR
Pattern sensitive range	1-6cpd OS	OS Frequencies unknown	2-3cpd PPR	2-6cpd PPR

Chapter 8 Experiment 1	Subject 21	Subject 24	Subject 26	Subject 27
Age at time of exam	25 years	28 years	9 years	27 years
Medication at time of exam	1000mg SV	1200mg SV	NONE	NONE
Number of seizure to date	Numerous	8	1	4-5
Time since last seizure	Continuing	7 years	4 months	7 years
Resting EEG	Spontaneous theta and spike and wave	WNL	WNL	WNL
Clinical response to hyper-ventilation	None recorded	None recorded	None recorded	None recorded
EEG during hyper-ventilation	Increased abnormality	No change	Little change	WNL
Clinical to visual stimulation	None recorded	None recorded	None recorded	None recorded
Photo/sen range	9fps OS 15-45fps PPR	8-50fps OS	7-60fps PPR	40+50fps OS
Pattern sensitive range	2-6cpd PPR	2-6cpd OS	1-6cpd PPR	2-6cpd OS

Chapter 8 Experiment 1	Subject 28	Subject 32	Subject 33	Subject 34
Age at time of exam	8 years	15 years	47 years	21 years
Medication at time of exam	400mg SV	1000mg SV	250mg SV	150mg LTG 700mg Cbz 2000mg Vig
Number of seizure to date	14	4	Numerous	70
Time since last seizure	12 months	6 months	Continuing absences	Continuing
Resting EEG	WNL	mid-temporal 3 cps spike and wave	3 cps spikes and wave coinciding with absence	WNL
Clinical response to hyper-ventilation	None recorded	None recorded	None recorded	None recorded
EEG during hyper-ventilation	WNL Some increased theta	Increased slow	Increase in abnormality	No change
Clinical to visual stimulation	None recorded	Whole body jerks during stimulation	Whole body jerks during PPR	None recorded
Photo/sen range	18-40fps PPR	11-17+ 40-50fps PPR	5-50fps PPR	35-60fps OS
Pattern sensitive range	2-6cpd PPR	0.25-6cpd PPR	0.25-6cpd PPR	NAD

Chapter 8 Experiment 1	Subject 35	Subject 36	Subject 37	Subject 38
Age at time of exam	32 years	16 years	12 years	35 years
Medication at time of exam	1500mg SV	300mg LTG	NONE	500mg SV
Number of seizure to date	8	Numerous	2	2
Time since last seizure	20 years	unknown	6 months	15 years
Resting EEG	WNL	Eyelid myoclonia	WNL	Generalised bursts of theta activity
Clinical response to hyper-ventilation	None recorded	None recorded	None recorded	None recorded
EEG during hyper-ventilation	No change	Induced sharp theta activity	WNL Some sharp waves	Increased abnormality
Clinical to visual stimulation	None recorded	None recorded	None recorded	None recorded
Photo/sen range	40-50fps OS	10-50fps PPR	8-25+55fps OS 40-50fps PPR	8-18+50fps PPR
Pattern sensitive range	Unknown	0.5-6cpd PPR	unknown	0.5-6cpd PPR

Chapter 8 Experiment 1	Subject 42	Subject 44	Subject 45	Subject 46
Age at time of exam	14 years	35 years	34 years	29 years
Medication at time of exam	NONE	NONE	NONE	1000mg SV
Number of seizure to date	1	10	1	10
Time since last seizure	1 month	12 years	12 years	10 years
Resting EEG	Focal temporal abnormality	WNL Low amplitude	WNL Some theta	WNL
Clinical response to hyper-ventilation	None recorded	None recorded	None recorded	None recorded
EEG during hyper-ventilation	Increased slow but no increase in abnormality	No change	WNL Increased theta	No change
Clinical to visual stimulation	None recorded	None recorded	None recorded	None recorded
Photo/sen range	7-20fps PPR	9-17+ 50-55fps OS	9-20fps PPR	13-15fps OS
Pattern sensitive range	Minimal abnormality	NAD	2-6cpd PPR	NAD

Chapter 8 Experiment 1	Subject 47	Subject 49	Subject 51	Subject 52
Age at time of exam	27 years	17 years	10 years	45 years
Medication at time of exam	1000mg SV	25mg LTG	NONE	NONE
Number of seizure to date	Numerous	4	3	4
Time since last seizure	12 years	2 months	1 month	1 month
Resting EEG	High amplitude sharp theta	Focal spike and wave	WNL	Sharpened theta
Clinical response to hyper-ventilation	None recorded	None recorded	None recorded	None recorded
EEG during hyper-ventilation	Increased theta	Increased abnormality	Little change Some increase theta	No change
Clinical to visual stimulation	None recorded	None recorded	None recorded	None recorded
Photo/sen range	5-20fps PPR	40fps PPR	9-18+ 45-50fps PPR	4-60fps OS
Pattern sensitive range	1-6cpd PPR	2-6cpd PPR	unknown	0.5-6cpd OS

Chapter 8 Experiment 1	Subject 53	Subject 54	Subject 55	Subject 57
Age at time of exam	22 years	11 years	8 years	6 years
Medication at time of exam	NONE	10 mg LTG	NONE	NONE
Number of seizure to date	3	Numerous	Numerous	1
Time since last seizure	Unknown	Unknown	Continuing	2 weeks
Resting EEG	Generalised bursts of theta	WNL	WNL	WNL
Clinical response to hyper-ventilation	None recorded	None recorded	None recorded	None recorded
EEG during hyper-ventilation	No change	No change	WNL	WNL Some increased theta
Clinical to visual stimulation	None recorded	None recorded	None recorded	None recorded
Photo/sen range	14+50fps PPR	11-17fps PPR	17-60fps PPR	6-25+ 50-60fps PPR
Pattern sensitive range	2-6cpd PPR	2-4cpd PPR	0.5-6cpd PPR	2-3cpd PPR

Chapter 8 Experiment 1	Subject 59	Subject 60	Subject 61	Subject 62
Age at time of exam	18 years	18 years	17 years	17 years
Medication at time of exam	400mg Cbz 400mg LTG	1250mg SV 400mg Cbz	600mg SV	NONE
Number of seizure to date	Numerous	Unknown	Numerous	20
Time since last seizure	Unknown	Unknown	1 week	Continuing
Resting EEG	Single spikes in right rolandic area	WNL	Spike and wave associated with absences	WNL
Clinical response to hyper-ventilation	None recorded	None recorded	None recorded	None recorded
EEG during hyper-ventilation	Increased abnormality	No change	No change	WNL Some increased theta
Clinical to visual stimulation	Whole body jerk at 12fps	None recorded	None recorded	None recorded
Photo/sen range	10-60fps PPR	13-47fps PPR	7-17fps OS	5-20+50fps OS
Pattern sensitive range	2-6cpd PPR	Unknown	OS Frequencies unknown	2.5-3.5cpd OS

Chapter 8 Experiment 1	Subject 64	Subject 65	Subject 66	Subject 67
Age at time of exam	19 years	10 years	15 years	20 years
Medication at time of exam	Cbz dose unknown	NONE	NONE	250mg LTG
Number of seizure to date	Numerous	NONE	1	Numerous
Time since last seizure	Unknown	N/A	1 year	Unknown
Resting EEG	Spiking in temporal regions	Sharp waves in right temporal region	WNL	WNL
Clinical response to hyper-ventilation	None recorded	None recorded	None recorded	None recorded
EEG during hyper-ventilation	Increased abnormality	Increased abnormality	WNL Increased slow	WNL
Clinical to visual stimulation	None recorded	None recorded	None recorded	None recorded
Photo/sen range	13-20fps PPR	7-11fps PPR	6-17+50fps PPR	50fps PPR
Pattern sensitive range	NAD	Minimal abnormality	Unknown	1.5-2.5cpd PPR

Chapter 8 Experiment 1	Subject 68	Subject 69	Subject 70	Subject 71
Age at time of exam	22 years	24 years	13 years	24 years
Medication at time of exam	200mg LTG	200mg Cbz	NONE	NONE
Number of seizure to date	Numerous	Numerous	3	6
Time since last seizure	Continuing	Continuing	Unknown	Continuing
Resting EEG	WNL	Spontaneous focal spike and wave	Generalised theta	Non-specific abnormalities
Clinical response to hyper-ventilation	None recorded	None recorded	None recorded	None recorded
EEG during hyper-ventilation	WNL Increased alpha	Increased abnormality	Increased theta	Increased abnormality and theta
Clinical to visual stimulation	None recorded	None recorded	None recorded	None recorded
Photo/sen range	13-17fps PPR	5+7fps OS 9-50fps PPR	7-14+50fps PPR	9-11+ 45-50fps PPR
Pattern sensitive range	PPR Frequencies unknown	2-3.5cpd PPR	2-3cpd PPR	1-6cpd PPR

Chapter 8 Experiment 1	Subject 72	Subject 74
Age at time of exam	35 years	20 years
Medication at time of exam	NONE	Cbz dose unknown
Number of seizure to date	Numerous	Numerous
Time since last seizure	Unknown	Unknown
Resting EEG	WNL	Spiking in left temporal region
Clinical response to hyper-ventilation	None recorded	None recorded
EEG during hyper-ventilation	No change	Increased abnormality
Clinical to visual stimulation	None recorded	None recorded
Photo/sen range	11-20fps PPR	7-11fps OS 13-25+ 40-45fps PPR
Pattern sensitive range	NAD	Minimal

Chapter 8 Experiment 2	Subject 2	Subject 4	Subject 6	Subject 7
Age at time of exam	16 years	35 years	37 years	11 years
Medication at time of exam	75mg LTG	2500mg SV	300mg SV	10mg LTG
Number of seizure to date	Numerous	8	Numerous	8
Time since last seizure	Continuing	23 years	3 years	3 weeks
Resting EEG	WNL	WNL	WNL	Suppression of normal background activity on left
Clinical response to hyper-ventilation	None recorded	None recorded	None recorded	None recorded
EEG during hyper-ventilation	WNL Occasional ragged complexes in temporal regions, rapid recovery	No change	No change	Increased abnormal sharp theta in anterior region
Clinical to visual stimulation	None recorded	None recorded	None recorded	None recorded
Photo/sen range	13+45-60fps PPR	9-11fps PPR	10-20fps PPR	40-50fps PPR
Pattern sensitive range	2.5cpd PPR	2-3cpd PPR	2-6cpd dPPR	2-3cpd PPR

Chapter 8 Experiment 2	Subject 8	Subject 9	Subject 10	Subject 11
Age at time of exam	8 years	29 years	17 years	18 years
Medication at time of exam	NONE	100mg LTG	1000mg SV	5mg LTG
Number of seizure to date	NONE	Numerous	NONE	1
Time since last seizure	N/A	Unknown	N/A	2 months
Resting EEG	WNL	WNL Some sharp theta	WNL	Abnormal posterior sharp theta
Clinical response to hyper-ventilation	None recorded	None recorded	None recorded	None recorded
EEG during hyper-ventilation	WNL	WNL Increased alpha	Induces slow rhythms of 6-7cps	Increased abnormality
Clinical to visual stimulation	None recorded	None recorded	Twitch of arms at 40fps	None recorded
Photo/sen range	40-45fps PPR	11-20+ 45-50fps OS	6-50fps PPR	NAD
Pattern sensitive range	2-6cpd PPR	0.5-6cpd OS	2-6cpd PPR	2-6cpd OS

Chapter 8 Experiment 2	Subject 12	Subject 14	Subject 16	Subject 18
Age at time of exam	23 years	20 years	13 years	17 years
Medication at time of exam	1000mg SV	NONE	NONE	700mg SV
Number of seizure to date	2	Numerous	1	2
Time since last seizure	10 years	2 months	1 year	2 years
Resting EEG	WNL	WNL	Abnormal sharp and slow in temporal and occipital regions	Spontaneous frontal spike and wave
Clinical response to hyper-ventilation	None recorded	None recorded	None recorded	None recorded
EEG during hyper-ventilation	WNL Some increased slow	WNL Increased theta and slow	Increased slow focus	Increased abnormality
Clinical to visual stimulation	None recorded	None recorded	None recorded	None recorded
Photo/sen range	5-17fps OS	NAD	5-20fps OS	16-30fps PPR
Pattern sensitive range	OS frequencies unknown	2-6cpd PPR	1-6cpd OS	2-3cpd PPR

Chapter 8 Experiment 2	Subject 19	Subject 21	Subject 22	Subject 23
Age at time of exam	34 years	25 years	21 years	27 years
Medication at time of exam	NONE	1000mg SV	NONE	2000mg SV
Number of seizure to date	Numerous	Numerous	6	50
Time since last seizure	16 years	Continuing	8 years	1 year
Resting EEG	Abnormal sharp theta	Spontaneous theta and spike and wave	Sharp waves and brief theta and delta discharges	WNL
Clinical response to hyper-ventilation	None recorded	None recorded	None recorded	None recorded
EEG during hyper-ventilation	No change	Increased abnormality	Increased abnormality	No change
Clinical to visual stimulation	None recorded	None recorded	None recorded	None recorded
Photo/sen range	10-25 fps PPR	9fps OS 15-45fps PPR	NAD	13+45-50fps dPPR
Pattern sensitive range	2-6cpd PPR	2-6cpd PPR	2-3cpd PPR	2-6cpd PPR

Chapter 8 Experiment 2	Subject 24	Subject 25	Subject 26	Subject 27
Age at time of exam	28 years	23 years	9 years	27 years
Medication at time of exam	1200mg SV	1000mg SV	NONE	NONE
Number of seizure to date	8	Numerous	1	4-5
Time since last seizure	7 years	Unknown	4 months	7 years
Resting EEG	WNL	WNL	WNL	WNL
Clinical response to hyper-ventilation	None recorded	None recorded	None recorded	None recorded
EEG during hyper-ventilation	No change	No change	Little change	WNL
Clinical to visual stimulation	None recorded	Subjective sensations with OS	None recorded	None recorded
Photo/sen range	8-50fps OS	8-20fps OS 12-14fps dPPR	7-60fps PPR	40-50fps OS
Pattern sensitive range	2-6cpd OS	2-6cpd PPR	1-6cpd PPR	2-6cpd OS

Chapter 8 Experiment 2	Subject 28	Subject 29	Subject 31	Subject 35
Age at time of exam	8 years	22 years	17 years	35 years
Medication at time of exam	400mg SV	NONE	400mg SV	1500mg SV
Number of seizure to date	14	4	20	8
Time since last seizure	12 months	4 years	6 months	23 years
Resting EEG	WNL	WNL	WNL	WNL
Clinical response to hyper-ventilation	None recorded	None recorded	None recorded	None recorded
EEG during hyper-ventilation	WNL Some increased theta	3cps spikes	No change	No change
Clinical to visual stimulation	None recorded	None recorded	None recorded	None recorded
Photo/sen range	18-40fps PPR	25+50-60fps dPPR	Minimal abnormality	Minimal abnormality
Pattern sensitive range	2-6cpd PPR	1-5cpd PPR	2-6cpd PPR	2-3cpd OS

Chapter 8 Experiment 2	Subject 36	Subject 38	Subject 39	Subject 41
Age at time of exam	16 years	35 years	37 years	32 years
Medication at time of exam	300mg LTG	500mg SV	700mg SV	1500mg SV
Number of seizure to date	Numerous	2	4	6
Time since last seizure	Unknown	15 years	20 years	4 years
Resting EEG	Eyelid myoclonia	Generalised bursts of theta activity	Sharp theta in left temporal	WNL
Clinical response to hyper-ventilation	None recorded	None recorded	None recorded	None recorded
EEG during hyper-ventilation	Induced sharp theta activity	Increases abnormality	Increases abnormality	No change
Clinical to visual stimulation	None recorded	None recorded	None recorded	None recorded
Photo/sen range	10-50fps PPR	8-18+50fps PPR	NAD	NAD
Pattern sensitive range	0.5-6cpd PPR	0.5-6cpd PPR	1.5-2cpd OS	2-6cpd PPR

Chapter 8 Experiment 2	Subject 44	Subject 48	Subject 49	Subject 50
Age at time of exam	36 years	38 years	17 years	30 years
Medication at time of exam	NONE	2000mg SV	25mg LTG	NONE
Number of seizure to date	10	50	4	1
Time since last seizure	13 years	2 years	2 months	4 years
Resting EEG	WNL Some sharpened theta	Non-specific abnormalities	Spontaneous focal spike and wave	WNL
Clinical response to hyper-ventilation	None recorded	None recorded	None recorded	None recorded
EEG during hyper-ventilation	No change	No change	Increased abnormality	No change
Clinical to visual stimulation	None recorded	Vaso-vagal attack	None recorded	None recorded
Photo/sen range	8-12+ 50-60fps OS	NAD	40fps PPR	8+12+20+ 40fps OS 10fps dPPR
Pattern sensitive range	2-3cpd OS	2-3cpd PPR	2-6cpd PPR	2-6cpd OS

Chapter 8 Experiment 2	Subject 52	Subject 53	Subject 54	Subject 55
Age at time of exam	45 years	22 years	11 years	32 years
Medication at time of exam	NONE	NONE	10mg LTG	1200mg SV started 15 weeks previous
Number of seizure to date	4	3	Numerous	Numerous
Time since last seizure	1 Month	Unknown	Unknown	12 years
Resting EEG	Sharpened theta	Generalised sharp theta burst	WNL	WNL
Clinical response to hyper-ventilation	None recorded	None recorded	None recorded	None recorded
EEG during hyper-ventilation	No change	No change	No change	Little change
Clinical to visual stimulation	None recorded	None recorded	None recorded	None recorded
Photo/sen range	4-60fps OS	14+50fps PPR	11-17fps PPR	12fps OS
Pattern sensitive range	0.5-6cpd OS	2-6cpd PPR	2-4cpd PPR	2-6cpd OS

Chapter 8 Experiment 2	Subject 57	Subject 59	Subject 62	Subject 63
Age at time of exam	6 years	18 years	17 years	27 years
Medication at time of exam	NONE	400mg Cbz 400mg LTG	NONE	500mg SV
Number of seizure to date	1	Numerous	20	NONE
Time since last seizure	2 weeks	Unknown	Continuing	N/A
Resting EEG	WNL	Single spikes in right rolandic	WNL	WNL
Clinical response to hyper-ventilation	None recorded	None recorded	None recorded	None recorded
EEG during hyper-ventilation	WNL Some increased theta	Increased abnormality	WNL Some increased theta	No change
Clinical to visual stimulation	None recorded	Whole body jerk at 12fps	None recorded	None recorded
Photo/sen range	6-25+ 50-60fps PPR	10-60fps PPR	5-20+50fps OS	NAD
Pattern sensitive range	2-3cpd PPR	2-6cpd PPR	2.5-3.5cpd OS	2-3cpd PPR

Chapter 8 Experiment 2	Subject 67	Subject 70
Age at time of exam	20 years	13 years
Medication at time of exam	250mg LTG	NONE
Number of seizure to date	Numerous	3
Time since last seizure	Unknown	Unknown
Resting EEG	WNL	Generalised theta
Clinical response to hyper-ventilation	None recorded	None recorded
EEG during hyper-ventilation	WNL	Increased theta
Clinical to visual stimulation	None recorded	None recorded
Photo/sen range	50fps PPR	7-14+50fps PPR
Pattern sensitive range	1.5-2.5cpd PPR	2-3cpd PPR

Chapter 9	Subject 12	Subject 13	Subject 24	Subject 36
Age at time of exam	27 years	24 years	29 years	19years
Medication at time of exam	1000mg SV	700mg SV	1200mg SV	300mg LTG
Number of seizure to date	3	NONE	8	Numerous
Time since last seizure	15 months	N/A	8 years	8 months
Resting EEG	WNL Minimal alpha	WNL	WNL	Eyelid myoclonia
Clinical response to hyper-ventilation	None recorded	None recorded	None recorded	None recorded
EEG during hyper-ventilation	No change	WNL Increased alpha	No change	No change
Clinical to visual stimulation	None recorded	None recorded	None recorded	None recorded
Photo/sen range	6-18+40fps OS	6-25+ 40-50fps OS	8-10+20fps OS 12-50fps dPPR	8+60fps OS 10-50fps PPR
Pattern sensitive range	2-6cpd OS	2-6cpd OS	2-6cpd PPR	0.5-6cpd PPR

Chapter 9	Subject 57	Subject 70
Age at time of exam	7 years	14 years
Medication at time of exam	NONE	100mg LTG
Number of seizure to date	2	3
Time since last seizure	2 weeks	Unknown
Resting EEG	WNL	Non-specific abnormalities
Clinical response to hyper-ventilation	None recorded	None recorded
EEG during hyper-ventilation	WNL Some increased theta	No change
Clinical to visual stimulation	None recorded	None recorded
Photo/sen range	8-16+ 40-60fps PPR	8-16+ 40-50fps PPR
Pattern sensitive range	Unknown	2-6cpd PPR