INVESTIGATIONS OF VISUAL FUNCTION IN MIGRAINE ~~USING~~ BY VISUAL EVOKED POTENTIALS AND VISUAL PSYCHOPHYSICAL TESTS

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ABSTRACT

Ninety two adult migraineurs and 62 age and sex matched controls were examined using visual evoked potentials (VEP) and visual psychophysical tests.

The VEP were recorded to chequerboard pattern and to single and repetitive flash at 4 to 24 Hz. The electroretinogram (ERG) was also recorded to pattern and single flash.

Psychophysical tests consisted of visual illusions, assessed with high contrast patterns, spatial contrast sensitivity (SCS) measured with whole-field and half-field sinusoidal gratings, and temporal contrast sensitivity (TCS) measured at 3.3, 10, 20 and 30 Hz.

The ERG was similar in migraine and control groups. Latencies of the P100 wave of the pattern and of the P1 and P2 waves of the single flash VEP were prolonged in migraineurs.

P100 amplitude was increased in common migraine and in classical migraine of short duration, but decreased in chronic cases. With repetitive flash the H-response was more prominent in migraineurs, especially in classical migraine and in patients with frequent attacks, but disappeared with successful prophylactic treatment.

Visual illusions were more frequent in migraine subjects, especially in classical migraine on the aura side, and in patients with frequent attacks or attacks triggered by visual stimuli. They did not change with duration of migraine, but were reduced in patients responding to prophylactic treatment.

Both spatial and temporal CS were normal in common

migraine subjects but were reduced in patients with chronic classical migraine, especially on the side of the visual aura. Reduction in temporal CS was greatest at 10 and 20 Hz.

Asymmetry of spatial CS and illusions was related to the side of the visual aura but not to the side of the headache.

The increased illusions, prolonged VEP latencies, high P100 amplitude and increased incidence of H-responses all suggest an underlying neural abnormality in migraine subjects. The reduction of P100 amplitude and CS in late classical cases may represent ischaemic damage caused by recurrent attacks.

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ABBREVIATIONS

A	Amplitude
CBF	Cerebral blood flow
CD	Contrast discrimination
CNS	Central nervous system
CNV	Contingent negative variation
CS	Contrast sensitivity
CT	Contrast threshold
EEG	Electroencephalogram
ERG	Electroretinogram
HF	Half-field
HFCD	Hemifield spatial contrast discrimination
L	Latency
LHF	Left half-field
MRI	Magnetic resonance imaging
OPs	Oscillatory potentials
PET	Positron emission tomography
PRVEP	Pattern-reversal visual evoked potentials
RFVEP	Repetitive flash visual evoked potentials
RHF	Right half-field
SCS	Spatial contrast sensitivity
SFVEP	Single flash visual evoked potentials
TCS	Temporal contrast sensitivity
VEP	Visual evoked potential(s)
WF	Whole-field

CHAPTER 1 VISUAL SYSTEM IN MIGRAINE

Visual symptoms have been recognised as part of the clinical picture of migraine for several thousand years. In some subjects attacks can be precipitated by bright, flashing or flickering light. Even without visual symptoms the reduction in cerebral blood flow which occurs in classical migraine often starts posteriorly. These observations suggest that some components of visual function in migraine might be different from normal, and make it appropriate to compare the function of the visual system in migraine subjects and controls. Furthermore, information about the visual system may offer guidelines to other components of cerebral organisation and function in migraine.

The visual system can be tested by clinical examination, visual evoked potentials and psychophysical tests. Clinical examination of the visual system in migraine has shown no abnormalities. Visual evoked potentials have been reported abnormal in migraine using various stimuli including pattern (section 4.2.4), single flash (section 4.3.4) and repetitive flash (section 4.4.2). Visual illusions on looking at high contrast patterns have been found to be increased (Wilkins et al. 1984). The oldest of the psychophysical tests is visual acuity, which is usually measured as part of the physical examination, and this is normal in migraine. The most recent psychophysical tests are those of contrast sensitivity function, and there have been no publications on these in migraine.

The various VEP studies have been performed separately and by different authors. Only one publication deals with various VEP's in combination (Winter 1987, based on Ph.D thesis 1985). No one has

previously combined neurophysiolog'cal and psychophysical tests, and the effect of various factors in the migraine subjects has not been examined in any detail.

The present study combined neurophysiological and psychophysical testing in large numbers of migraine and control subjects, using standard visual tests that have proved valuable in exploring various aspects of visual physiology. Thus, visual evoked potentials were recorded to pattern and to various flash stimuli, and measurements were made of spatial and temporal contrast sensitivity and the responses to high contrast patterns.

The large size of the study group made it possible to look for variations according to age, sex, trigger factors, type of migraine, duration of illness, unilaterality of headache and visual aura and the effect of prophylactic treatment.

The Headache Classification Committee of the International Headache Society (1988) has recently recommended that the terms "classical" and "common" migraine should be replaced by "migraine with aura" and "migraine without aura". Although these new terms are satisfactory as definitions they are remarkably awkward to use for the range of purposes one needs in writing English sentences, and since this is quite difficult for me anyway, I have found it more convenient to use the old terminology.

CHAPTER 2 MIGRAINE

2.1 Historical review

According to several authors, the earliest description of migraine is found in the poetry of Mesopotamia (3500 B.C.). Descriptions like "I am sick-eyed", "I am sick-headed" "flashing like lightning" and "flashing like a heavy star" appear (see Alvarez 1945, Sigerist 1955).

However, the first precise description of visual symptoms preceding an intense headache was by Hippocrates (460-377 B.C.), and he also noted that the act of vomiting would often alleviate the suffering. His words were as follows: "Most of the time he seemed to see something shining before him like a light, usually in part of the right eye; at the end of a moment, a violent pain supervened in the right temple, then in all the head and neck, where the head is attached to the spine. Vomiting, when it became possible, was able to divert the pain and render it more moderate" (Adams 1939).

The first identification of migraine as an entity distinct from other headaches was made by Aretaeus of Cappadocia (A.D. 30-90), who distinguished three types of headache. These were cephalagia, an acute headache lasting for days, cephalea or chronic headache, and heterocrania, which we recognise as migraine because of his description of severe, recurrent pain confined to half of the head, associated with nausea and vomiting. "....In certain cases, the parts on the right side, or those on the left solely, so far that a separate temple, or ear, or

one eyebrow, or one eye, or the nose which d vides the head into two equal parts; and the pain does not pass this limit, but remains in the half of the head. This is called heterocrania, an illness by no means mild, even though it intermits, and although it appears to be slight. For if at any times it sets in acutely, it occasions unseemly and dreadful symptoms... nausea; vomiting of bilious matters, collapse of the patient; but if the affection be protracted, the patient will die; or if more light and not deadly, it becomes chronic" (Critchley 1967)

However, it was Galen (A.D. 131-201) who introduced the term "Hemicrania". The Romans altered "Hemicrania" into the Latin "Hemicranium", which became by successive changes, Emigranea, Migranea, Migrim and Migrana. The French modified migrana to migraine which is now universally accepted (Lance 1982). Galen also recognised precipitating factors and mentioned the cause as a disturbance in parts of the body that dispatch vapour or liquid containing harmful properties to the brain.

In Arabian medicine, Avicenna (A.D. 980-1037) divided "sudàa" which is the name of headache in Arabic, into three types; ordinary headache, headache caused by brain damage, and "shaqiqa" the name given to migraine, meaning severe pain which divides the head into two parts. He formulated the first mature idea about the underlying pathophysiology: "migraine is due to hyperexcitability of brain tissue which causes the brain to react unusually to noises and to light stimuli" (Isler 1987)

There are no references to migraine during the next, generally blank, period in medical history, unt'l the seventeenth

century, when important observations were made by Thomas Willis (1621-1675) a pioneer clinical neurologist. He noted a premonitory enhancement of appetite before the attack, and also trigger factors including wine, overeating, oversleeping, lying in the sun and sexual activity. In addition, he considered that the pain in migraine was due to distension of blood vessels rather than radiating from brain tissue (Sacks 1985). Subsequently Charles Le Pois in 1681 (Riley 1932) described a case with transient sensory loss and weakness on the left side of the body, accompanying severe headache.

During the eighteenth century additional data about the symptoms and pathophysiology of migraine came to light. The Swiss physician J.J. Wepfer in 1726 noted that migraine headache can alternate from side to side. He attributed the pain to stasis of the cerebral circulation, dilation of blood vessels and defective reabsorption of fluid (Isler 1985). John Fothergill (1784), himself a migraine sufferer, described the visual disturbances of classical migraine and first used the term fortification spectra to describe the zigzag appearance of the aura. He also mentioned the dietary triggers of migraine, specifically chocolate (Schiller 1975).

In the nineteenth century came the discovery of ergot, and Woakers (1868) in England described the use of its derivatives in the treatment of migraine. Edward Liveing (1873) has been credited as the father of the neurogenic theory of migraine. He stated that migraine is primarily caused by disturbance of function of nerve cells of the brain, referred to as a "nerve storm", and that the visible vasomotor disturbances are of secondary origin. This theory was supported by Gowers (1888)

whose description has influenced all those who have attempted to define migraine: "Migraine is an affection characterised by paroxysmal nervous disturbance, of which headache is the most constant element. The pain is seldom absent and may exist alone, but it is commonly accompanied by nausea and vomiting, and it is often preceded by some sensory disturbance, especially by some disorder of the sense of sight. The symptoms are frequently one-sided, and from this character of the headache the name is derived, the Greek 'hemicrania' furnishing the French 'Migraine', the German 'Migran' and the English 'Megrim' "

The twentieth century is marked by the work of Wolff and his colleagues, beginning in the 1930s, which contributed a great deal to our understanding of the pathophysiology of migraine. This focussed attention on the vascular changes, and established ergotamine tartrate as the treatment of choice. Wolff's vascular theory, which dominated thought about migraine mechanisms for several decades, stated that the initial preheadache phase consists of intracranial vasoconstriction and that this is followed by extracranial vasodilation during the headache. Additionally he suggested that sterile inflammation of the arterial walls produces pain (Wolff 1963). This work merged into the present day concepts of migraine.

2.2 Visual disturbances in migraine

Visual disturbances are the most common aura symptoms in migraine. They commonly precede, but may occur concomitantly

with, headache, and may occur alone without the headache (migraine equivalents) or may persist after the headache has stopped (complicated migraine). The visual disturbances may take the form of unstructured flashes or spots before the eyes, fortification spectra or transient field defects (Klee and Willanger 1966). The size and density of the visual field defect vary considerably, from general dimness of vision to dots and spots, hemianopia and even total visual loss (Alvarez 1960). In one series visual symptoms occurred in 41% of 484 migraineurs and photophobia in 82% of 435 (Selby and Lance 1960).

Transient and permanent monocular disturbances can occur in migraine (Hupp et al. 1989), and such episodes have been called retinal or ocular migraine. The latter is more accurate since either the ciliary or retinal circulation may be involved. The condition is extremely rare.

A more disturbing visual symptom is that objects may appear distorted, so that proportions of human body may look wrong, with changes in the shape or size of eyes, ears, face, hands etc (Wilkinson 1986).

Typically the visual aura starts as a hazy spot at or near the macular field and spreads outwards up to 50 degrees from fixation (Richards 1971). However, spread from the periphery to the macular region may also occur. It is almost symmetrical in the two eyes, and does not impinge on the midline. The time taken to spread from the centre to the periphery is about 20 to 25 minutes (Lashley 1941). As it spreads and expands star-shaped figures with shining and flickering curved zig-zag lines (fortification spectra) may become apparent. However, some

auras are negative, consisting only of scotomata without the scintillations. Although visual disturbances are mostly uncoloured, colour may appear close to the zigzag lines (Bücking and Baumgartner 1974, quoted by Olesen 1988):

The visual aura is commonly in one hemifield only . However, the side and composition of aura symptoms may vary between attacks in the same individual. The side of the aura is not necessarily correlated with the side of headache (Peatfield et al. 1981).

Study of the visual disturbances has shed light on important pathophysiological aspects of migraine (see section 2.3.1).

2.3 Pathophysiology of migraine

The pathophysiology of migraine is poorly understood, and a unified concept must take into account not only the wide range of precipitating factors, including food, alcoholic drinks, sleep deprivation, stress, cold, head trauma, visual stimuli, loud noises and strong smells, but also the multiple symptomatology and the widely variable individual vulnerability to the condition.

2.3.1 Current ideas on pathophysiology of migraine

Current ideas on the pathophysiology of migraine started with Lashley (1941), who mapped his visual aura at brief intervals during migraine attacks, and concluded that "a wave of intense excitation is propagated at a rate of 3 mm/minute across the visual cortex. This wave is followed by complete inhibition of activity with recovery progressing at the same rate. Sometimes

the inhibition spreads without the preceding excitatory wave". He thought that inhibition alone produced an aura consisting only of a "negative" scotoma with no "positive" scintillation.

Three years later the Brazilian physiologist Leão (1944a, 1944b) described the phenomenon of spreading depression (SD) of electrical activity of the cerebral cortex in animals following a variety of stimuli. The rate of spread of this wave of inhibition was about 3 mm/min, and subsequently Grafstein (1956) showed that at its advancing margin the cortical neurones were thrown into violent activity for a period of several seconds. Leão himself suggested a relationship between this phenomenon and migraine (Leão 1945), and this idea was taken further by Milner (1958) who suggested that SD is the underlying mechanism of all the sensory symptoms of migraine, involving different areas of cerebral cortex. He did not offer any explanation for the headache.

Subsequent theories have concentrated on vascular disorders. Grahame and Wolff (1938) showed that the amplitude of the pulse wave of the superficial temporal artery was increased during an attack of migraine, and that administration of ergotamine reduced the amplitude of the pulsations. It was subsequently found that the pulse pressure in the temporal arteries was larger and more variable in migraine patients than in normal controls even between attacks (Tunis and Wolff 1953). Later, vasoconstriction and increased sensitivity to norepinephrine were demonstrated in the small vessels of the bulbar conjuctiva during the pre-headache phase (Wolff 1963). Because of these observations Wolff considered that the headache phase of migraine attacks was due to extracranial vasodilatation and the neurological symptoms were

produced by intracranial vasoconstriction (Wolff 1963). This was the accepted view of migraine pathophysiology for some 20 years.

However, cerebral blood flow studies have shown that in classical migraine there is a reduction of cerebral blood flow which usually starts posteriorly and spreads forward over the cortex from one arterial territory to another at a speed of 2-3 mm/min (Olesen et al. 1981a, Lauritzen et al. 1983). The anatomical character of this spread, from one arterial territory to another, cannot be primarily vascular and is probably secondary to a reduction in metabolic requirements. The speed of the spread is similar to that of cortical impairment as calculated by Lashley (1941) and to the experimental spreading depression of Leão. This has revived interest in the suggestion that spreading depression might be the initiating event in the migraine attack, with secondary effects on blood vessels, and this suggestion accords well with many clinical features including the nature of the premonitory phase, the march of visual or sensory symptoms and other chronological aspects of the attack (Blau 1986).

Spreading depression is now largely accepted as the underlying pathophysiological mechanism of the migraine aura, but it does not account for the headache. Cerebral blood flow may be increased in some cases after the phase of oligaemia, but there is no evidence that this is responsible for the headache of classical migraine. Indeed, headache may begin at a time when cerebral blood flow is still diminished (Lauritzen et al. 1983). Moreover several authors (Olesen et al. 1981b, Lauritzen and Olesen 1984 and Davies et al. 1990) have shown that cerebral blood flow does not alter during attacks of common migraine (migraine without

aura), yet there is pain.

We have to ask whether the headache itself is primarily neuronal or vascular. Headache, like any other pain, must be felt as a result of activation of neural pathways, but the critical question is the site and nature of the pain-sensitive structures. In particular, does the pain arise in blood vessels, i.e is it due to changes in blood vessels, stimulating pain fibres in their walls? If so, which vessels are involved? Are they peripheral cerebral blood vessels, proximal vessels around the circle of Willis, extracranial vessels or meningeal vessels? Are there changes in any of these vessels which would fit this hypothesis?.

There are certainly changes in those cerebral vessels responsible for autoregulation, at least in classical migraine, but the changes are physiological, and there is no direct relationship between headache and cerebral blood flow. Furthermore, intracerebral vesse s do not have any C fibre innervation and are thus insensitive to pain. C fibres do however exist in the walls of meningeal vessels, extracranial vessels in the scalp, the circle of Willis, the terminal carotid and basilar arteries, and the proximal anterior, middle and posterior cerebral arteries, and changes have been observed in some of these (Markowitz et al. 1987).

Following the work of Wolff (1963) it has generally been supposed that the headache is caused by dilatation of extracranial blood vessels. However, this is unlikely to be the whole story. The pain is in fact pulsatile in only 50% of migraine patients (Olesen 1978). Compression of the temporal artery relieves pain in only a third of migraine patients (Drummond and Lance 1982, 1983, 1984) and facial pallor, rather than flushing, is present in half of them (Blau and Dexter 1981). In addition, measurements of pulse

pressure in the superficial temporal artery have given variable results. Heyck (1969) found no consistent difference in pulse amplitude between the headache side and the headache-free side, and Feuerstein (1983) found only small differences which did not reach statistical significance. However, Drummond and Lance (1983) showed that the pulse pressure was sometimes significantly greater on the side of unilateral migraine, but in only one third of cases, and in these compression of the superficial temporal artery diminished the intensity of headache. Similarly these patients had increased heat loss during the attack from the frontotemporal region ipsilateral to the headache as measured thermographically (Drummond and Lance 1984). Thus, extracranial vascular dilatation may be the source of pain in some migraine patients but not all.

Are there general systemic changes which could modify any of these blood vessels? Disturbances in the serotoninergic system in migraine have been widely studied. Platelet serotonin level falls during a migraine attack, with an increased urinary excretion of 5-hydroxy-indole-acetic acid (Anthony et al. 1969). In addition, reserpine, which triggers serotonin release, causes migraine in some patients (Kimball et al. 1960). Intravenous administration of serotonin can stop the attack (Anthony et al. 1967) and so can the 5HT1-like receptor agonist, sumatriptan (Doenicke et al. 1988), and all antimigraine drugs have a stabilising effect on serotonin neurotransmission through a variety of mechanisms (Fozard 1975). However, it is difficult to understand how changes in intravascular serotonin, which has little direct effect on vessel contraction, could induce the vascular changes responsible for migraine. In

particular it is difficult to see how it could induce a unilateral headache which may alternate from side to side from one attack to another. Internal carotid infusions of serotonin have no effect on rCBF in man (Olesen 1981).

Studies have been made also on the catecholamines, norepinephrine and epinephrine. There is no agreement on whether the sympathetic nervous system is under- or overactive in migraine. Some studies have shown elevation of plasma catecholamine concentration (Anthony 1981, Pradalier et al. 1985), or of urinary vanillylmandelic acid during an attack (Sicuteri et al. 1961, Curran et al. 1965) whereas Fog-Möller et al. (1978) reported a fall in plasma level of norepinephrine (NE) in the first stage of an attack. Gotoh et al. (1976) found no elevation of plasma NE, and a significant decrease of blood pressure with head-up tilt, in the headache-free period. The role of catecholamines is thus far from clear, and the possibility that they exert local effects on blood vessels has not been excluded.

Are there known local mechanisms which could operate on the various compartments of the vascular system to cause changes that initiate pain?

First, we have already excluded the metabolic blood flow changes which take place at the level of small intracererebral blood vessels, since these vessels lack C fibres. Regarding the extracranial vessels, two different explanations have been offered to explain the dilatation and/or increase in extracerebral blood flow. Heyck (1969, 1970) observed a reduced arteriovenous oxygen saturation difference in the presence of skin pallor on the side of the headache during an attack, and postulated that this might be

due to the opening of arteriovenous shunts in scalp and meningeal vessels. He suggested that this would result in a passive increase in arterial blood flow and distension of scalp and meningeal arteries proximal to the shunts. Drummond and Lance (1983 and 1984) and Drummond (1987 and 1990) suggested that the greater heat loss from the frontotemporal region on the headache side in some migraineurs might be due to impaired cutaneous sympathetic control of the facial skin vessels, especially in view of associated evidence for disturbed autonomic function in the pupils. Experimentally, several local mechanisms are known which cause changes in intracranial and extracranial vessels, which may be highly relevant to the pathophysiology of migraine (section 2.3.3), but these have not so far been documented in man.

2.3.2 Endogenous pain modulating systems

The most remarkable attempt to explain the complex pathophysiology of migraine focuses on the brainstem pain modulating systems and trigeminal system. Two systems originating in the brainstem appear to participate in the modulation of pain. The descending system originates in the midbrain periaqueductal gray matter (PAG), in the median raphe nuclei of the medulla and in the adjacent reticular formation, and it acts on the dorsal horn (laminae IV and V) and on the spinal nucleus of the trigeminal nerve. This system is enkephalinergic, and hence is also called the opioid system, because of the high density of opiate receptors and opioid peptides in its relay cells. This system inhibits peripheral nociceptive stimuli by "gating" mechanisms. The second system is an ascending modulating

system which originates in the dorsal raphe nuclei (DRN) of the midbrain, which constitute the main central serotonin-containing cell group, and projects to the thalamus and cortex. There is a reciprocal innervation between the locus coeruleus (LC) of the pons, which has the largest store of norepinephrine in the brain, and the DRN, and the DRN neurones are connected to the hypothalamus, the limbic system, the vomiting centre in the medulla, the retina and the visual pathways. In addition, these neurones send out fibres which provide a perivascular serotoninergic innervation of the cortical vessels (Reinhard et al. 1979, and Edvinsson et al. 1983). The exact role of this complex system is not yet understood.

Is there direct evidence for involvement of these systems in migraine?

As far as the descending system is concerned there is some suggestive evidence of an abnormality, in that CSF enkephalins were found to be reduced both during the migraine attack (Anselmi et al. 1980) and also in the headache-free period (Genazzani et al. 1984). Moreover, this reduction was greater in patients with a longer duration of migraine and more frequent attacks (Genazzani et al. 1984). However, opioid dysfunction could be the result of exhaustion, induced by continuous activation of the system, rather than a primary deficiency, so any specific relevance of the descending system to migraine is doubtful, although it is of course relevant to all pain syndromes.

Raskin et al. (1987) reported migraine-like headache syndromes in 15 patients immediately or soon after electrode implantation in PAG for the control of pain, mostly intractable

backache, responsive to opioids. Two patients died, and necropsy showed that the electrodes were indeed in PAG but also very close to the DRN, the origin of the ascending serotoninergic system. It was surmised that the headaches were caused by activation of DRN neurones, and suggested that migraine is likely to be related to a disturbance of the ascending system rather than the descending system (Raskin 1988). It is tempting, but difficult, to try and relate the known changes in serotonin metabolism to this anatomical system.

2.3.3 Experimental data

Experiments on animals have suggested other ways in which brainstem neurones and the trigeminal system may be linked to the phenomena of migraine, since these structures can influence both blood flow and nociception. Stimulation of LC in the monkey causes a 20% reduction of intracerebral blood flow, comparable with the reduction during the aura of classical migraine (Sakai and Meyer 1978), and it also causes vasodilation of extracerebral vessels (Goadsby et al. 1982). This is mediated by the facial nerve/greater superficial petrosal nerve (GSPN) pathway, is distributed to the periphery via the sphenopalatine and otic ganglia, and employs vasoactive peptide (VIP) as its peripheral transmitter (Goadsby and McDonald 1985). Stimulation of DRN produces an increase of flow in both the cerebral and the extracerebral circulation. The latter is also mediated through the facial/GSPN pathway and employs a noradrenergic, noncholinergic, nonhistaminic transmitter agent (Goadsby and Lance 1989). The

changes in cerebral blood flow following stimulation of DRN and LC are due to a direct action on the cortical microcirculation and are not secondary to metabolic demand caused by changes of neuronal activity (Adams et al. 1989)

Stimulation of the trigeminal ganglion in cats also causes dilation of extracranial blood vessels via a reflex pathway with its afferent path in the trigeminal root and the efferent in the greater superficial petrosal nerve (Lambert et al. 1984). Thus dilation of extracranial vessels can be produced by stimulation of either the trigeminal ganglion, the DRN or the LC via the so-called trigeminovascular reflexes.

Vascular pain could possibly result not only from vasodilation but also by the release of vasoactive/nociceptive peptides such as substance P. Recent work has concentrated on the role of neurotransmitters found in nerve fibres of the cerebral vasculature. NE, acetylcholine (ACH) and VIP have been most clearly established as vasomotor neurotransmitters in the cerebral circulation, and evidence is now accumulating rapidly that other substances such as substance P, adenosine triphosphate, neuropeptide Y, and calcitonin gene-related peptide (CGRP) must be seriously considered as potential vasomotor neurotransmitters, acting alone or in concert with the more classical molecules. However, the specific role of each one is not clear yet. Moskowitz et al. (1983) showed that either potassium or capsaicin could stimulate the *in vitro* release of substance P from trigeminal nerve endings in a bovine pia-arachnoid preparation. In addition it has been recently demonstrated in rats that neurogenic inflammation develops within and around the blood vessels in the dura mater, but not in the brain, following intravenous chemical

(capsaicin) administration or electrical stimulation of the trigeminal ganglia (Markowitz et al. 1987). This inflammation was selectively blocked by ergot alkaloids (Saito et al. 1988) and by the 5HT1-like agonist, sumatriptan (Buzzi and Moskowitz 1989). These findings suggest a role for substance P in the genesis of vascular pain. Furthermore, Goadsby et al. (1990) have recently demonstrated a substantial elevation of CGRP level in the external jugular but not in the cubital vein ipsilateral to the side of the headache in both classical and common migraine.

2.3.4 Unified concepts

The preceding presentation shows that current theories about the pathophysiology of migraine are extremely complex. Thus, a unified concept explaining the varied symptomatology in the light of the available experimental and clinical knowledge is naturally speculative. The following suggestions are based on current data and hypotheses.

Various trigger factors cause migraine, which suggests that migraine is a response of the brain and of cranial blood vessels to external stimuli or to internal, perhaps biochemical, changes. Welch (1987) has suggested that there is a threshold for migraine above which the mechanisms of the attack are set into motion. This threshold depends on the functional state of the noradrenergic system, and it is through modulation of sympathetic activity that potentiators of migraine, including psychological factors, exert their effect. This concept implies functional differences between individuals that determine migraine threshold, some of which may

be general biochemical, some immunological, some neurological. Visual trigger factors are the ones which most obviously have their immediate effect on a specific neurological substrate when they initiate attacks.

The trigger factors appear to funnel through the cortex or the hypothalamus or both. These structures are the the anatomical substrates of premonitory symptoms. Thence, activation spreads gradually to involve the monoaminergic nuclei in the brainstem i.e DRN and LC. Their activation will then result in reduction of regional cerebral blood flow and possibly induce the phenomenon of spreading depolarisation in the cerebral cortex, both of them starting posteriorly and spreading forward from one arterial territory to the other. This temporal progression of SD is widely accepted as the basic mechanism of aura symptoms in classical migraine, and there may be a similar but less marked cortical event in common migraine.

The cause of headache is even more speculative: several factors and mechanisms could contribute to the production of pain.

1. (a) Pain-sensitive fibres of trigeminal origin innervating blood vessels on the ventral surface of the brain and the surrounding pia-arachnoid mater could be stimulated by the ionic shifts in extracellular fluid (high potassium and low pH) produced by SD itself (Lauritzen 1988). Alternatively these fibres could be depolarized directly by the excitatory wave which is at the advancing edge of the spreading depression in the underlying cortex. Either way nociceptive impulses will be transmitted to the nervous system.

(b) In the mean time, depolarisation of these pain-sensitive

fibres causes vasoactive substances such as substance P and CGRP to be released from trigeminal nerve terminals in and around the wall of blood vessels in the pia-arachnoid and dura. These substances, together with locally produced histamine and bradykinin, can initiate vascular dilation, with increased permeability and sterile inflammation, which then causes pain.

2. The opening of arteriovenous shunts could also cause pain not only by distending the walls of meningeal and scalp vessels, but also by producing local hypoxia and acidosis by a steal mechanism, which could lower the pain threshold.

3. The release into the circulation of amines, such as NE from the adrenal medulla and 5HT from platelets, might influence the sensitivity of the blood vessels to other stimuli.

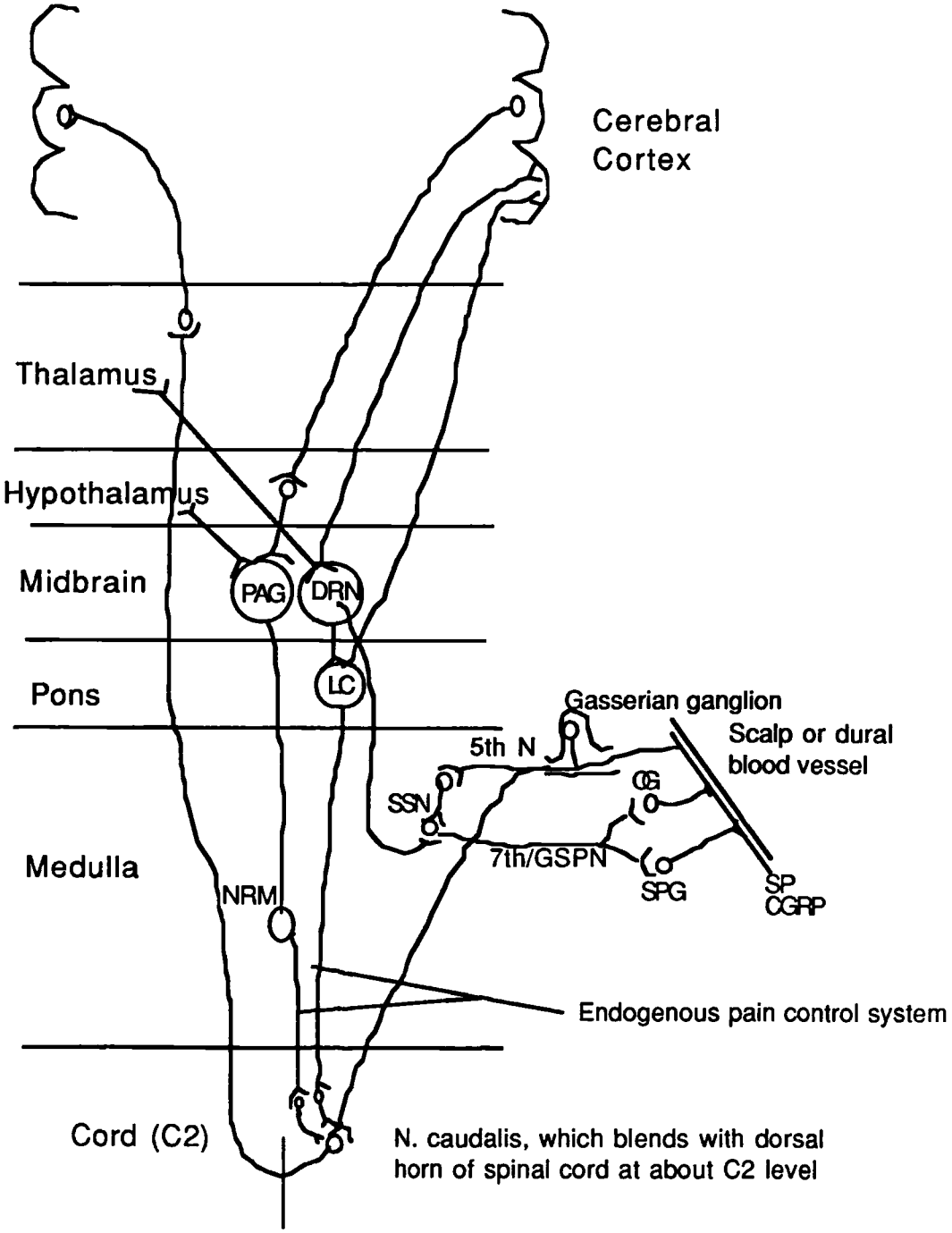
4. Pain might also be initiated or exacerbated by dysfunction of the endogenous pain modulating system. Discharges in the DRN and LC might cause extracranial vasodilation via the facial/GSPN system. The primary trigeminal nerve endings are then stimulated secondarily to this vascular dilatation. The resultant impulses through the trigeminal afferents are conveyed to the spinal trigeminal nucleus and thus to its central connections which will in turn activate this vicious circle.

Excessive activity in DRN and LC might also lead to reduced function of the descending inhibitory control system, opening the "gating" at the spinal nucleus level and leading to enhanced transmission of nociceptive impulses (Lance 1988) (Fig 1).

Figure 1

Schematic representation of the principal neural and vascular components of migraine (Modified from Goadsby and Lance 1989)

CGRP = calcitonin gene-related peptide, DRN = dorsal raphe nuclei, GSPN = greater superficial petrosal nerve, LC = locus coeruleus, NRM = nucleus raphe magnus, OG = otic ganglion, PAG = periaqueductal gray, SP = substance P, SPG = sphenopalatine ganglion, SSN = superior salivary nucleus



CHAPTER 3 VISUAL SYSTEM

3.1 Anatomical properties of the visual system

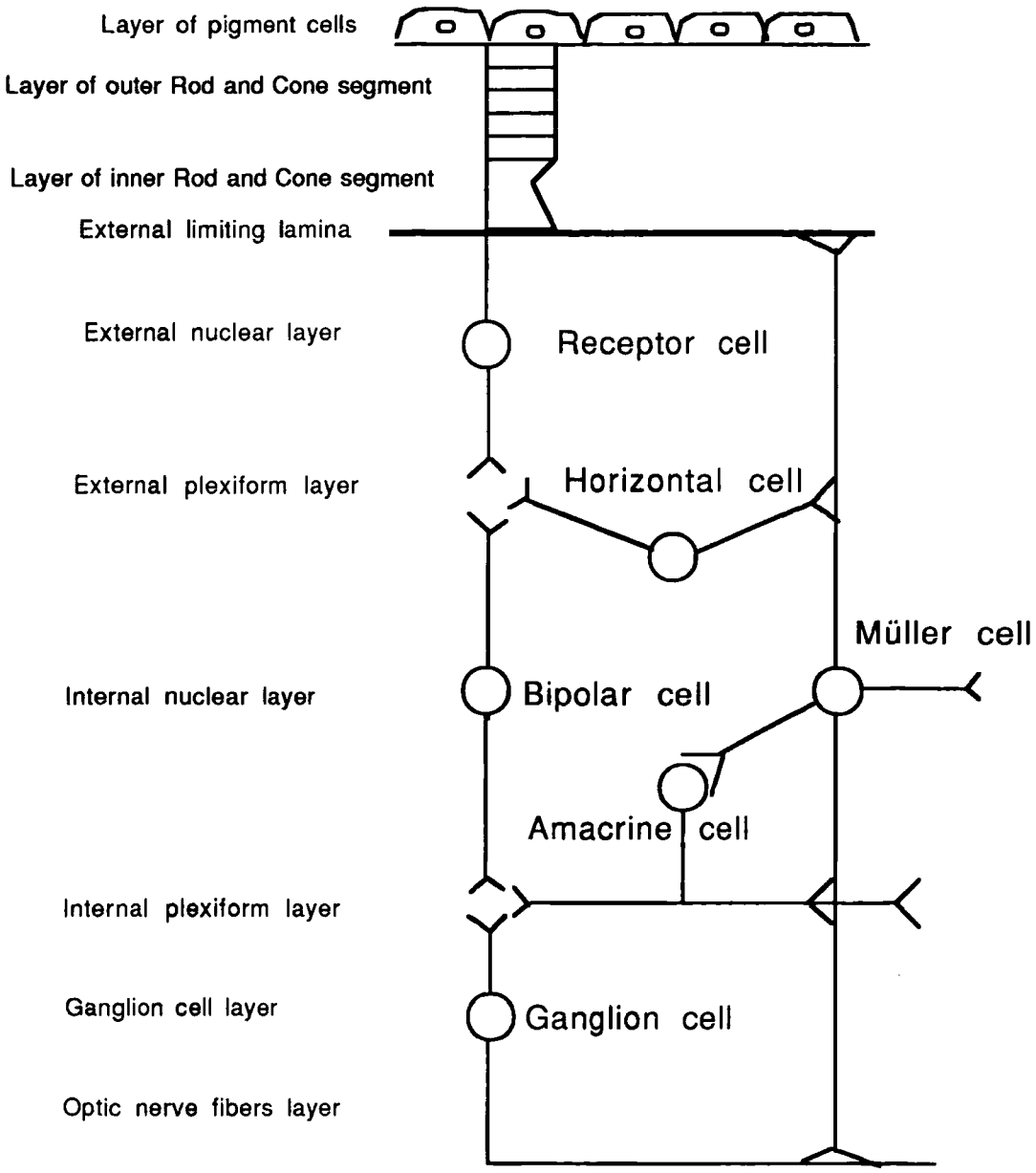
The neural pathway of vision, like all sensory pathways except the sense of smell, is arranged in three neuronal levels. The cell bodies of the first order neurones, which are comparable to dorsal root ganglion cells, lie in the inner nuclear layer of the retina and are called bipolar cells. They collect visual signals from the photoreceptors and transmit them to the ganglion cells, which are comparable to the cells of the nucleus gracilis and nucleus cuneatus, and which lie in the ganglion cell layer. The axons of these second order neurones pass to the lateral geniculate nucleus (LGN) which is part of the thalamus, where they synapse with the cell bodies of the third order neurones, whose axons terminate in the visual cortex.

The retina consists of ten structural layers in which six types of functional cell are recognized. These are photoreceptor cells (cones and rods), bipolar cells, ganglion cells, horizontal cells, amacrine cells and Müller cells, which are glial cells. The ganglion cells can be distinguished into small and large cells. The small cells predominate in the central retina, and are known as β cells, the large cells are found in the periphery and are known as α cells.

The photoreceptors synapse with the bipolar cells which in turn synapse with the ganglion cells. In addition to this serial connection there are lateral connections linking horizontal cells to bipolar cells and amacrine cells to ganglion cells, which control the information passing through the serial system (Fig 2).

Figure 2

Schematic diagram showing structure of retina and interconnections between cells in the retina.



The density of the retinal receptors is highest in the fovea and diminishes towards the retinal periphery. The higher the density of the receptors the smaller their individual receptive fields and the greater is the visual acuity. The receptors convert the light from the visual image into neural signals. There are some 7 million cones and 120 million rods, but only one million ganglion cells, which indicates the degree of convergence in the system. However, the convergence is not uniform, being greater in the periphery and least in the centre; in the area centralis there is a one-to-one ratio between receptor, bipolar and ganglion cells.

On leaving the eyeball at the optic disc the axons of the ganglion cells acquire a myelin sheath and form the optic nerve, which contains about one million fibres. The nerve fibres from the macular area have a smaller diameter and lower conduction velocity than those of the peripheral retina. At the chiasm fibres from the nasal half of each retina cross to the opposite side while those from the temporal half remain uncrossed.

In primates the axons of most ganglion cells terminate in the LGN. Each LGN is divided into six layers numbered from the ventral to the dorsal aspect. The first two layers, consisting of large cells, are called the magnocellular layers, and the other four consist of small cells and are called the parvocellular layers. Layers 2,3 and 5 receive uncrossed fibres from the temporal half of the ipsilateral retina, and layers 1,4 and 6 receive crossed fibres from the the nasal half of the contralateral retina. Thus the right half of each retina projects to the right LGN and the left half to the left LGN. This arrangement is maintained in the geniculate projection to the primary visual cortex (area 17 or striate cortex),

i.e the right half of each retina projects to the right visual cortex and the left half to the left occipital cortex. The calcarine fissure divides the visual cortex into upper and lower halves. The upper retina projects to the upper visual cortex and the lower retina to the lower visual cortex. The light rays reflected from an object are refracted by the cornea and lens before falling onto the retina, so that the visual image formed on the retina is both inverted (upside-down) and reversed (turned right for left and vice versa). As a result the right visual cortex receives information from the left visual field and the left cortex from the right field.

The area of cortical representation is directly proportional to the density of the retinal receptors. Thus the macula, which is quite small in the eye, has a large cortical representation, which is at the posterior occipital pole. The peripheral fields are represented anteriorly and on a smaller scale. The representation of the visual field is repeated in prestriate cortex with a different orientation (Zeki 1969).

The visual cortex includes the striate or primary visual cortex (Brodmann area 17) and the prestriate or extrastriate or parastriate cortex or secondary visual cortex (Brodmann areas 18 and 19). However, a dozen distinct visual areas have been identified in the cerebral cortex of macaque monkey (for a review see Van Essen and Munsell 1983). The most important functional ones in man correspond to primate areas V1, V2, V3, V4 and V5. Areas V1, V2 and V3 are located in Brodmann areas 17, 18 and 19 respectively. Recently it has been found in man (Lueck et al. 1989, Zeki et al., in press), using PET techniques, that colour and motion, corresponding to areas V4 and V5, have separate locations in area

19; V4 is in the fusiform gyrus, and V5 in the parieto-temporo-occipital pit.

The visual cortex consists of six structural layers, numbered I-VI, and three functional cell types, stellate, pyramidal and granular cells. Layer IV is further subdivided into IV A, IV B, IV Cα and IV Cβ. The connections between layers of the primary visual cortex are achieved by the axons of stellate cells while the projection to other cortical areas and to subcortical structures is via the axons of the pyramidal cells. From the viewpoint of connectivity, the primary visual cortex can be distinguished into two parts receiving afferents and two parts projecting to other cortical layers and to the two major sources of input, the superior colliculus and the LGN. Layers, I, II and III receive crossed callosal fibres from the opposite visual cortex, and layer IV receives LGN afferents. There are no efferent projections from layer IV. Axons of pyramidal cells in the superficial layers, especially layers II and III, go to the ipsilateral extrastriate cortex, whereas those in deeper layers (V and VI) terminate subcortically; layer V projects to the inferior olive, superior colliculus and pretectum, and layer VI to the LGN (Estèvez and Spekreijse 1974). In the cat there are as many corticofugal fibres passing through the optic radiation to the LGN as there are fibres passing from the LGN to the cortex. Incidentally, LGN neurones also receive input from ascending reticular pathways (see Singer 1977 for a review).

Although most of the retinal ganglion cells in primates terminate in the LGN, other fibres project to various subcortical structures, including the pretectal nuclei, the suprachiasmatic nucleus of the hypothalamus, the pregeniculate nucleus, the accessory optic nuclei, the reticular nucleus of the thalamus, the

basal ganglia and the pons (Tigges et al. 1977). However, the most important of these extrageniculate projections is the projection to the superior colliculus, which in turn projects to the inferior pulvinar complex and then primarily but not exclusively to the extrastriate cortex (areas 18 and 19 or secondary visual cortex). This is the tectopulvinar-extrastriate system.

3.2 Functional properties of the visual system

The area in the visual field or the corresponding area in the retinal surface within which an adequate stimulus influences the activity of a neurone is termed the receptive field of that neurone. Kuffler (1953) studied the reponses of ganglion cells to a spot of light moving over their receptive fields, and found that these fields had a centre-surround organization. Two types of receptive field could be recognised; in one, the centre of the receptive field was excited by an increase in light intensity ("on-centre") and in the other it was excited by a decrease in light intensity ("off-centre"), above and below a background level respectively. The centre of the receptive fields was surrounded by an annular region giving the opposite response. The size of the receptive field centre increases with retinal eccentricity, i.e fields located near the fovea have a smaller centre than do fields in the retinal periphery. Using sinusoidal grating stimuli the ganglion cells have been divided by Enroth-Cugell and Robson (1966), according to their spatial-summation properties over their receptive fields, into X and Y cells. Those ganglion cells for which summation was approximately linear were called X-cells, those for which it was non-linear were

called Y cells. These X and Y cells show differences in a number of other properties. X cells correspond to β retinal cells, they are small in size, have thin axons, slow conduction velocity (17-20 m/sec), small receptive fields and can resolve fine visual patterns (higher spatial frequencies) and recognise colour. They are more in the centre than the periphery, where Y-cells predominate (Lennie 1980). Y cells correspond to α cells, and are large ganglion cells, with thick axons, high conduction velocity (30-40 m/sec), and large receptive fields. They do not recognise colour and at low frequencies they have higher contrast sensitivity than X cells, so they can resolve coarse patterns i.e patterns of low spatial frequency. Cleland et al. (1971) noted that X and Y cells responded differently to a stationary flashing spot centred in their receptive fields; the X-cells showed sustained (tonic) responses to this stimulus and the Y-cells showed brief (phasic) responses, also called transient responses. Both on-centre and off-centre varieties of each type were found, although off-centre X cells were rather uncommon.

These physiological criteria suggest that X-cells subserve spatial contrast and colour discrimination, and Y-cells are probably concerned with detection of more general changes in the visual environment. Most of the primate ganglion cells are X cells, and Y cells make up a relatively small population.

Primate W cells represent a poorly understood small population of remaining neurones which has been difficult to characterize in terms of their responses to visual stimuli. Their role in vision is unclear, but their slow conduction velocities suggest they have a different functional role from X and Y cells

(Weller and Kaas 1981)

There is electrophysiological evidence that the X and Y ganglion cells relay on to different types of neurone in the LGN, in cat and monkey. The Y-cells project to the magnocellular layer and the X-cells to the parvocellular layer (Dreher et al. 1976, Scherman et al. 1976, Schiller and Malpeli 1978). The LGN magnocellular cells (M-cells) have the same properties as Y-cells and the parvocellular cells (P-cells) have the same properties as X-cells (Shapley and Hochstein 1975).

Retinal ganglion cells and LGN neurones can be activated not only by flashing spots of light but also by elongated, straight contrast patterns such as bright or dark bars, edges, etc, moving across their receptive field in any direction. Cells in the visual cortex are also sensitive to moving bars, but in both cat (Hubel and Wiesel 1962, 1965) and monkey (Hubel and Wiesel 1968) they are selective both for orientation and direction. In the striate cortex inputs from the two eyes converge and interact on single neurones, and this constitutes the beginning of binocular vision. The striate neurones have been divided by Hubel and Wiesel (1962, 1965 , 1968) into three main types; simple, complex and hypercomplex cells, depending on the spatial organization of their receptive fields. Simple cells are sensitive to one stimulus orientation and usually one direction of motion across their receptive fields. These simple cells are mostly found around layer IV, receiving their input directly from several excitatory on-centre geniculate cells so that a line stimulus with specific orientation will give maximum stimulation. Complex cells are maximally stimulated by a line or a bar of appropriate orientation from anywhere in the field, i.e the actual position of the bar in the receptive field is not important.

About half are direction-specific, although not as strongly as simple cells. It is thought that this is the first level at which the signals from the two eyes converge. Hypercomplex cells display sensitivity not only to the orientation but also to the length of the stimulus.

In addition to their orientation and direction selectivity, visual cortical cells exhibit selectivity to colour and depth in the visual space.

3.3 Processing of visual information

The characteristics and localisation of the visual cortical neurones mentioned above prompted Hubel and Wiesel (1962, 1965) to propose a hierarchical or serial model for the processing of visual information in the visual cortex. This model is based on the successive convergence of sets of neurones with similar properties on to other cortical neurones subserving a higher order function. The geniculate cells project directly on to simple cells, then a number of simple cells with slightly different receptive field positions converge on to complex cells, which will in turn provide a drive to hypercomplex cells. This functional model is consistent with the anatomical distribution of the cells. The simple cells are found in layer IV and the complex and hypercomplex cells in layers II, III, V and VI. Colonnier (1968) produced evidence to suggest that cells with simple characteristics correspond to stellate cells in layer IV and complex cells correspond to pyramidal cells which are found in layers II and V.

Work carried out since the Hubel and Wiesel research has

indicated a much more complex picture of the processing of visual information. In particular, evidence is accumulating that parallel processing may also occur starting with the X-Y cell system in the retina and the magnocellular (M) and the parvocellular (P) cells in the LGN. The P-cells have slow-conducting axons to the simple cells and the M-cells have fast-conducting axons to the complex cells (Hoffmann and Stone 1971, Schiller and Malpeli 1978) forming two functionally distinct pathways currently known as the M- and P- pathways, which project to two different areas in layer IV of primary visual cortex (Fig 3). P-cells project to IV A and IV Cβ in area V1, then from IV Cβ to layers II and III of V1, and then from V1 to V2. M-cells project to IV B and IV Cα of V1 and then on to V2 (Kulikowski 1989, Tootell et al. 1988). Even at higher cortical levels there are two major pathways for the processing of visual input. There is a pathway leading from area V2 to area V4 concerned with spatial and colour discrimination, and a pathway from V2 to V5 concerned with motion (temporal modulation) (Shipp and Zeki 1985).

There is also evidence for chemical selectivity of these pathways. Ikeda and Sheardown (1982) found in the cat that aspartate is the excitatory neurotransmitter for X and acetylcholine for Y ganglion cells for both on- and off-centre cells in each class. However, the inhibitory transmitter for retinal on-centre cells is GABA and for off-centre cells it is glycine, irrespective of the X or Y types.

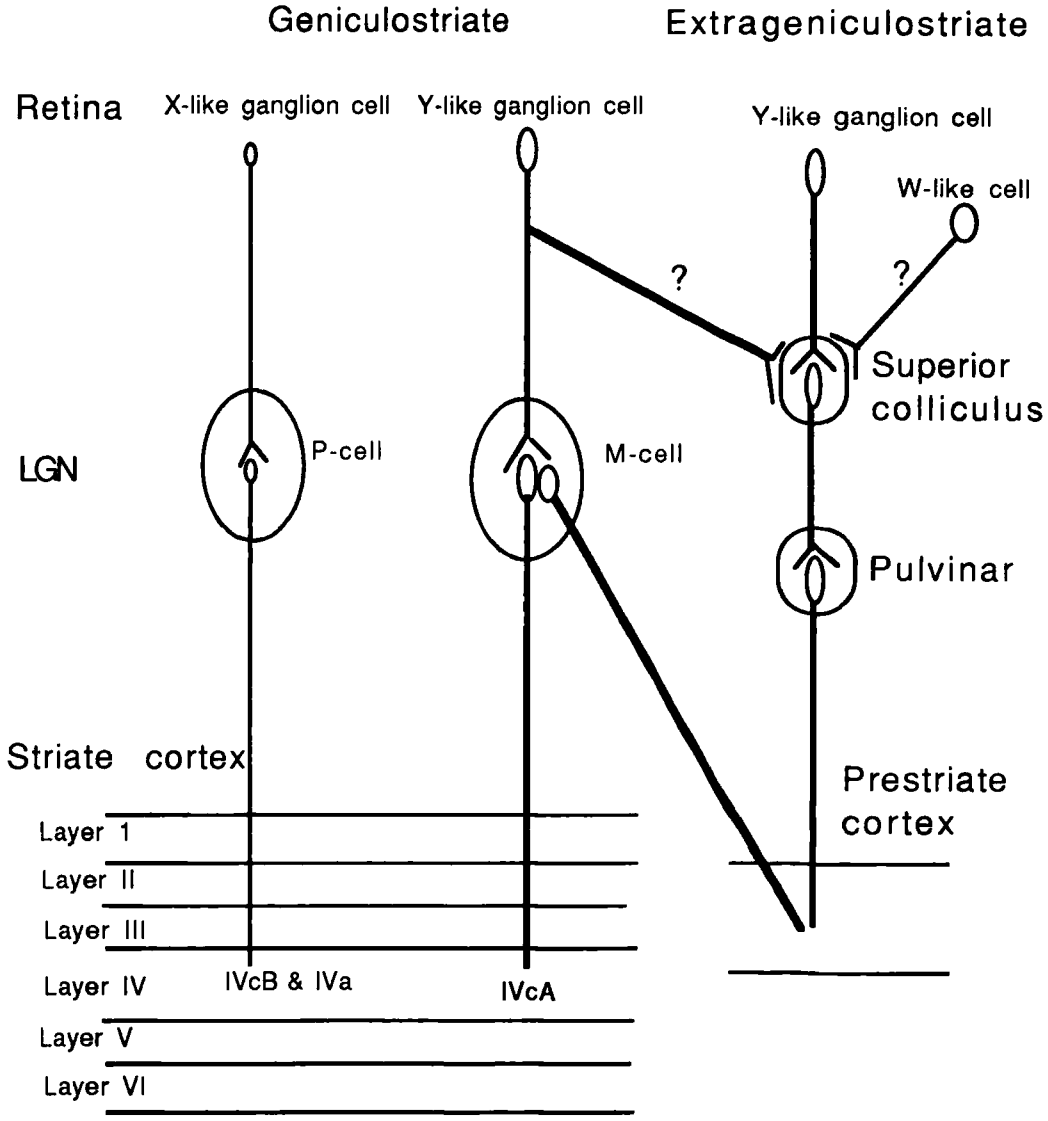
In addition to these neurophysiological, anatomical and chemical data in animals, psychophysical data in man support the presence of two parallel systems. Using temporally modulated

sinusoidal grating stimuli, two thresholds can be distinguished: the contrast at which flicker can be perceived and the contrast at which spatial structure becomes distinct. The flicker detection threshold and the pattern recognition threshold each vary independently as functions of both the spatial and temporal frequencies, suggesting that the two thresholds represent the activities of two independent systems (Kuilokowski and Tolhurst 1973, Tolhurst 1975, Stone et al. 1979, Bodis-Wollner and Camisa 1980, Green 1981).

The X cells with their small receptive fields, linear summation across their receptive fields and preponderance in the centre of the retina are probably responsible for spatial contrast and colour discrimination (Bodis-Wollner and Camisa 1980). In contrast, the larger and less well-defined receptive fields of the Y cells make them poor spatial discriminators and it is thought that they transmit temporal information (Ikeda and Wright 1972, Stone 1972, Green 1981). However, there is an interaction between the two systems and both contribute to the spatial and temporal properties of vision.

Figure 3

Diagram of the principal connections of the visual pathways M- and P- pathways to the striate cortex and the tectopulvinar system to the prestriate cortex



CHAPTER 4 ELECTROPHYSIOLOGICAL TESTS

In this study retinal function was tested with pattern and single flash stimuli and the visual evoked potentials were recorded to pattern and to single and repetitive flash stimuli.

4.1 Electroretinogram (ERG)

The function of the retina has commonly been tested with flash, and more recently by pattern stimuli too.
The ERG is usually recorded with corneal electrodes such as a contact lens electrode, gold foil (Arden et al. 1979) or a fine wire (Dawson et al. 1979). However skin electrodes can be used reliably to record both flash ERG (Papakostopoulos 1982) and pattern ERG (Adachi-Usami and Murayama 1985, Leguire and Rogers 1985, Kakisu et al. 1986), and these were employed in this study.

There are two main ERG components for both flash and pattern responses. The usual convention for naming the ERG components has been positive/up and negative/down, which is unfortunately the reverse of the convention used for VEP analysis, and this has led to confusion. Hence there is now a tendency to use the negative/up and positive/down nomenclature for ERG's, and this is what I shall do. The negative and positive components of the flash ERG will be referred to as the a and b waves respectively, and the pattern ERG components α and β waves.

4.1.1 Flash ERG

The main components of the flash ERG are the a and b waves. The a-wave is a negative wave, generated by photoreceptors (rods and cones) and the b-wave is a positive wave, generated by photoreceptors and Müller cells in the inner nuclear layer. These latter cells absorb extracellular potassium liberated by the photoreceptor cells and it is this which produces the potential change recorded as the b-wave (Miller and Dowling 1970). Hence, production of a b-wave involves rods and cones as well as Müller cells. Rods and cones both contribute to the flash ERG, but we can separate the ERG into cone-ERG and rod-ERG by appropriate changes in retinal adaptation, or in the intensity or colour of the stimulus. Rods are more sensitive than cones across almost the entire visible spectrum. However, this difference diminishes in the long wavelength spectrum, and with very long wavelength (deep red) stimuli cone function may be isolated. The rod contribution to the ERG can be separated by recording from the dark adapted subject and stimulating with relatively dim, short wavelength (blue) stimuli.

If the stimulus is well above the rod threshold, as it is with the usual white light stimulus used for testing patients with suspected retinal disease, the a and b waves are generated by both rod and cone systems. Thus the flash ERG to relatively intense white light stimuli, used in this study, represents contributions from both rods and cones.

Other ERG components include the c-wave and the oscillatory potentials (OPs). The c-wave is a fairly slow negative wave which

follows the b-wave. It represents a slow potential change occurring in the retinal pigment epithelium and is of little use clinically (Steinberg et al. 1970). The electro-oculogram is usually preferred as an indicator of the integrity of pigment epithelium (Ikeda 1976).

The oscillatory potentials (OPs) appear as oscillations on the b-wave. Up to 6 oscillations may be present. OPs are only recorded to bright flash and may be enhanced by the use of a red filter on the flash. They are a sensitive indicator of retinal circulation, and are affected when this is involved in any pathological process..

4.1.2 Pattern ERG

Pattern ERG is now commonly used in combination with pattern VEP to study the visual pathway. It is of a longer latency than flash ERG and consists of two main components, the α and β waves. The α-wave is a negative wave occurring at a mean latency of 50 msec, and the β-wave is a positive wave with a mean latency of 95 msec. The pattern ERG is thought to arise from retinal ganglion cells. This is supported by experimental evidence from sectioning the optic nerve in the cat (Maffei and Fiorentini 1981) and monkey (Maffei et al. 1985), which abolishes the pattern ERG but leaves the flash ERG intact. These observations have been confirmed in man by the finding that the pattern ERG is absent in optic nerve disease, but the flash ERG, which arises from preganglionic cells in the retina, remains intact (Fiorentini et al. 1981, Dawson et al. 1982). However, there is evidence that the preganglionic cells do influence the human pattern ERG, as a result of local luminance effects

(Arden and Vaegan 1983, Sherman 1986, Drasdo et al. 1987). Thus the normal pattern ERG is not completely pattern-specific: there is a contribution from local luminance effects, which are maximal when mean luminance and contrast of the pattern are high and when large areas of the retina are stimulated.

In fact the two components of the pattern ERG represent the contributions of luminance and pattern. The α-wave is a luminance function and the β-wave is mainly pattern-specific. This is indicated by the fact that these two components can be selectively involved in different pathological states: macular or generalized retinal pathology invariably affects the first negative component, whereas optic neuropathies affect mainly the late positive component (Arden et al. 1984, Holder 1987).

4.1.3 Clinical value of ERG

Combining the flash and pattern ERG provides not only a useful measure of retinal function, but also enables one to identify the site of retinal dysfunction, in the preganglionic photoreceptor cells or the retinal ganglion cells.

The flash ERG is of use in investigating the preganglionic cells, and is only abnormal when they are affected by widespread pathology. An abnormal a-wave of the flash ERG indicates a photoreceptor problem, and the relative contribution of rod and cone disorders can be distinguished by flicker and dark adaptation tests and by recording the focal cone ERG. If the a wave is abnormal the b and c waves will also be abnormal because they all depend on the photoreceptors. If the a wave is normal the b wave becomes a test of the integrity of the the inner nuclear layer.

The flash ERG is usually normal when a reduction in visual acuity is due to maculopathy but the rest of the retina is intact. In such a case the α-wave of the pattern ERG may be abnormal and the focal cone ERG will usually be abnormal. The β-wave, the main positive component of the pattern ERG, is usually abnormal in diseases of the ganglion cell layer and optic nerve.

4.1.4 ERG in migraine

Winter (1985) found no significant difference in either latency or amplitude of the a and b waves of the flash ERG between 45 migraine and 30 control subjects. Puca et al. (1985) also found normal latency and amplitude of the a and b waves in 13 migraineurs.

4.2 Pattern-reversal visual evoked potential (PRVEP)

4.2.1 General features:

Pattern stimulation was first introduced into the clinical testing of patients with optic neuritis by Halliday et al. in 1972. The pattern VEP has less interindividual variability and greater inter-trial and test-retest stability of its components than the flash VEP (Halliday 1982, Stockard et al. 1979). Therefore, it has become the main method of investigating the visual system in clinical practice.

Pattern stimuli can be either chequerboards or gratings. Several methods have been used to produce these, including

oscilloscope displays, television displays, a slide projector with mirror, light emitting diodes, rotating polaroid discs, and tachistoscopic display (Arden et al. 1977). The most commonly used methods are the television display and the mirror/projector method. The pattern responses are obtained by viewing the stimulus with both eyes or with each eye separately, and can be presented to the whole field or to one half-field.

The mode of stimulation can be either reversal of the pattern or appearance and disappearance. The shape of the potential varies according to the type of stimulus and mode of stimulation. In this study a reversing chequerboard was used, and the following considerations apply to this method.

The amplitudes and waveforms of the response obtained to whole-field stimulation of each eye in the same individual are very similar. There is a simple algebraic summation at the scalp of the responses from different areas of the field in such a way that the sum of the responses from each half-field of the same eye equals the response from the whole field of that eye (Blumhardt et al. 1977, Halliday 1982).

The potential field distribution of the normal "whole-field" chequerboard pattern has been studied by several authors (Barrette et al. 1976, Shagass et al. 1976, Blumhardt et al. 1978, Blumhardt and Halliday 1979, Blumhardt et al. 1982, Haimovic and Pedley 1982, Onofrj et al. 1982). All of these used multichannel recording, with a mid-occipital electrode and two laterally placed electrodes on each side at 5 and 10 cm from the midline, referred to Fz. This is the classical montage developed by the Halliday group. These studies showed that the pattern response from a

binocular or monocular whole-field stimulus has a characteristic triphasic waveform with a major positive component preceded and followed by smaller negative peaks (negative-positive-negative configuration). The major positive component has a peak latency of about 100 msec , hence it is commonly known as the P100. The two negativities have latencies of about 75 and 145 msec respectively. The amplitude is largest at the midline, 5 cm above the inion, and decreases gradually at more lateral positions on each side but maintains a similar waveform (Blumhardt and Halliday 1982). Peak to peak amplitudes at homologous positions over the two hemispheres may differ by a factor of 2 (e.g Hoeppner et al. 1984).

The P100 latency with the TV method is usually greater than that with the mirror/projector stimulus by some 4.2 msec (Chiappa 1989).

With half-field stimulation it is possible to separate responses from the right and left hemispheres, since the retinocortical pathways from each half-field terminate in the visual cortex of the opposite occipital lobe.

The response to half-field stimulation shows a striking difference from the full field response. Barrett et al. (1976) found the responses to half-field stimulation to be "paradoxically" distributed along the transverse chain over the occipital region. That is, the largest and most consistent response was a negative-positive-negative (NPN) pattern which appeared at the midline and in lateral electrodes ipsilateral to the half-field stimulated (Fig 15). Their explanation of this finding was that the cortical generator areas for the pattern stimulus response are largely situated on the medial and postero-medial surface of the visual

cortex. Thus, the electrodes over the non-stimulated hemisphere are optimally placed to record from these generator areas on the other side. This was confirmed by recordings from patients with an occipital lobectomy, in whom the NPN response was preserved over the excised lobe and absent over the intact hemisphere (Blumhardt and Halliday 1979, 1981, Blumhardt et al. 1982).

The contralateral electrodes i.e those over the stimulated hemisphere, show a triphasic complex of opposite polarity i.e a positive-negative-positive pattern, with a maximal amplitude at the electrode 10 cm from the midline (Halliday 1982). The main component of this contralateral response is a negative wave which occurs at approximately the same latency as the P100, and is hence known as N100. These contralateral (PNP) components show greater variability in both latency and morphology than the ipsilateral (NPN) components (Blumhardt et al. 1978) and indeed, nearly one third of normal individuals fail to show a contralateral N100 (Haimovic and Pedley 1982).

The PNP complex is not simply a phase reversal of the ipsilateral NPN complex. Progressive occlusion of the central 0-16 degrees of the pattern caused a progressive attenuation of the ipsilateral NPN complex but a progressive enhancement of the PNP complex (Halliday et al. 1979, Blumhardt et al. 1978). Furthermore, with progressive occlusion of the pattern stimulus from the central region of the visual half-field, the ipsilateral P100 was increasingly attenuated, while the contralateral complex was relatively unaffected. By contrast, reducing the radius of the stimulus area, so that stimulation is applied to central vision alone, does not affect the P100, but does affect the contralateral

response. These findings suggest that both central and peripheral vision contribute to the generation of the P100 but that peripheral vision is especially important in producing the contralateral N100.

4.2.2 Factors affecting PRVEP

The latency and amplitude of the principal pos tive wave of PRVEP are sensitive to many subject variables such as sex, age and pupil size, and to stimulus variables such as luminance, contrast and size of stimulus field and check size.

1. Sex: females have a shorter latency and larger amplitude than males (Stockard et al. 1979, Halliday et al. 1982).
2. Age: P100 latency does not vary significantly with age in the range from 15 to 60 years, using check sizes larger than 15-20 minutes (Halliday et al. 1973a, Allison et al. 1979, Halliday 1982) and nor does P100 amplitude (Sokol et al. 1981, Snyder et al. 1981, Halliday et al. 1982).
3. Pupil diameter: changes in pupillary diameter will influence retinal illumination, but the change has to be gross to produce a significant effect on PRVEP (See, e.g Penne and Fonda 1981, Hawkes and Stow 1981).
4. Luminance or stimulus intensity: reduction in the mean luminance of the pattern stimulus results in an increase in latency and a reduction in amplitude (Halliday et al. 1973b).
5. Contrast: VEP latency increases and amplitude decreases linearly with the log of stimulus contrast. However, this effect saturates at a contrast level of 20 to 40% (Halliday and McDonald 1981), and since much higher degrees of contrast are most commonly used this

factor has practically no effect.

6. Field size and check size are important in determining which part of the retina is giving rise to the response. Small checks are considered to be stimulating predominantly the fovea (Oishi et al. 1985) and larger checks stimulate both the fovea and the peripheral retina (Meredith and Celesia 1982, Behrman et al. 1972). This depends on the size of the receptive field which varies across the retina and the magnitude of the cortical area activated by the stimulus. It has been shown that a VEP of approximately equal amplitude can be obtained from each retinal location if the stimulus is so structured as to stimulate an equal number of cortical neurones (Meredith and Celesia 1982, Celesia and Meredith 1982).

4.2.3 Origin/Neural generators of PRVEP

The widespread distribution of the pattern VEP generators has been inferred from studies on patients with lesions restricted to the primary or secondary visual cortex. Bodis-Wollner et al. (1977) found that the steady-state pattern VEP was present in a patient with bilateral destruction in areas 18 and 19 but preservation of area 17, and Celesia et al. (1980) found essentially normal transient and steady-state pattern VEP in a patient with bilateral destruction of area 17 and relative preservation of areas 18 and 19. These observations have been recently supported by positron emission tomographic scanning, which has shown that both primary and association visual cortical areas are strongly activated when a reversing chequerboard pattern is used as a visual stimulus (Celecia et al. 1982). However, the PRVEP represent a

predominantly macular-paramacular response. Numerous workers have shown that the main contribution to the response comes from within the cortical representation of the central 10 degrees of the retina (Harter 1970, Asselman et al. 1975, Bartl et al. 1978, Blumhardt et al. 1978, Yiannikas and Walsh 1983). The predominance of the central response is partly due to the proximity of the central field to the scalp electrode, and also to the higher receptive field density and consequent cortical magnification of this area (Armington and Brigell 1981)

4.2.4 PRVEP in migraine

The first study on PRVEP in migraine (Kennard et al. 1978) showed an increased latency of P100 (which they called P2), and its amplitude was increased as well in certain patients.

Diener et al. (1984) found that P100 latency was similar in patients and controls but amplitude was higher in migraineurs.

Winter (1985) found that migraineurs had longer latencies (5 msec) than controls, particularly of the P100 and N140 components, and this was more evident with half-field stimulation. The duration of migraine had no effect on the results. The P100 amplitude was normal. However, Benna et al. (1985) found no abnormality of either latency or amplitude of P100 in migraineurs.

Recently, Marsters et al. (1988) found that "fast activity" (>14Hz) during the period of 200 to 500 msec after the stimulus was increased in migraineurs, especially in classical cases.

4.3 Single flash visual evoked potentials (SFVEP)

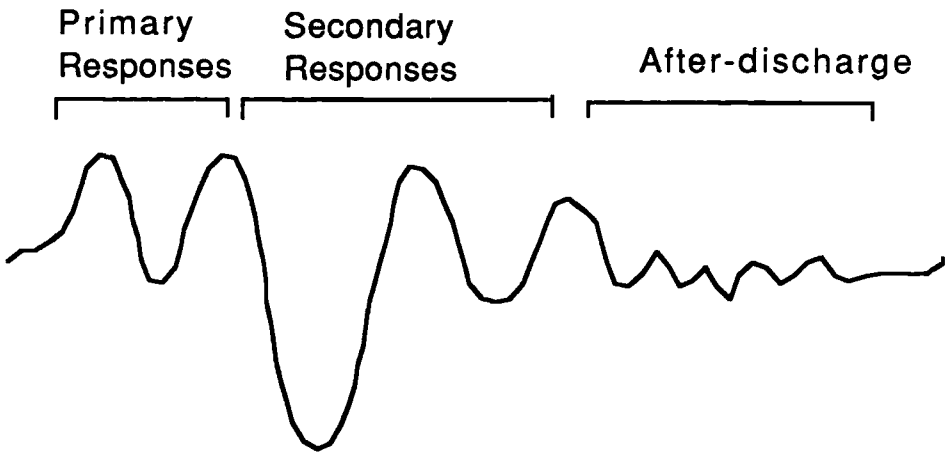
4.3.1 General features of SFVEP

The SFVEP elicited over the back of the head by brief flashes of light with the subject's eyes open consists of six major waves. Cigánek (1961,1969) has distinguished two principal components and an after-discharge. The early or primary component occurs between 0 and 90 msec and the late or secondary component occurs between 90 and 160 msec. The rhythmic after-discharge has a frequency about the same as the alpha rhythm. Various labelling systems have been used to identify the components of the responses. These systems use Arabic numerals (Gastaut and Reigs 1967), Roman numbers (Cigánek 1961), polarity (Harding 1974) and polarity-mean latency (Borda 1977) for nomenclature. Figure 4 shows a typical example of a flash response and demonstrates the four types of labelling system. It consists mainly of two major positive waves, which are preceded, separated and followed by three negative waves. According to Harding (1974) the most consistent components of the response are the P1 and P2 waves i.e the two positive waves of the early and late components. These are the only waves measured in this study.

The flash VEP shows greater interindividual variability than the pattern VEP, and amplitude shows greater variability than latency. This is especially so for the early components, due to contamination with spontaneous alpha activity (Cigánek 1969).

Figure 4

Diagram showing a typical single flash visual evoked response with various systems of nomeneclature.



I	II	III	IV	V	VI	Ciganek (1961)
1	2	3	4	5	6	Gastaut and Reigs (1967)
A	B	C	D	E	F	Dustan and Beck (1969)
N1	P1	N2	P2	N3	P3	Harding (1974)
N40	P70	N90	P114	N154		Borda (1977)

Interhemispheric asymmetry is usual. The right occipital VEP is almost always larger than the left (Borda 1977). Harmony et al. (1973) have shown that the amplitude difference can be up to 50% and the latency difference is up to 5 msec.

The responses recorded at the vertex are different in morphology, latency, amplitude and polarity from those recorded over the occipital region (Contamin and Cathala 1961, Kooi and Bagchi 1964, Beaumont and Mayes 1977, Borda 1977)

4.3.2 Factors affecting flash responses

1. Pupil diameter has no effect on latency or amplitude of the SFVEP (Kooi and Bagchi 1964).
2. Age: There is no significant change in latency or amplitude between the ages of 16 and 40 years, but after that the components within the first 100 msec start to increase both in latency and amplitude (Dustman and Beck 1966, Wright et al. 1985) and P2 latency is also increased after this age.
3. Sex: amplitude is higher in adult females (Buchsbaum et al. 1974) which may be due to physical properties of the head.
4. Stimulus intensity: Latency is prolonged and amplitude is reduced with reducing stimulus intensity (Creutzfeldt and Kuhnt 1967, Kinney 1977). A reduction of one log unit increases latency by 5-12 msec. The amplitude increases gradually when the stimulus intensity is increased gradually from a low level and saturates at moderate intensity.

4.3.3 Origin of SFVEP

The flash stimulus commonly used for eliciting the VEP is a diffuse white light, and this causes stimulation of both central and peripheral retinal elements. The responses represent summation of activity from retinal fibres dealing primarily with luminance function. They are more variable than the pattern VEP, which deals primarily with contrast function.

Most attention has been paid to the occipital responses. The primary component of these responses does not change between waking and the various stages of sleep, and it remains present at high flash frequencies, up to 35 Hz, at which the secondary component and the after-discharge have become negligible. It is therefore generally agreed that it originates from the primary visual cortex (Vaughan 1966, Cigánek 1969, Reits 1975). The secondary component is associated with higher integrative processes affected by motivation, attention and state of arousal. It seems most likely that it originates outside the primary visual cortex, perhaps through a mechanism involving the non-geniculostriate pathway (Wright et al. 1987). Vaughan (1969) reported that a subcortical lesion resulting in complete homonymous hemianopia abolished the early component but left the later components intact. He inferred that only the earliest component was due to the geniculo-calcarine input into the cortex. Celesia et al. (1984) utilizing the technique of PET scanning found that flash stimulation produced an increase in regional CBF not only in the mesial surface of the occip'tal lobe (area 17) but also in lateral occipital regions (areas 18 and 19). They concluded that the

scalp VEP distributions reflect "the complex interaction of the electrical field potentials within at least three cortical areas rather than the sole volume transmission of striate dipoles". They also showed that the flash VEP does not show any paradox as does the pattern VEP; in one patient visual stimulation produced no metabolic change over the right occipital cortex in PET studies, and the flash VEP was absent over this region, whereas the PRVEP was present (section 4.2.1).

Chalupa et al. (1972, 1973), by cooling different layers of LGN in the cat, demonstrated that the primary and secondary components of the SFVEP are processed by different neural pathways. The direct geniculostriate pathway, through layer A of the LGN, is mainly responsible for the primary components of the response and a non-geniculostriate pathway, through layer B of the LGN via the pulvinar to the suprasylvian gyrus, for the secondary components and after-discharge.

There is no agreement upon the mechanisms underlying the vertex potentials. However, from their morphology, and from human pathology and animal experiments, they appear to be generated by conduction through pathways not involving the geniculostriate system. Winter (1985) showed differences in harmonics and phase angle between occipital and vertex potentials. In addition, patients who suffer occipital lobe damage resulting in cortical blindness and loss of the occipital response may still have a vertex response (Kooi and Sharbrough 1966), and unilateral striate ablation or optic tract section in monkeys produces no change in this response (Vaughan and Cross 1969).

4.3.4 SFVEP in migraine

Most of the previous studies with slow flash stimuli at 1-3 f/sec, like the present one, were performed on patients free from headache.

Richey et al. (1966) found that N1 latency was reduced and P1 latency was prolonged. P2 amplitude was significantly reduced in females. Vertex flash responses were normal. Migraineurs had on average a slightly smaller pupil size than controls, but this did not affect the results.

Lehtonin (1974) found that N1, P1, N2 and P2 latencies were normal and amplitudes tended to be higher in migraineurs.

Lehtonin et al. (1979) examined 11 women with menstrual migraine and found prolongation of P1 latency and low amplitude of N3 and P3 waves in all phases of the menstrual cycle.

Connolly et al. (1982) used different stimulus parameters and recording montage. The stimulus was xenon light at six intensities and 500 msec duration. Recordings were made at Cz, T3 and T4, to linked ears, and they identified a triphasic response, P100, N120 and P200. They tested 16 patients and 21 controls, and found increased latency of N120 at the vertex and of P200 at the temporal sites, especially to brighter flashes, and high N120 amplitudes at both sites.

Winter (1985) found no differences in the early responses but a shorter N3 latency in young migraineurs under photopic conditions.

There are only few studies during a migraine attack. In classical cases MacLean et al. (1975) found marked reduction in the amplitude of the the first three waves in the hemisphere

contralateral to the field defect, two of whom also showed asymmetry when they were headache-free. Conversely, with serial recordings Lehtonin et al. (1979) found a transient asymmetry in the flash VEP of some subjects during a headache, but there was no relationship between the direction of the asymmetry and the side of visual symptoms. Patients with common migraine did not show any asymmetry in flash VEP (Richey et al. 1966, MacLean et al. 1975) during an attack.

4.4 Repetitive flash visual evoked potentials (RFVEP)

4.4.1 General features

Flash stimulation at a rate greater than 4 /sec produces after some time a complex, sinusoidal wave variously known as photic driving, photic following, steady-state response, flicker VEP or repetitive flash response. These responses are usually composed of complex waves made up of fundamental, harmonic and subharmonic frequencies.

The components of the repetitive flash response can be grouped in the frequency domain into three distinct frequency subsystems (Spekreijse et al. 1977). These are the high frequency (35-60 Hz), medium frequency (14-25 Hz) and low frequency (9-12 Hz) subsystems. These have different latencies, waveforms, distributions and spectral properties (Regan 1989). This implies utilisation of different cortical pathways and possibly different cortical areas and functionally different group of neurones. Furthermore, they may be differentially affected by disease processes. For example demyelination increases the latency of medium frequency but not high frequency responses (Milner et al. 1974).

Spekreijse et al. (1977) studied the topographical distribution of the VEP flicker responses over the scalp. The low frequency subsystem has a diffuse distribution, which led to the suggestion that it may possibly originate in centres where EEG alpha rhythm is produced. The high frequency subsystem has a more limited distribution over the back of the head, and is thought to be

processed in the primary visual cortex. The med'um frequency subsystem has a different topological distribution from the high and low frequency subsystems. Its largest amplitude is found at about 5 cm above the inion and 4 cm to the right and left of the midline. Reits (1975) has suggested that this component originates in the secondary cortex (area 18 and 19) because the equivalent dipole of the secondary response lies above area 17. .

It is possible to investigate these subsystems by choosing stimuli of different frequencies in the low, medium and high frequency ranges. Using this method Spekreijse et al. (1977) stimulated the visual system with sine wave modulated light of constant mean luminance and modulation depth, and plotted the amplitude of the fundamental VEP component as a function of the stimulus frequency. Starting at 3 Hz the amplitude reached a maximum at around 10 Hz and reduced to a minimum at 25-45 Hz.

The same authors compared the time-domain of single flash responses with the different frequency subsystems of the repetitive flash reponses. They suggested that the early, 30-msec component of the transient flash VEP corresponds to the high frequency steady-state response, the 100-200 msec component to the intermediate-frequency response, and the rhythmic after-discharge, whose frequency approximates to that of the alpha frequency, to the low frequency response. However, it is not clear whether the single and repetitive flash responses provide complementary information or not.

The amplitude of the repetitive flash responses depends on the luminance, modulation of flicker, electrode position and field size.

Several methods have been used to record and analyse these

responses. These include analogue filtering techniques, digital methods using a fast Fourier transform, and averaging techniques

1. The analogue filtering technique is the oldest method, and was originally used by Golla and Winter (1959) to obtain the H-response (see later). In this method a frequency analyser was used to separate the frequency components of the response to provide an on-line analysis by writing frequency histograms of 10 second epochs of data directly on to the primary EEG record.

2. Digital method: Fourier analysis using a fast Fourier transform with small computers (Cooley and Tukey 1965) allows on-line analysis over wide frequency ranges, much easier and faster than the old Fourier analyser used by previous workers (e.g Regan 1966). This analysis has been used to provide amplitude/frequency plots, and a phase lag/frequency plot can be obtained for the fundamental and harmonics of the stimulus frequency.

One method of quantifying the responses in the frequency domain of interest is by power and amplitude spectra. The power spectrum is obtained by squaring and adding the sine and cosine components for the frequency of interest. The amplitude spectrum is the square root of the power spectrum

3. Averaging technique: this method has been used in this study. It was originally used by Townsend (1966) and Lehtonin (1974) to analyse flicker reponses in migraine. The principle of the method is that the signal-to-noise ratio is improved with progression of stimulation as the signal is time-locked to the stimulus while the background noise has no fixed relationship to the stimulus and is therefore cancelled out with progression of stimulation.

Both the digital and the averaging methods have their own limitations. In the digital method only frequencies harmonic to the

stimulus frequency are picked up. Thus the original configuration of the response may be lost and the latency and amplitude parameters cannot be studied accurately. In the averaging method phase information is lost if not combined with Fourier analysis.

For further details on these methods and their limitations see Cooper et al. (1980)

4.4.2 RFVEP in migraine

All the publications on this subject stem from the original publication of Golla and Winter (1959) who examined 115 subjects with classical migraine. They coined the term "H-response" to describe two ratios, the first between the response amplitude at 18 or 20 Hz and the peak amplitude in the alpha frequency range, and the second between the smallest amplitude and that at 18 or 20 Hz. They defined a positive H-response as the first ratio greater than 1/3 and the second ratio greater than 1/2. They found an H-response in 96% of migraine subjects and 16% of normal controls. The H-response could be recorded both during and between attacks, and it was not altered by conventional migraine medications, but was temporarily normalised by blocking the cervical sympathetic chain with procaine.

Smyth and Winter (1964) studied 202 migraine patients, 97 patients following head injury, and 66 controls, using the same technique. They found an H-response in 95% of migraineurs, 14% of normal controls and 66% of head injury patients. Slatter (1968) showed photic following responses at 20 f/sec or more in 85% of 147 migraine subjects.

Townsend (1966), using averaging techniques, found that photic following responses persisted with large amplitude up to frequencies well above 20 f/sec in three migraine subjects, but not in two normal subjects.

Lehtonin (1974), using an averaging technique, showed that 33 migraine subjects had a higher amplitude of responses to 22 f/sec than 11 controls. This was confirmed in a later study of 11 patients with menstrual migraine (Lehtonin et al. 1979).

Jonkman and Lelieveld (1981), using a digital method, found a relatively high power induced by photic stimulation at 18 Hz in 55% of migraine subjects compared to 5% of normal controls, and the spontaneous EEG in these patients showed significant asymmetry in the alpha frequency power.

Simon et al. (1982) analysed responses by a digital method to find the power spectra at 24, 34, and 38 f/sec and the highest power in the alpha frequency range. Their findings fulfilled the Golla and Winter (1959) criteria for an H-response in 10 out of 11 patients and in only 1 of 11 controls.

Nyrke and Lang (1982) applied a fast Fourier transform to measure the frequency power spectrum of the fundamental and the second harmonic components of the response evoked by sine wave-modulated light at frequencies of 10-22 Hz. They found no significant difference between migraine and control groups at 10 Hz stimulation, but increased power of the fundamental response component at around 20 Hz and reduction of the second harmonic response at 16-22 Hz in migraineurs. They argued that this was evidence for selective disturbance of two of the three frequency VEP subsystems in migraine: exaggeration of the medium frequency

subsystem and attenuation of the high frequency subsystem.

The original observations of Golla and Winter (1959) on migraine were extended into the Ph.D studies of Winter (1985), who examined 45 patients with classical migraine and 30 normal controls using digital methods of frequency analysis. He found an H-response in 75% of migraineurs and 11% of controls with the eyes closed. The difference was less with the eyes open.

Puca et al. (1987) found an H-response in 16 out of 20 migraine subjects.

CHAPTER 5 PSYCHOPHYSICAL VISUAL TESTS

Psychophysical tests are different in nature from the electrophysiological tests in that the reaction of the visual system is indicated by the subject's verbal response instead of by an objective measurement. Hence, they depend on the judgment of the patient, whose cooperation is very important for a reliable result. Three tests have been used in this study, the spatial contrast sensitivity (SCS), the temporal contrast sensitivity (TCS) and visual illusions. SCS and TCS have proved valuable in discovering abnormalities in other neurological problems involving the visual system, e.g multiple sclerosis (Regan and Maxner 1986) and Parkinson's disease (Bodis-Wollner et al. 1987). The visual illusion test was used because it was found by Wilkins et al. (1984) in a pilot study that migraine subjects developed more illusions than healthy subjects on looking at patterns of high contrast.

CS is measured using the contrast threshold, which is the minimum contrast needed to detect an object. The basic principle of detecting a visual image, whether a structured (spatial) pattern or nonstructured flicker, is by detecting a variation in luminance either in space or in time. SCS is assessed using a sinusoidal spatial contrast pattern, and TCS with a sinusoidally modulated flash. Each test can establish the contrast threshold either by the method of limit or by the forced-choice method.

In the method of limit the stimuli may be presented in ascending or descending series. Thus, the stimulus can be presented below threshold level and the contrast increased gradually until the subject can detect it, or the test can be started

above threshold level and the contrast decreased until the subject reports that it has disappeared. The point at which the stimulus appears or disappears is recorded as the contrast threshold.

In the forced choice method (Blackwell 1953), the observer's task is to choose among several carefully specified stimuli, only one of which contains the contrast. These stimuli may be presented sequentially or simultaneously in different locations. In both cases the contrast is increased stepwise in successive trials. The threshold is usually defined as the contrast at which the subject achieves three correct responses out of four, or two correct responses in succession.

In the method of limit the subject's decision involves subjective criteria for what he perceives as threshold stimuli. By contrast, the forced choice method involves no criteria. However, in practice no one method has proved superior and all are used without preference.

In this study temporal CS and whole-field spatial CS were measured by the ascending limit of contrast, which is the most commonly employed, and hemifield spatial CS (later referred to as hemifield CD, see section 6.2.2.3) was measured by a forced-choice method.

5.1 Visual Illusions

An illusion is defined as the false interpretation of a genuine perception e.g seeing a rope and thinking it is a snake, but broadly speaking any perceptions which do not harmonize with physical measurements of the stimulus may be termed illusions. They may

occur in any of the five senses, but visual illusions are the best known. They are widely encountered in nature, and in paintings, decorations and architecture (Luckiesh 1922). In addition, they may occur in a variety of diseases involving the brain, including schizophrenia and temporal lobe epilepsy, and they may also be produced by pathology restricted to the brainstem (Ropper 1983).

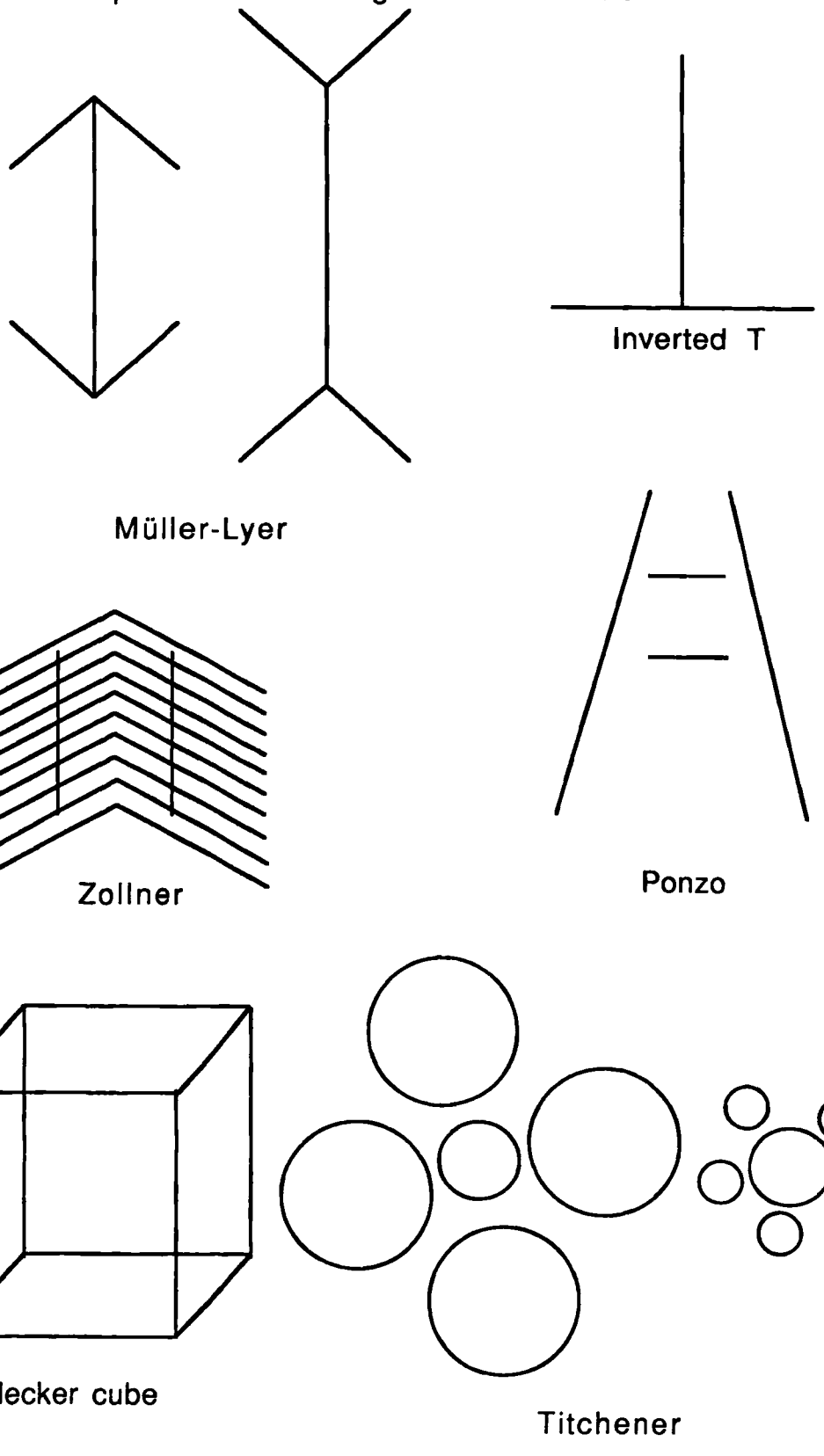
5.1.1 Classification of visual illusions

There is no satisfactory classification of illusions, but they may be roughly separated into two groups.

1. Geometrical illusions: These are the most widely known and studied (Fig 5). They are line figures in which the length, orientation, curvature or direction of lines is wrongly perceived. For example in the Müller-Lyer figure the line with outward pointing arrowheads appears longer than the line with inward pointing arrowheads, in the Zollner illusion there is distortion of the parallel lines, and in the Titchener figure the two inner circles appear of different sizes. In the Ponzo illusion the figure near the converging lines appears larger than another, placed where the lines are farther apart, and the Necker cube changes orientation so that sometimes one face, sometimes another, appears the nearer. These figures are thought to consist of two components; an inducing or distorting component and a test or distorted component (Gillam 1980). For example in the Müller-Lyer figure the arrowheads are the inducing component and the lines are the test component.

Figure 5

Examples of common geometrical illusions



2. High contrast black and white patterns, composed of radially arranged or parallel stripes or concentric circles, produce illusions involving shape, movement and the appearance of different colours (MacKay 1957). These include expanding concentric circles at right angles to radial lines, or wavy lines of different colours moving up and down perpendicular to parallel lines, or distortion and instability of the lines of any pattern.

5.1.2 Theories of illusions

The lack of any proper classification of illusions indicates the difficulty in understanding their underlying mechanism. Several theories have been put forward (see Wade 1982 for a review).

Theories attributing illusions to abnormal eye movements induced by the illusionary object have been disproved, as the illusion can occur undiminished when figures are stabilized on the retina with an optical stabilizing device (Pritchard 1958, 1961).

Psychologists explain geometrical illusions as conceptual rather than perceptual. For example the psychological explanation of the Müller-Lyer illusion depends on considerations of culture; the segment with inward arrows is read as an internal corner, and the outward arrows as an external corner. Owing to a hypothetical scaling faculty, our perceptual system judges external corners to be larger than internal corners. A tree appears longer when standing than when lying on the ground, and for the same reason we overestimate vertical lines in comparison with horizontal lines (Fig 5).

Other theories have concentrated on the stimulus properties themselves which produce illusions. Gregory (1963) presented the idea that the illusionary figures possess the property of producing "inappropriate constancy scaling". The distortion of visual space is produced if the scaling is set inappropriately to the distance of an observed object. "The parts of the figure corresponding to distant objects are expanded and the parts

corresponding to nearer objects are reduced. Thus, in the Müller-Lyer figure the vertical line would be further away in the diverging case, and is expanded in the illusion, and vice versa".

The discovery of orientation-specific neurones in the cat and monkey visual cortex by Hubel and Wiesel (1959, 1962, 1968) has encouraged several investigators to look for neural mechanisms underlying illusions. Theories have been put forward especially for illusions involving a single dimension, like the length or orientation of lines (Wallace 1969, Blakemore et al. 1970, Klein et al. 1974 and Tolhurst and Thompson 1975) which prove more amenable to study than the more complex illusions involving shape, motion and colour.

Neural interactions between neighbouring cells in the visual system, known as lateral inhibition, have been a central feature of the theories. Neighbouring columns of neurones in the visual cortex have sequential preferred orientations, producing a complete array of orientation neurones. Thus an illusion of orientation could be produced by inhibitory interactions between detectors responding to similar orientation. A stimulus at one orientation will excite a population of neurones which are most sensitive to a given orientation, but neurones sensitive to other orientations will also be excited, although less strongly. If a second stimulus is added, at a nearby orientation, the neurones responding to this stimulus will inhibit those responding to the first. The amount of inhibition will fall off with increasing differences between the optimal orientations of the interacting neurones. Thus the population of neurones responding to the first stimulus will not be uniformly inhibited by the second, and it is

this non-uniformity which is thought to give rise to an illusion. This hypothesis will explain the orientation or tilt illusion (Blakemore et al. 1970, Bouma and Anderiessen 1970, Lennie 1971), the distortion of acute angles so that they appear larger (Carpenter and Blakemore 1973) and a number of other geometrical illusions.

Furthermore, Georgeson (1973) has demonstrated that the tilt illusion depends on spatial frequency; illusion is maximal between patterns with similar spatial frequency, and declines as the difference in frequency increases. This fits the presence in the human visual system of "channels" selective for orientation and for a fairly narrow band of spatial frequencies (Blakemore and Campbell 1969).

The mechanism of illusions induced by high contrast patterns will be discussed later (section 8.2.6).

Several observations suggest that all types of illusion have an underlying cortical mechanism.

1. The effects are more striking with binocular than monocular stimulation (MacKay 1957).
2. Illusions can be lateralised to one hemifield (Wilkins et al. 1984).
3. Patterns that induce illusions can also induce paroxysmal EEG activity in patients with photosensitive epilepsy (Wilkins et al. 1984, Wilkins 1986), which led Wilkins (1986) to suggest that "the neural mechanisms responsible for illusions may resemble to some extent those that trigger epileptic disturbances".
4. Sleep deprivation increases both illusions and epileptic seizure frequency (Wilkins et al. 1984)
5. Illusions do not originate in the retina, because they are

equa ly present when the inducing component is presented to one eye and the test component to the other. Therefore, they must originate behind the LGN where the images from the two eyes first come together (Gillam 1980).

The illusions studied were those induced by high contrast striped patterns of the kind used by Wilkins et al. (1984) in headache patients.

5.1.3 Illusions in migraine

Wilkins et al. (1984) found that people suffering from headache reported more illusions than control subjects on looking at high contrast patterns of square-wave luminance profile and a spatial frequency of 4 cycles/ degree. They also examined 46 subjects suffering from migraine, 9 men and 32 women, who also saw more illusions than healthy controls. They found that when headache tended to be lateralised illusions tended to be lateralised too, but there was no relationship between the side of illusions and the side of headache.

Recently Marcus and Soso (1989) examined 32 subjects with migra'ne, 22 with "non-migraine" headache, and 42 "non-headache" subjects. Thirty one of those with migraine were found to have an aversive response to vertical black and white stripes, but only four of those with other headaches and none of the "non-headache" subjects were affected.

5.2 Spatial contrast sensitivy

5.2.1 General features

Spatial contrast discrimination involves the ability to differentiate objects of different sizes at various contrast levels. The measurement of visual acuity by conventional charts, such as the Snellen chart, measures only one aspect of this, the ability to detect small objects at the highest contrast, and provides no information about sensitivity to large targets of lower contrast, which are commonly encountered in the visual world. For comprehensive measurement of the spatial aspect of vision a striped grating pattern of sinusoidal luminance profile has been used. This was originally employed by Schade (1956), because it is the simplest object from which any spatial pattern or visual image can be constructed by superimposing a sufficient number of sine waves of the appropriate spatial frequencies, amplitude, phases and orientation.

Two variables in this grating pattern are essential for spatial CS measurements, namely the contrast and the width of the bars. The perceived width of the bars will obviously vary with distance of the pattern from the observer's eye. Width is therefore usually specified in terms of the visual angle it subtends. A dark and a bright bar are called a cycle and the number of cycles subtending one degree of visual angle is called the spatial frequency of the pattern. Thus a low spatial frequency indicates wide bars and a high spatial frequency narrow bars. The second variab e, contrast, is defined as the ratio of the difference between maximum and

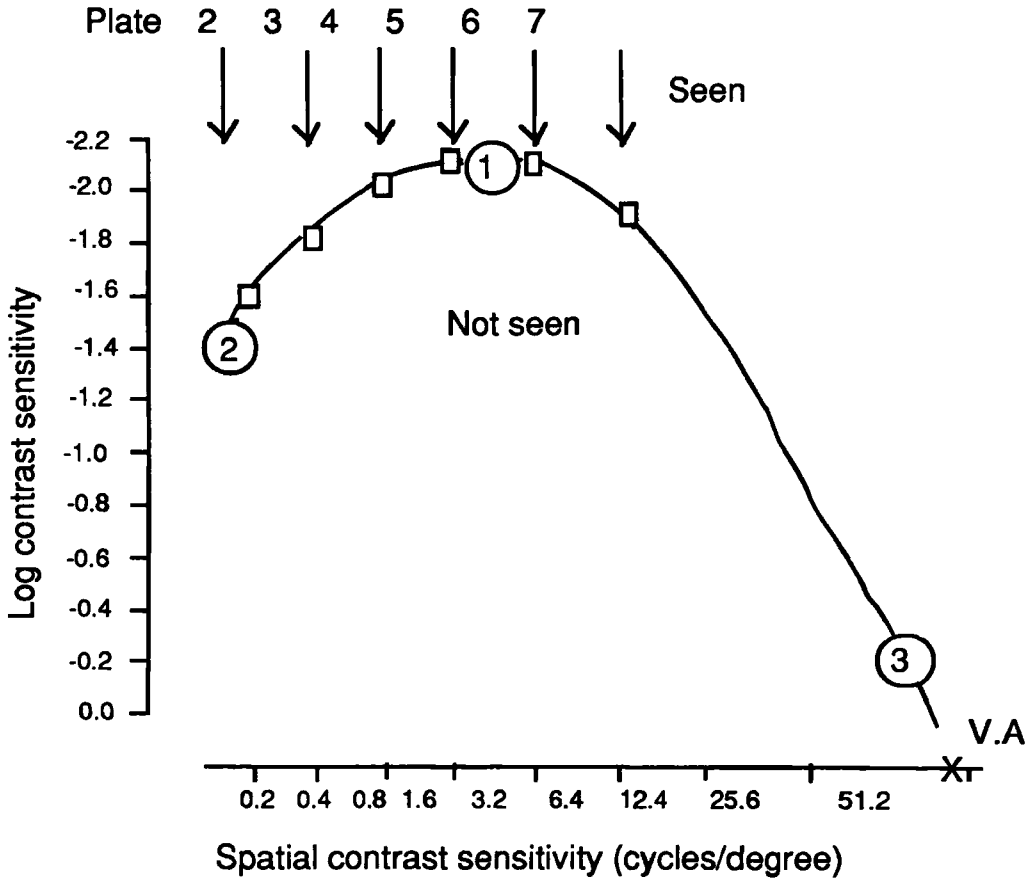
minimum luminance over their sum. It is usually expressed as a percentage i.e contrast = (Lmax-Lmin)/(Lmax+Lmin) x 100, where Lmax is the luminance of the bright bar and Lmin is the luminance of the dark bar, measured by a photometer.

These two variables must be chosen so that they do not affect the average luminance of the pattern, which is (Lmax+Lmin)/2. This is necessary to ensure a constant retinal adaptation, and to confine the test to the effect of contrast rather than brightness levels on spatial resolution.

Measuring spatial CS involves determining the contrast threshold at different spatial frequencies. The contrast threshold is the minimum contrast required to see the grating pattern. The reciprocal of contrast threshold is the contrast sensitivity, and the graphic representation of contrast sensitivity as a function of spatial frequency is called the contrast sensitivity curve or the modulation transfer function (MTF). This curve is bell shaped (Fig 6). This means at point 1 (3-4 cycles per degree) the human eye has the highest sensitivity (i.e lowest threshold) and at points 2 and 3 the sensitivity is lowest. The grating is visible above this curve and invisible below it. The curve intersects the abscissa at between 30 and 40 c/deg., which represents the smallest resolvable image, i.e the highest spatial frequency which can be seen at 100% contrast (Bodis-Wollner 1972, Arden 1978). This value theoretically corresponds to a visual acuity of 6/6 on a Snellen chart, as each bar of a 30 c/deg grating subtends one minute of arc at the eye, which is the same as the lines making up the letters, at the specified distance, on the 6/6 section of the Snellen chart.

Figure 6

Spatial CS curve. Note the range of spatial vision that can be tested with Arden gratings (Modified from Arden 1978). V.A = visual acuity. ①, ②, ③ - see text



5.2.2 Factors affecting spatial CS

Important factors affecting SCS include:

1. Luminance: This is important mainly at high spatial frequencies. High frequency sensitivity can be increased by increasing the average luminance within the mesopic range (up to 24 cd/m^2). Further increases have little effect (Kulikowski 1971, Bodis-Wollner and Camisa 1980). With decreasing luminance the peak of the curve is shifted toward lower spatial frequencies due to the use of larger receptive fields at lower adaptation levels (Kulikowski 1971, Kelly 1977, Bodis-Wollner and Camisa 1980).

2. Stimulus area and retinal eccentricity: CS is optimum, or maximal, at all spatial frequency ranges when a field of between 3 degrees and 6 degrees is used (e.g Campbell and Green 1965, Campbell and Robson 1968, Arundale 1978, Derefeldt et al. 1979). The stimulus area affects CS mainly at low frequency ranges, i.e CS at low spatial frequency is decreased with a decreasing size of stimulus (Kulikowski 1971, Kelly 1975). This has been attributed to an increase in receptive field size with eccentricity and to summation within the receptive fields of the detectors involved (Hoekstra et al. 1974, Savoy and McCann 1975 Robson and Graham 1981). There is a progressive decline in CS for all spatial frequencies with increasing retinal eccentricity. The decline is greater for high spatial frequency gratings than for low, so that the peak sensitivity (see Fig 6) is shifted to the left, since the fovea is more sensitive to stimuli of high spatial frequency and the peripheral retina to stimuli of low spatial frequency (Hilz and Cavonius 1974, Koenderink et al. 1978a, 1978b, Robson and Graham

1981).

3. Effect of age: Using T.V. screen presentation (see below, section 5.2.3), age has been found to affect CS mainly in the medium and high frequency regions. Arundle (1978) found a reduction in medium and high frequency regions in the age group 45 to 66 years, and Ross et al. (1985) found the same in the age group 50 to 87 years. However, Drefeldt et al. (1979) found that the reduction occurred only after the age of 60, and that there was no significant difference in CS in the range of 0.5 to 40 c/deg between the ages of 6 and 60 years. Sensitivity to low spatial frequency was not affected by age except in one unusual study, in which Sekuler et al. (1980) found that older observers had a normal CS to high spatial frequencies but a remarkably reduced CS to low spatial frequencies.

There is no agreement about the effect of age on spatial CS as measured by Arden gratings (see section 8.1.2).

5.2.3 Techniques for measuring SCS:

SCS is tested by using sinusoidal gratings, which have been generated electronically on oscilloscope or television screens, and more recently have been printed on sheets of paper. Gratings can either be made photographically, like the Arden type gratings (Arden 1978) and the Vistech Vision Contrast Test System (Ginsbury 1984) or can be printed by computer like the Cambridge low contrast grating (Della Sala et al. 1985, Wilkins et al. 1987). Other patterns, apart from gratings, have also been used, including low contrast test types (Regan and Neima 1984) and the low

contrast letter chart (Pelli et al. 1988). The aim of all these variants is to produce a simple, reliable and portable method that can be used clinically to supplement Snellen acuity, or to provide useful information that acuity measurements fail to provide.

The gratings used in this study are those produced by Arden (1978). These are simple and reliable, and the frequency range can discover visual defects in the presence of normal visual acuity. The gratings are supplied in a booklet containing 6 plates, each at one spatial frequency, covering a spatial frequency range of 0.2- to 6.4 c/deg. which is sufficient to reveal neural defects while remaining unaffected by refractive errors (Marmor 1986).

5.2.4 Neural basis of spatial vision

The SCS curve represents the responses of different channels each sensitive to a narrow band of spatial frequencies. The visual system acts according to Fourier principles, with information about each of the constituent sinusoidal components of an image transmitted through a separate neural channel (Campbell and Robson 1968). High frequency channels are present mainly in the fovea and low frequency channels in the peripheral retina. Thus the X cells, the ganglion cells which predominate centrally, contribute to the high frequency portion of the curve, and the Y cells, which predominate in the periphery, to the low frequency portion (Bodis-Wollner 1980).

The spatial resolution properties of ganglion cells are continued beyond the retina. Neurones in the LGN are selectively sensitive to narrow bands of spatial frequencies (Maffei and Fiorentini 1973), and so are the neurones in the visual cortex

(Campbell et al. 1969, Maffei and Fiorentini 1973 . Furthermore, the spatial frequency discrimination measured for single cortical cells in cat visual cortex corresponds to the frequency threshold estimated behaviourally (Bradley et al. 1987).

Pathological processes can selectively affect CS in certain spatial frequency ranges, providing further evidence that these different frequencies are processed by different channels. For example selective CS deficits in the medium frequency range have been reported in multiple sclerosis. (Regan et al. 1977) and other cerebral lesions (Bodis-Wollner 1972, Bodis-Wollner and Diamond 1976).

Since the properties of the LGN and simple cortical neurones reflect faithfully the properties of the spatial CS curve one can reasonably infer that spatial discrimination is processed in the primary visual cortex.

5.2.5 Contrast sensitivity in migraine

There is no previous report about CS, as normally understood, in migraine. However, there is one very brief but relevant abstract describing the use of sinusoidal gratings to elicit VEP's. Orban and Orban (1987) measured a neurophysiological version of "CS" in 33 migraine subjects and 26 patients suffering from tension headache using contrast modulated steady-state (CMSS) VEP at five spatial frequencies (0.25 to 10 c/deg). In this method (Orban and Orban 1985) an electronically generated vertical sinusoidal grating was phase reversed at 16 Hz. A linear modulation of contrast from 0 to 80% was superimposed upon this phase reversal at a frequency of 1

Hz. Thus the contrast of the grating was reduced from 80% to 0 during eight phase reversals and increased back to 80% during the next eight. Evoked potentials were obvious at high contrast and absent at low contrast. The portion of the VEP trace where the evoked potential were absent was referred to as the "null interval". The width (W) of the "null interval" (in msec) was converted into the contrast threshold (T) by the formula T = W x 80/1000. Thus defined, CS was reduced in all migraine patients, but was normal in patients with tension headache. In classical migraine the reduction in CS occurred mainly at 0.25 c/deg, and in common migraine mainly at 4 c/degree.

5.3 Temporal contrast sensitivity (TCS): the psychophysics of flicker.

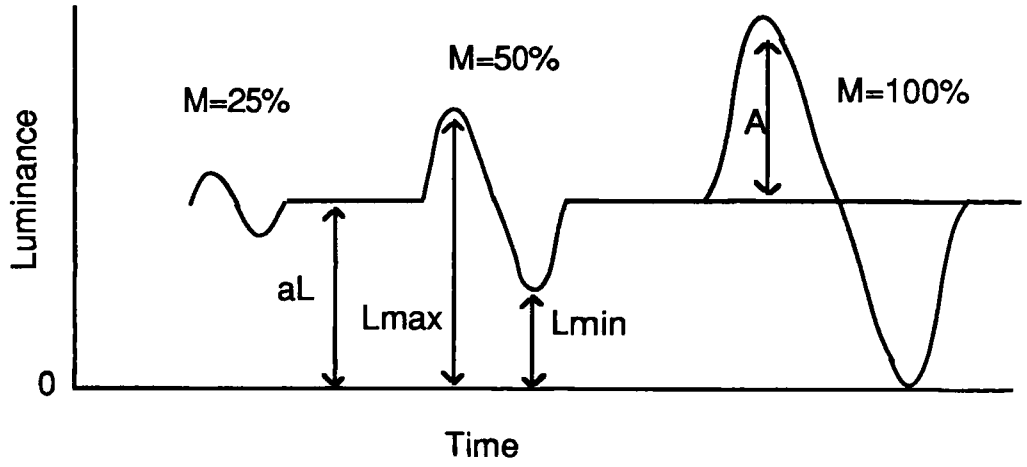
5.3.1 General features

The determination of flicker sensitivity depends on finding the contrast threshold at which an oscillating source of light is seen flickering. The usual stimulus is a light of sinusoidally varying luminance profile, and the appearance of flicker depends on both the amplitude and the frequency of variation. The amplitude of variation of light from a mean background level of illumination is described as the depth of modulation (M), usually expressed as a percentage of the average luminance (Fig 7). M reaches 100% if the amplitude of the sinusoidal variation is equal to the average luminance, and in this case the luminance reaches zero during each cycle.

The flicker threshold (T), the depth of modulation at which the flicker is perceived, can be expressed either as relative modulation, T = A/aL x 100, where A is the amplitude of sinusoidal change and aL is the average luminance, or as absolute modulation, which is the variation around average luminance, or Lmax-Lmin.

Figure 7

Schematic representation of sinusoidally modulated light showing one cycle at different levels of modulation (Modified from van der Tweel and Estevez 1974)



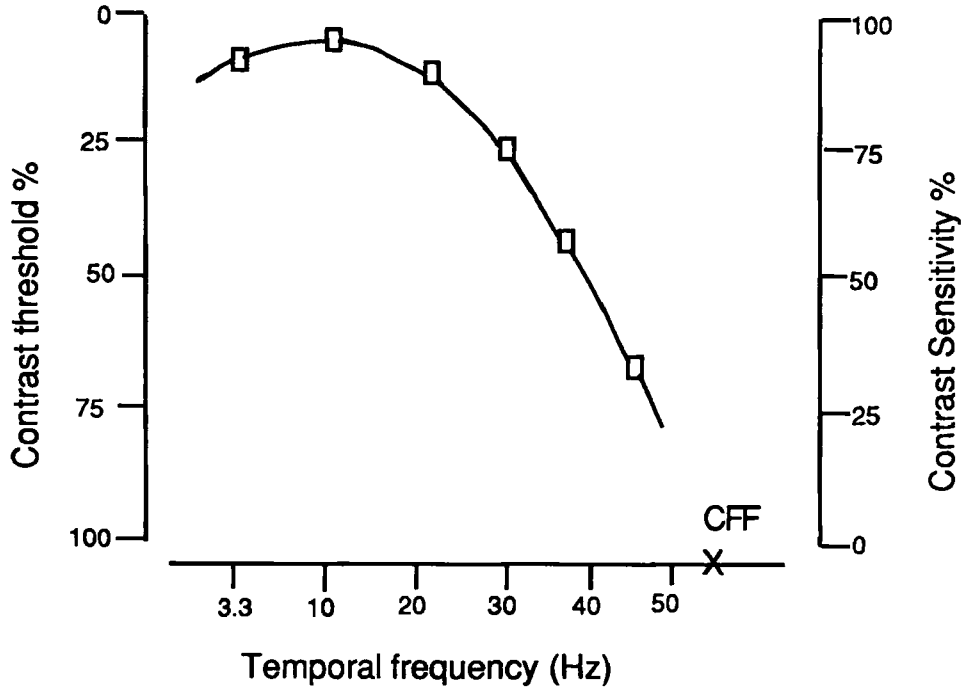
L = luminance
A = amplitude of modulation
Contrast% = (Lmax-Lmin)/(Lmax+Lmin) x 100
Relative modulation (M) = A/aL X 100
Absolute modulation = Lmax-Lmin

Temporal contrast sensitivity is usually measured by using a source of sinusoidally modulated light subtending 1 or 2^{o} of visual angle (Brukink and Ten Doesschate 1963), surrounded by a field illuminated by another source producing a luminance equal to the average intensity of the oscillating test field. This matched surround is important in order to light-adapt a large area of the retina, thus reducing the possible effect of stray light, as dissimilar states of retinal adaptation affect the TCS measurement.

Studies on the entire spectrum of human perception of flicker were first made by a telecommunication specialist De Lange (1954, 1958a, 1958b). Using a sinusoidally modulated light stimulus subtending a 2^{0} field, he found that the lowest relative modulation required to reach threshold was at 10 Hz, i.e flicker sensitivity was maximal at this frequency (Fig 8). Above this frequency the relative modulation required to see the flicker increased rapidly, and at some point above 50 Hz even a light modulated 100 percent did not appear to flicker. The point at which the curve intersects the abscissa is the maximum temporal frequency discernible by the visual system. This is known as the critical flicker frequency (CFF) (Kelly 1964, van der Tweel and Estèvez 1974), and it used to be the only criterion for investigating the temporal responsiveness of the visual system (Porter 1902).

Figure 8

Temporal CS curve at various frequencies. Illustration based on personal and published figures. CFF = Critical flicker frequency



5.3.2 Factors affecting TCS

TCS is influenced by stimulus variables such as luminance, target size, and eccentricity in the visual field, and by subject variables such as age and pupil size.

1. Luminance of the field: a decrease of the mean luminance level leads to a lowering of the whole curve, in particular the medium and high frequency regions (Brukink and ten Doesschate 1963). An increase in mean luminance, within a fairly wide range of luminances, leads to an increased sensitivity for frequencies above 10 Hz. This was described separately by Ferry (1892) and Porter (1902) and is commonly known as the Ferry-Porter Law.

2. Depth of Modulation: modulation of the light source is the most important factor in determining the perception of flicker, and is of course the criterion by which TCS is measured, but its effect varies with the frequency. At low frequencies the perception of flicker is dependent on the relative modulation of the stimulus, according to Weber's law which states that the smallest difference in intensity which can be detected is directly proportional to the background intensity. However, at high frequency perception influenced also by luminance, so it can be said to depend on absolute modulation.

3. Size of the stimulus and retinal eccentricity: TCS at high frequency increases with increasing stimulus size (Granit-Harper law). Wolf and Vincent (1963) showed that at high frequencies CFF increases substantially when the test field size increases from 2' to 1 or 2^{o} but with further increases the change in CFF is only slight. They attributed this to the overlap of the test field into

inhibitory areas of the retinal receptive field. The opposite effect occurs at low frequencies i.e TCS is markedly reduced with an increasing test field, and this is explained by enhanced inhibitory interactions (Kelly 1964).

Temporal CS decreases linearly with retinal eccentricity when measured with a constant stimulus size. However, CFF varies with stimulus size in the periphery but not in the centre. With a stimulus subtending 2^{o} or more CFF is higher in the periphery than in the centre, but with a stimulus of less than 2^{o} peripheral CFF is less than central CFF (Granit and Harper 1930, Kugelmass and Landis 1955, Wolf and McGown 1963).

The effects of field size and retinal eccentricity on TCS may be due to the interaction of several factors; the relative sensitivities and summative ability of the X and Y ganglion cell subsystems, the receptive field density, and lateral inhibitory interactions, which are more probable with large than with small test areas.

4. Age: CFF declines with age. It is about 45 Hz at age 13, and diminishes to between 19 and 30 Hz at age 80 to 89 (Domey 1964). Wright and Drasdo (1985) showed that temporal CS at 3 Hz and 10 Hz peaks at age 30-39 years, and there is then an overall decline with age of 0.21 log units at 3 Hz and 0.23 log units at 10 Hz. At high temporal frequency (30 Hz) they found a progressive reduction in sensitivity between the age groups 10-19 years and 70-79 years of 0.68 log units. They attributed the reduction in high frequency sensitivity to optical rather than neural factors, principally the reduction of pupil area with age, causing a reduction in retinal illumination.

6. Pupil size: a decrease in pupil size leads to lowering of the whole TCS curve which roughly corresponds to the loss in retinal illumination.

5.3.3 Neural factors in processing of flicker perception

Experiments involving ablation of cortical and subcortical structures in the cat (Norton and Clark 1963, Schwartz and Cheney 1966) and monkey (Mishkin and Weiskrantz 1965) have elucidated the neural processing of flicker. Higher frequency flicker perception was reduced by lesions of the striate cortex, whereas lesions of the superior colliculus reduced it at low frequency. Spekreijse et al. (1971) have found that there is a similarity between the characteristics of human psychophysical flicker detection and the electrophysiological responses of LGN neurones in monkey, by demonstrating that the response strength (impulses/sec) of LGN neurones to low flicker frequency (<10 Hz) is dependent on the relative modulation of the stimulus, in accordance with Weber's law, whereas in the high frequency region (>10 Hz) the response depends on absolute modulation, in accordance with the Ferry-Porter law. Furthermore, microelectrode recordings from single neurones of the LGN in monkey (Schiller and Malpeli 1978, Kaplan and Shapley 1982) have demonstrated that the magnocellular cells (M-cells) have high frequency properties and the parvocellular cells (P-cells) have low frequency properties.

In man TCS at different frequencies can be differentially affected by pathology. Ambylopia affects the low temporal frequency range, with little involvement of the high frequencies.

Selective loss in the high frequency range has only been observed in some cases of optic nerve pathology (Brukink and Ten Doesschate 1963). Wright et al. (1987) showed that the temporal CS was affected by optic neuritis across the whole frequency range, whereas in Alzheimer's disease only the medium frequencies were involved.

The sum of these animal and human data suggest that the pathway leading from the Y-cells to the magnocellular system and the striate cortex is responsible for processing high frequency flicker. The medium frequency range is processed in the extrastriate cortex (18 and 19), through either a geniculostriate pathway and on to the extrastriate cortex or a nongeniculostriate pathway leading from the LGN to the tectopulvinar/extrastriate pathway. The neural basis for low frequency flicker is ill understood, but may perhaps represent the activity of W-cells passing to the tectum and prestriate cortex.

5.4 Spatiotemporal interactions

Although spatial and temporal CS have been considered separately, there is clearly an interaction between the perceptions of form and of movement in the visual world. This interaction has been studied by psychophysical procedures using a grating pattern temporally modulated at different rates by drifting the contrast at high velocity or by contrast reversal of a stationary grating. Such temporal modulation increases the sensitivity of spatial contrast perception (Robson 1966, Van Nes et al. 1967), but only at low spatial frequencies modulated about 8 Hz (Robson 1966, Kelly

1977). This increased spatial contrast sensitivity might be due to activation of a distinct population of channels by temporally modulated stimuli. Furthermore, several investigators have proposed two distinct mechanisms for spatial and temporal vision, as two distinct contrast thresholds can be observed when viewing flickering gratings: as contrast is reduced spatial contrast fades and disappears but the flicker can still be seen (Riggs and White 1967, van Nes et al. 1967, Keesey 1970, 1972). However, some authors claim that these two thresholds correspond to nothing more than two levels of excitation of the same mechanism (Burbeck 1981, Derrington and Henning 1981). This argument has been pursued by Kulikowski and Tolhurst (1973), who showed that the thresholds behaved differently in different spatial frequency ranges. At low spatial frequencies (below 3-4 c/deg) the threshold for detecting flicker is much lower than that for spatial pattern, whereas at high spatial frequencies the two thresholds coincide. These authors concluded that there are two sets of channels. One, responsible for temporal vision, responds to high temporal frequency but is sensitive only to low or medium spatial frequencies. The other, responsible for pattern vision, responds well to high spatial frequencies and to low temporal frequencies.

One can see a possible correlation between the two types of channel implied by these psychophysical experiments and the two classes of retinal ganglion cells in the cat, called X- and Y-cells by Enroth-Cugell and Robson (1966) and sustained and transient channels by Cleland et al. (1971) (see section 3.2). The sustained/transient distinction exists among neurones in the LGN also (Cleland et al. 1971), so that each class receives its input

from the corresponding class of retinal ganglion cell. These two systems may well continue separately into the striate cortex (Stone and Hoffman 1971, Maffei and Fiorentini 1973), which is consistent with the idea that their activities could yield quite distinct sensations, of spatial pattern and of flicker (or movement) respectively.

CHAPTER 6 SUBJECTS AND METHODS

The electrophysiological and psychophysical tests used in this study were performed with approval from the ethics committee of Hammersmith Hospital. The objectives of the tests were explained to all subjects at the beginning of the test session.

6.1 Subjects

6.1.1 Migraine subjects

Migraine patients were recruited from the neurology outpatient clinics of Hammersmith and Ealing hospitals, and from members of the British Migraine Association in response to an article in the association's newsletter.

All patients fulfilled the criteria for a diagnosis of migraine and those for a diagnosis of migraine with aura (classical migraine) or migraine without aura (common migraine), according to the Headache Classification Committee of the International Headache Society (1988).

For the main part of the study a total of 100 migraine volunteers were examined. In eight patients the studies were inadequate because of technical problems or lack of time. Results were therefore available from 92 migraine subjects, 72 females and 20 males, aged 17-62 years. 80 patients were right-handed, 7 were left-handed and 5 were ambidextrous. All patients had a visual acuity of 6/6 or better using a standard

Snellen chart at a distance of 6 meters; 15 needed correction to achieve this. None were taking prophylactic treatment.

47 patients had classical migraine, 37 had common migraine and 8 had both common and classical migraine attacks. In these 8 patients at least 10% of the attacks were classical. All patients with classical migraine had a visual aura. Seven also had other aura symptoms including motor, sensory and speech disturbances. The duration of migraine ranged from one month to 55 years, and the frequency of attacks varied from several a year to more than one a week.

Migraine was assessed for type, site, severity, duration, frequency, triggering factors, and associated symptoms by a preliminary questionnaire (Appendix). At a consultation subjects were then questioned further about details of their migraine, and also about a history of neurological or ophthalmological problems, and received a thorough neurological examination, with special concentration on the optic fundi, visual fields, visual acuity and pupils. No disorders were found other than refractive errors.

15 out of the 92 patients started prophylactic treatment shortly after being tested, and these were examined again after three months. The results of their first study were used in the general analysis. An additional group of eight patients were examined for the first time while they were on prophylactic treatment, which was later withdrawn from four of them, and these four were examined again. Their results were not used for the general analysis (see section 6.3.6).

6.1.2 Control subjects

65 control subjects were recruited from friends, colleagues, hospital staff, relatives and friends of migraine patients, and volunteers responding to an advertisement in "The Friend". They were assessed by a modified questionnaire and consultation to establish that they were free from migraine and from neurological or ophthalmological problems other than refractive errors, and their visual system was fully examined clinically.

In three subjects studies were incomplete, leaving 62 subjects for analysis, 44 females and 18 males, aged 19-58 years. 56 were right-handed, 4 were left-handed and 2 were ambidextrous. All had a visual acuity of 6/6 or better, 11 with correction.

6.2 Methods

The testing session lasted 3-4 hours. Subjects were encouraged throughout the tests, to maintain their interest and concentration, and a break was taken for refreshment halfway through. Subjects who needed glasses wore them throughout all tests.

6.2.1 Electrophysiological tests

6.2.1.1 General considerations

All investigations were carried out with the laboratory

lights switched off. The background luminance was then about 1 cd/m^2 as checked by a photometer. Cort'cal visual evoked potentials were elicited to pattern stimuli and to both single and repetitive flash stimuli. The ERG was recorded simultaneously to pattern and single flash stimuli.

The equipment used to elicit the visual evoked potentials was as follows.

1. SLE Neuroscribe 8-channel Electroencephalograph, used for all recordings. The evoked responses were amplified with a bandwidth of 0.16 to 150 Hz, the sensitivity was set to 10 μV/cm and the paper speed to 15 mm/sec. The channel input selection (the montage) can be automatically changed on the panel of the machine.

2. SLE SA 2000 Townsend averaging system, used for averaging all recordings, and containing a st'mulus programme for repetitive flash, designed and installed by Dr. Horace Townsend. It consists of two microprocessors each looking at four channels. Alternate responses are averaged into different parts of the memory and when the results are displayed the pens are arranged to switch rapidly between the two estimates of the average so that the size of the 'shaded' region (Fig 9) provides a guide to the consistency of the estimate. Subsequently the two estimates are combined to form a grand average, which is displayed with "ticks" which are time markers. The averager was set to a total sweep duration of 200 msec, which was found to be the most suitable for producing clear and well formed recordings.

3. Barco 2432 T.V. Monitor, used to display the chequerboard pattern stimuli.

4. Medelec Visual Stimulator 47791: this was used to generate the pattern stimuli, consisting of a chequerboard on the T.V. screen in which all squares reverse between light and dark without any change in total light output (luminance) from the screen. The check size, stimulus rate, luminance and contrast can all be easily changed.

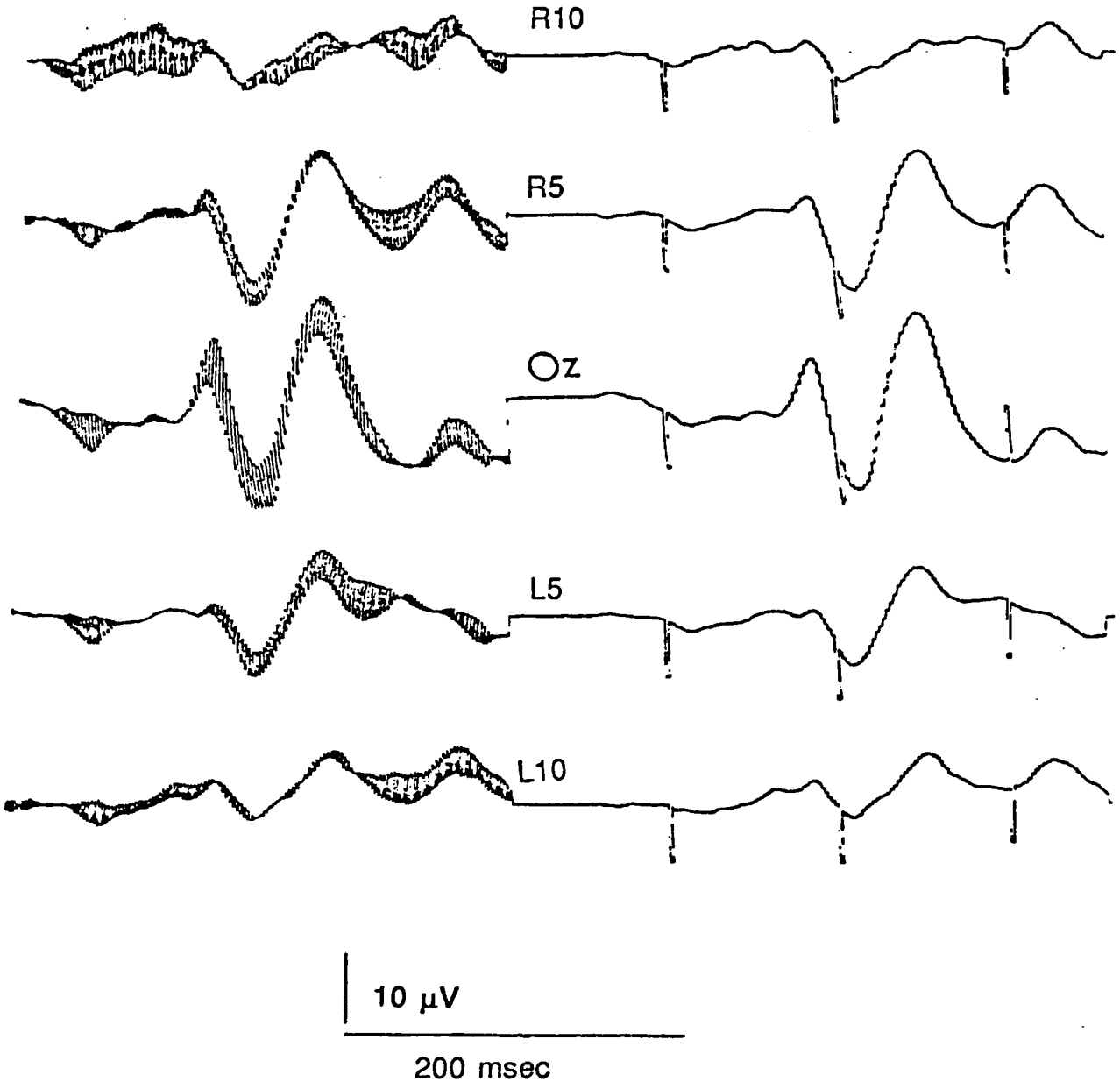
5. SLE PS100 Photic Stimulator: this provided the flash stimuli, constituting change in luminance. It delivered single flashes of 65 μsec at 2/sec or was driven by the Townsend system to provide repetitive flashes at various frequencies.

6. Silver/silver chloride EEG electrodes: these were standard EEG electrodes with a central hole, held in place by crossed surgical tape.

7. Textronix J16 Photometer with J6503 probe, used to measure luminance.

Figure 9

Pattern-reversal visual evoked potentials recorded at 5 positions showing the write-out in two displays. The first display compares two concurrently acquired averages and the second display shows the combined average with time markers at 0 msec, 100 msec and 200 msec.



Calibration checks were carried out weekly on the EEG machine and the averager. These included sensitivity, pen alignment, pen centering, base line shifting (hysteresis), paper speed, amplifier filters and amplifier noise. In addition a calibration signal of approximately the same amplitude as the biological signal was averaged at the same rates, repetitions, filters and gain settings as those used for the evoked potential signal. This provided a comprehensive check of the polarity, amplitude and latency and filter characteristics of the system.

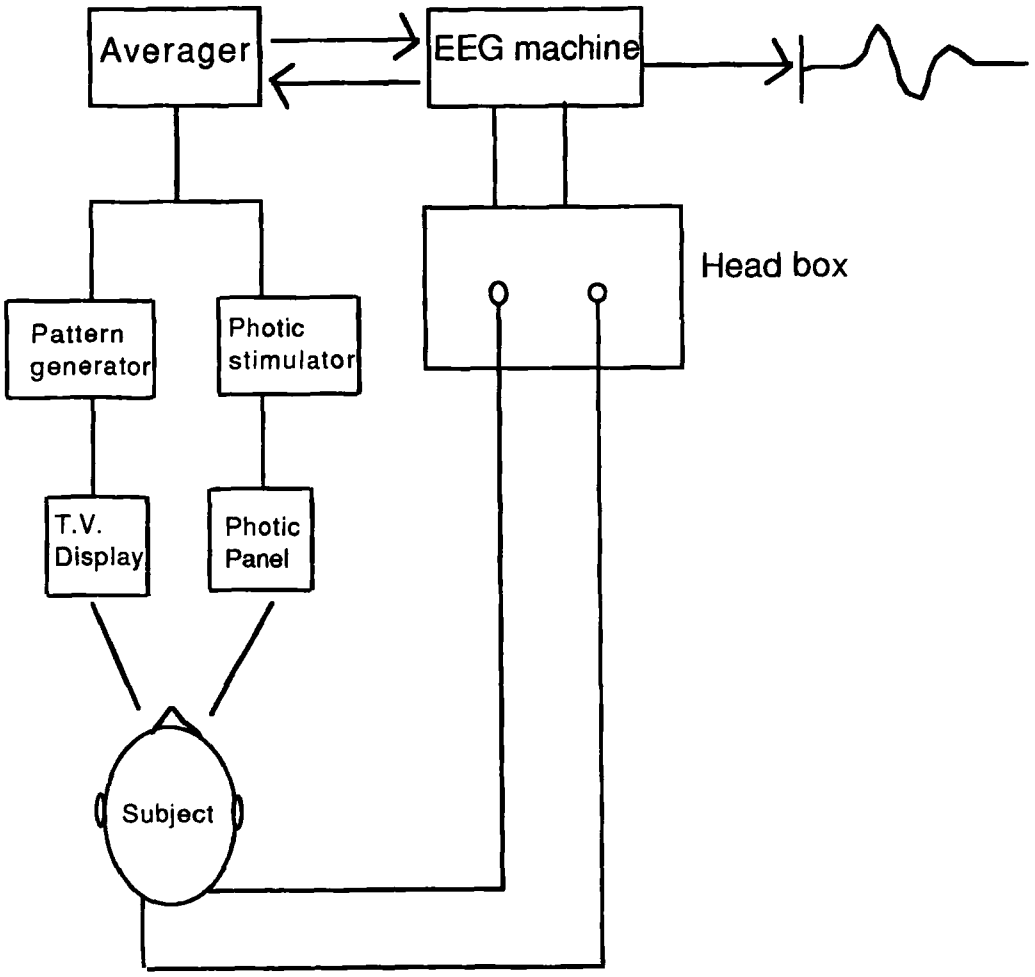
With the subject seated in a comfortable chair the recording electrodes were placed according to a protocol based on the standard 10/20 system of EEG electrode application, and the Queen Square montage for recording the visual evoked potentials, i.e at Oz, Pz and at 5 and 10 cm lateral to Oz on both sides (R5, R10, L5 and L10 respectively), with an Fz reference for recording pattern responses and linked-ears reference for recording flash responses. In addition, two electrodes were placed infraorbitally for ERG recording. The ground electrode was placed on the forehead. An 18-gauge needle with a blunt tip was used to fill the electrodes with saline electrode gel and also to lower the skin resistance by moving it back and forth against the scalp until the resistance was down to below 3 Kohms, as measured by an impedance meter built into the head box. Figure 10 shows a block diagram to illustrate the processing of the visual evoked potential signal through the system. The averager triggers the stimulator (the pattern generator or the photic stimulator), and the evoked response generated by viewing the T.V screen or the stroboscope panel is then recorded via the scalp electrodes,

which are plugged into the head box of the SLE machine. The responses are filtered, amplified, and then stored in the averager to be plotted directly by the EEG pens on EEG paper.

In order to ensure that the visual evoked responses are clear and reproducible the usual recommendation is that two trials, each averaging 100 or so repetitions, should be superimposed. However, it was not possible to superimpose two trials with the available equipment, so the averaging procedure was performed in two steps. Initially 120 responses were averaged and displayed on EEG paper, and if the waveform was reasonably clear the averaging procedure was continued until 240 stimulus repetitions had been accomplished, and the grand average of the 240 responses was then printed on EEG paper at a suitable gain setting. In most subjects a clear set of waveforms was obtained after 120 repetitions. However, if the written out waveforms after one minute were unclear, or if there were several waveforms whose consistency was in doubt, the averager memory was cleared and a fresh 120 responses were averaged and displayed. The equipment was positioned so that the subject could be carefully watched, and if there was excessive movement or blinking averaging was stopped immediately. The procedure was then restarted when the patient was relaxed.

Figure 10

Block diagram showing how the evoked potential signal is processed



6.2.1.2 Analysis of evoked potentials

The amplifiers are constructed in such a way that when lead 1 (the black lead) becomes more negative than lead 2 (white lead) or when lead 2 becomes more positive than lead 1, there is an upward deflection of the pen. This is the EEG convention of polarity and is used for the evoked potentials in this study.

The two important parameters of the VEP, the latency and the amplitude, were measured on the EEG paper directly. The latency was measured in milliseconds (msec) from the stimulus to the peak of the response and the amplitude was measured in microvolts (μV) from peak to peak.

There are two main systems of wave nomenclature. In the first, the components are numbered in sequence by polarity e.g P1, P2, N1, N2. In the second, the components are labelled according to their polarity and mean latency in normal subjects e.g P100. In accord with the published literature on the subject, the first system was used for the flash VEP and the second system for the pattern VEP.

6.2.1.3 Procedure for evoked potentials

6.2.1.3.1 Electroretinogram (ERG)

The pattern ERG (PERG) was recorded at the same time as the pattern reversal visual evoked potentials with binocular viewing. So, the method of recording was the same as that for recording the binocular whole-field pattern reversal visual

evoked potentials (see section 6.2.1.3.2). The recording electrodes were placed infraorbitally (Papakostopoulos 1982) on each side, held in place by double-sided self-adhesive tape, and were referred to the ipsilateral temple. The stimulus was a chequerboard reversing at 2 per second. Initially, the technique used by Papakostopoulos (1982) and by Winter (1985) for eliciting flash ERG was employed, by collecting two sets of 120 responses over one minute. This technique was used for the first 21 migraine patients and the first 10 controls, but it produced low amplitudes and unclear responses, due to prominent blink reflex artifact. The method was therefore changed, and the responses were collected in four steps, each taking half a minute. It proved easy for subjects to avoid blinking for half a minute, and they were then allowed to blink and look away from the pattern briefly before another half minute of responses was collected. The procedure was continued for 2 minutes of recording i.e a total of 240 repetitions were obtained. This produced much better and clearer responses, and only those obtained by this method have been used for analysis.

The flash ERG was recorded at the same time as the flash VEP, on two channels with skin electrodes referred to ipsilateral temple. The details of the method are given below (section 6.2.1.3.3).

6.2.1.3.2 Pattern-reversal VEP (PRVEP)

The PRVEP were elicited by using a chequerboard displayed on a Medelec T.V. type visual stimulator with a central fixation

point. This allows the stimulus to be delivered without overall change in luminance. The mean luminance of the screen was 54.2 cd/m^2 and the contrast was 95%

The subject was seated in front of the chequerboard at an eye-screen distance of 100 cm. At this distance the stimulus field subtends 30X25 degrees of visual angle, and the individual squares 38 minutes.

The subject was instructed to gaze at the dot in the centre of the pattern. Although absolutely precise fixation is not important, and minor wanderings of gaze do not significantly affect P100 latency or amplitude, it is important that the subject maintains gaze fixation near the centre of the screen (Chiappa 1989).

First the test was performed with binocular viewing. Then each eye was tested separately with the opposite eye covered by an eye patch. Then half-field responses were obtained by blanking half of the screen with cardboard and also leaving blank a 1 cm strip adjacent to the vertical meridian, because this is an area of overlap between the two fields. The binocular responses were collected in four steps, each lasting half a minute. The monocular and half-field responses were collected in two steps, each lasting one minute. This made a total of 240 responses, which were averaged and displayed on paper print-out at different gain settings.

6.2.1.3.3 Single flash VEP (SFVEP)

The SFVEP were elicited with binocular viewing using a xenon flash tube (PS100 SLE) at a frequency of 2 f/sec, with a

mean single flash luminance of 11 cd/m^2 measured at the eye (when the tube was placed at 15 cm distance) and a flash duration of 65 µsec. Averaging was started 5 seconds after the photic stimulator was switched on to allow time for the pupil to establish a steady diameter.

The recording electrodes were placed at Oz, Pz, Cz, Fz and at 5 cm lateral to Oz on both sides, and connected to a common linked-ear reference.

The subject was instructed to gaze at the central fixation point of the stroboscope lamp. 240 responses were then averaged and displayed, as follows. First, 120 responses were recorded over one minute, and were averaged and displayed as for the monocular pattern VEP. A second collection of 120 responses was then made, starting 5 minutes after the room lighting had been switched off. This time was kept constant to ensure that all subjects had the same degree of retinal adaptation during the time of testing, because the flash ERG was being recorded at the same time, and for this it is important for consistency that all subjects should have the same degree of retinal adaptation during the period of testing.

6.2.1.3.4 Repetitive Flash VEP (RFVEP)

The repetitive flash responses were recorded using a programme made and installed into the averager by Dr. Horace R.A. Townsend. The rate of presentation started at 4 f/sec, increased to 6 f/sec, then increased stepwise by 1 f/sec up to 12 f/sec and thereafter by 2 f/sec up to 24 f/sec. Thus the frequencies used

were 4, 6, 7, 8, 9, 10, 11, 12, 14, 16, 18, 20, 22 and 24 Hz. The luminances at these frequencies were 50, 72, 81, 94, 104, 117, 126, 137, 158, 180, 202, 220, 244, and 260 cd/m^2 respectively. Each presentation lasted 10 seconds and the averaged responses were recorded on to 4 channels representing R5, Oz, L5 and Cz with linked-ears reference. The recordings were made with the subject's eyes both open and closed. Two trials were collected in each case to ensure reproducibility.

The responses during the first epoch, at 4 f/sec, were not used, since this stimulation period was allowed for pupillary adaptation. Starting with the 6 Hz epoch, the amplitudes at all frequencies and at all four positions were measured in all subjects.

6.2.2 Psychophysical tests

Unlike the visual evoked potentials, the acquisition of psychophysical measurements depends on the judgement of the patient. The characteristics of the illusions elicited by high contrast patterns were assessed, and measurements were made of spatial and temporal contrast sensitivity, using the ascending limit of detecting contrast threshold. In addition, hemifield SCS was measured, using a different technique and a forced choice method. These results were used solely for comparing the two hemifields, and from now on will be referred to as hemifield contrast discrimination (HFCD).

6.2.2.1 Visual illusions

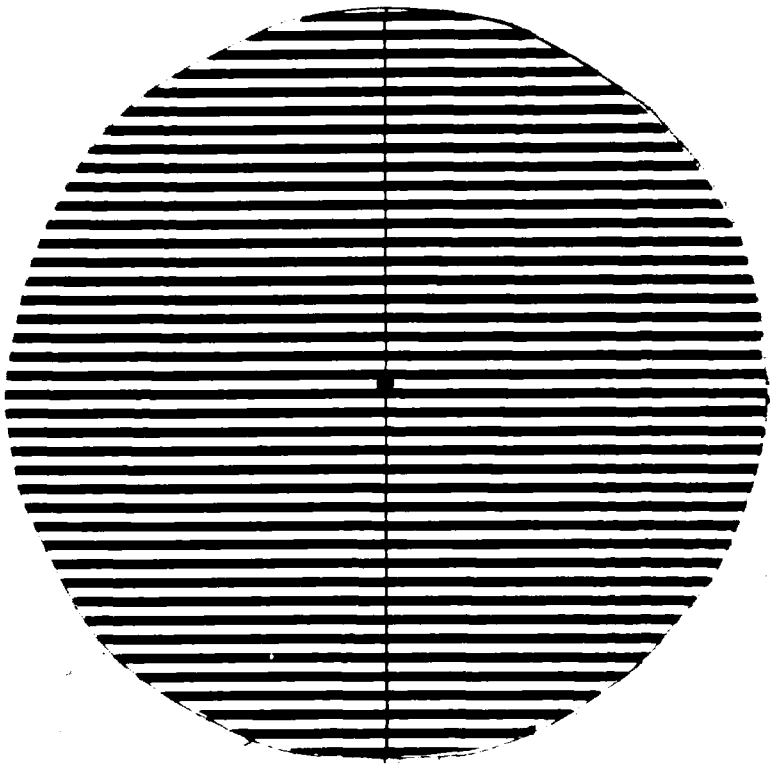
These were tested using high contrast patterns of stripes, made by the Letraset Company, and kindly provided by Dr. Arnold Wilkins. Each pattern is circular in outline, marked with a vertical midline and a central fixation point, and consists of black and white horizontal stripes with a square-wave luminance profile at 70% contrast and a frequency of 4 cycles per degree. Six patterns were used. The first four had diameters of 2.5, 5, 10 and 20 cm respectively, and the other two consisted of the right and left halves of the largest pattern. At 50 cm distance the first four patterns subtended about 3, 6, 11 and 22 degrees of visual angle respectively, and the last two subtended 11 degrees. The overall luminance was 74 cd/m^2 when the patterns were illuminated by a 100 watt spot light. All patterns were mounted on grey card with a mean luminance similar to that of the black and white stripes. Figure 11 is one of these patterns.

The subject was seated on a chair and all patterns were presented for 5-10 seconds each. The whole-field patterns were presented first, starting with the smallest and progressing to the largest, followed by the half-field patterns. The subjects recorded on a checklist the illusions seen after each presentation of each pattern. The checklist of illusions was as follow; blurring, shimmering, flickering, fading of stripes, intermingling of lines, zigzags, colours (red, green, blue, yellow), shadowy shapes and any other illusions. The total number of illusions of all kinds was then recorded for all the whole-field patterns. To look for asymmetry of illusions, initially subjects were asked to

record the number of illusions on each side of the pattern, when viewing both the whole-field and the hemifield patterns. However, many subjects found that the number of illusions was the same on the two sides but that there was nevertheless a marked asymmetry, in that illusions were more prominent on one side than the other. Therefore, the criterion for asymmetry of illusions was a qualitative judgment about their relative prominence on the sides. In addition, subjects were asked to rate their experience of the whole-field patterns on a discomfort scale (very comfortable, moderately comfortable, neither comfortable nor uncomfortable, slightly uncomfortable, moderately uncomfortable, very uncomfortable).

Figure 11

High contrast, square-wave pattern used to assess illusions.



6.2.2.2 Spatial contrast sensitivity (SCS)

Contrast sensitivity was measured using Arden type sinusoidal gratings (Arden 1978), made by the American Optical Company. They consist of a series of 7 photographic plates. Each plate is 28 cm wide and 22 cm high, subtending 26 x 21 degrees of visual angle at 57 cm from the observer's eye, thus covering both central and peripheral fields of vision. The first plate is for demonstration purposes and has exaggerated contrast. On plate 2-7 the spatial frequencies of the grating are 0.2, 0.4, 0.8, 1.6, 3.2, 6.4 cycles per degree of visual angle, at 57 cm, and the contrast increases gradually from top to bottom of each plate by 0.08 log units per cm, over the whole 22 cm. The luminance is 70 cd/m2 with a 60 watt incandescent bulb 14" above the plates. The threshold scores at the sides of each plate range from zero at the top, low contrast end, to 20 at the bottom, high contrast end of the plate. Figure 12 is one of such plate (Plate 3).

The special pocket containing the plates was supported on a slightly sloping easel, designed to minimise reflection from overhead lights. Because of this the subject was positioned with the eyes slightly higher than the middle of the plate, so that the visual axis was perpendicular to the face plate. However, testing is not sensitive to minor variations.

The principle of the test was explained to the subject using plate 1. The dark and light spaces were pointed out together with the change in contrast. Then the plate was placed in its pocket and exposed gradually at a rate of about 1 second per division on the scale. The subject was constantly instructed to scan the top

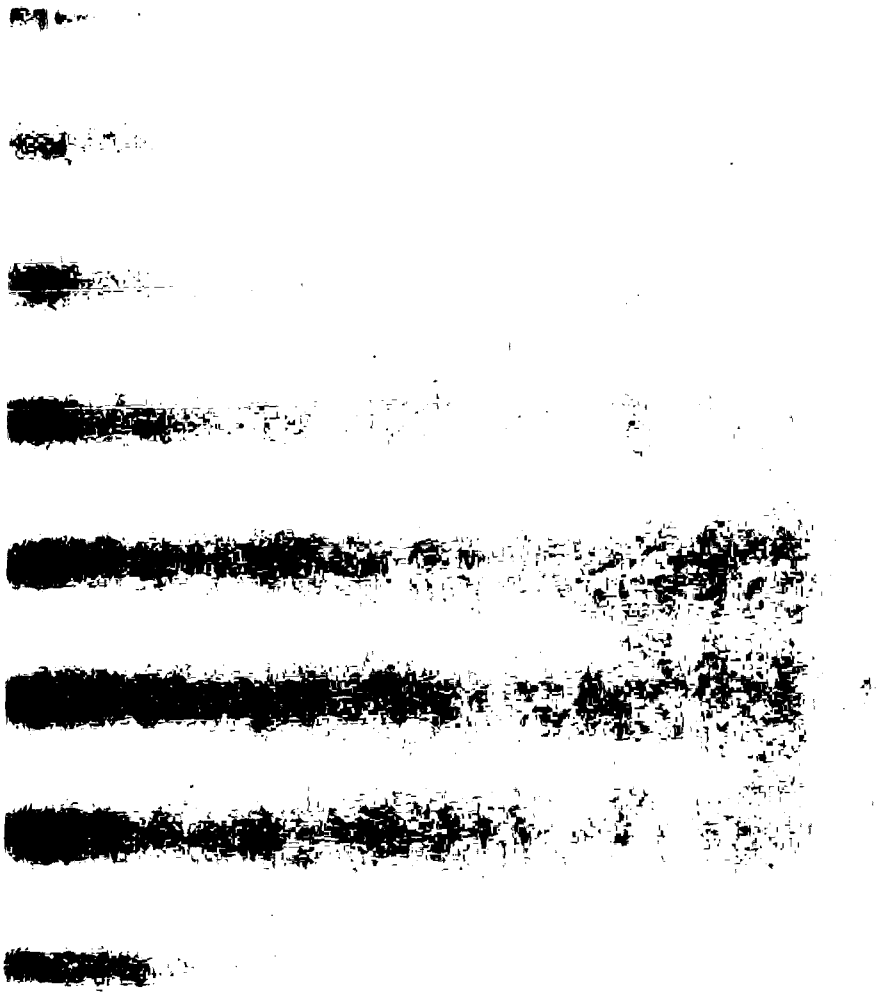
edge of the pocket rather than to fix and hold on any part of the moving plate, and was asked to say "now" as soon as the pattern was seen. This procedure was repeated until the subject had gained some experience. Then the subject was told that the same type of pattern was present on the next test plates but the changes were more subtle.

The presentation started with plate 2 and progressed to plate 7. The point at which the subject started seeing the pattern was the subject's threshold score for that plate. Each plate was presented four times and each eye was tested separately on each plate. The contrast threshold score for each plate was taken as the mean score of the four presentations. The total contrast threshold for the eye was the sum of scores for the six plates.

Contrast sensitivity is defined as the reciprocal of the contrast threshold, and presentation of results thus gives rise to a degree of confusion. In common with other authors who have used Arden gratings, the results here are presented as contrast threshold. Thus, the higher the score the poorer the contrast sensitivity.

Figure 12

Plate 3 of Arden gratings. Notice the sinusoidal wave pattern and the threshold scores on the side of the plate.



6.2.2.3 Hemifield spatial contrast discrimination (HFCD)

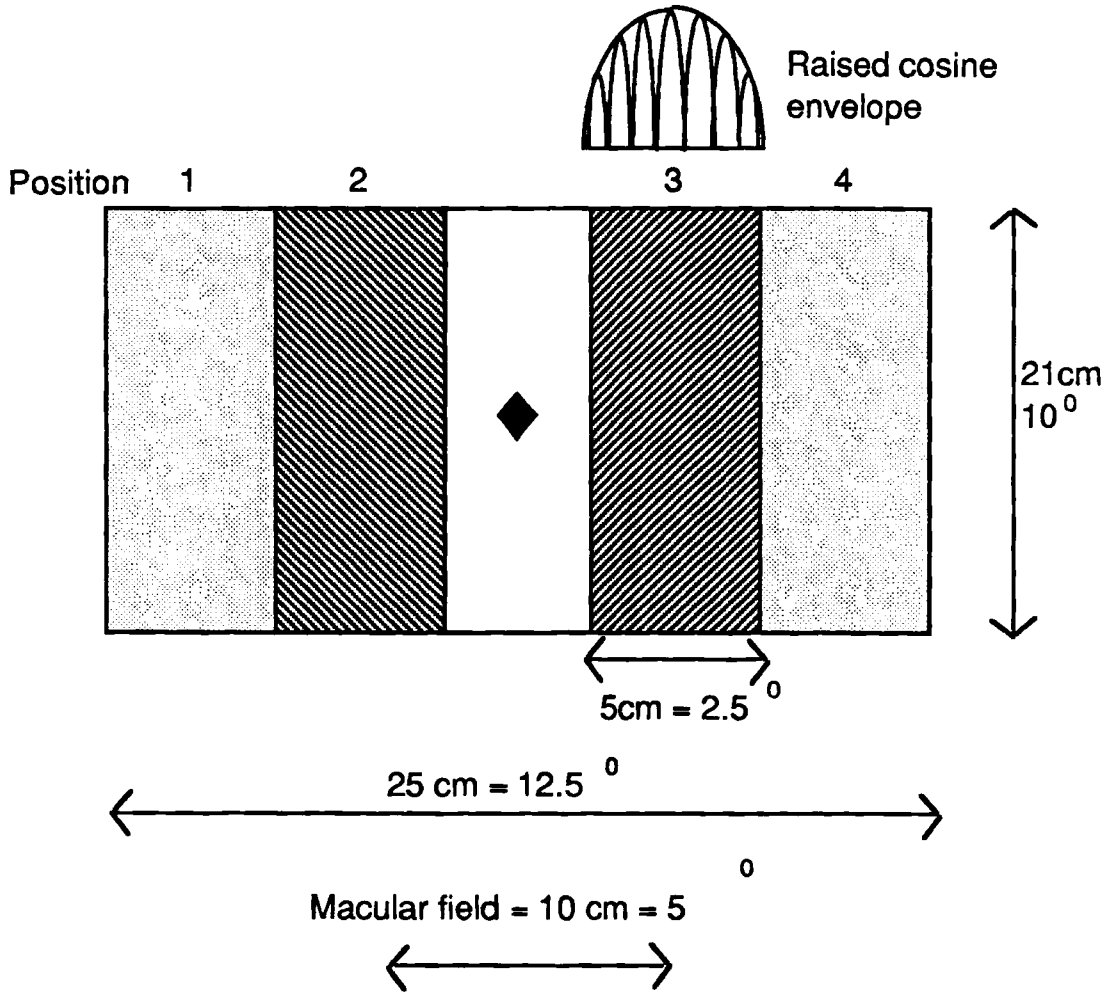
The testing of spatial contrast discrimination in each visual hemifield separately is a relatively new method for investigating visual field defects. This was accomplished by using a Grating generator (Prisma VR 1000) made by Millipede Electronic Graphics, which consists of a board fitting in an IBM computer (IBM PS/2 model 30) and appropriate software made by Dr. Arnold Wilkins of the Applied Psychology Department, Cambridge. The system generates grating patterns at various contrasts on a monochrome oscilloscope with P4 phosphor coating. The screen has a central fixation point, a red diamond of 10 mm width and 7 mm height, and the gratings are presented as vertical oblongs, subtending 10 by 2.5 degrees of visual angle, at one of four positions in the visual field (Fig 13). Positions 2 and 3 overlap the macular field, positions 1 and 4 are outside it at about 6 degrees from fixation.

The grating pattern contains vertical stripes with a sinusoidal luminance profile and a spatial frequency of 4 cycles per degree at a distance of 114 cm. The contrast varies across the pattern according to a raised cosine envelope (Fig 13), the extremes of which subtend 2.5 degrees of visual angle.

The subject was asked to fixate the central fixation point and was told to expect to see a pattern of vertical stripes in one of the four positions. The pattern was presented for 200 msec, (so that the subject did not have time to move his eyes) in each of the four positions.

Figure 13

Diagram illustrating presentation of gratings in four positions in the visual field for hemifield contrast discrimination



The pattern was presented at each position in a random order and in the following sequence of reducing contrast; 13%, 9.19%, 6.5%, 4.6%, 3.25%, 2.29%, 1.62%, 1.31% (values differ by one decibel) until the subject started making errors. At this contrast level the test measurements were started. The pattern was presented sixteen times at each position in random order, and the same procedure was then repeated at the next lower contrast, so that there were altogether 32 presentat ons at each position. The number of errors at each position was recorded.

Hemifield contrast discrimination for the right and left hemifields was measured by the total number of errors made on each side at both levels of contrast. The higher the number of errors the lower the contrast discrimination.

It is important to emphasize that this error score method does not represent the SCS obtained by the convent'onal method of recording the last contrast at which the pattern was seen, because error scores were obtained here at two contrast levels. The objective of this procedure was to look for asymmetry between the two hemifields, not to establish an abso ute measure of contrast threshold, which had already been obtained with Arden gratings. Therefore to distinguish it from spatial CS it is referred to as spatial contrast discrimination. In fact the errors made at the first contrast level were mainly at the periphery, with very few in the central macular fields, and occurred with less than 50% of the presentations. The second, lower contrast level does probably approximate to the contrast threshold. Most normal subjects started making errors at a contrast level of 3.25%, so their score represents the number of errors collected at

3.25% and 2.29%. The latter contrast was close to the contrast threshold obtained with conventional methods of CS measurement at 4 cycles/degree.

6.2.2.4 Temporal contrast sensitivity (TCS)

Temporal CS is the ability to detect minor changes in luminance of a flickering light source at various frequencies measured by using sinusoidally modulated flickering light against a background luminance equal to the mean luminance of the light source. This was accomplished by using a CH Electronics LED Photostimulator, which consists of a viewing box and a control box. The viewing part consists of a 5 mm yellow LED set in a circular background surround of white perspex, 15 cm in diameter. The control box is composed of a waveform generator, a contrast card and a frequency meter. The background luminance of the LED was set to 50 cd/m^2 and the surround was matched for luminance and colour. The LED subtends 1 degree of visual angle at a distance of 28 cm, and the surround 30 degrees.

The control box was used to control the frequency and also the contrast, i.e the sinusoidal variation in luminance of the LED. A multiturn potentiometer with a digital readout knob was used to modulate the luminance and was calibrated in 0.1% increments.

The subject was instructed to look at the LED while the contrast was slowly increased, and to indicate as soon as flickering was perceived. The procedure was repeated several times until the subject had gained some experience in recognising the flicker at different frequencies. Four frequencies were chosen, 3.3 Hz, 10 Hz, 20 Hz and 30 Hz to represent the low, medium, intermediate and high frequency ranges. The patient was presented with these frequencies in ascending order. Modulation was set to zero and was increased gradually until the the subject

saw the flicker. Four trials were performed at each frequency and the mean of the four contrast threshold readings was taken as the contrast threshold for that frequency. The contrast threshold (CT) at each frequency was obtained for each eye separately. As with spatial CS, the results for temporal CS are presented as threshold values, so the higher the threshold value the lower the CS.

6.2.3 Statistical analysis

Statistical analysis was performed with the Macintosh statistical programmes (Statwork, Statv ew SE and Extatix) and with the Maxitab on an IBM computer. Analysis of the data was done with the help of Mr. Aber and Mr Alexander of the Department of Medical Physics, RPMS. The differences between sets of data from migraine and control subjects were tested for significance by the unpaired t-test. The effects on the results of various factors in the migraine group were tested with analysis of variance, chi-square, Fisher's exact test, McNemar's test and simple and multiple regression analysis

CHAPTER 7 RESULTS

7.1 Analysis of migraine and control subjects:

Migraine patients were age- and sex-matched with normal controls. There were 92 migraine patients, with an age range of 16-59 years (mean±SD 40±13) , 72 females (78%) and 20 males (22%). There were 62 normal controls, age range 17-58 years, (mean±SD 37±13), 44 females (71%) and 18 males (29%). 37 patients (40%) had common migraine (migraine without aura), 47 (51%) had classical migraine (migraine with aura) and 8 (9%) had mixed classical and common migraine.

34 patients (37%) said that their attacks were triggered by visual stimuli, and 14 (15%) said they were triggered by other stimuli e.g stress, strong smells, alcoholic drinks etc. 39 (42%) said that their attacks were triggered by both visual and non visual stimuli and 5 (5%) said there were no clear triggering factors.

The proportion of classical migraine cases and the number of patients with attacks triggered by visual stimuli are both higher than in the general migraine population, and this was a deliberate emphasis when volunteer patients were being sought for the study.

The duration of migraine ranged from 0.12 to 55 years (mean±SD 18.49 ±14.80 years). The frequency of attacks varied from several times a week to several times a year.

With respect to the side of the headache patients fell into four groups. 30 patients (33%) had headache consistently on the

right, 16 (17%) had headache consistently on the left, 30 (33%) bilateral and 16 (17%) inconsistent. The same grouping was applied with respect to the visual aura in classical migraine. 11 (23%) had aura consistently on the right, 12 (26%) on the left, 14 (30%) bilateral and 10 (21%) inconsistent.

The data will be presented in two steps:

1. The results of a direct comparison between migraine and control subjects with respect to the electrophysiological and psychophysical data. These data were analysed for right and left eyes separately, and are presented in tables as the mean and standard deviation for each investigation, and number of subjects studied by each test together with the t and p values.

2. The effect of various factors in the migraine group on those responses which were significantly different from control subjects. These factors include: age, sex, type of migraine, triggering factors, duration of migraine, lateralisation of headache and aura and effect of treatment. Here the values used were an average of values from right and left eyes since there was no significant difference between the values of the right and left eyes.

Significant values in the tables are marked with an asterisk, and the error bars in the figures represent one standard deviation.

7.2 Test results for migraine and control subjects:

7.2.1 Electrophysiological tests

7.2.1.1 Electroretinogram (ERG)

The pattern ERG recorded with skin electrodes consisted of one positive (α) and one negative (β) wave, with similar morphology in the control and migraine subjects. The flash ERG recorded in this manner also consisted of two waves, a and b (Fig 14). The subcomponents of the a and b waves, representing the contribution of the photopic and scotopic systems, cannot be recorded clearly using this technique. As mentioned under methods (section 6.2.1.3.1) the pattern ERG was collected by two different procedures. Results from those control and migraine subjects who were studied early on with a 2-step procedure were not used for analysis, and the comparison between the two groups is based on those subjects who were studied with the 4-step procedure. This consisted of 71 migraineurs and 52 controls.

Table 1a shows no significant difference in latency or amplitude of α and β waves in the pattern ERG, and table 1b shows the same for the flash ERG.

Figure 14

Example of a pattern and a flash ERG in a normal subject.

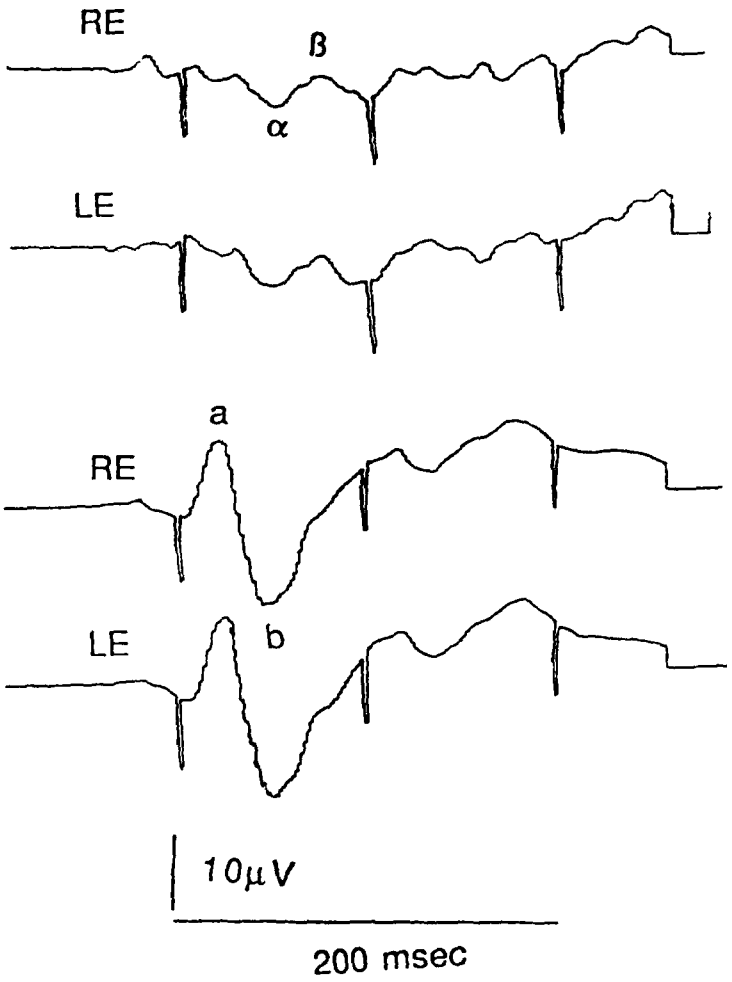


Table 1

a) Pattern ERG latency (L) in msec and amplitude (A) in μV in migraine and control subjects

			Controls (52)	M'graine (71)		
		Wave	M ± SD	M ± SD	t	p
L	RE	α	72.6 ± 4.5	74.1 ± 5.7	1.53	0.127
		β	98.2 ± 5.3	97.2 ± 6.2	0.56	0.578
	LE	α	73.2 ± 4.3	74.3 ± 5.8	1.18	0.240
		β	99.3 ± 5.4	98.2 ± 6.1	0.23	0.222
A	RE	α	4.2 ± 1.3	4.3 ±1.43	0.37	0.708
		β	5.3 ± 1.9	5.4 ± 1.67	0.56	0.577
	LE	α	4.15 ± 1.4	4.38 ± 1.4	1.18	0.239
		β	5.64 ± 2.1	5.35 ± 1.5	0.71	0.478

b) Flash ERG latency (L) in msec and amplitude (A) in μV in migraine and control subjects

			Controls (62)	Migraine (92)		
		Wave	M ± SD	M ± SD	t	p
L	RE	a	22.6 ± 1.9	22.7 ± 1.8	0.28	0.782
		b	48.9 ± 6.7	48.8 ± 5.2	0.09	0.926
	LE	a	23.7 ± 5.9	22.9 ± 1.9	1.09	0.276
		b	49.4 ± 5.7	49.0 ± 5.3	0.34	0.735
A	RE	a	9.4 ± 2.9	9.32 ± 3.4	0.14	0.893
		b	29.7 ± 11.7	27.2 ± 9.1	1.45	0.151
	LE	a	9.4 ± 2.8	9.9 ± 5.4	0.72	0.474
		b	30.0 ± 12.5	27.6 ± 9.9	1.28	0.203

RE= right eye, LE= left eye

7.2.1.2 Pattern-reversal VEP (PRVEP)

The pattern reversal VEP were recorded on 6 channels representing the R10, R5, Oz, L5, L10 and Pz positions, all referred to Fz. Recordings were made at Pz because the anatomy of the visual cortex is variable and sometimes the responses are clearer at Pz than at Oz (Chiappa 1989).

Full field stimulation with binocular viewing was performed first, then full field with monocular viewing, followed by half-field presentation to each eye separately.

The typical responses for binocular and monocular viewing consisted of a triphasic wave NPN recorded at Oz, with similar responses at lower amplitude at R5 and L5, and at even lower amplitude at L10 and R10 (Fig 9).

Half-field stimulation produced an NPN response at Oz and at the 5 cm position ipsilateral to the stimulus, and a PNP response at 5 cm, and more clearly at 10 cm, contralateral to the stimulus (Fig 15).

The most consistently recorded component was the P100 wave, so its latency and amplitude at R5, Oz and L5 positions were recorded for binocular and monocular presentation. For the half-field responses the latency and amplitude of the ipsilateral P100 were measured at the ipsilateral electrode 5 cm from the midline.

The binocular and half-field responses were of slightly shorter latency than the monocular responses. The binocular responses were of slightly smaller amplitude and less well formed than the monocular responses, and sometimes the

binocular P100 had two distinct peaks, the so-called "W-shape" pattern. For these reasons the binocular responses have been used only in the preliminary comparison between migraine and control subjects in this section (7.2) and not for the later analysis (section 7.3).

The P100 latency of the monocular PRVEP was significantly longer in the migraine group as a whole than in normal controls at all recorded positions, i.e at Oz, R5 and L5, and for both eyes (Table 2a). The mean P100 amplitude of the monocular pattern response was slightly greater in the total migraine group than in controls, especially at Oz, but the difference was not significant at any position (Table 2b).

The mean P100 latency of the binocular PRVEP was significantly greater in migraineurs than controls at all positions, and the difference was of the same order as that for P100 latency of the monocular PRVEP. P100 amplitude was not significantly different at any position (Table 3). Similar results were found for the ipsilateral P100 latency and amplitude of the half-field PRVEP (Table 4).

Figure 15

Example of left half-field pattern-reversal VEP showing the NPN pattern at L5 ipsilateral to the stimulated field and the PNP at R10 contralateral to it.

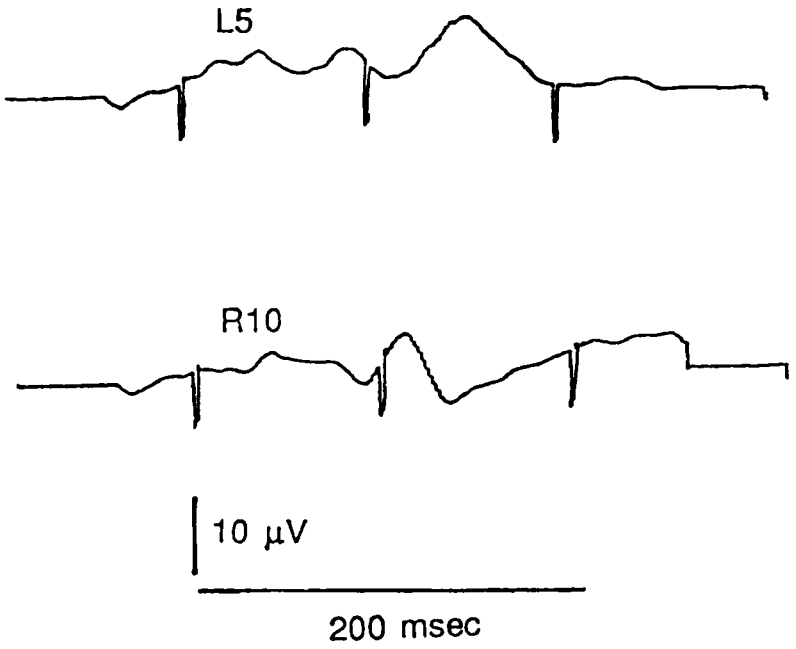


Table 2

a) Monocular wholefield pattern-reversal VEPs in migraine and control subjects

a) Latency (msec)

		Controls (62)	Migraine (92)		
	Position	M ± SD	M ± SD	t	p
RE	Oz	112.1 ± 5.6	117.9 ± 5.4	6.51	0.000*
	R5	112.5 ± 5.7	118.1 ± 5.6	5.19	0.001*
	L5	112.5 ± 6.7	118.5 ± 5.8	6.35	0.000*
LE	Oz	113.1 ± 5.5	118.8 ± 5.3	6.53	0.000*
	R5	113.3 ± 5.5	119.1 ± 5.5	6.40	0.000*
	L5	113.3 ± 5.5	119.0 ± 5.6	6.46	0.000*

b) P100 amplitude (μV)

		Controls (62)	Migraine (92)		
	Position	M ± SD	M ± SD	t	p
RE	Oz	15.4 ± 4.9	17.0 ± 5.6	1.82	0.071
	R5	11.6 ± 4.5	11.5 ± 4.5	0.02	0.983
	L5	10.4 ±4.0	11.4 ± 4.6	1.42	0.157
LE	Oz	14.9 ± 5.1	16.5 ± 5.3	1.39	0.056
	R5	11.3 ± 4.8	11.7 ± 4.6	0.58	0.561
	L5	10.4 ± 3.9	11.5 ± 4.9	1.46	0.146

Table 3

P100 latency (L) in msec and amplitude (A) in μV of the binocular PRVEP in migraine and control subjects

		Controls (62)	Migraine (92)		
	Position	M ± SD	M ± SD	t	p
L	Oz	110.5 ± 5 8	115.2 ± 5.6	5.08	0.000*
	R5	110.9 ± 5.9	116.5 ± 5.7	5.94	0.000*
	L5	110.9 ± 6 0	116.9 ± 6.1	6.08	0.000*
A	Oz	15.4 ± 4.6	16.1 ± 5.9	0.76	0.463
	R5	11.7 ± 4.5	11.9 ± 4.6	0.23	0.820
	L5	10.8 ± 3.9	11.8 ± 4.8	1.38	4.792

Table 4

Ipsilateral P100 Latency (L) in msec and amplitude (A) in μV of the half field PRVEP in migraine and control subjects

			Controls (62)	Migraine (92)		
		Position	M ± SD	M ± SD	t	p
L	RE	RHF	112.1 ± 5.8	117.3 ± 5.2	5.82	0.000*
		LHF	112.3 ± 5.6	117.1 ± 5.6	5.30	0.000*
	LE	RHF	112.5 ± 5.7	117.4 ± 5.3	5.45	0.000*
		LHF	111.9 ± 5.6	117.2 ± 5.3	5.81	0.000*
A	RE	RHF	8.2 ± 3.1	7.8 ± 2.84	0.71	0.480
		LHF	7.9 ± 3.1	8.1 ± 3.3	1.14	0.254
	LE	RHF	7.5 ± 3.1	7.9 ± 3.3	0.15	0.883
		LHF	7.4 ± 3.2	7.7 ± 3.1	0.44	0.662

RE= right eye LE= left eye
RHF= right half f'eld LHF= left half field

7.2.1.3 Single flash VEP (SFVEP)

The flash responses, unlike the pattern responses, show much variability of the waveforms in both groups of subjects.

The SFVEP were recorded from electrodes located at Oz, R5, L5, Pz, Cz and Fz positions referred to linked ears. With recording from the occipital region, the results showed several waves in most cases (Fig 16a), predominantly two major positive waves alternating with three negative waves. The most consistent waves were the two positive waves recorded at Oz, R5 and L5, called P1 and P2. With recording over the vertex, at Cz, the responses had different morphology. Instead of the major second positive wave (P2) seen at the back of the head there was a major negative wave which came at a different latency from P2. Accordingly the only waves considered for measurements and comparison between migraine and control subjects were the P1 and P2 waves of the occipital responses and the P1 and N2 waves at Cz, and in some cases even these waves were not clear. In others the whole morphology was different and it was difficult to identify any consistent waveform. Figure 16b illustrates some examples of these difficulties. In such cases the flash responses could not be used for analysis. The proportion of such cases was similar in migraine and control subjects, and the number of cases used from each group are shown in brackets in tables 5a and 5b.

The occipital and vertex flash responses can both be seen at Pz, where they form a composite pattern (Fig 17). This indicates that they have separate origins, and are not simply two manifestations of the same response.

Table 5a shows the latencies of the two components of the

occipital responses, P1 and P2, and the P1 and N2 of the vertex responses. The amplitudes are presented in table 5b.

Posteriorly, P1 latency was significantly longer in migraine subjects but only at the Oz position. P2 latency was significantly longer at all positions. The increase of P2 latency was comparable to the prolongation of P100 latency of the PRVEP. The mean P1 and P2 amplitudes of SFVEP were higher than controls at several positions but the difference did not reach significance at any (Table 5b).

The P1 and N2 latencies and amplitudes of the vertex responses were not significantly different between the two groups (Table 5a and 5b).

Figure 16

Examples of single flash VEP recorded at the occipital region a) typical morphology b) different morphologies..

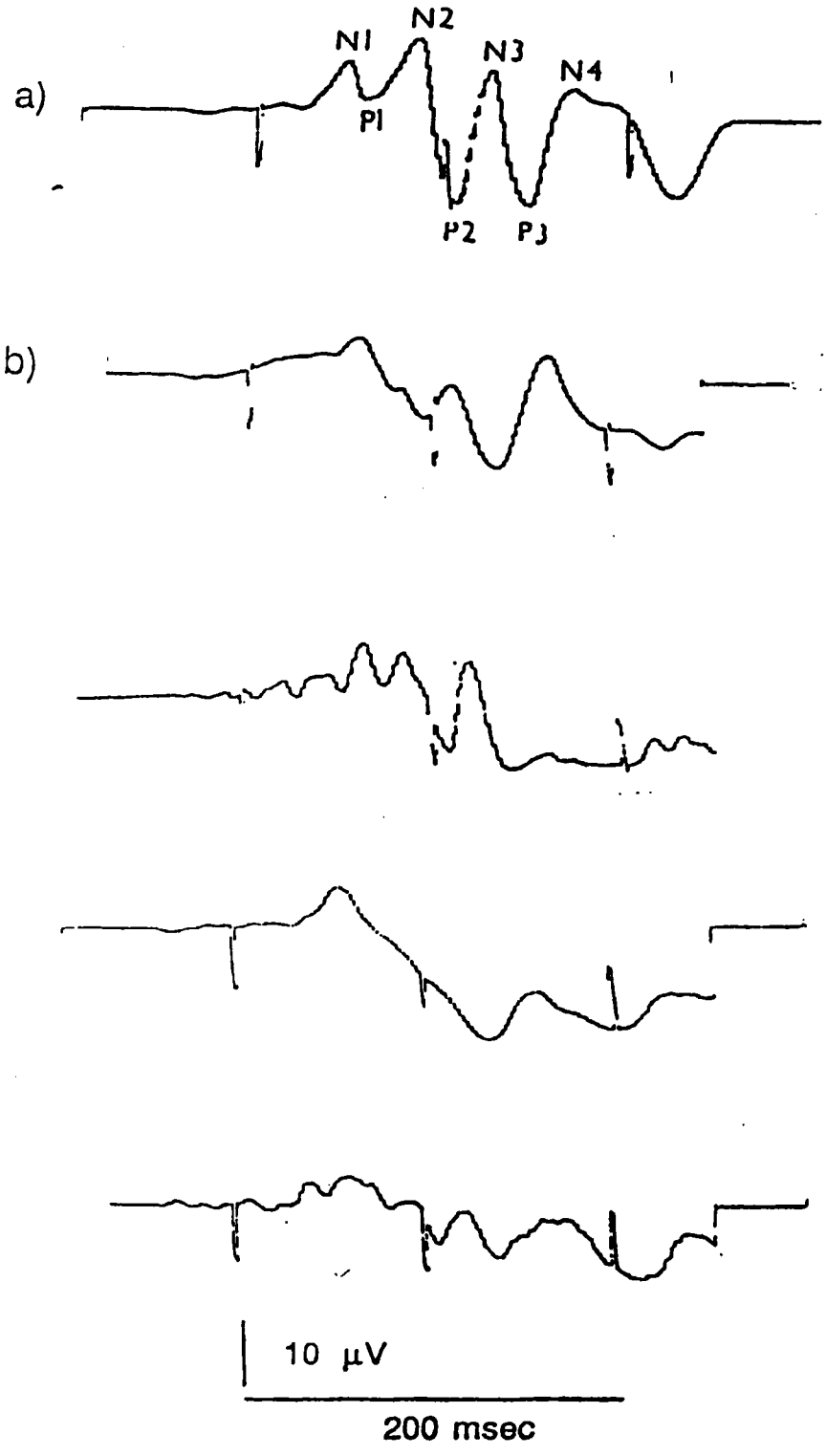


Figure 17

Example of single flash VEP showing different morphologies of the occipital (Oz) and vertex (Cz) flash responses with overlap of these responses at Pz position. The response at Fz is similar to that at Cz.

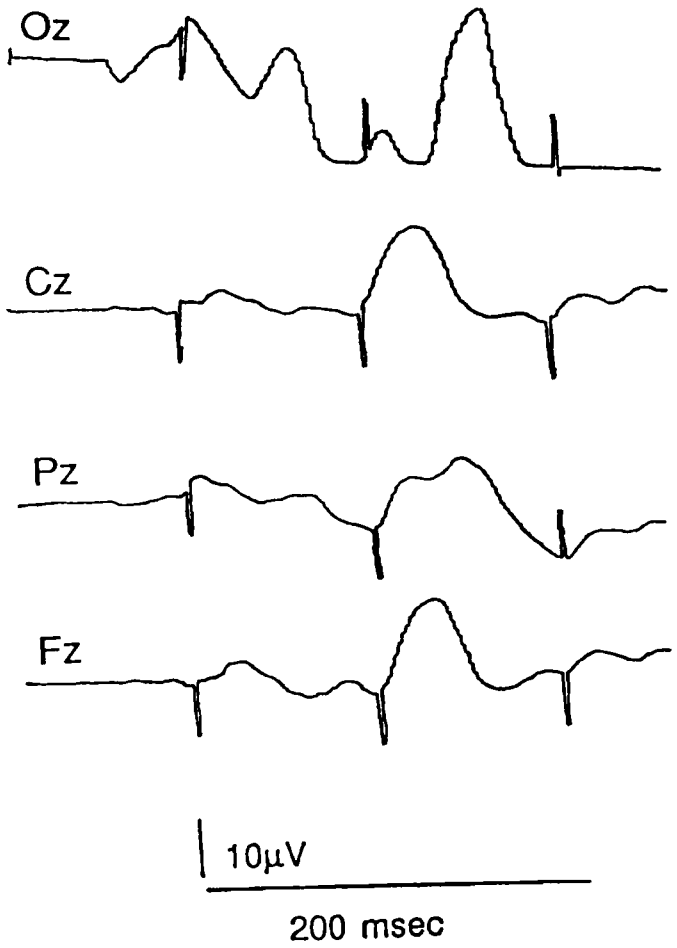


Table 5

Single flash VEP in migraine and control subjects (numbers in brackets).

a) Latency (msec)

		Controls	Migraine		
Position	Wave	M ± SD (n)	M ± SD (n)	t	p
Oz	P1	71.6 ±10.7 (51)	76.2±10.2 (75)	2.45	0.016*
	P2	124.8 ± 10.0 (56)	129.6 ± 10.3 (89)	2.79	0.006*
R5	P1	72.1 ± 11.81 (49)	75.9 ± 9.9 (72)	1.89	0.061*
	P2	125.4 ± 10.0 (54)	129.6 ± 9.9 (88)	2.44	0.016*
L5	P1	73.1 ± 11.53 (50)	75.9 ± 10.05 (71)	1.34	0.183
	P2	125.0 ± 9.9 (55)	130.0 ± 10.3 (88)	2.88	0.005*
Cz	P1	74.5± 11.91 (41)	77.1 ± 12.9 (64)	1.017	0.312
	N2	120.4 ± 11.1 (49)	121.4 ± 10.2 (81)	0.505	0.614

b) Amplitude (μV)

		Controls	Migraine		
Position	Wave	M ± SD (n)	M ± SD (n)	t value	p value
Oz	P1	6.9 ± 5.9 (49)	7.6 ± 4.6 (75)	0.79	0.434
	P2	13.8 ± 6.3 (54)	14.0 ± 6.9 (89)	0.176	0.861
R5	P1	5.5 ± 4.81 (49)	5.3 ± 3.5 (73)	0.279	0.781
	P2	10.7 ± 5.1 (53)	11.2 ± 5.8 (87)	0.450	0.654
L5	P1	5.6 ± 4 47 (48)	5.5 ± 3.5 (71)	0.092	0.927
	P2	10.6 ± 5.1 (53)	11.2 ± 5.8 (88)	0.596	0.559
Cz	P1	5.6 ± 3.5 (41)	5 6 ± 3.3 (65)	0.015	0.988
	N2	11.7 ± 5.0 (48)	10.3 ± 4.72 (80	1.522	0.130

7.2.1.4 Repetitive flash VEP (RFVEP)

These responses were recorded with four channels representing the R5, Oz, L5 and Cz positions referred to linked ears, at frequencies of 4, 6, 7, 8, 9, 10, 11, 12, 14, 16, 18, 20, 22 and 24 Hz. One patient, who had a high P100 amplitude and a lot of illusions, could not tolerate the test. Otherwise all patients and controls were tested with eyes closed. 74 migraineurs and 49 controls were also tested with eyes open, but this test was discontinued when a preliminary analysis showed that it was less specific in separating migraineurs from controls.

The response at 4 Hz was excluded (see section 6.2.1.3.4). The mean amplitude of responses at the 13 flash frequencies at the Oz position are shown for both migraine and control subjects with eyes closed (Fig 18) and eyes open (Fig 19) The amplitude of response was highest in the alpha frequency range, especially at 10 Hz, and it declined with higher frequencies. However, the decline in migraine subjects was less than in normal controls, and there was a considerable separation between the two groups for amplitudes at 18-20 Hz with the eyes closed. The responses at the Cz position, whether with eyes closed (Fig 20) or eyes open (Fig 21) did not follow the same pattern. They did not diminish as much as the posterior flash responses with increasing flash frequencies.

The mean amplitudes at Oz with the eyes closed (Table 6a) were greater in the migraine subjects at all flash frequencies from 6 Hz to 24 Hz. However, the differences were significant only at 6 Hz, 18 Hz and 20 Hz. With eyes open (Table 6b) the

amplitudes were also higher at all frequencies except at 12 Hz and 16 Hz but the differences were not significant at any position.

The response amplitudes at Cz were smaller than those at Oz and there were no significant differences between the two groups at any flash frequency with eyes closed (Table 7a) or eyes open (Table 7b). This finding is comparable to those for single flash responses i.e there was no difference between the groups in responses recorded at Cz for either single or repetitive flash stimuli.

In view of the inherent variability of the repetitive flash responses Golla and Winter (1956) introduced the concept of the "H-response" for direct comparison of repetitive flash responses between migraine and control subjects. They defined the H-response by relating the amplitude of the responses at 18 Hz to the peak amplitude in the alpha frequency range and the smallest amplitude between these two peaks. This comparison was expressed as two ratios; the ratio of the amplitude at 18 Hz to the peak amplitude in the alpha frequency range, and ratio of the smallest amplitude between these two peaks to the amplitude at 18 Hz. They defined the H-response as present when the first ratio was equal to or greater than 1/3 and the second ratio was equal to or greater than 1/2. For the present study these criteria were slightly modified. For both ratios the highest amplitude at either 18 or 20 Hz was taken, instead of invariably that at 18 Hz, because sometimes the response at 20 Hz is greater than that at 18 Hz, and for the first ratio the criterion taken was a figure of 1/2 instead of 1/3, in order to enhance the specificity of the

test. Thus, the criteria of the H-response were defined as follow:

$$\frac{\text{Highest amplitude at 18 or 20 Hz}}{\text{Highest amplitude in the alpha frequency range}} \geq 0.5$$

$$\frac{\text{Smallest amplitude between the above two}}{\text{Highest amplitude at 18 or 20 Hz}} \geq 0.5$$

When the RFVEP was elicited with eyes closed there was a significantly higher prevalence of H-response n the migraine group (77%) than the control group (13%) as shown in table 8. In the migraine group the prevalence was somewhat greater with eyes open than with eyes closed (85% compared w th 77%), but in controls the prevalence was much greater (53% compared with 13%). The difference between the two groups was thus less significant with eyes open than with eyes closed (Table 8). This means that the H-response test separates migraine from control subjects best with the eyes closed. Figures 22 and 23 show an example of repetitive flash VEP in a control and a migraine subject with eyes closed and figures 24 and 25 with eyes open.

In all patients in whom the first ratio was greater than 0.5 the second ratio was always greater than 0.5 too. Since the responses in the alpha frequency range were normal, this means that the increased amplitude at 18/20 Hz is the crucial point of the H-response.

Table 6

Comparison of repetitive flash response amplitudes (μV) at various frequencies in migraine (m) and control (c) subjects recorded at Oz position with a) eyes closed and b) eyes open.

Controls n = 62
Migraine n = 91

a)	6Hz	7Hz	8Hz	9Hz
M±SD (c)	18.2 ± 7.9	20.3 ± 8.1	20.8 ± 9.9	25.0 ± 13.9
M±SD (m)	22.8 ± 11.5	20.6 ± 9 3	22.8 ±13.7	25.5 ± 12.7
t	2.78	0.47	1.00	0.42
p	0.006*	0.639	0.320	0.676
	10Hz	11Hz	12Hz	14Hz
M±SD (c)	27.6 ± 14.9	21.5 ± 12.1	17.2 ± 9.06	12.9 ± 6 4
M±SD (m)	28.3 ± 13.5	24.4 ± 13.5	20 0 ± 11.98	15.2 ± 7.4
t	0.28	1.38	1.61	1.80
p	0.777	0.169	0.110	0.074
	16Hz	18Hz	20Hz	22Hz
M±SD (c)	11.8 ± 6.2	10.75±6.10	9.7 ± 6.6	9.1 ± 5.6
M±SD (m)	13.6 ±7.1	13.39±6.97	12.7 ±8.7	10.4 ±6.0
t	1.69	2.23	2.29	1.60
p	0.093	0.027*	0.023*	0.111
	24Hz			
M±SD (c)	8.6 ± 5.9			
M±SD (m)	10.2 ± 6.7			
t	1.50			
p	0.128			

Controls n = 49
Migraine n = 74

b)	6Hz	7Hz	8Hz	9Hz
M±SD (c)	22.7 ± 11.5	24.6 ± 12.3	24.5 ± 12.1	24.0 ± 13.2
M±SD (m)	23.6 ± 10.4	26.4 ± 10.5	25.6 ±11.0	25.6 ±10.1
t	0.15	0.91	0.52	0.75
p	0.884	8.366	0.603	0.453
	10Hz	11Hz	12Hz	14Hz
M±SD (c)	22.6 ± 9.9	20.6 ± 9.4	19.6 ± 10.1	17.1 ± 8.8
M±SD (m)	25.4 ± 10.7	22.9 ± 11.3	18.6 ± 8.9	17.9 ± 7.9
t	1.45	1.22	0.56	0.50
p	0.149	0.226	0.578	0.619
	16Hz	18Hz	20Hz	22Hz
M±SD (c)	17.8 ± 8.9	15.9 ± 7.6	15.3 ± 7.8	12.8 ± 6.8
M±SD (m)	16.9 ± 8.2	16.9 ± 8.2	16.1 ± 8.1	14.6 ± 6.3
t	0.54	0.68	0.54	1.43
p	0.587	0.498	0.590	0.154
	24Hz			
M±SD (c)	12.7 ± 7 2			
M±SD (m)	13.4 ± 6.9			
t	0.54			
p	0.591			

Table 7

Comparison of repetitive flash response amplitudes (μV) at various frequencies in migraine (m) and control (c) subjects recorded at Cz position with a) eyes closed and b) eyes open.

Controls n = 62
Migraine n = 91

a)

	6Hz	7Hz	8Hz	9Hz
M±SD (c)	15.2 ± 6.5	16.7 ± 7.3	16.6 ± 7.7	17.5 ± 8.6
M±SD (m)	16.3 ± 7.6	17.2 ±7.7	16.7 ± 8.4	18.5 ± 8.6
t	0.94	0.41	0.06	0.74
p	0.349	0.684	0.956	0.461
	10Hz	11Hz	12Hz	14Hz
M±SD (c)	19.4 ± 10.2	15.3 ± 7.4	12.9 ± 6.4	12.5 ± 6.0
M±SD (m)	19.8 ± 9.7	17.2 ± 7.9	14.6 ± 6.5	12.9 ± 6.7
t	0.06	1.49	1.65	0.43
p	0.955	0.148	0.101	0.666
	16Hz	18Hz	20Hz	22Hz
M±SD (c)	10.3 ± 5.5	9.3 ± 5.0	8.6 ± 4.9	8.2 ± 4.8
M±SD (m)	11.9 ± 6.2	9.9 ± 3.9	9.4 ± 4.1	8.6 ± 5.0
t	1.65	0.80	1.16	0.50
p	0.101	0.424	0.247	0.621
	24Hz			
M±SD (c)	7.8 ± 4.4			
M±SD (m)	8.6 ± 6.3			
t	0.88			
p	8.382			

Controls n = 49
Migraine n = 74

b)

	6Hz	7Hz	8Hz	9Hz
M±SD (m)	17.3 ± 10.3	17.7 ± 7.3	18.2 ± 8.0	18.1 ± 8.2
M±SD (c)	15.5 ± 8.5	16.3 ± 6.8	16.8 ± 6.9	17.4 ± 7.3
t	1.04	1.12	1.04	1.53
p	0.299	1.265	0.301	0.600
	10Hz	11Hz	12Hz	14Hz
M±SD (c)	18.8 ± 8.4	15.0 ± 7.1	14.3 ± 6.5	13.5 ± 7.2
M±SD (m)	18.4 ± 7.8	17.4 ± 6.9	14.5 ± 5.9	13.2 ± 4.9
t	0.25	1.82	0.17	0.29
p	0.803	0.071	0.864	0.769
	16Hz	18Hz	20Hz	22Hz
M±SD (c)	13.5 ± 9.0	11.8 ± 5.1	10.6 ± 5.9	8.8 ± 3.9
M±SD (m)	12.9 ± 5.6	11.6 ± 4.7	10.6 ± 5.6	10.3 ± 5.1
t	0.20	0.15	0.05	-1.72
p	0.841	0.880	0.964	0.087
	24Hz			
M±SD (c)	8.4 ± 4.7			
M±SD (m)	10.2 ± 5.4			
t	1.92			
p	0.058			

Table 8

Prevalence of the H-response of RFVEP in migraine and control subjects.

	Eyes Closed					Eyes Open				
	H	n	%	X^2	p	H	n	%	X^2	p
Controls	8	62	13	60.03	0.000	26	49	53	13.6	0.000
Migraine	71	91	77			63	74	85		

Figure 18

Amplitudes of the repetitive flash VEP in migraine and control subjects recorded at Oz at various flash frequencies with the eyes closed (n = M 91, C 62)

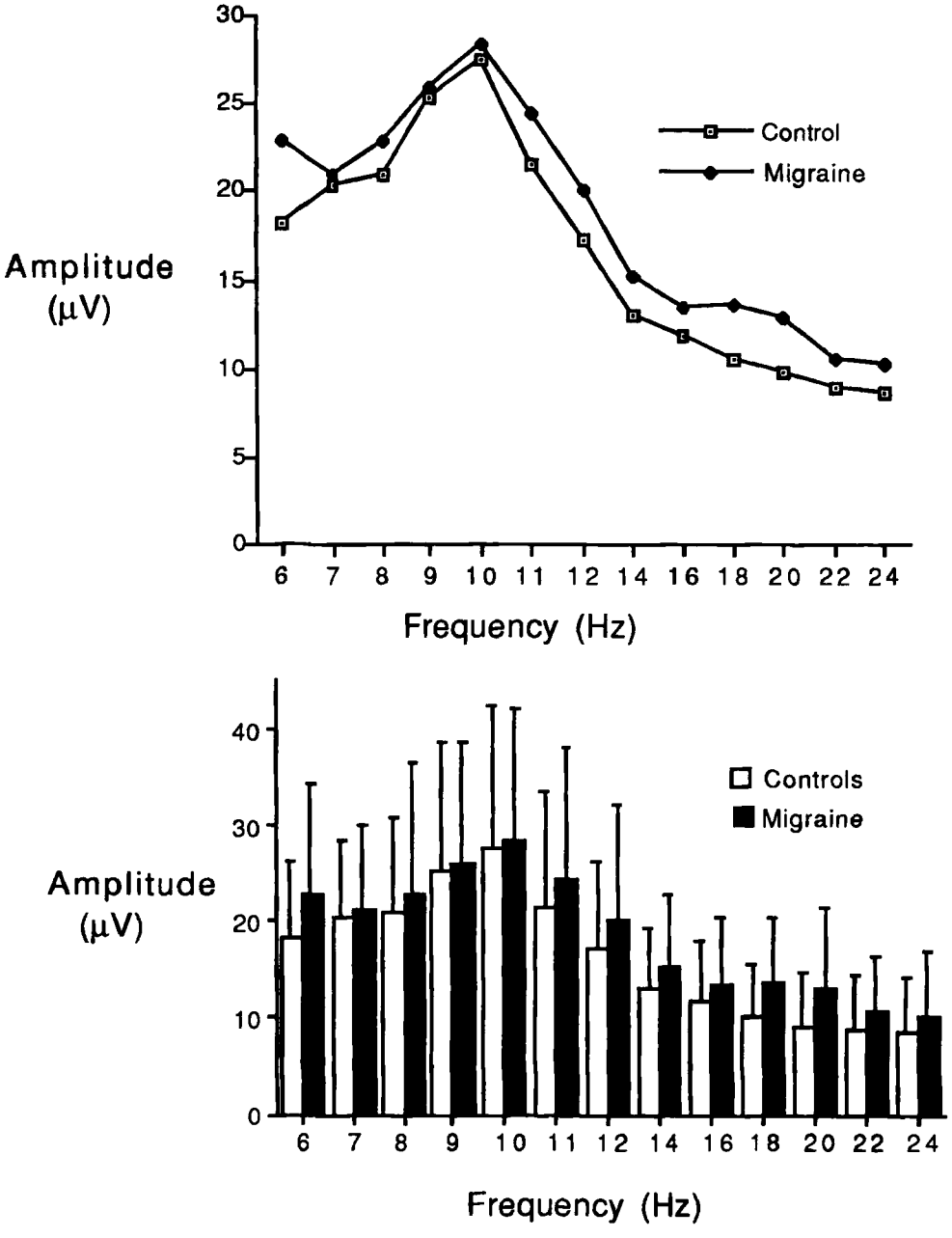
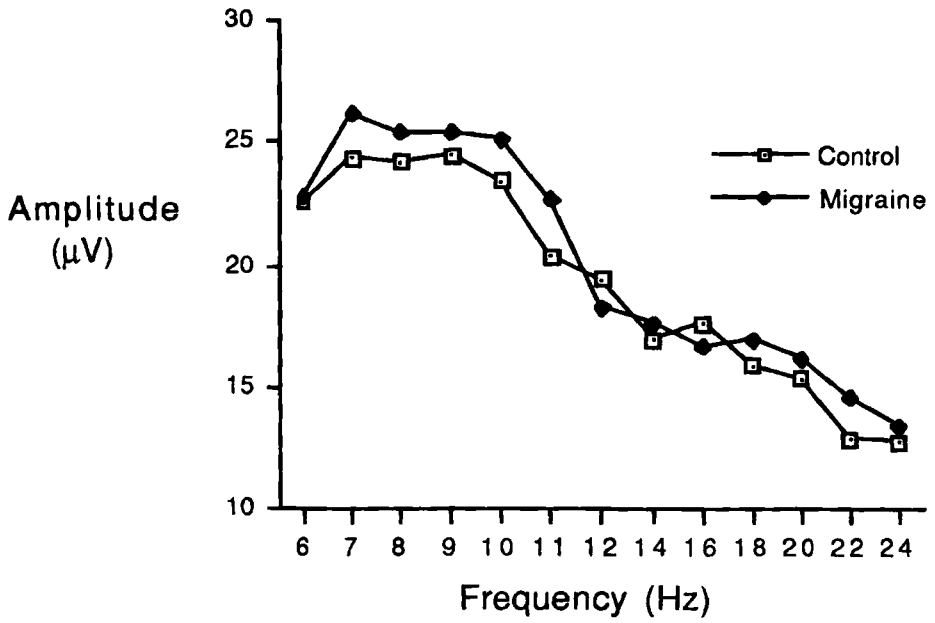


Figure 19

Amplitudes of the repetitive flash VEP in migraine and control subjects recorded at Oz at various flash frequencies with the eyes open (n = M 74, C 49)



□Control

Figure 20

Amplitudes of the repetitive flash VEP in migraine and control subjects recorded at Cz at various flash frequencies with the eyes closed (n= M 91, C 62)

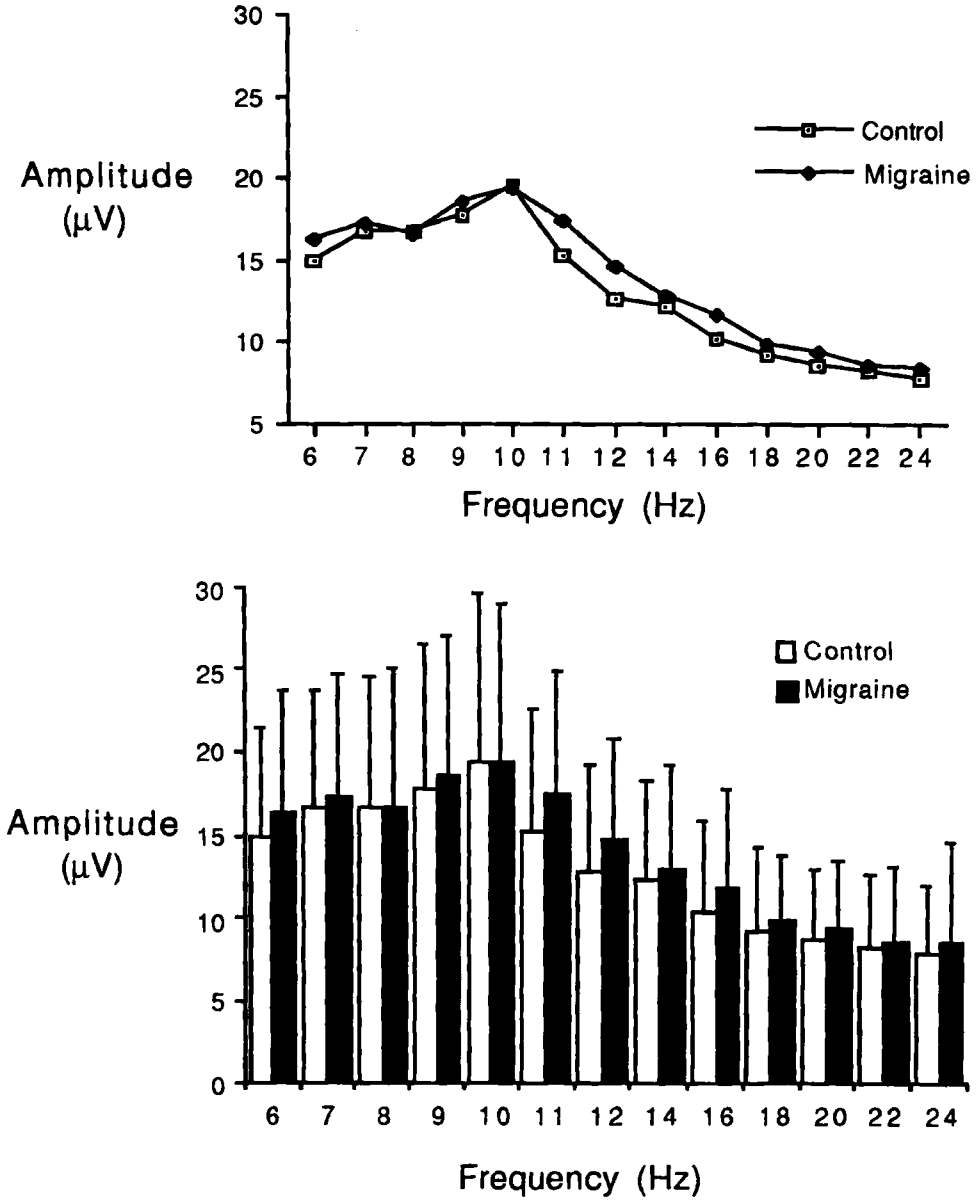


Figure 21

Amplitudes of the repetitive flash VEP in migraine and control subjects recorded at Cz position at various flash frequencies with the eyes open (n= M 74, C 49)

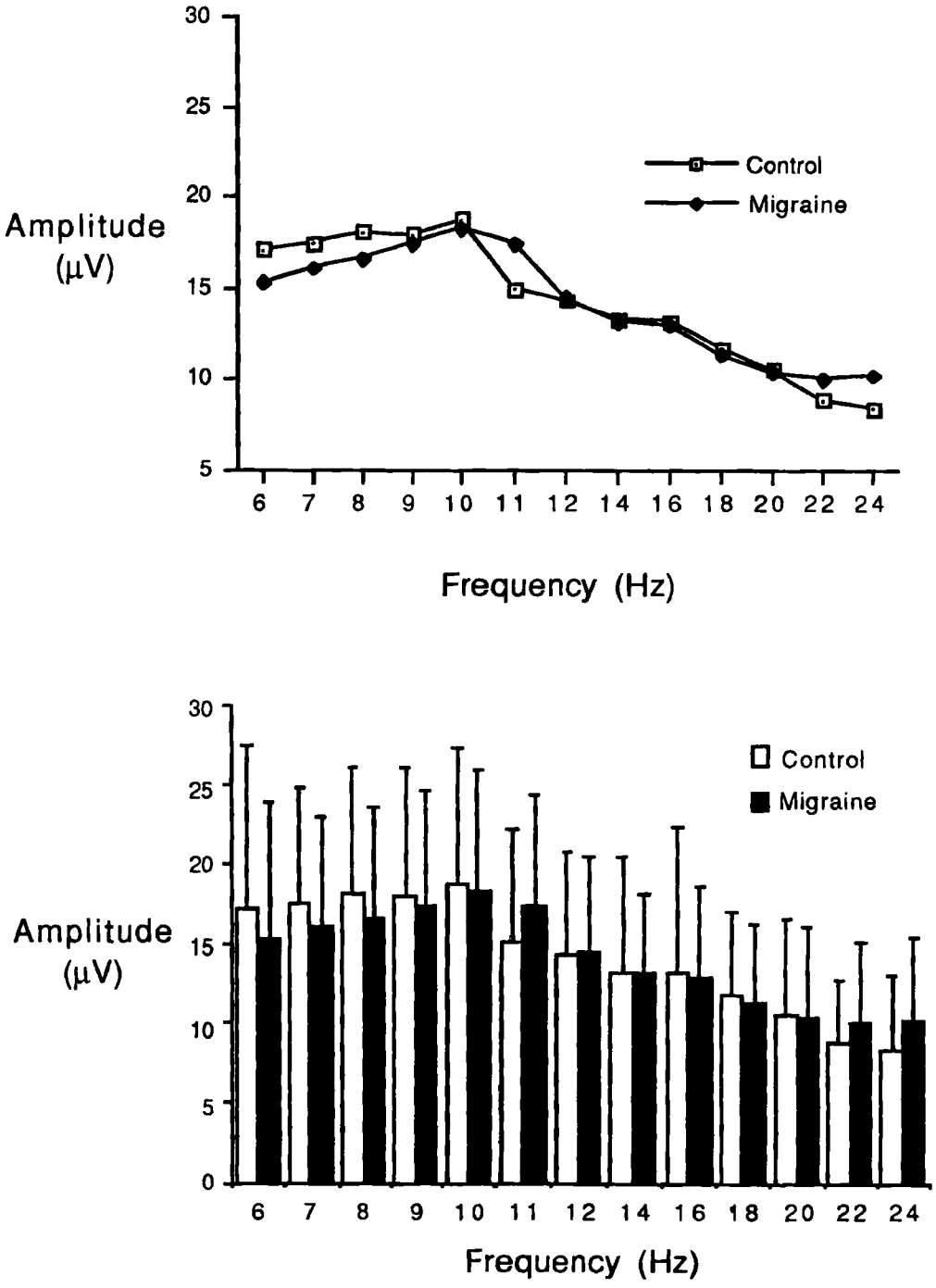


Figure 22

Example of repetitive flash VEP in a control subject with eyes closed. Notice the attenuation of responses at 20 Hz and the different morphologies of the occipital (Oz, R5, L5) and vertex (Cz) responses.

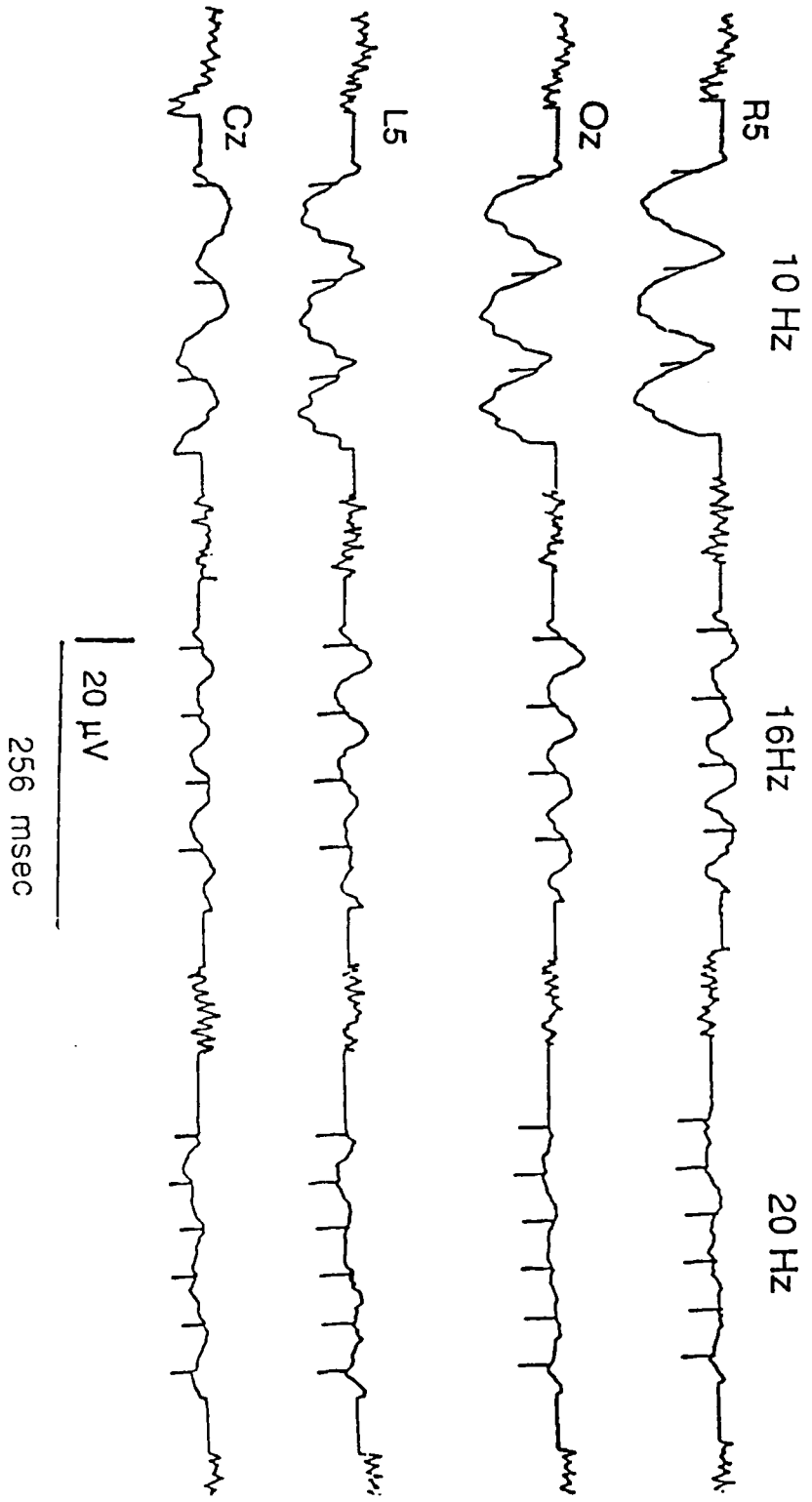


Figure 23

Example of repetitive flash VEP in a migraineur with eyes closed. Notice high amplitude responses at 20Hz.

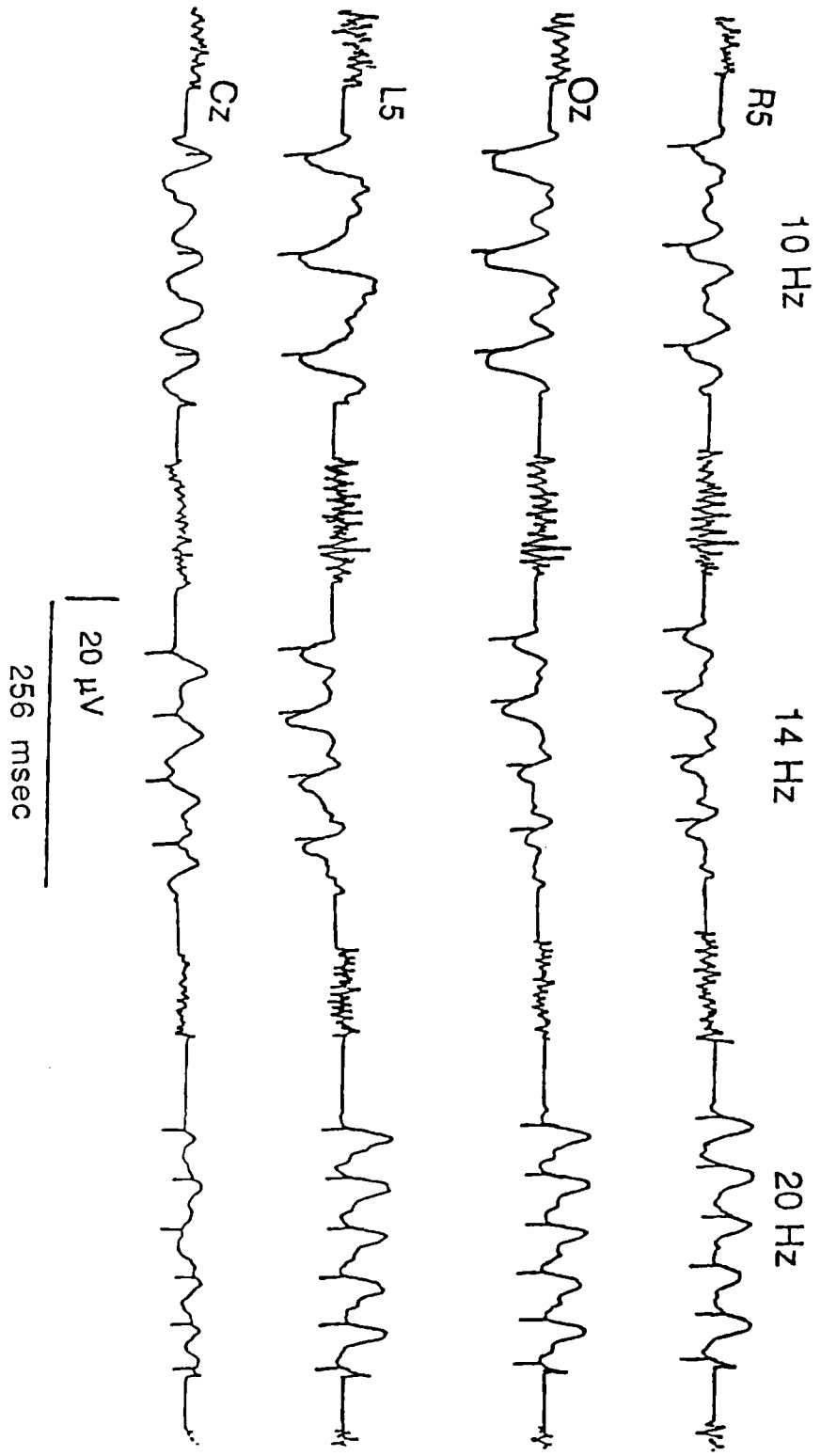


Figure 24

Example of repetitive flash VEP in a control subject with eyes open.

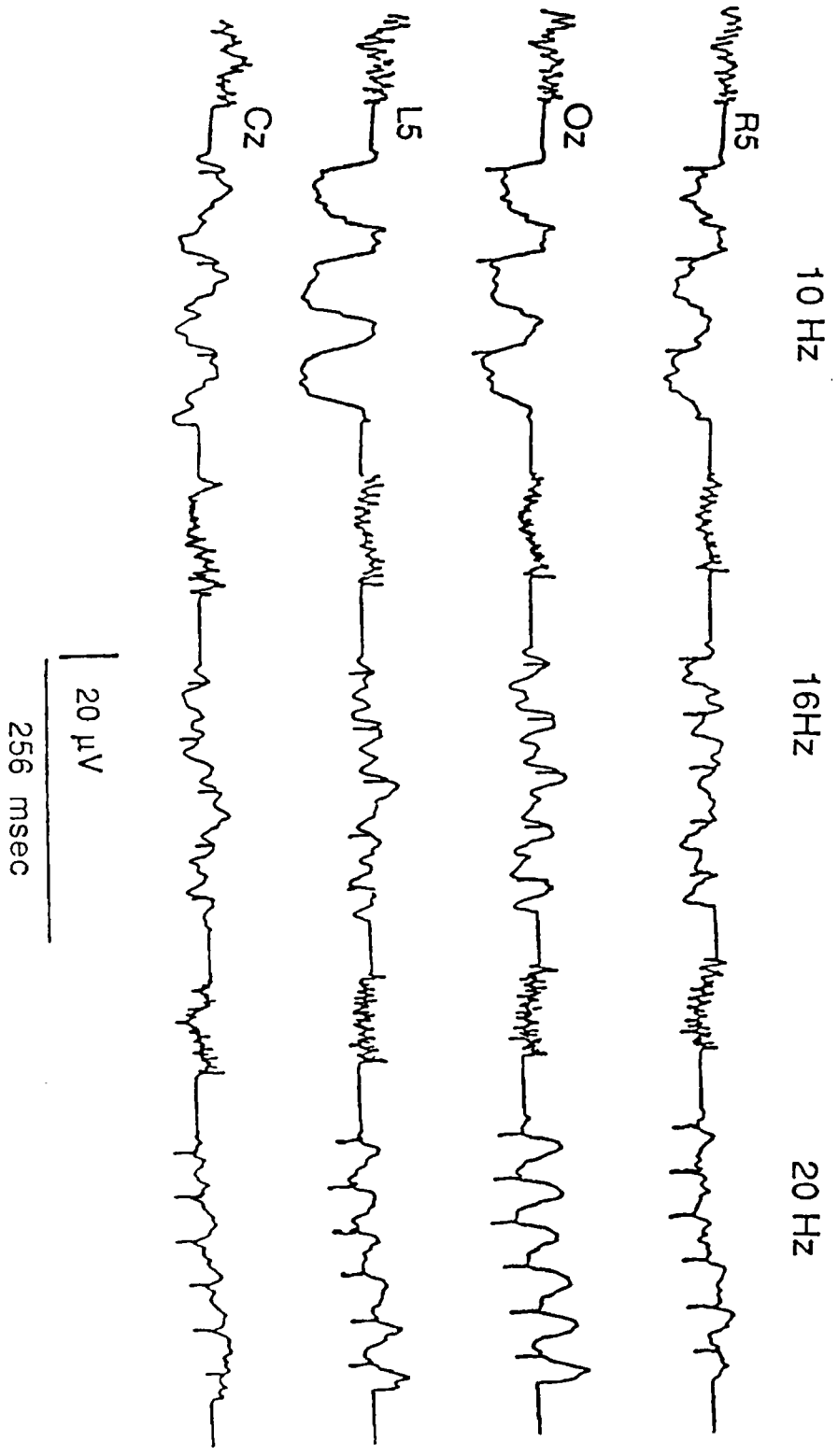
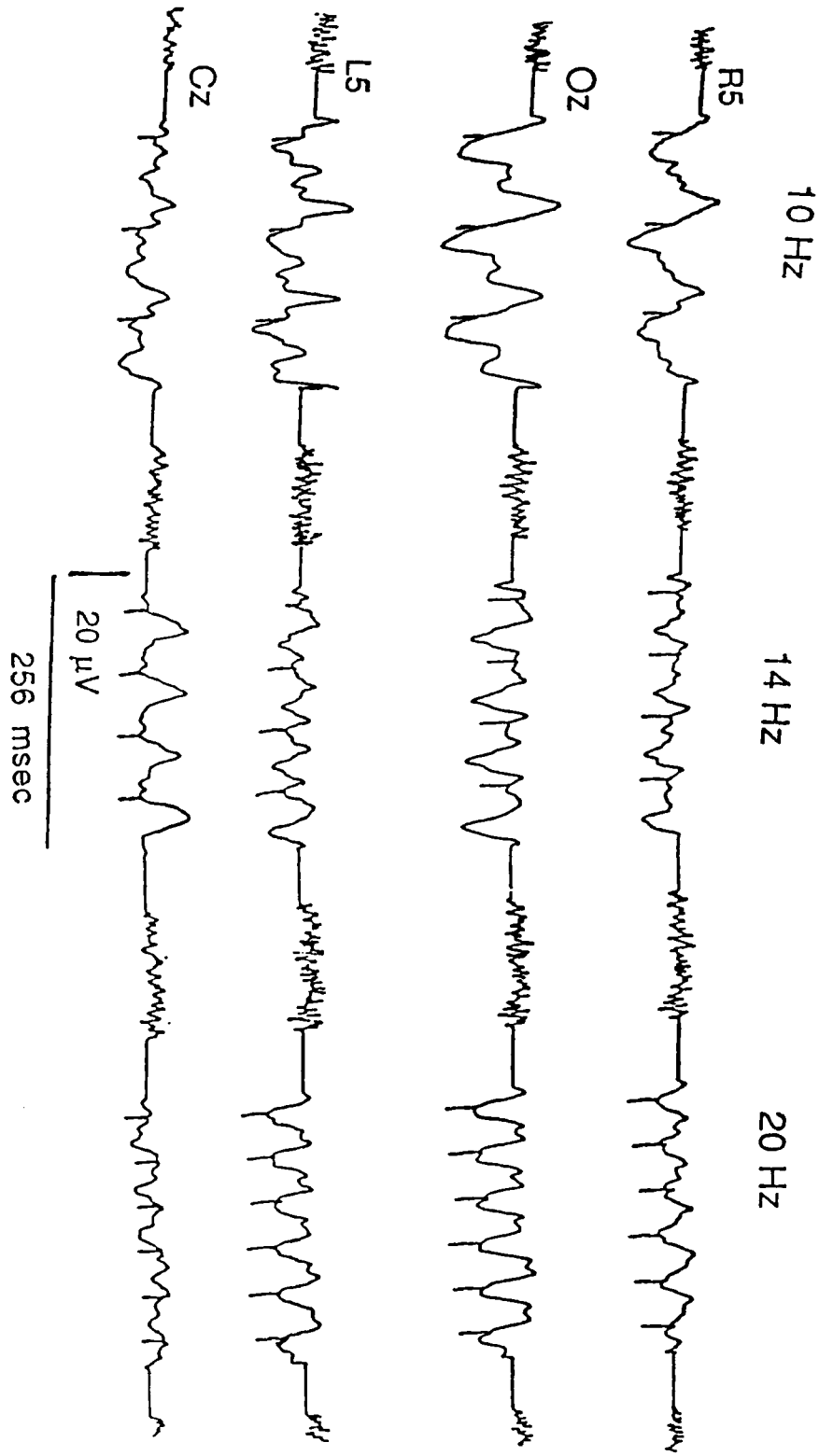


Figure 25

Example of repetitive flash VEP in a migraineur with eyes open.



7.2.2 Psychophysical tests

7.2.2.1 Illusions

Four high contrast patterns, with overall diameters of 25, 50, 100 and 200 millimeters, were used to test for illusions.

Figure 26 shows the number of illusions seen by migraine and control subjects as a function of the size of the pattern. There is a direct relationship between the size of the pattern and the number of illusions, presumably related to the magnitude of cortical area activated with increasing size of the pattern.

Migraine subjects saw significantly more illusions than normal controls (Table 9a). This applied to all the patterns used (Table 9b and Fig 26). There was no relationship between the numbers of illusions seen by patients and the time since their last attack of migraine.

Migraine subjects also experienced more discomfort on looking at these patterns (Fig 27). About 70% of control subjects rated the patterns as neutral or slightly uncomfortable, and the rest as moderately or severely uncomfortable. This proportion was reversed in the migraine group. More than 70% of migraineurs rated the patterns as moderately or severely uncomfortable, and only 30% as neutral or slightly uncomfortable.

There was a correlation between the number of illusions seen and the discomfort experienced ($r=0.82$, $t=13.50$, $p=0.000$).

Table 9

Comparison of illusions between migraine and control subjects

a) Total scores

Controls	Migraine	t	p
6.3 ± 2. 9	11.5 ± 4.5	7.96	0.000*

b) Illusions at different sizes of the pattern

	Controls	Migraine	t	p
Pattern 1	0.3 ± 0.5	0.9 ± 0.8	5.82	0.000*
Pattern 2	0.9 ± 0.7	2.3 ± 1.3	7.43	0.000*
Pattern 3	1.9 ± 0.9	3.25 ± 1.4	7.79	0.000*
Pattern 4	3.2 ± 1.3	4.7 ± 1.6	6.51	0.000*

Figure 26

Illusions in migraine and control subjects as a function of the radius of the pattern

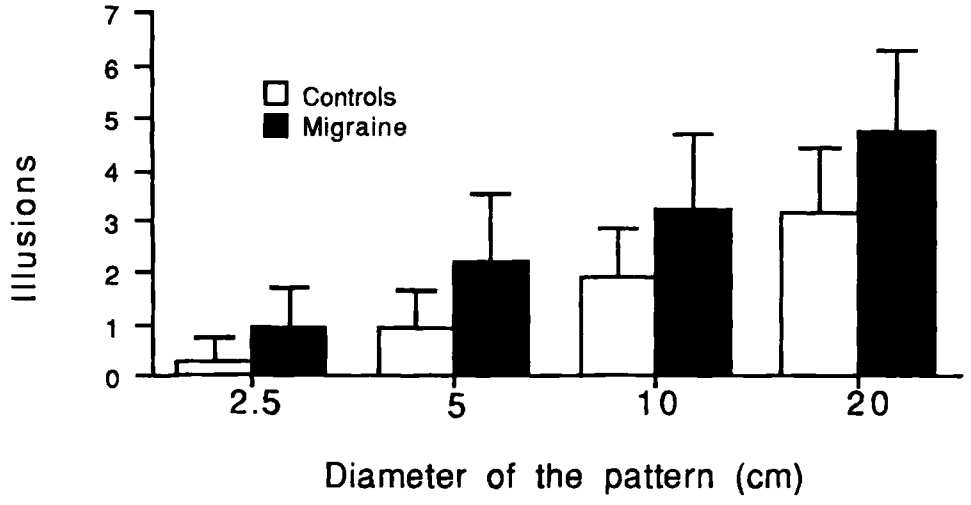
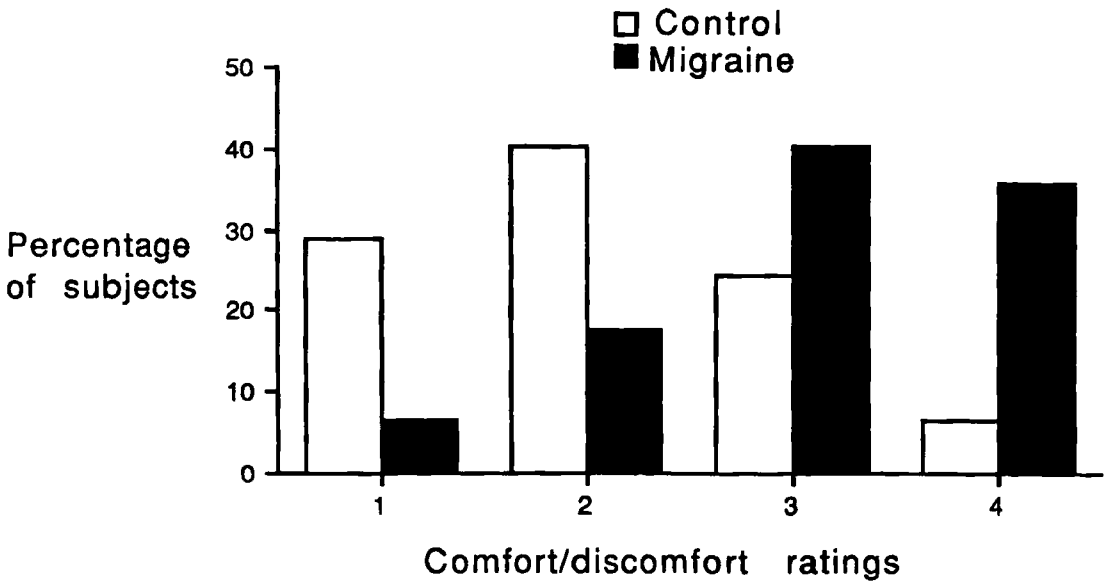


Figure 27

Comfort/discomfort ratings for the high contrast patterns



1. Neutral
2. Slightly uncomfortable
3. Moderately uncomfortable
4. Very uncomfortable

7.2.2.2 Spatial CS (SCS)

Table 10 and figure 28 show the results for spatial CS, expressed as Arden threshold scores at different spatial frequencies. Total Arden threshold scores in the migraine subjects were significantly higher than those of normal controls (Table 10a), i.e contrast sensitivity in the migraine group was lower than in normal controls, and this applied to all the spatial frequencies tested (Table 10b and Fig 28). Subsequent analysis showed that this reduction was accounted for by classical cases only (sections 7.3.3 and 7.3.5).

The tests of hemifield contrast discrimination (CD) were designed to detect asymmetries between the two hemispheres, but the data can also be used to give an indication of whole-field spatial CS. Hemifield CD was expressed by the error score for each hemifield, measured at two contrast levels (see section 6.2.2.3). Most normal subjects started making errors at a contrast level of 3.25%, so their score represents the number of errors collected at 3.25% and 2.29%. Only three normal subjects started making errors at 4.60% and their error scores were thus collected at 4.60% and 3.25%. Out of 37 patients with common migraine only three started making errors at 4.60%. Out of 47 classical migraine subjects, 23 started making errors at 3.25%, 17 at 4.6% and 7 at 6.5%. These results are thus another indication of lower CS in patients with classical migraine.

7.2.2.3 Hemifield contrast discrimination

Hemifield CD was greater in the left hemifield than the right in normal subjects i.e more errors were made on the right. Only two of the present normal subjects made more errors on the left, and both were ambidextrous. The mean excess of right-sided errors over left-sided errors in normals was 2.29, S.D. 1.94. Thus, the normal range of asymmetry, mean ± 2SD is -1.59 to 6.17, where minus scores denote more errors on the left and plus scores indicate more errors on the right. Abnormal asymmetry is therefore present if errors on the left exceed those on the right by 2 or more, or if errors on the right exceed those on the left by 6 or more. Eighty nine patients were examined with hemifield CD.

Using these criteria 57 migraine patients had "normal" asymmetry of hemifield CD and 32 had abnormal asymmetry; 18 had abnormal asymmetry favouring the left hemifield. and 14 had abnormal asymmetry favouring the right hemifield. This difference from normal controls is highly significant ($X^2 = 20.6$, $p<0.001$). The relation of this asymmetry to the side of headache is dealt with in section 7.3.4.

Table 10

Comparison of spatial CS expressed as Arden threshold scores between normal and migraine subjects

a) comparison of the total Arden threshold scores

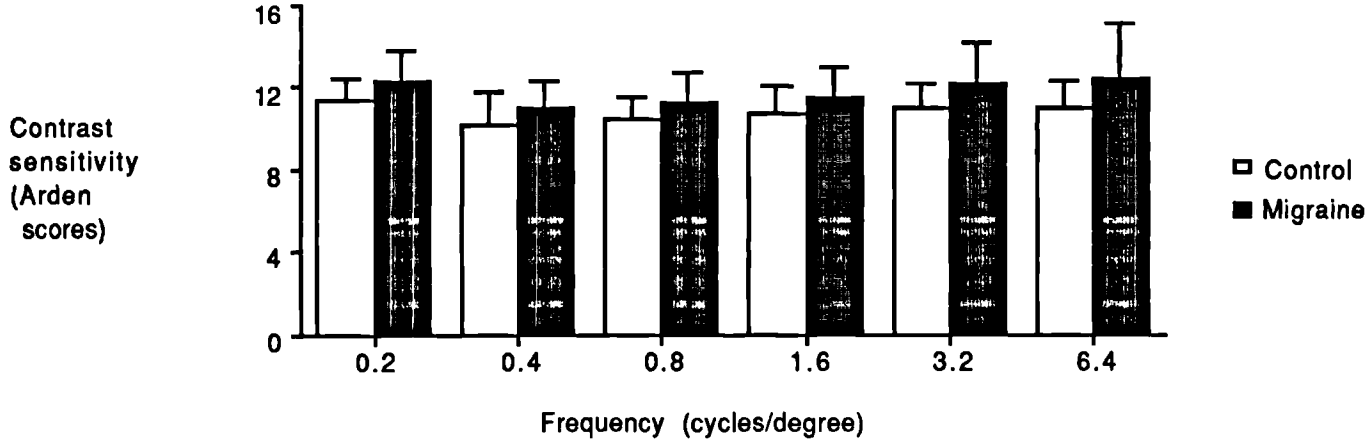
	Controls (n=62)	Migraine (n=92)	t	p
R eye	64.2 ± 5.5	70.3 ± 8.4	5.1	0.000*
L eye	64.9 ± 6.0	69.6 ± 8.3	3.8	0.000*

b) comparisons at different spatial frequencies (cycles/degree)

	0.2 c/d	0.4 c/d	0.8 c/d	1.6 c/d	3.2 c/d	6.4 c/d
Controls	11.4 ± 1.0	10.1 ± 1.6	10.3 ± 1.1	10.6 ± 1.3	10.9 ± 1.2	10.9 ± 1.4
Migraine	12.2 ± 1.5	10.9 ± 1.3	11.2 ± 1.4	11.5 ± 1.4	12.1 ± 2.1	12.4 ± 2.6
t	4.02	3.56	4.40	3.79	3.78	4.16
p	0.000*	0.000*	0.000*	0.000*	0.000*	0.000*

Figure 28

Spatial CS measured by Arden scores at different spatial frequencies in migraine and control subjects



7.2.2.4 Temporal contrast sensitivity (TCS)

TCS was measured at low (3.3 Hz), middle (10 Hz), intermediate (20 Hz) and high (30 Hz) frequencies. Each eye was tested separately.

Table 11 and figure 29 show the results. The migraine group showed significantly greater threshold scores than normal controls i.e their temporal CS was lower than normal controls. This occurred at all frequencies and for both eyes.

This reduction in temporal CS proved to be accounted for by classical migraine subjects only (see sections 7.3.3 and 7.3.5)

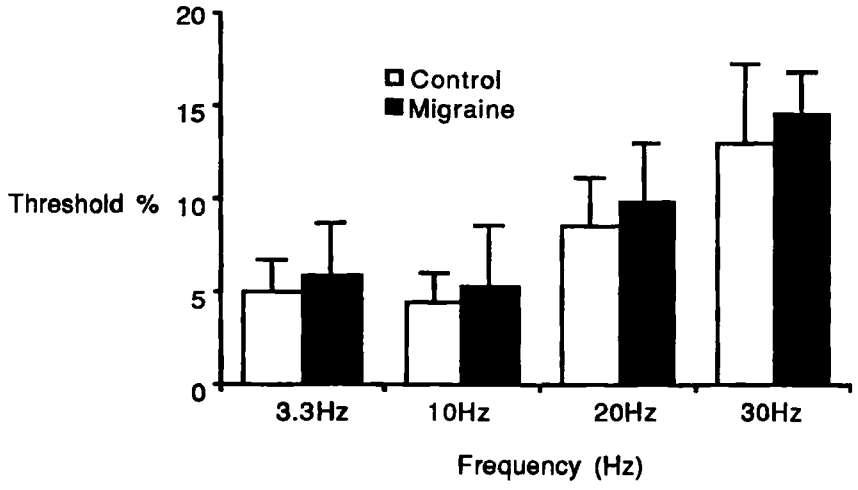
Table 11

Temporal CS expressed by threshold % in migraine and control subjects

		Controls n=62	Migraine n=92	t	p
R EYE	3.3 Hz	5.1 ± 1.6	5.9 ± 1.6	2.84	0.005*
	10 Hz	4.4 ± 1.6	5.4 ± 1.8	3.31	0.001*
	20 Hz	8.6 ± 2.6	9.9 ± 2.4	3.12	0.002*
	30 Hz	12.9 ± 4.3	14.6 ± 4.6	2.25	0.026*
L EYE	3.3 Hz	5.2 ± 1.5	6.2 ± 1.9	3.68	0.000*
	10 Hz	4.6 ± 1.7	5.6 ± 1.8	3.56	0.000*
	20 Hz	8.7 ± 2.7	10.2 ± 2.6	3.54	0.001*
	30 Hz	12.9 ± 4.5	15.9 ± 5.2	3.30	0.001*

Figure 29

Temporal CS measured by threshold % at four frequencies in migraine and control subjects



7.3 Effect of various factors in the migraine group

The effect was investigated of various factors in the migraine subjects on those electrophysiological and psychophysical parameters which were significantly different from normal controls. These were P100 latency and amplitude, P1 and P2 latencies, illusions, spatial CS and temporal CS. For the P100 latency and amplitude, SCS and TCS the values from the averaged measurements for right and left eyes were used because there were no significant differences in these measurements between the two eyes.

7.3.1 Effect of triggering factors

Migraine patients were divided according to the effect of triggering factors on their migraine, as follows: migraine triggered by visual stimuli (n=34), migraine triggered by other stimuli e.g stress (n=14), migraine triggered by both visual and other stimuli (n=39), and migraine with no clear trigger stimuli (n=5).

Initially, patients with no triggers were excluded from the analysis, and no differences were found between the first three groups in respect of any of the measurements listed above (Table 12). However, when all patients with a visual trigger (groups 1 and 3) were compared with all patients without a visual trigger (groups 2 and 4), it was found that illusions were significantly greater in patients whose attacks were triggered by visual stimuli (Table 13).

Table 12

Effect of triggering factors on electrophysiological and psychophysical data in migraine population. Numbers in brackets

L= latency, A = amplitude, SCS = spatial CS, CT = contrast threshold, TCS= temporal CS

	Visual	Nonvisual	Both	F	p
P100 L (msec)	118.1 ± 5.2 (34)	120.2 ± 6.2 (14)	118.1 ± 4.6 (39)	1.21	0.305
P100 A (μV)	16.9 ± 5.1 (34)	17.9 ± 6.3 (14)	15.9 ± 4.7 (39)	0.69	0.506
Flash P1 L (msec)	78.0 ± 10.4 (27)	72.4 ± 9.0 (11)	75.4 ± 10.9 (32)	0.99	0.378
Flash P2 L (msec)	128.6 ± 9.8 (34)	128.3 ± 10.7 (13)	131.3 ± 10.6 (37)	0.60	0.552
Illusions	12.1 ± 4.4 (34)	9.4 ± 4.5 (14)	12.1 ± 4.3 (39)	1.80	0.163
SCS (CT score)	71.2 ± 10.3 (34)	70.1 ± 8.3 (14)	69 5 ± 6.1 (39)	0.32	0.725
TCS (CT %) 3.3Hz	6.5 ± 1.8 (34)	6.1 ± 1.4 (14)	5.9 ± 1.7 (39)	0.28	0.755
10 HZ	5.7 ± 1.9 (34)	5 5 ± 1.3 (14)	5.4 ± 1.7 (39)	0.22	0.802
20Hz	9.6 ± 1.9 (34)	9.9 ± 2.0 (14)	10 3 ± 2 3 (39)	0.87	0.425
30Hz	13.78±4.56 (34)	16 26±5.40 (14)	14.80±4.24 (39	1.21	0.303
H response prevalence	79%	79%	84%	X^2 0.93	0.61

Table 13

Effect of trigger factors on electrophysiological and psychophysical data in patients with visual triggers and patients without visual triggers. Numbers in brackets.
Abbreviations as in table 12

	Visual trigger	No visual trigger	t	p
P100 L (msec)	117.8 ± 5.1 (73)	118.6 ± 6.7 (19)	0.55	0.582
P100 A (μV)	16.9 ± 5.8 (73)	18.8 ± 6.0 (19)	1.27	0.209
Flash P1 L (msec)	76.6 ± 5.8 (59)	74.8 ± 8.4 (16)	0.65	0.508
Flash P2 L (msec)	129.9 ± 10.2 (71)	128.2 ± 10.5 (18)	0.65	0.508
Illusions	12.10 ± 4.3 (73)	9.05 ± 4.6 (19)	2.70	0.008*
SCS (Arden score)	70.5 ± 8.5 (73)	69.5 ± 7.8 (19)	0.47	0.642
TCS (CT %) 3.3Hz	6.1 ± 1.3 (73)	6.0 ± 1.7 (19)	0.30	0.764
10Hz	5.4 ± 1.84 (73)	5.1 ± 1.4 (19)	0.66	0.509
20Hz	10.0 ± 2.15 (73)	9.8 ± 1.8 (19)	0.37	0.710
30Hz	15.9 ± 5.0 (73)	14.3 ± 4.4 (19)	1.36	0.178
H response prevalence	82%	83%	x^2 0.05	0.91

7.3.2 Effect of sex difference

Table 14a shows the comparison of measurements between females and males in the migraine group. Only the P100 latency was significantly different. Female migraineurs had significantly shorter latency (mean 117 msec) than male migraineurs (mean 120 msec). In normal subjects also the latency was shorter in females (112 msec compared to 114 msec) but the difference was not significant (Table 14b). Because of this normal difference between the sexes female migraineurs were compared with female controls (Table 14c) and male migraineurs with male controls (Table 14d). The migraineurs showed significantly longer latency in both cases i.e P100 latency is longer in female and male migraineurs than in female and male controls.

Table 14

Difference between females and males in electrophysiological and psychophysical measurements. Abbreviations and units as in table 12.

a) In migraine population

	Females n=72	Males n=20		
	M±SD	M±SD	t	p
P100 L	117.8 ± 4.7	120.6 ± 6.2	2.13	0.036*
P100 A	16.7 ± 5.1	16.8 ± 5.6	0.04	0.965
Flash P1 L	76.9 ± 10.1	74.1 ± 10.5	1.00	0.321
Flash P2 L	129.9 ± 10.3	128.4 ± 10.1	0.59	0.556
Illusions	11.5 ± 4.6	11.5 ± 4.6	0.02	0.985
SCS (CT score)	70.1 ± 8.1	69.8 ± 8.8	0.11	0.911
TCS 3.3Hz	6.0 ± 1.6	6.1 ± 1.9	0.14	0.886
10Hz	5.5 ± 1.7	5.1 ± 1.7	1.10	0.274
20Hz	10.0 ± 2.1	9.5 ± 1.2	1.02	0.316
30Hz	14.8 ± 4.8	13.9 ± 3.4	0.83	0.411
H response prevalence	80%	77%	X^2 0.01	0.95

b) In normal population

	Females n=44	Males n=18	t	p
P100 L	112.1 ± 5.2	113.8 ± 5.9	1.12	0.269

c) Female controls and female migraineurs

	Controls n=44	M graine n=72	t	p
P100 L	112.1 ± 5.2	117.8 ± 4.7	6.08	0.000*

d) Male controls and male migraineurs

	Contro s n=18	M gra ne n=20	t	p
P100 L	113.8 ± 5.9	120.0 ± 6.2	3.42	0 007*

7.3.3 Effect of type of migraine

The measurements listed above were compared in the two major types of migraine, classical (n=47) and common (n=37) migraine (Table 15). Eight patients with mixed attacks of classical and common migraine were excluded from this analysis.

P100 latency and the flash P1 and P2 latencies were similar in the two groups.

P100 amplitude was significantly higher in common migraineurs than in classical migraineurs. P100 amplitude was higher than controls in common migraine but comparable to controls in classical migraine as shown in table 16 and figure 30 (but see section 7.3.5). The prevalence of an H-response was greater in classical than common migraine, but the difference was not significant.

Illusions were more frequent in classical than common migraine subjects, but in each they were more frequent than in normal controls (Table 17), for all the patterns used (Fig 31). Visual discomfort showed a similar trend (Fig 32).

Spatial CS and temporal CS were significantly lower in classical than common migraine. Compared with controls, common migraine subjects had normal CS and classical migraine had lower CS. This was true for both spatial CS (Table 18 and Fig 33), and temporal CS (Table 19 and Fig 34), i.e the differences between controls and the migraine group as a whole are due to the classical migraine subjects only (but see 7.3.5 for further clarification).

Table 15

Difference between classical and common migraine in electrophysiological and psychophysical data.
Abbreviations and units as in table 12

	Classical (47)	Common (37)	t	p
P100 L (msec)	118.4 ± 5.3	118.9 ± 5.4	0.42	0.674
P100 A (μV)	15.1 ± 4.5	18.6 ± 5.3	3.25	0.002*
Flash P1 L (msec)	75.4 ± 10.2	78.2 ± 9.2	1.16	0.252
Flash P2 L (msec)	131.3 ±10.8	128.8 ± 8.5	1.15	0.255
Illusions	13.4 ± 3.9	9.5 ± 4.4	4.16	0.000*
SCS (CT score)	71.2 ± 8.9	66.6 ± 4.6	2.82	0.006*
TCS (CT %) 3.3Hz	6.4 ± 1.7	5.5 ± 1.5	2.35	0.021*
10Hz	5.7 ± 1.8	4.9 ± 1.5	2.06	0.042*
20Hz	10.7 ± 1.8	9.0 ± 1.9	4.21	0.000*
30Hz	15.3 ± 4.6	13.9 ± 4.6	1.40	0.165
H response prevalence	83%	73%	x^2 1.30	0.25

Table 16

Comparison of P100 amplitude (μV) between controls and the two types of migraine. Numbers in brackets

	Controls (62)	Classical (47)		
	M±SD	M±SD	t	p
R eye	15.4 ± 4.85	15.1 ± 4.90	0.30	0.762
L eye	14.9 ± 5.07	15.4 ± 4.95	0.53	0.595

	Controls (62)	Common (37)	t	p
R eye	15.4 ± 4.85	19.4 5 ± 5.69	3.70	0.000*
L eye	14.9 ± 5.07	18.9 ± 5.93	3.61	0.000*

Figure 30

P100 amplitude (μV) in controls, all migraine and the two types of migraine

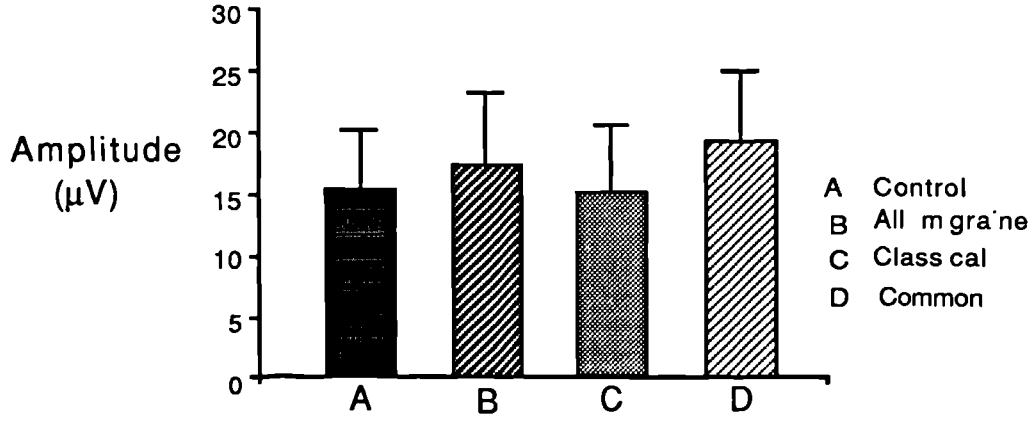


Table 17

Comparison of illusions between controls and the two types of migraine.

Controls (n=62)	Common (n=37)	t	p
6.3 ± 2.9	9.5 ± 4.4	4.35	0.000*

Controls (n=62)	Classical (n=47)	t	p
6.3 ± 2.9	13.3 ± 3.9	10.70	0.000*

Figure 31

Illusions in controls, all migraine, classical migraine and common migraine as a function of the diameter of the pattern

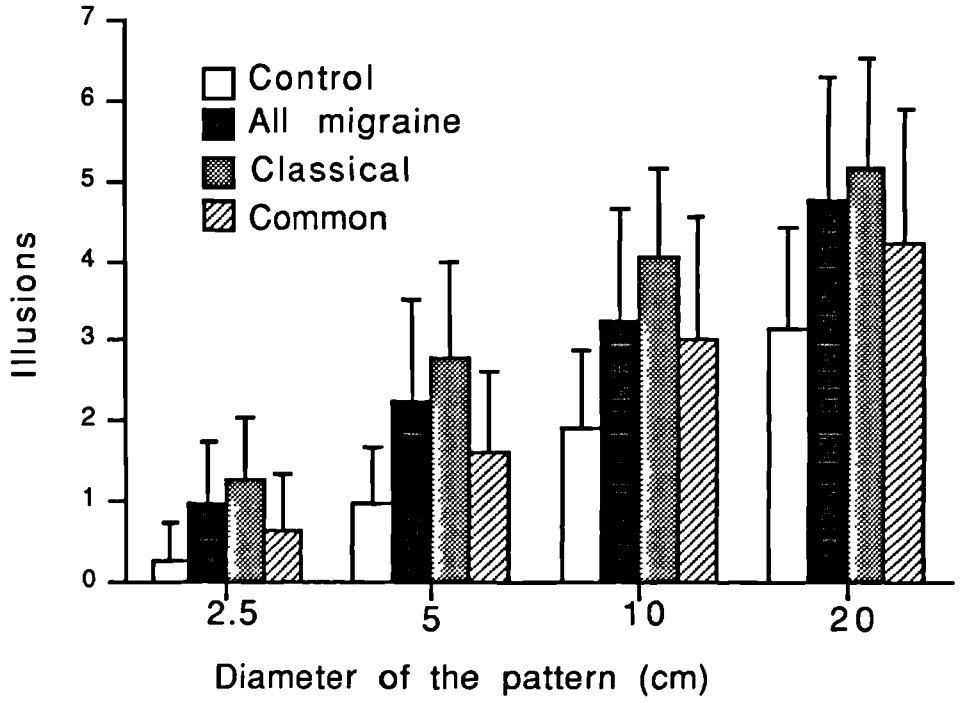
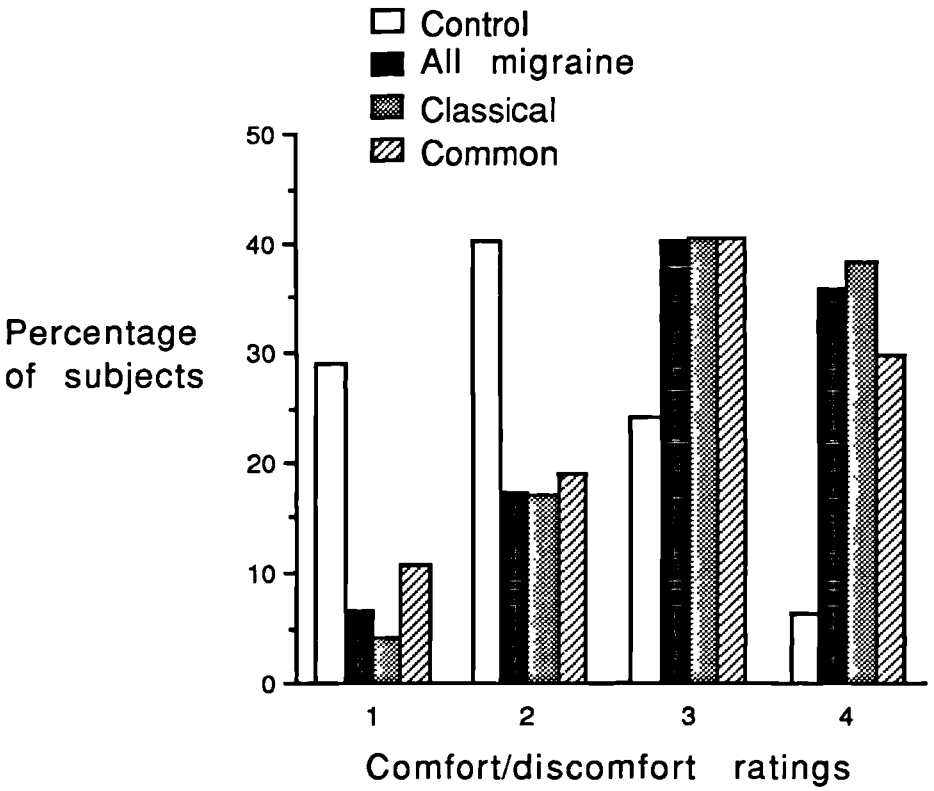


Figure 32

Comfort/discomfort ratings for the high contrast patterns in controls, all migraine, classical and common migraine



1. Neutral
2. Slightly uncomfortable
3. Moderately uncomfortable
4. Very uncomfortable

Table 18

Comparison of spatial CS between normals and the two types of migraine with a) total Arden CT scores, b) individual CT scores at different spatial frequencies

a)	Controls (n=62)	Classical (n=47)		
	M ± SD	M ± SD	t	p
RE	64.2 ± 5.5	71.8 ± 8.8	5.52	0.000*
LE	64.9 ± 6.0	70.5 ± 9.3	3.79	0.000*

	Controls (n=62)	Common (n= 37)	t	p
RE	64.2 ± 5.5	66.4 ± 4.6	1.75	0.083
LE	64.9 ± 6.0	66.81 ±4.9	1.59	0.114

b)	PL2	PL3	PL4	PL5	PL6	PL7
Controls	11.4 ± 1.0	10.1 ± 1.6	10.3 ± 1.1	10.6 ± 1.3	10.9 ± 1.2	10.9 ± 1.4
Classical	12.7 ± 1.5	11.2 ± 1.4	11.3 ± 1.5	11.6 ± 1.6	12.4 ± 2.1	12.4 ± 2.6
t	5.43	3.76	4.24	3.46	4.65	4.34
p	0.000*	0.000*	0.000*	0.000*	0.000*	0.000*

	PL2	PL3	PL4	PL5	PL6	PL7
Controls	11.4 ± 1.0	10.1 ± 1 6	10.3 ± 1.1	10.6 ± 1.3	10.9 ± 1.2	10.9 ± 1.4
Common	11.5 ± 1.2	10.5 ± 0.8	10.6 ± 1.0	11.0 ± 0.9	11.2 ± 1.4	11.5 ± 1.9
t	0.514	1.207	1.26	1.633	0.858	1.903
p	0.9609	0.230	0.212	0.106	0.393	0.060

Figure 33

Contrast sensitivity measured by Arden scores at different spatial frequencies in controls, all migraine, classical migraine and common migraine subjects.

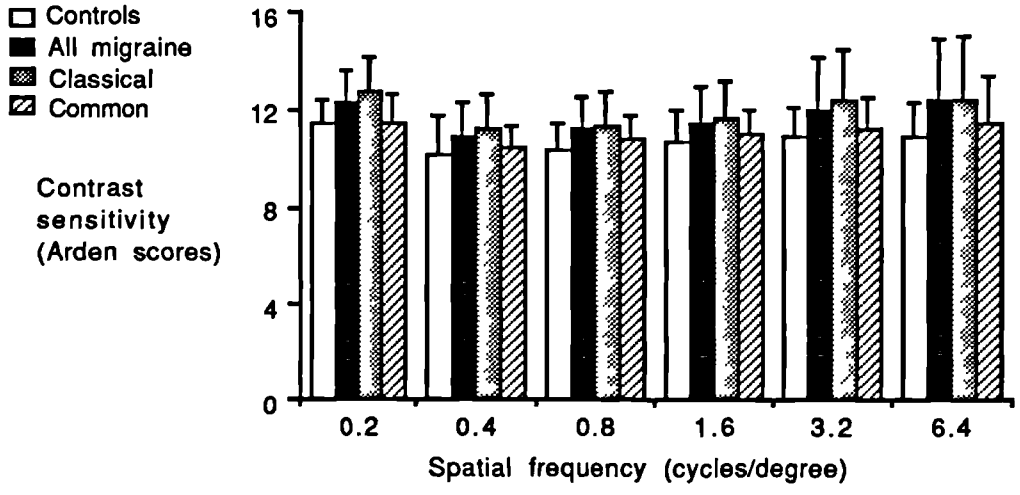


Table 19

Temporal CS in threshold % in controls and the two types of migraine.

a) Controls and classical migraineurs

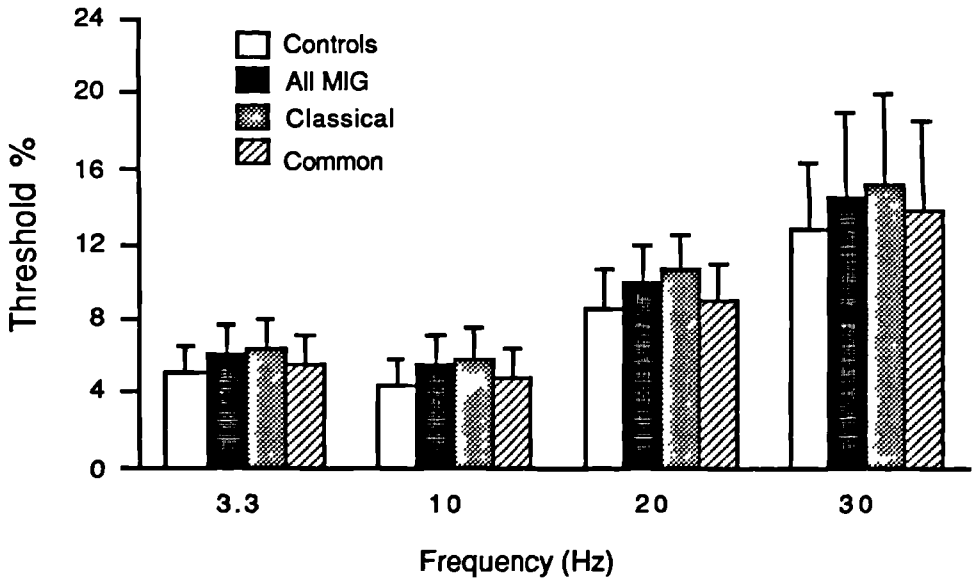
	Controls (n=62)	Classical (n=47)	t	p
3.3Hz	5.2 ± 1.5	6.4 ± 1.7	3.98	0.000*
10Hz	4.4 ± 1.5	5.7 ± 1.8	4.26	0.000*
20Hz	8.5 ± 2.1	10.7 ± 1.8	5.86	0.000*
30Hz	12.7 ± 3.7	15.3 ± 4.6	3.28	0.001*

b) Controls and common migraineurs

	Controls (n=62)	Common (n=37)	t	p
3.3Hz	5.2 ± 1.5	5.5 ± 1.5	1.23	0.222
10Hz	4.4 ± 1.5	4.9 ± 1.5	1.81	0.073
20Hz	8.5 ± 2.1	9.0 ± 1.9	1.27	0.208
30Hz	12.7 ± 3.7	13.9 ± 4.6	1.41	0.161

Figure 34

Temporal CS in threshold % in controls and in classical and common migraineurs



7.3.4 Effect of headache side and aura side:

Those abnormal electrophysiological results which were recorded separately from the two hemispheres, i.e at R5 and L5 positions, were examined in relation to headache side (Table 20) and aura side (Table 21). The migraine subjects were divided, both for headache and for aura, into four groups; consistently right, consistently left, bilateral, and inconsistent. The last group was excluded from the analysis. The results showed no significant differences in the measurements between the other three groups (but see section 7.3.5).

Table 20

Effect of headache side on electrophysiological data. Number of patients in brackets

RE = right eye, LE = left eye, WF = wholefield, RHF = right half field, LHF = left half field
R5 = responses recorded over the right hemisphere, 5 cm lateral to Oz
L5 = responses recorded over the left hemisphere, 5 cm lateral to Oz

a) P100 latency (msec) of monocular PRVEP

	R headache (30)	L headache (16)	Bilateral headache (30)	F	p
RE/WF/R5	118.2 ± 6.0	119.3 ± 5.2	117.2 ± 6.3	0.63	0.535
RE/WF/L5	118.2 ± 6.0	119.3 ± 5.2	117.7 ± 6.3	0.55	0.579
LE/WF/R5	119.0 ± 5.5	120.2 ± 5.4	118.5 ± 6.4	0.42	0.660
LE/WF/L5	118.9 ± 5.6	120.1 ± 5.4	118.6 ± 6.3	0.29	0.747
RE/RHF/R5	117.1 ± 5.4	117.6 ± 4.5	116.8 ± 5.6	0.08	0.921
LE/RHF/R5	117.3 ± 6.1	116.8 ± 4.6	117.5 ± 5.1	0.09	0.911
RE/LHF/L5	117.2 ± 6.1	117.3 ± 4.3	116.5 ± 5.8	0.13	0.881
LE/LHF/L5	117.3 ± 5.6	116.6 ± 4.3	116.8 ± 5.6	0.07	0.934

b) P100 amplitude (μV) of monocular PRVEP

	R h'ache (30)	L h ache (16)	Bilat h'ache (30)	F	p
RE/WF/R5	11.3 ± 3.9	11.3 ± 5.5	11.5 ± 4.9	0.01	0.990
RE/WF/L5	11.5 ± 3.8	10.9 ± 5.5	11.6 ± 5.1	0.11	0.895
LE/WF/R5	11.9 ± 4.3	11.6 ± 5.5	11.8 ± 4.7	0.03	0.976
LE/WF/L5	11.7 ± 4.8	11.6 ± 4.8	11.7 ± 4.9	0.00	0.998
RE/RHF/R5	8.3 ± 2.7	7.8 ± 3.0	7.6 ± 3.2	0.30	0.743
LE/RHF/R5	8.7 ± 3.7	7.3 ±2.0	7.7 ± 3.6	0.97	0.385
RE/LHF/L5	9.0 ± 3.3	7.2 ± 2.3	8.1 ± 3.7	1.69	0.193
LE/LHF/L5	8.3 ± 2.8	6.9 ± 2.1	7.6 ± 3.6	1.11	0.337

c) P1 and P2 latencies (msec) of the binocular SFVEP

	R h ache	L h ache	B at h ache	F	p
P1/R5	76.9 ± 12.4 (22)	75.0 ± 7.8 (12)	75.1 ± 10.0 (25)	0.83	0.367
P1 L5	76.6 ± 11.9 (22)	76.4 ± 9.5 (12)	74 6 ± 10.2 (24)	0.39	0.533
P2 R5	133.0 ± 10.5 (27)	131.7 ± 8.8 (15)	127.4 ± 8 9 (30)	2.38	0.101
P2/L5	132.9 ± 10.8 (27)	133.5 ± 10 34 (15)	127.7 ± 9 1 (30	2.36	0.103

Table 21

Effect of aura side on electrophysiological data. Number of patients in brackets

RE = right eye, LE = left eye, WF = wholefield, RHF = right half field, LHF = left half field
R5 = responses recorded over the right hemisphere, 5 cm lateral to Oz
L5 = responses recorded over the left hemisphere, 5 cm lateral to Oz

a) P100 latency (msec) of monocular PRVEP

	R aura (11)	L aura (12)	Bilat aura (14)	F	P
RE/WF/R5	115.6 ± 4.6	117.7 ± 7.3	119.6 ± 6.0	1.39	0.262
RE/WF/L5	116.0 ± 5.2	117.7 ± 7.2	119 8 ± 6.3	1.13	0.335
LE/WF/R5	116.7 ± 4 1	118.4 ± 6.7	119.9 ± 6 3	0.88	0.426
LE/WF/L5	116.7 ± 4.1	118.3 ± 6.5	120.0 ± 6.6	0.94	0.399
RE/RHF/R5	115.1 ± 4.3	116.5 ± 5.9	117.7 ± 5.4	0.76	0.475
LE/RHF/R5	115.8 ± 4.2	117.6 ± 5.2	118.8 ± 6.9	0.67	0.519
RE/LHF/L5	115.1 ± 4.5	116.9 ± 5.4	117.6 ±6.9	0.58	0.563
LE/LHF/L5	117.6 ± 5.9	116.6 ± 4.3	116.8 ± 5.6	0.07	0.934

b) P100 amplitude (μV) of monocular PRVEP

	R aura (11)	L aura (12)	Bilat aura (14)	F	P
RE/WF/R5	9.7 ± 4.80	9.5 ± 3.6	11.1 ± 3.7	0.64	0.533
RE/WF/L5	10.3 ± 4.9	10.4 ± 3.5	10.5 ± 3.5	0.01	0 989
LE/WF/R5	11.3 ± 4.9	9.1 ± 3.9	11.57 ± 4.33	0.18	0.318
LE/WF/L5	11.4 ± 4.2	9.8 ± 4.1	11.36 ± 4.13	0.55	0.580
RE/RHF/R5	6.6 ± 1.9	6.3 ± 1.9	7.6 ± 3.1	0.54	0.586
LE/RHF/R5	6.9 ± 2.1	7.3 ± 1.6	8 4 ± 3 9	0.96	0.394
RE/LHF/L5	8.6 ± 2.1	7.1 ± 3.2	7.9 ± 3.4	1.78	0.467
LE/LHF/L5	8.2± 2.1	6.9 ± 3.9	7.5 ± 2 6	0.44	0.640

c) P1 and P2 latencies (msec) of binocular SFVEP

	R aura	L aura	B at aura	F	P
P1/R5	74.9 ± 13.3 (8)	79.7±3.24 (9)	72 5± 8.82 (12)	0.22	0.647
P1/L5	74.1 ± 12 2 (8)	81.5 ± 6.5 (8)	72.6 ± 8.9 (12)	0.10	0.755
P2/R5	132.9 ± 10.8 (10)	129.2 ± 8.04 (11)	132.4 ± 10.9 (14)	0.44	0.650
P2/L5	133.3 ± 11.2. (10)	131.7 ± 10.4 (11)	132.7 ± 11.2 (14)	0.05	0.947

For the psychophysical data, asymmetries in hemifield CD and illusions were analysed in relation to the side of headache and aura.

The distribution of the whole patient group with regard to headache laterality and asymmetry is shown in table 22a. When patients with bilateral headache were compared with those with unilateral headache (Table 22b), it was found that asymmetry in hemifield CD was much commoner in patients with unilateral headache than patients with bilateral headache However, when the results in the 25 patients with asymmetrical CS and unilateral headache were examined (Table 22c) there was no significant correlation between the side of the headache and the reduction in hemifield CD. This means that when the headache was lateralised the reduction in contrast sensitivity was lateralised too but the direction of asymmetry bore no relation to the side of headache. The explanation for this observation is suggested below.

The same analysis was done for patients with a visual aura, and the overall data are shown in table 23a. It was found that those with bilateral aura tended to have symmetrical CD and those with unilateral aura tended to have asymmetrical CD (table 23b). The reduction in CD occurred on the side of the visual aura; among the 10 patients with a right-sided aura only 2 patients had a reduction in CD on the left, and only one patient out of ten with a left-sided aura had a reduction of CD on the right (Table 23c). Thus, when aura tends to be lateralised the reduction in hemifield CD tends to be lateralised as well, and the reduction is usually on the side of the visual aura.

Table 22

Relationship between symmetry of headache and of HFCD in migraine subjects. Data represent number of patients.
R < L = CD worse in the right hemifield
L < R = CD worse in the left hemifield

a) Distribution of migraine subjects according to symmetry of headache and HFCD

	Symmetry of HFCD		
Symmetry of headache	R = L	R < L	L < R
Bilateral (n=29)	26	2	1
Right (n=29)	13	6	10
Left (n=16)	7	6	3
Inconsistent (n=15)	11	3	1

b) Relationship between laterality of headache and HFCD

	Symmetrical HFCD	Asymmetrical HFCD	X^2	p
Bilateral H'ache (29)	26	3	13.46	0.000
Unilateral H'ache (45)	20	25		

c) Relationship between side of headache and side of HFCD

	HFCD R < L	HFCD L < R	p
R headache (16)	6	10	0.326
L headache (9)	6	3	

(p value from Fisher exact test)

Table 23

Relationship between symmetry of aura and of HFCD.
Data represent number of subjects.
R < L and L < R as in table 22

a) Distribution of migraine subjects according to symmetry of aura and hemifield CD

	Symmetry of HFCD		
Symmetry of aura	R = L	R < L	L < R
Bilateral (n=14)	11	2	1
Right (n=11)	1	8	2
Left (n=12)	2	1	9
Inconsistent (n=10)	4	0	6

b) Relationship between laterality of aura and HFCD

	Symmetrical HFCD	Asymmetrical HFCD	X^2	p
Bilateral Aura (14)	11	3	13.22	0.000*
Unilateral Aura (23)	3	20		

c) Relationship between side of aura and side of HFCD

	HFCD R < L	HFCD L < R	p
R Aura (10)	8	2	0.005*
L Aura (10)	1	9	

(p value from Fisher exact test)

The relationships were then examined between the laterality and side of headache and aura and the laterality and side of illusions. An analysis of variance showed no difference in the average number of illusions perceived between the three headache groups or the three aura groups.

Table 24a shows the distribution of patients according to headache side and the side of more prominent illusions. Table 24b and 24c show that when headaches were lateralised illusions also tended to be lateralised, but not consistently to either the same or the opposite side.

Table 25a shows the distribution of patients according to aura side and the side of more prominent illusions. Patients with a bilateral aura tended to see symmetrical illusions while patients with a unilateral aura tended to see asymmetrical illusions (Table 25b). This lateralisation in illusions was correlated with the side of aura (Table 25c) i.e more illusions were seen on the side of the visual aura.

Table 24

Relationship between symmetry of headache and of illusions. Data represent number of subjects.
R > L = more illusions on right hemifield
L > R = more illusions on left hemifield

a) Distribution of migraine subjects according to symmetry of headache and illusions

	Symmetry of illusions		
Symmetry of headache	R = L	R > L	L > R
Bilateral (n=30)	23	4	3
Right (n=30)	15	5	10
Left (n=16)	6	7	3
Inconsistent (n=16)	12	1	3

b) Relationship between laterality of headache and illusions

	Symmetrical illusions	Asymmetrical illusions	X^2	p
Bilateral H'ache (30)	23	7	5.95	0.015*
Unilateral H'ache (46)	21	25		

c) Relationship between side of headache and side of illusions

	Illusions R > L	Illusions L > R	p
R Headache (15)	5	10	0.367
L Headache (10)	7	3	

(p value from Fisher exact test)

Table 25

Relationship between symmetry of aura and of illusions.
Data represent number of subjects

a) Distribution of migraine subjects according to symmetry of aura and illus ons

	Symmetry of illusions		
Symmetry of aura	R = L	R > L	L > R
Bilateral (n=14)	10	3	1
Right (n=11)	0	10	1
Left (n=12)	4	0	8
Inconsistent (n=10)	7	0	3

b) Relationship between laterality of aura and illusions

	Symmetrical illusions	Asymmetrical illusions	X^2	p
Bilateral Aura (14)	10	4	8.63	0.003*
Unilateral Aura (23)	4	19		

c) Relationship between side of aura and side of illusions

	Illusions R > L	Illusions L > R	p
R Aura (11)	10	1	0.000*
L Aura (8)	0	8	

(p value from Fisher exact test)

Relationship between the side of illusions and of HFCD

Patients tended to see more illusions on the side of the aura and there was a reduction in hemifield CD on the side of the aura. This suggests a relationship between the side of reduced CD and the side of illusions.

Table 26a shows the distribution of subjects according to these factors. Table 26b shows that patients who saw symmetrical illusions tended to have symmetrical errors (HFCD) while patients with asymmetrical illusions tended to have asymmetrical errors. In fact, eight of the 11 subjects with more illusions on the right had more errors on the right and seven of the 11 patients with more illusions on the left had more errors on the left, but this difference is not significant. Thus, when the illusions were asymmetrical the errors also tended to be asymmetrical, but the correlation between the sides did not reach significance.

Table 26

Relationship between symmetry of Illusions and of HFCD. Data represent number of subjects.

a) Distribution of migraine subjects according to symmetry of illusions and hemifield CD

	Symmetry of HFCD		
Symmetry of illusions	R = L	R < L	L < R
R = L (n=55)	46	5	4
R > L (n=18)	7	8	3
L > R (n=16)	5	4	7

b) Relationship between laterality of illusions and HFCD

	Symmetrical errors	Asymmetrical errors	X^2	p
Bilateral Illusions (55)	46	9	19.56	0.000*
Unilateral Illusions (34)	12	22		

c) Relationship between side of illusions and side of HFCD

	HFCD R > L	HFCD L > R	X^2	p
Illusions R>L (11)	8	3	1.65	0.20
Illusions L>R (11)	4	7		

(p value from Fisher exact test)

Relation between aura side and headache side

Distribution of the classical migraine subjects according to aura side and headache side is illustrated in table 27a.

After excluding patients with inconsistent lateralisation of aura and headache, six out of 11 patients with bilateral aura had bilateral headache and 17 out of 20 patients with unilateral aura had unilateral headache, a significant relationship (Table 27b). The relationship between side of aura and side of headache shows a trend (Table 27c), but it does not reach statistical significance. Clearly it might do so if the groups contained larger numbers.

We have already seen that the side of reduction in CD and increased illusions correlates with the side of aura but not with the side of headache, and clearly this is because there is no consistent relationship between side of aura and side of headache.

Table 27

Relationship between side of aura and headache in classical migraineurs. Data represent number of subjects.

a) Distribution of migraine subjects according to side of headache and aura.

		Side of headache			
		Bilateral	R	L	Inconsistent
Bilateral aura	(14)	6	3	2	3
Right aura	(11)	1	3	6	1
Left aura	(12)	2	6	2	2
Inconsistent aura	(10)	3	3	1	3

b) Relationship between laterality of headache and aura

	Bilateral headache	Unilateral headache	p
Bilateral aura (11)	6	5	0.038
Unilateral aura (20)	3	17	

(p value from Fisher exact test)

c) Relationship between side of headache and side of aura

	Right h'ache	Left h'ache	p
Right aura (9)	3	6	0.150
Left aura (8)	6	2	

(p value from Fisher exact test)

Relation between half-field P100 amplitude and HFCD

Since an overall reduction in CS was correlated with an overall reduction in P100 amplitude in classical migraine subjects, half-field P100 amplitude was examined in relation to HFCD in the 8 patients with reduced CD in the right hemifield (Table 28) and the 9 patients with reduced CD in the left hemifield (Table 29). There proved to be a significant reduction in P100 amplitude in the hemifield with reduced CD when compared to the the opposite field in the same subject (Table 28a and 29a) and to the corresponding field in controls (Table 28b and 29b). P100 amplitude was normal in the hemifields with normal CD. The P100 amplitudes of whole-field responses in these patients were also asymmetrical (Table 28c and 29c), but the reductions over the relevant hemisphere were less significant.

Table 28

P100 amplitude (μV) of monocular PRVEP in 8 migraine subjects with reduced CD in the RIGHT hemifield.

a) Differences between right and left half fields for each eye in these migraine subjects

	RHF	LHF	t	p
RE	5.75 ± 1.0	8.75 ± 2.3	3.31	0.013*
LE	5.50 ± 1.2	8.00 ± 2.8	2.76	0.028*

b) Differences between the half field responses of these migraine subjects and controls

		Migraine (8)	Controls (62)	t	p
RHF	RE	5.8 ± 1.0	8.2 ± 3.1	2.19	0.032*
	LE	5.5 ± 1.2	7.9 ± 3.1	2.14	0.036*
LHF	RE	8.8 ± 2.3	7.5 ± 3.1	1.13	0.264
	LE	8.0 ± 2.8	7.4 ± 3.2	0.49	0.629

c) Differences between the wholefield responses of these migraine subjects and controls

		Migraine (8)	Controls (62)	t	p
RE	Oz	11.5 ± 2.9	15.4 ± 4.9	2.20	0.031*
	R5	7.9 ± 1.5	11.6 ± 4.5	2.28	0.026*
	L5	9.5 ± 4.6	11.3 ± 4.8	0.97	0.334
LE	Oz	11.4 ±1.4	14.9 ± 5.1	1.94	0.057*
	R5	7.9 ± 2.1	10.4 ± 4.0	1.79	0.078
	L5	9.8 ± 3.7	10.4 ± 3.9	0.46	0.649

Table 29

P100 amplitude (μV) of monocular PRVEP in 9 migraine subjects with reduced CD in the LEFT hemifield

a) Differences between right and left half fields for each eye in these migraine subjects

	RHF	LHF	t	p
RE	7.11 ± 2.1	4.89 ± 1.05	4.50	0.002*
LE	7.22 ± 2.0	4.67 ± 1.22	3.82	0.005*

b) Differences between the half field responses of these migraine subjects and controls

		Migraine (9)	Controls (62)	t	p
RHF	RE	7.11 ± 2.1	8.15 ± 3.1	0.98	0.331
	LE	7.22 ± 2.0	7.85 ± 3.1	0.60	0.551
LHF	RE	4.89 ± 1.05	7.40 ± 3.1	2.46	0.016*
	LE	4.67 ± 1.22	7.42 ± 3.2	2.52	0.014*

c) Differences between the whole field responses of these migraine subjects and controls

		Migraine	Controls	t	p
RE	Oz	12.00 ± 2.1	15.37 ± 4.85	2.05	0.044*
	R5	9.11 ± 2.5	10.35 ± 4.03	0.90	0.373
	L5	8.11 ± 1.8	11.55 ± 4.49	2.26	0.027*
LE	Oz	11 78 ± 3.3	14.89 ± 5.07	1.78	0.079
	R5	9.00 ± 2.87	10.42 ± 3.92	1.04	0.300
	L5	7.89 ± 2.47	11.26 ± 4.83	2.04	0.045*

7.3.5 Effect of duration of migraine

The effect was examined of duration of migraine on those electrophysiological and psychophysical parameters which showed significant differences from normal controls (Table 30). The results showed an effect on the P100 amplitude, the spatial CS and and the temporal CS at 10 and 20 Hz. These correlations are illustrated in figures 35, 36 and 37. With longer duration of migraine the P100 amplitude was lower, the contrast threshold was higher i.e the spatial CS was reduced, and the temporal CS was also reduced. This was not an age effect (section 7.3.6).

As shown previously (section 7.3.3) the overall difference in CS between migraine and control subjects is due only to classical migraine subjects. The effects of migraine duration on P100 amplitude spatial CS, and temporal CS were therefore considered separately for the two types of migraine. Table 31 shows that P100 amplitude and CS were affected by migraine duration only in classical migraine subjects. The effect of migraine duration in these subjects is therefore greater than for the group of migraine subjects as a whole, as this contains common migraineurs as well. This can be seen by comparing figures 35, 36, and 37 with figures 38, 39 and 40. Hence, the reduction in P100 amplitude and CS in the migraine group is caused by classical migraine subjects who have had migraine for a long time. Figure 41 shows an example of PRVEP in a control subject and in two patients with short and long histories of classical migraine.

The reduction in P100 amplitude with duration of migraine was correlated with the reduction in spatial CS ($r=0.56$, $p=0.000$),

and with temporal CS at 10 Hz (r=0.59, p=0.000), and 20 Hz (r=0.32, p=0.030). However, the amplitude of the RFVEP at 10 Hz and 20 Hz was not related to the temporal CS at 10 and 20 Hz. There was no relationship between P100 latency and either spatial or temporal CS.

Tab e 30

Correlations of duration of m grane with VEP and psychophysical data in all m grane subjects. S'gnificant results represent reduction of parameter with duration of migraine

		Duration of migraine		
		r	t	p
P100 latency (PRVEP)		0.06	0.53	0.599
P100 amplitude (PRVEP)		0 26	2.51	0.014*
P1 latency (SFVEP)		0.07	0.63	0.533
P2 latency (SFVEP)		0 02	0.17	0.863
Illusions		0.16	1.56	0.122
Spatial CS		0.37	3.83	0.000*
Temporal CS	3.3 HZ	0.13	1.20	0.232
	10 HZ	0.46	4.15	0.000*
	20 HZ	0.27	2.60	0 010*
	30HZ	0.00	0.04	0 966

Figure 35

Effect of duration of migraine on P100 amplitude in all migraine subjects

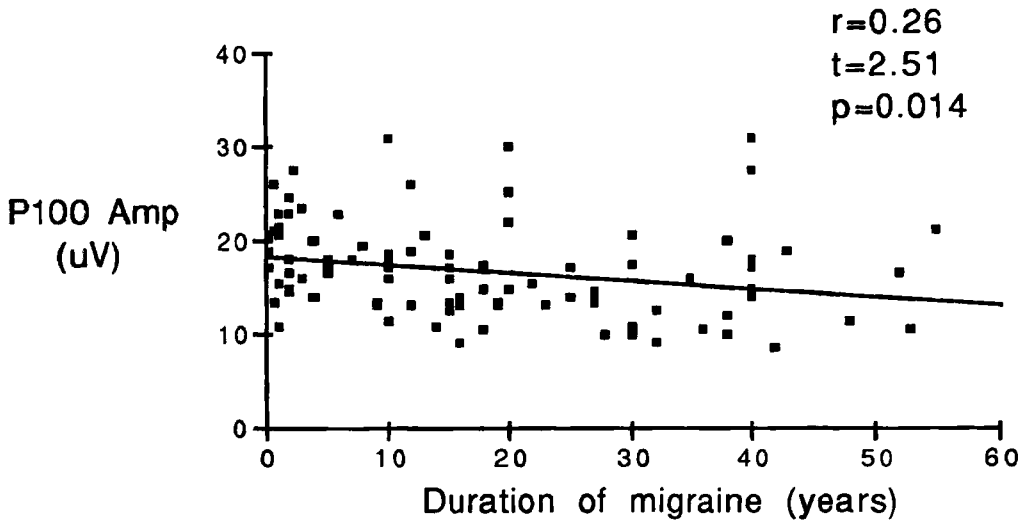


Figure 36

Effect of duration of migraine on spatial CS measured by the Arden threshold scores in all migraine subjects

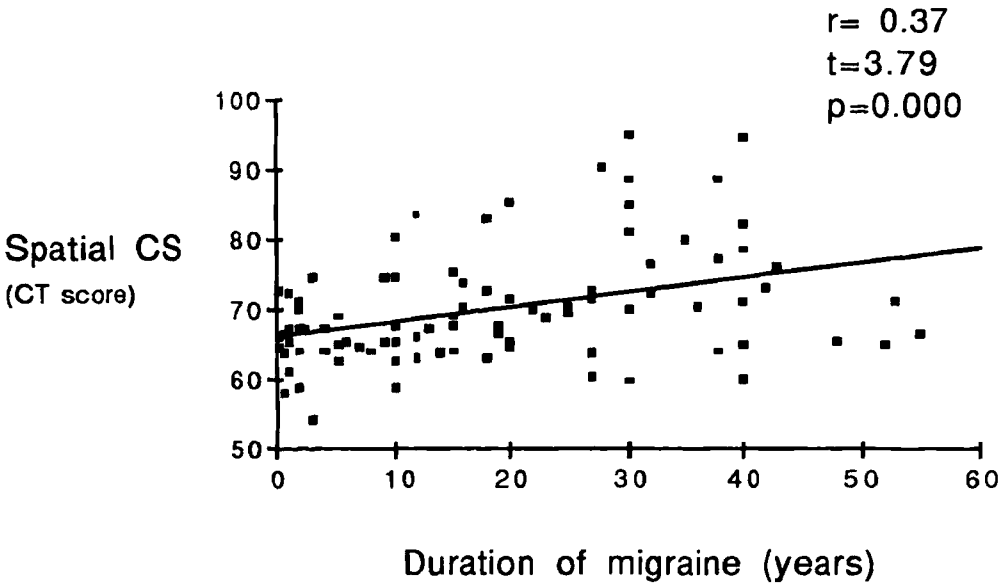
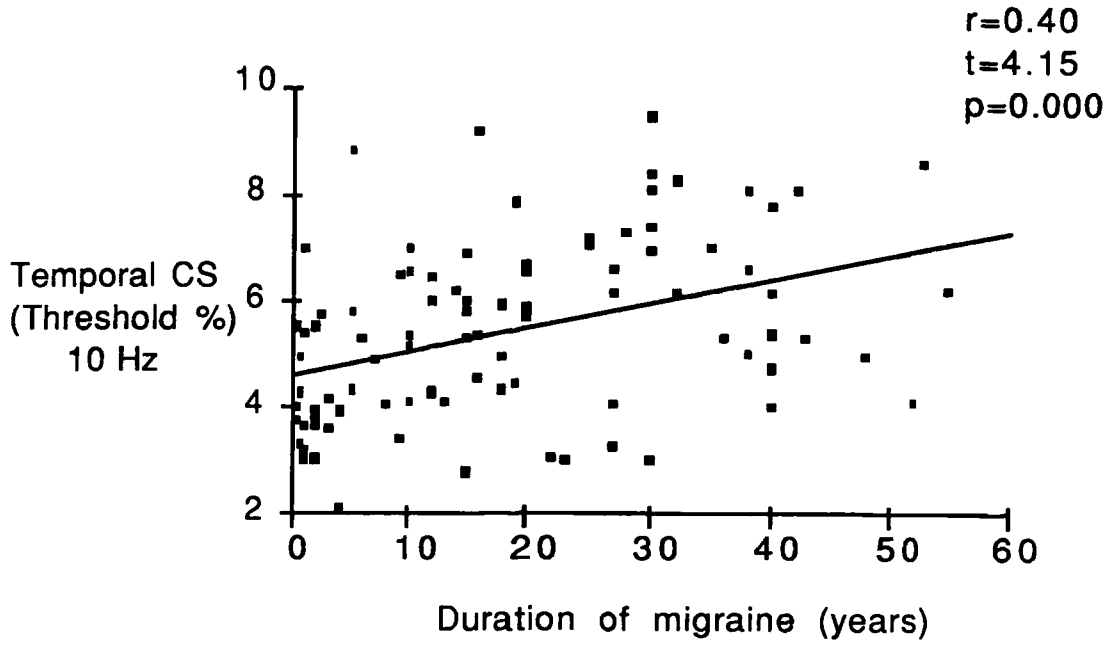


Figure 37

Effect of duration of migraine on temporal CS at 10 Hz and 20 Hz in all migraine subjects



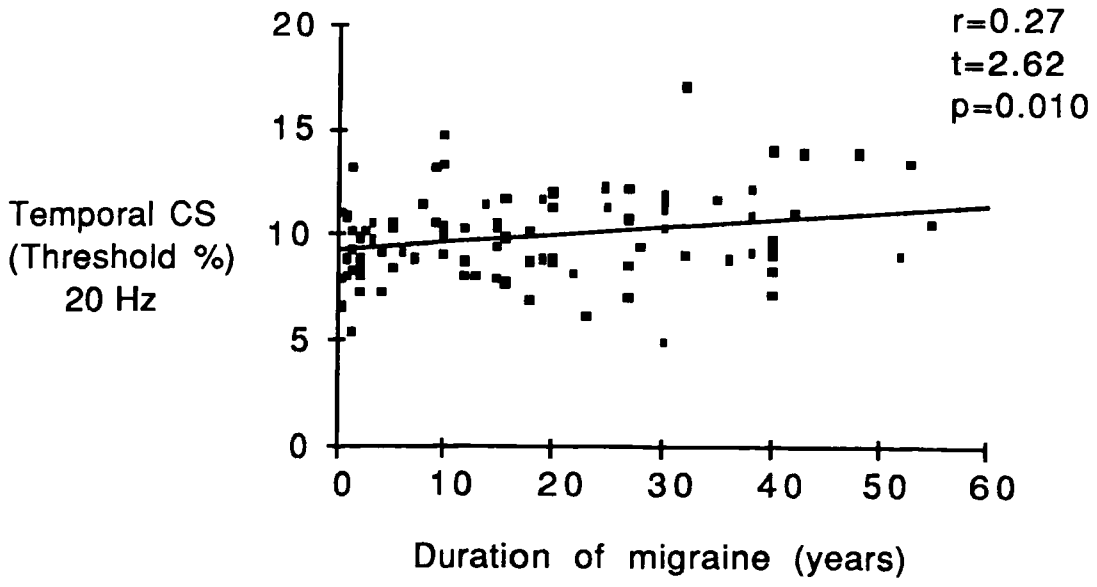


Table 31

Correlations of duration of migraine with visual evoked potentials and psychophysical data in a) classical migraine and b) common migraine. Significant results represent reduction of parameter with duration of migraine

a) Classical migraine

		Duration of migraine		
		r	t	p
P100 latency		0.02	0.12	0.904
P100 amplitude		0.60	5.04	0.000*
Wholefield CS		0.61	5.10	0.000*
Temporal CS	3.3Hz	0.05	0.35	0.726
	10Hz	0.61	5.16	0.000*
	20Hz	0.55	4.43	0.000*
	30Hz	0.14	0.91	0.365

b) Common migraine

		Duration of migraine		
		r	t	p
P100 latency		0.22	0.37	0.193
P100 amplitude		0.06	0.37	0.500
Wholefield CS		0.11	0.68	0.500
Temporal CS	3.3Hz	0.04	0.24	0.809
	10Hz	0.05	0.29	0.772
	20Hz	0.12	0.71	0.485
	30Hz	0.27	1.64	0.110

Figure 38

Effect of duration on P100 amplitude in classical migraine subjects

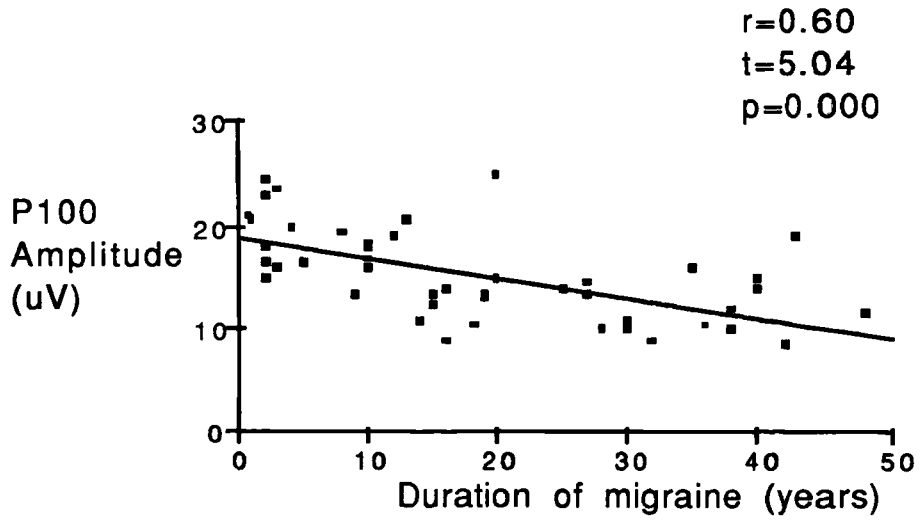


Figure 39

Effect of duration of migraine on spatial CS measured by Arden threshold scores in classical migraine subjects

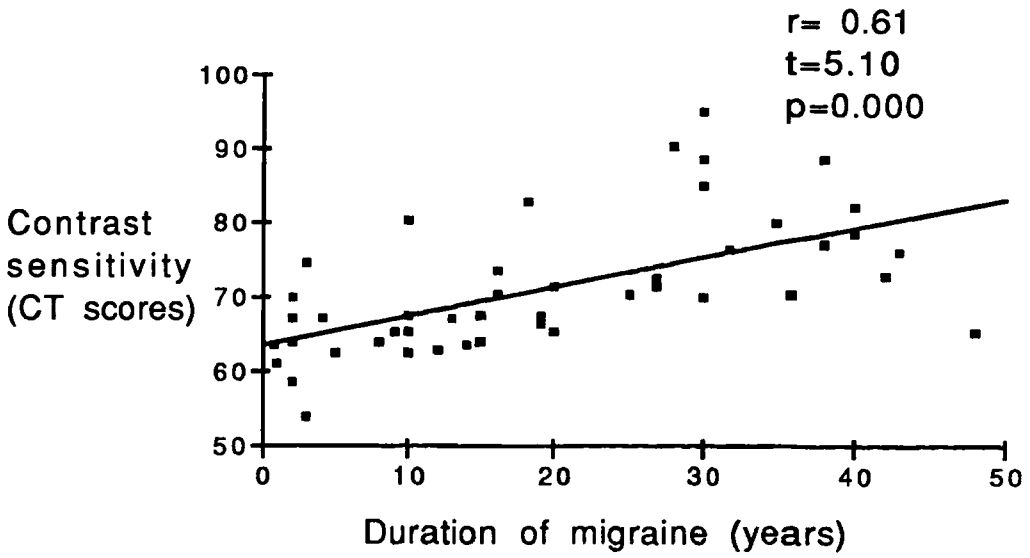
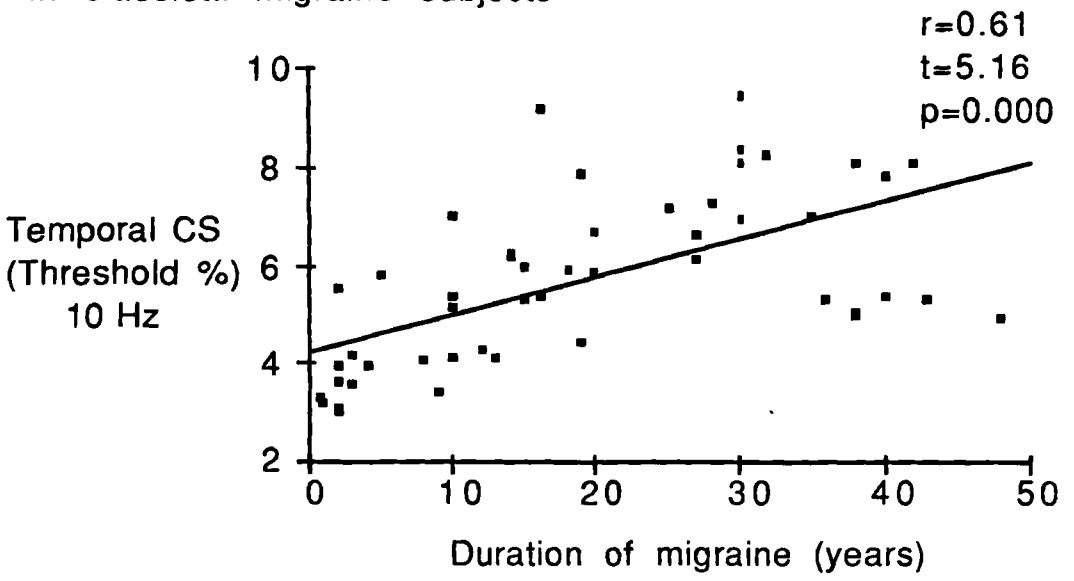


Figure 40

Effect of duration of migraine on temporal CS at 10 and 20 Hz in classical migraine subjects



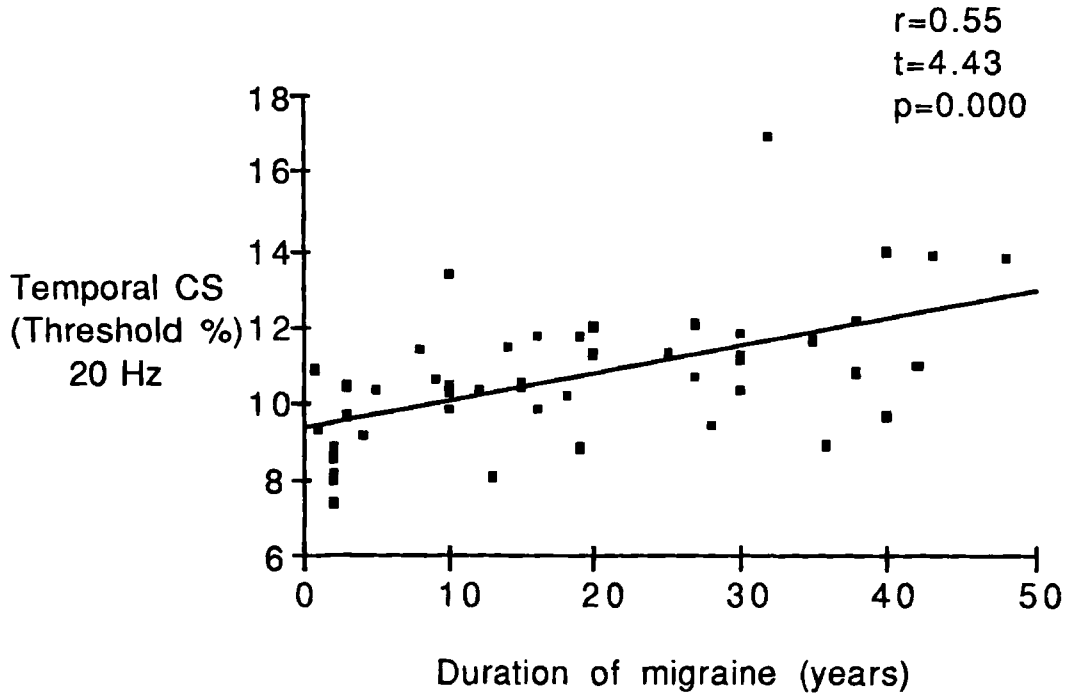
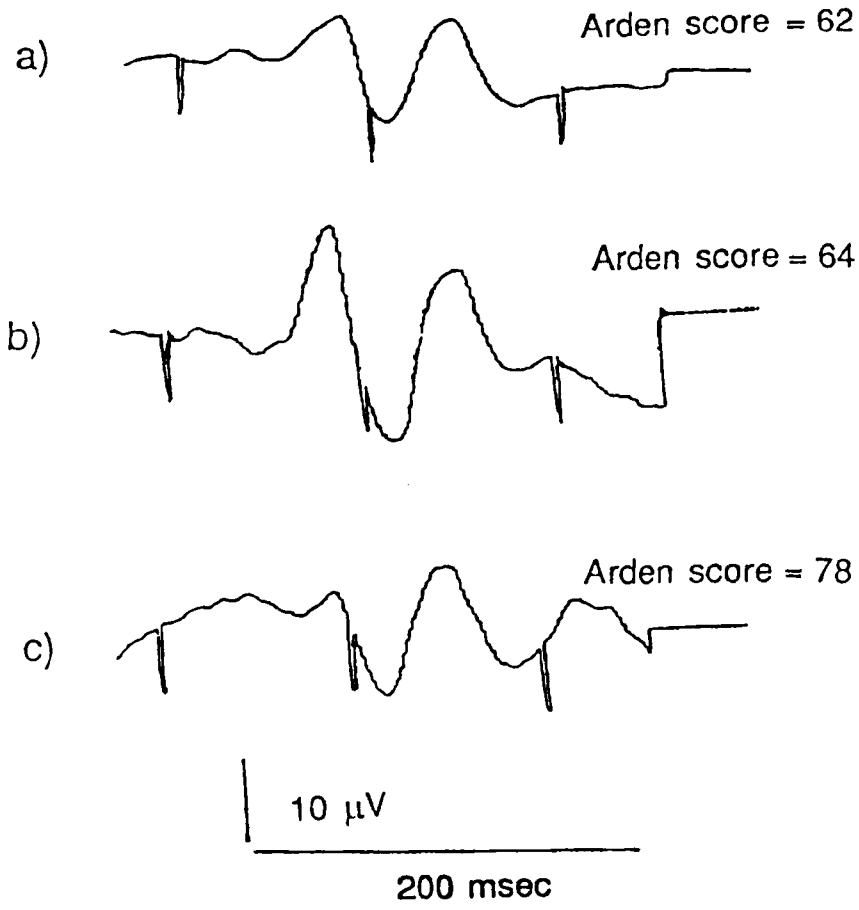


Figure 41

Examples of PRVEP in a) normal subject b) patient with an eight month history of classical migraine and c) patient with 26 year history of classical migraine. Notice high amplitude and normal CS in the patient with a short history and reduced amplitude and CS in the patient with a long history.

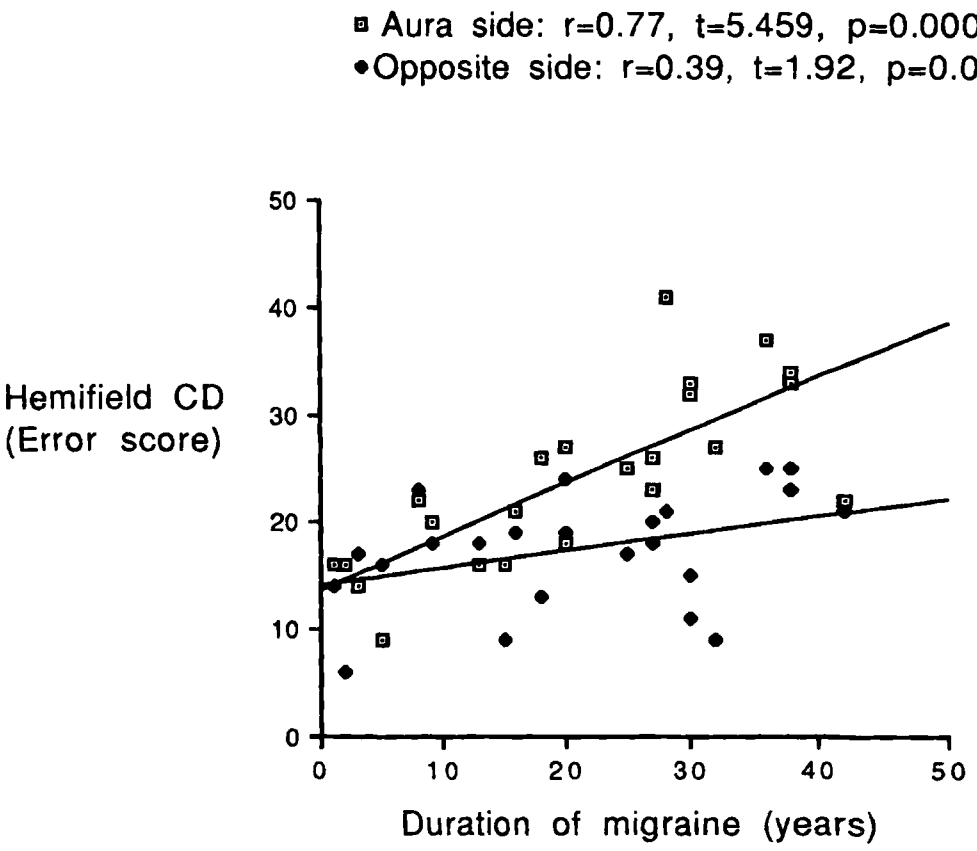


In classical migraine subjects with a strictly unilateral aura the effect of duration of migraine on HFCD on the aura side and the opposite side were looked at separately (Fig 42). The results showed that the hemifield CD was normal in early cases, but in later cases was reduced on the side of the aura.

Thus, the differences between migraine subjects and normal controls, for the spatial CS, hemifield CD and temporal CS are all accounted for by a deterioration in CS with increasing duration of migraine in classical migraineurs only, and predominantly on the side of the visual aura.

Figure 42

Effect of duration of migraine on hemifield CD expressed by error score on the side of the visual aura and on the opposite side of visual aura in classical migraine.



For further analysis of the effect of duration of migraine on electrophysiological and psychophysical tests, the classical migraine subjects were divided into two groups (Table 32), those with duration of migraine $\leq$ 10 years and those with $\geq$ 30 years. The results showed that P100, P1, and P2 latencies, illusions, and H-responses were similar in the two groups, while P100 amplitude, SCS and TCS at 10 and 20 Hz were different. P100 amplitude was significantly larger in the first group than the second group. Further, it was significantly higher than normal in the first group ($p=0.005$), and lower than normal in the second group ($p=0.019$). The SCS and the TCS at 10 and 20 Hz were comparable to controls in the first group, but significantly lower than controls in the second group ($p= 0.000$). Thus, people with classical migraine of short duration had a higher than normal P100 amplitude but a normal CS, while those with a long duration had a reduction in both CS and P100 amplitude.

Table 32

Electrophysiological and psychophysical data in patients with short (≤ 10 years) and long (≥ 30 years) history of migraine

	≤10 years (n=17)	≥30 years (n=14)		
	M±SD	M±SD	t	p
P100 L (msec)	119.3 ± 4.9	119.4 ± 5.7	0.05	0.962
P100 A (μV)	18.7 ± 3.1	11.9 ± 2.9	6.06	0.000*
Flash P1 L (msec)	71.4 ± 8.8	73.9 ± 7.4	0.83	0.413
Flash P2 L (msec)	132.3 ± 9.6	132.0 ± 6.2	0.10	0.922
Illusions	12.1 ± 3.3	12.9 ± 2.6	0.74	0.467
SCS (CT score)	65.4 ± 5.9	79.0 ± 8.2	5.36	0.000*
TCS 3.3 Hz	6.6 ± 1.7	7.01 ± 1.74	0.62	0.542
10Hz	4.3 ± 1.1	7.02 ± 1.5	5.78	0.000*
20Hz	9.2 ± 1.5	12.0 ± 2.1	3.37	0.002*
30Hz	15.2 ± 4.8	16.3 ± 4.9	0.62	0.540
H response prevalence	85%	82%	$X^2_{0.04}$	0.90

7.3.6 Effect of age

Since people with migraine of long duration are obviously older than those with short duration the data were examined for a possible effect of age on those measurements which were different in migraine and control groups, especially on P100 amplitude and contrast sensitivity which were affected by the duration of migraine. This was done for both control subjects and migraineurs.

In normal controls these measurement were not affected by age (Table 33). In migraine subjects both the spatial CS and the temporal CS at 10 Hz were apparently affected by age, but not P100 amplitude. However, multiple regression analysis showed that age itself was not significant, and the apparent age effect was due solely to the duration of migraine (Table 34).

Table 33

Effect of age on electrophysiological and psychophysical data in controls

		Age		
		r	t	p
P100 latency (PRVEP)		0.16	1.25	0.215
P100 amplitude (PRVEP)		0.16	1.23	0.225
P1 latency (FVEP)		0.08	0.52	0.568
P2 latency (FVEP)		0.18	1.34	0.184
Illusions		0.19	1.54	0.129
Spatial CS		0.19	1.49	0.141
Temporal CS	3.3 HZ	0.17	1.32	0.193
	10 HZ	0.10	0.75	0.453
	20 HZ	0.03	0.26	0.798
	30HZ	0.22	1.78	0.080

Table 34

Effect of age on electrophysiological and psychophysical data in migraine subjects.

		Age		
Measurements		r	t	p
P100 latency (PRVEP)		0.06	0.55	0.586
P100 amplitude (PRVEP)		0.17	1.62	0.109
P1 latency (SFVEP)		0.09	0.76	0.451
P2 latency (SFVEP)		0.07	0.67	0.505
Illusions		0.01	0.11	0.914
Spatial CS		0.32	3 25	0.002*
Temporal CS	3 3 HZ	0.02	0.20	0.845
	10 HZ	0.29	2.86	0.005*
	20 HZ	0.15	1.45	0.151
	30HZ	0.13	1.28	0.206

Multiple Regression

	Wholefield CS		Temporal CS	
	t	p	t	p
Duration	2.23	0.028	2.89	0.005
Age	1.30	0.260	0.45	0.655

7.3.7 Effect of frequency of migraine attacks

To look for an effect of frequency of attacks the two extremes of frequency were chosen, subjects who had one or more attacks per week and those who had 5-10 a year. Tests which were affected by the duration of migraine, i.e P100 amplitude and CS, were not included. The types of migraine were comparable in the two groups, 10 classical and 12 common in the first group and 7 classical and 8 common in the second.

The results (Table 35) showed that the H-response was more frequent in patients with frequent attacks (82% compared to 53%), but the difference was not significant. Illusion scores were also higher in the first group, and this difference was significant at 10% but not at 5%. There was no difference in P100, P1 and P2 latencies between the two groups.

In view of the trends found for the H-response and illusion scores, all data on these for the whole group of migraine subjects were then examined for a possible correlation with frequency of attacks. No correlations were found. The data were then examined for classical and common migraine subjects separately, and again no correlations were found.

Table 35

Effect of frequency of attack on electrophysiological and psychophysical tests which were not affected by the duration of migraine.

	≥ One/week M±SD (n=22)	5-10/year M±SD (n=15)	t	p
P100 latency (msec)	118.6 ± 4.6	118.9 ± 4.9	0.24	0.812
P1 latency (msec)	76.01 ± 10.9	75.9 ± 7.5	0.01	0.990
P2 latency (msec)	128.2 ± 11.1	125.9 ± 9.1	0.63	0.530
Illusions	12.5 ± 4.7	9.8 ± 3.3	1.94	0.060
H-response prevalence	82%	53%	X^2 2.3	0.130

7.3.8 Effect of treatment

15 patients were started on prophylactic treatment as part of their routine clinical management, shortly after their first study, receiving propranolol (n=10), atenolol (n=1), pizotifen (n=2) or amitriptyline (n=2). They were studied again after 3 months of continuous treatment and the results of electrophysiological and psychophysical tests before and during treatment are shown in tables 36, 37 and 38.

The measurements shown in table 36 for the group as a whole were similar before and during treatment. The repetitive flash responses (Table 37) showed very interesting results. Direct comparison of the amplitudes of response at various flash frequencies with the eyes open showed no differences. However, with eyes closed there was a significant reduction in amplitude at 18 Hz and a tendency towards lower amplitudes at both 16 Hz and 20 Hz. Furthermore, it will be seen that amplitudes tended to increase at frequencies from 6 to 11 Hz and tended to fall at frequencies from 12 to 24 Hz (Fig 43).

Using the criteria described earlier, 12 of the 15 patients had a positive H-response with eyes closed before starting treatment and only 5 out of 15 wh le they were on treatment. This difference is highly significant (p= 0.016, McNemar's test). There was no difference in H-responses with the eyes open.

Patients kept a diary of their headaches while they were on treatment. The number of attacks recorded while they were on treatment was compared with the number of attacks in the last three months prior to the treatment, as elicited by the original

Table 36

Comparison of visual evoked responses before and during treatment with antimigraine therapy. L = latency (msec), A = amplitude (μV), WF = wholefield, RHF = right half f eld, LHF = left half field

		Before ℞	On ℞		
		M±SD	M±SD	t	p
PRVEP	WF/ P100 L	117.7 ± 4.5	118.9 ± 4.9	1.78	0.086
	WF/P100 A	17.2 ± 7.4	17.4 ± 5.9	0.15	0.884
	RHF/P100 L	117.1 ± 4.3	118.4 ± 4.6	1.61	0.118
	LHF/P100 L	117.4 ± 4.9	118.7 ± 5.3	1.84	0.076
	RHF/P100 A	8.6 ± 4.3	9.8 ± 4.0	0.94	0.354
	LHF/P100 A	7.7 ± 3.3	8.3 ± 2.7	0.83	0.414
SFVEP	P1 L	75.1 ± 11.5	72.8 ±10.2	0.43	0.677
	P2 L	1.32.2 ± 8.8	131.5 ± 7.7	0.24	0.817
	P1 A	8.7 ± 4.8	8.0 ± 6.3	0.41	0.693
	P2 A	13.3 ± 7.7	15.0 ± 7.4	1.20	0.225

Table 37

Comparison of the amplitudes of repetitve flash VEP at various frequencies before and during treatment with antimigraine therapy.

a) eyes closed

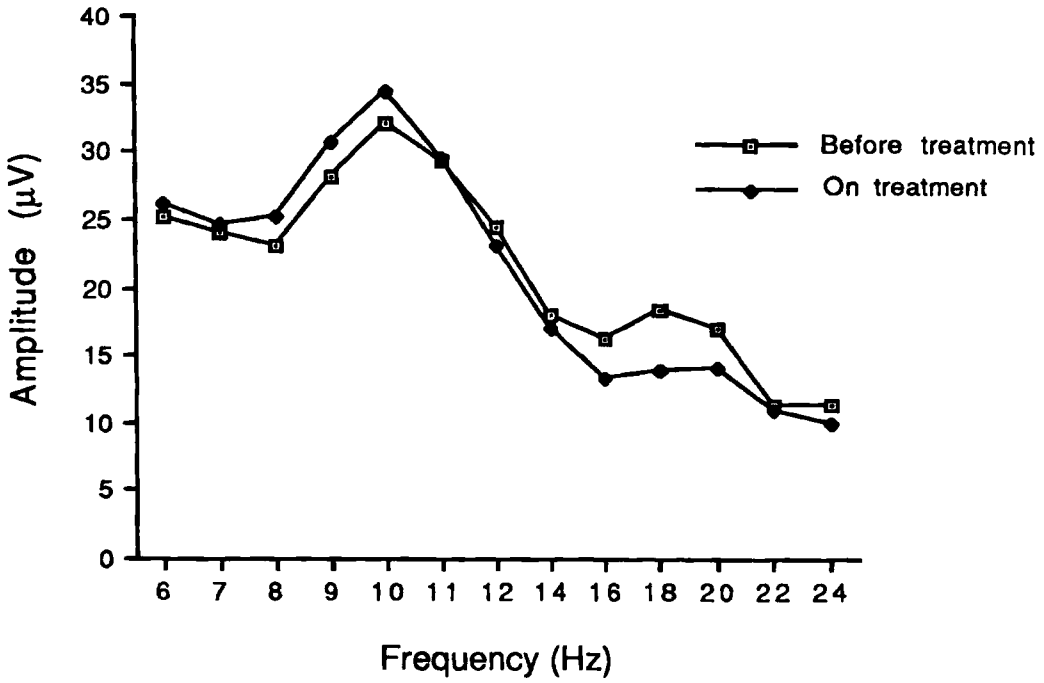
	Before Rx	On Rx		
6Hz	25.2 ± 14.4	26.1 ± 12.3	0.45	0.660
7Hz	24.1 ± 10.2	24.5 ± 9.6	0.14	0.888
8Hz	23.0 ± 12.7	25.1 ± 10.5	0.67	0.512
9Hz	28.0 ± 12.0	30.7 ± 10.6	0.92	0.372
10Hz	32.1 ± 15.9	34.3 ± 12.7	0.79	0.440
11Hz	29.2 ± 16.3	29.4 ± 15.4	0.04	0.971
12Hz	24.3 ± 16.8	23.1 ± 10.4	0.26	0.800
14Hz	17.9 ± 9.5	16.9 ± 8.2	0.38	0.709
16Hz	16.1 ± 7.4	13.2 ± 6.7	1.39	0.187
18Hz	18.3 ± 8.9	13.8 ± 5.7	2.17	0.048*
20Hz	17.0 ± 11.9	14.1 ± 5.6	1.07	0.303
22Hz	11.3 ± 7.3	10.9 ± 5.7	0.71	0.491
24Hz	11.3 ± 9.7	10.0 ± 4.1	0.55	0.591

b) eyes open

	Before Rx	On Rx		
	M ± SD	M ± SD	t	p
6Hz	22.3 ± 2.8	23.5 ± 10.7	0.30	0.768
7Hz	24.6 ± 9.8	25.8 ± 13.6	0.36	0.729
8Hz	20.2 ± 6.2	24.4 ± 11.7	1.29	0.224
9Hz	23.1 ± 7.0	21.5 ± 10.2	0.44	0.669
10Hz	24.4 ± 11.5	22.3 ± 5.3	0.89	0.395
11Hz	25.8 ± 10.4	24.9 ± 11.3	0.25	0.808
12Hz	21.6 ± 8.0	22.9 ±11.1	0.38	0.71.3
14Hz	19.4 ± 8.7	18.5 ± 8.1	0.29	0.779
16Hz	17.4 ± 8.3	17.5 ± 8.8	0.03	0.979
18Hz	18.0 ± 9.8	16.3 ± 7.9	0.56	0.584
20Hz	16.8 ± 7.1	15.0 ± 6.4	0.92	0.378
22Hz	15.7 ± 5.9	14.8 ± 7.0	0.41	0.687
24Hz	14.8± 9.8	15.7 ± 6.5	0.39	0.702

Figure 43

Comparison of the amplitudes of repetitive flash VEP at various frequencies, with eyes closed, before and during treatment with antimigraine therapy.



questionnaire. The reduction in H-response then proved to be related to clinical improvement. In patients who maintained their H-response the mean reduction in frequency of attacks was 56%, and in those who lost their H-response it was 89%. One patient took propranolol for three months and then amitriptyline for three months. Reduction in headache frequency was only 25% for each drug, and she retained her H-response. The 7 patients who lost their H-response all had a more than 80% reduction in frequency of attacks, and the attacks were less severe. Figure 44 (a and b) shows an example of one of these patients and a normal control.

Comparison of psychophysical data before and during treatment showed no differences in spatial or temporal CS (Table 38). However, there was a significant reduction in the illusions and visual discomfort induced by high contrast patterns when patients were on successful treatment (Table 38 and Fig 45).

A second group of eight patients, not forming part of the main study, were examined for the first time while on prophylactic treatment. All of them had had a good response to treatment i.e the antimigraine drugs had significantly reduced the frequency and intensity of attacks. Only three had a positive H-response at this stage. The mean number of illusions was 7.3, with a SD of 1.5, which is comparable to the score found during prophylactic treatment in the previous group of 15 patients. Four of the patients, none of whom had an H-response, stopped prophylactic treatment, and these were examined again one month later. In three patients clinical improvement was maintained, the H-response remained absent and the number of illusions stayed

Figure 44

Examples of effect of treatment on RFVEP. a) and b) migraineur before starting prophylactic treatment and after 3 months on treatment with propranolol 40 mg b.d. c) and d) normal control before and one hour after intake of 40 mg propranolol.

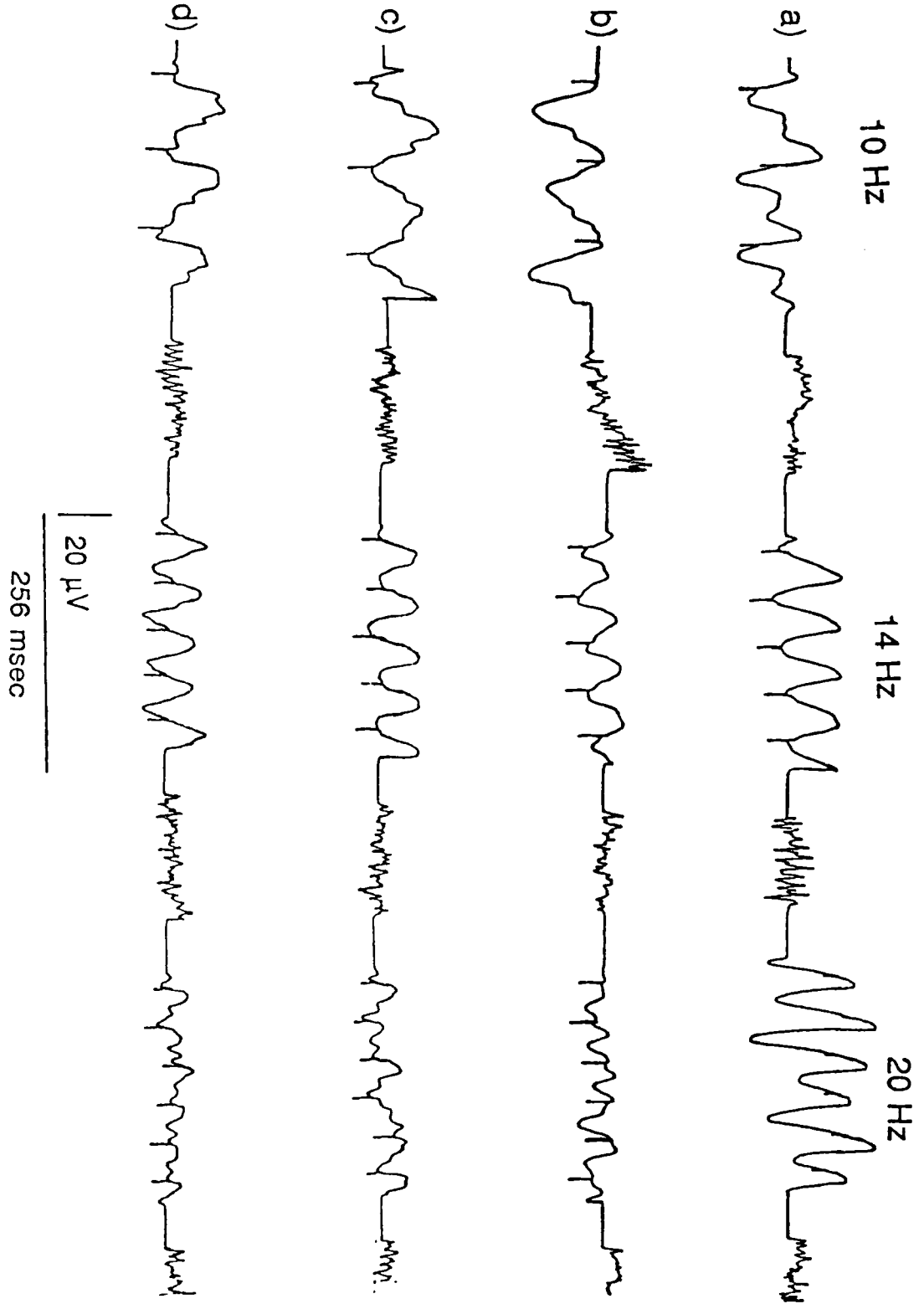


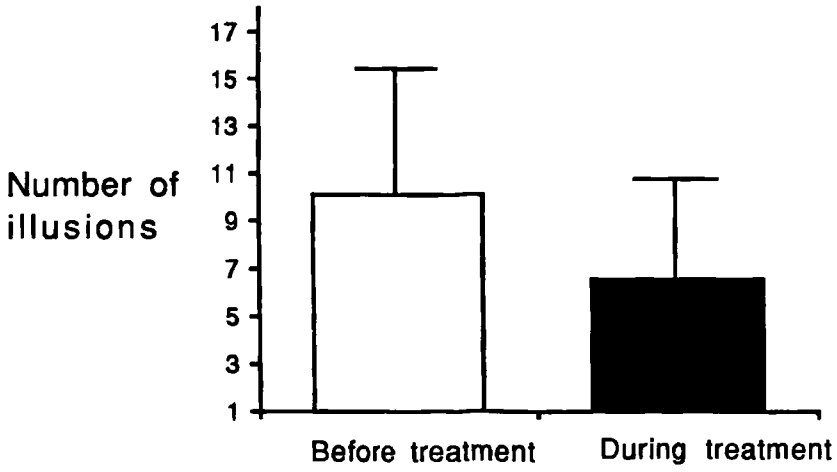
Table 38

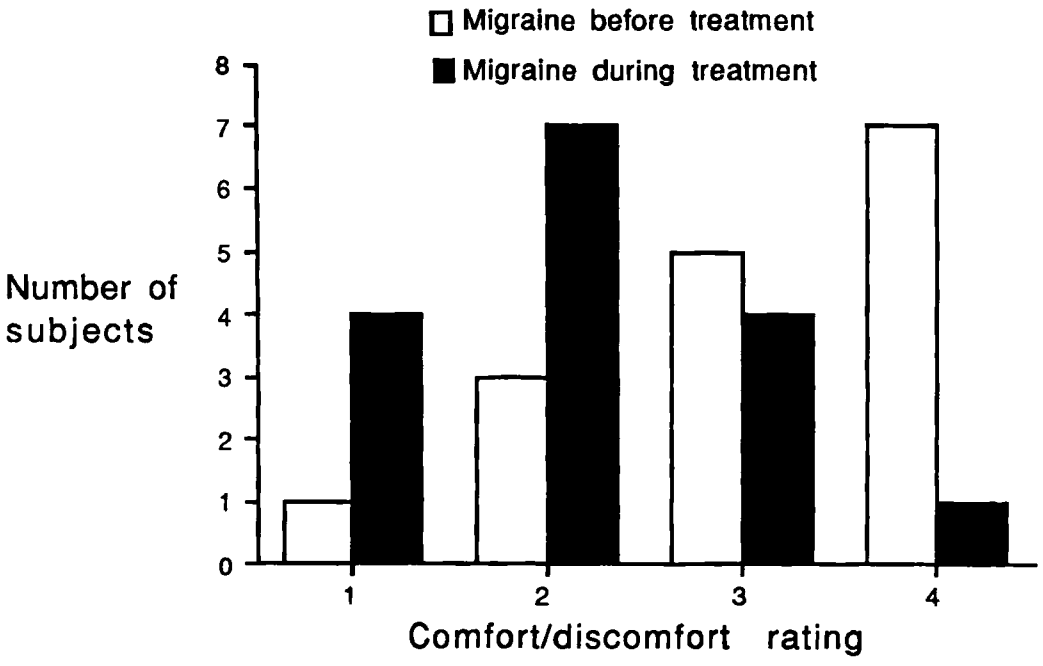
Comparison of psychophysical data before and during treatment with antimigraine therapy in 15 migraine patients

	Before Rx	On Rx		
	M ± SD	M ± SD	t	p
Illusions	10.1 ± 5.4	6.6 ± 4.2	3.33	0.005*
SCS (CT score)	65.5 ± 5.5	65.0 ± 4.3	1.20	0.241
TCS 3.3Hz	5.5 ± 1.4	5.5 ± 1.1	0.11	0.913
10Hz	4.3 ± 1.4	4.2 ± 1.2	0.44	0.661
20Hz	8.5 ± 2.2	8.3 ± 2.1	1.03	0.311
30Hz	13.5 ± 4.6	12.9 ± 3.6	0.54	0.595

Figure 45

Effect of treatment on illusions and visual discomfort in 15 migraine subjects





1. Neutral
2. Slightly uncomfortable
3. Moderately uncomfortable
4. Very uncomfortable

the same. In the fourth patient attacks of migraine recurred two weeks after stopping the treatment, and testing showed that the H-response had become positive, and the number of illusions had increased from 6 to 14.

Because of these results observations were made on five colleagues who volunteered to be tested before and one hour after 40 mg propranolol orally. The amplitudes of RFVEP (Fig 44 c and d, and Table 39), and the experience of illusions and visual discomfort (Fig 46) were not affected by the drug in these subjects.

Table 39

Comparison of the amplitudes of repetitive flash visual evoked potentials at various frequencies, before and after one hour of taking 40 mg propranolol in 5 normal controls

a) with eyes open

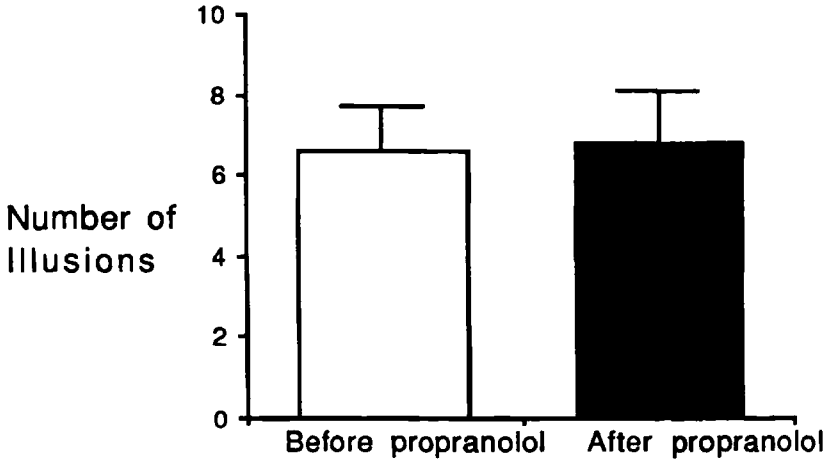
	Before Rx	On Rx		
6Hz	25.7 ± 4.4	27.7 ± 6.4	0.46	0.644
7Hz	25.7 ± 3.4	26.2 ± 3.5	0.22	0.836
8Hz	28.8 ± 6.9	29.2 ± 4.6	0.09	0.933
9Hz	25.8 ±1.9	23.7 ± 4.9	1.14	0.307
10Hz	21.8 ± 4.5	22.7 ± 4.6	0.96	0.383
11Hz	19.0 ± 3.7	20.2 ± 5.0	0.82	0.450
12Hz	23.0 ± 8.1	20.0 ± 4.2	1.14	0.306
14Hz	24.3 ± 10.1	22.0 ± 4.2	0.75	0.485
16Hz	18.3 ± 5.9	22.2 ± 3.7	1.28	0.258
18Hz	11.3 ± 4.9	13.8 ± 7.3	1.81	0.131
20Hz	10.5 ± 4.8	12.3 ± 7.2	1.53	0.186
22Hz	12.3 ± 5.0	12.2 ± 3.4	0.11	0.920
24Hz	10.3 ± 3.0	10.5 ± 3.0	0.12	0.913

b)with eyes closed

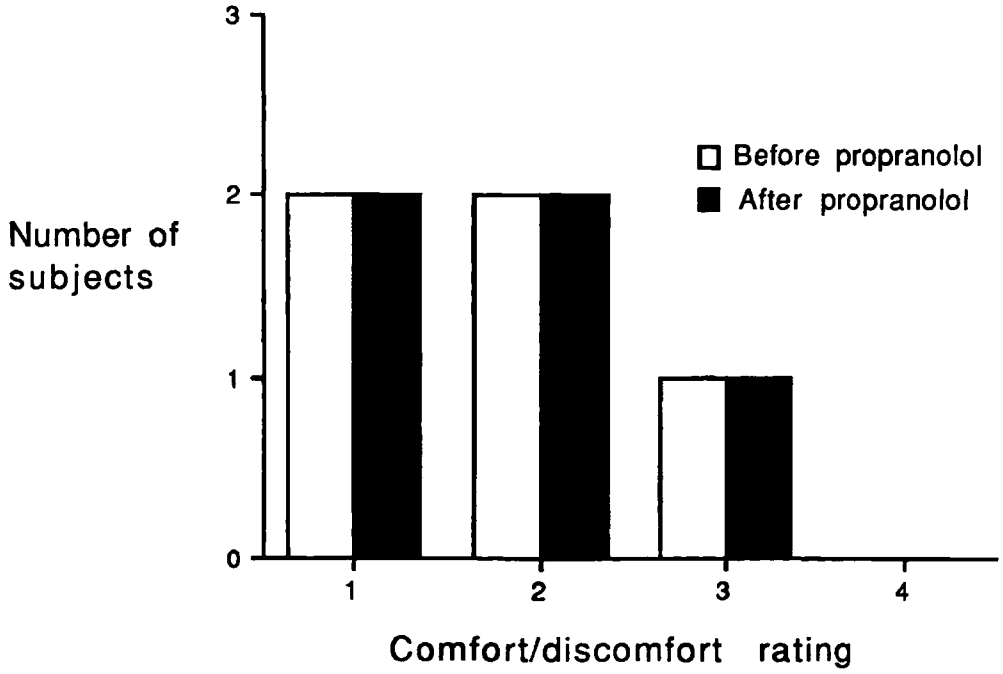
	Before Rx	On Rx		
6Hz	14.60±3.02	17.90±2.76	1.96	0.107
7Hz	19.10±4.87	19.80±2.98	0.72	0.503
8Hz	22.10±2.94	18.50±4.36	1.55	0.182
9Hz	34.00±9.70	32.40±9.00	0.65	0.544
10Hz	36.92±3.88	33.50±7.00	1.22	0.277
11Hz	23.82±9.48	20.90±13.05	0.48	0.653
12Hz	21.30±11.03	23.50±10.07	1.03	0.350
14Hz	19.50±4.58	16.50±5.15	1.27	0.260
16Hz	12.40±4.19	14.70±8.30	1.29	0.254
18Hz	13.10±4.12	11.40±2.52	0.92	0.401
20Hz	10.50±1.90	9.80±2.25	1.47	0.201
22Hz	12.20±4.99	12.10±7.26	0.03	0.977
24Hz	10.20±5.89	9.50±4.58	0.23	0.827

Figure 46

Illusions and visual discomfort in 5 normal subjects before and one hour after intake of 40 mg propranolol



M±SD	M±SD	t	p
6.60±1.14	6.80±1.30	0.34	0.749



1. Neutral
2. Slightly uncomfortable
3. Moderately uncomfortable
4. Very uncomfortable

7.4 Summary of results

1. ERG: Pattern and flash ERG were normal in both common and classical migraine.

2. PRVEP: P100 latency was significantly prolonged in migraine subjects, both common and classical. It was not affected by the duration of migraine. P100 amplitude was higher than normal in common migraine of any duration and in classical migraine of short duration. It was reduced in proportion to the duration of migraine in classical migraine, especially in the hemifield in which the visual aura was consistently experienced.

3. SFVEP: Latencies of both P1 and P2 waves at the occiput were prolonged in migraine of both types, but were not affected by the duration of migraine. Amplitudes were normal. Latencies and amplitudes of the vertex flash responses were normal

4. RFVEP: With occipital recording migraine subjects had a higher prevalence of H-responses than controls. The difference was greater with eyes closed. H-responses tended to be more prominent in classical than common migraine, and to be less in subjects with infrequent attacks, and disappeared in patients responding to prophylactic treatment. They were not affected by the duration of migraine.

The vertex responses recorded at Cz were normal, like the single flash responses.

4. Illusions were more frequent and varied in migraine subjects, and caused more discomfort. They were more common in patients with migraine triggered by visual stimuli, and in patients with frequent attacks. They were more common in classical than in common migraine, and more prominent on the side of a consistently unilateral visual aura. Illusions were asymmetrical in patients with lateralised headache but the sides did not correspond. They were not affected by the duration of migraine, but they were reduced when pat ents received effective prophylactic treatment.

5. Spatial and temporal CS were normal in patients with common migraine, and in those with classical migraine of short duration. Both spatial CS and temporal CS at 10 and 20 Hz were significantly reduced in patients with classical migraine of long duration, and this was not an age effect. In patients with a consistently lateralised visual aura hem field CD was reduced on the side of the aura, and in these patients the P100 amplitude of the half-field PRVEP was reduced too.

The reduction in spatial CS was correlated with P100 amplitude. The change in temporal CS at 10 and 20 Hz was not correlated with H-response, which declined as a function of headache frequency but not duration of migraine.

6. Patients with bilateral headache tended to have a bilateral aura and patients with asymmetrical headache tended to have an asymmetrical aura, but the trend of the headache to be on the opposite side from the aura was not significant.

Asymmetry of both hemifield CD and illusions was related to the side of visual aura but not to the side of headache.

There was a correlation between asymmetry of illusions and of hemifield CD, and there was a trend for the side of the prominent illusions to show a reduction in hemifield CD. However, hemifield CD was influenced by the duration of migraine but illusions were not.

7.5 Relation of present results to previously published results:

The following are previous observations which have been confirmed.

1. Normal flash ERG.
2. Prolonged pattern P100 latency, not affected by duration of migraine.
3. High P100 amplitude
4. Prolonged P1 and P2 latencies of the occipital response to single flash.
5. Normal vertex responses to single and repetitive flash.
6. Increased prevalence of H-response especially with eyes closed.
7. Increased illusions and visual discomfort from high contrast patterns.

The following are new observations:

1. Normal pattern ERG.
2. Prolongation of P1 and P2 latencies, like the P100 latency, was not affected by the duration of migraine.
3. P100 amplitude was higher than normal in common migraine, regardless of its duration, and in classical migraine of short duration. In classical migraine of longer duration it was reduced in

proportion to the duration of migraine, predominantly in the hemifield in which a visual aura was consistently experienced.

4. H-responses tended to be more prominent in classical than common migraine. They were not affected by duration of migraine, but were less prominent in subjects with infrequent attacks, and disappeared in patients responding to prophylactic treatment.

5. Illusions and visual discomfort were commoner in classical than common migraine, and more prominent on the side of a consistently unilateral visual aura. They were more common in patients with migraine triggered by visual stimuli and in patients with frequent attacks, and they lessened on successful prophylactic treatment. Illusions were asymmetrical in patients with lateralised headache but the sides did not correspond. They were not affected by the duration of migraine.

6. Spatial and temporal CS were normal in patients with common migraine, and in those with classical migraine of short duration. However both spatial CS and temporal CS at 10 and 20 Hz were significantly reduced in patients w'th classical migraine of long duration.

7. In patients with a consistently lateralised visual aura hemifield CD was reduced predominantly on the side of the aura, and in these patients the P100 amplitude of the half-field PRVEP was reduced too.

8. The reduction in spatial CS was correlated with P100 amplitude. The change in temporal CS at 10 and 20 Hz was not correlated with repetitive flash response amplitudes at 10 and 20 Hz.

9. Patients with bilateral headache tended to have a bilateral aura and patients with asymmetrical headache tended to have an

asymmetrical aura, but the trend of the headache to be on the opposite side from the aura was not significant.

10. Asymmetry of both hemifield CD and illusions was related to the side of visual aura but not to the side of headache.

11. There was a correlation between the laterality of illusions and hemifield CD and there was a trend for the side of the prominent illusions to show a reduction in hemifield CD.

Incidental observations which have not previously been described include:

1. The overlap of occipital and vertex flash reponses at Pz, supports the notion of two different flash response systems.

2. Left hemifield CD is better than right hemifield CD.

3. If the first ratio of the H response is defined as ≥ 0.5 then the second ratio can be omitted. Since the response amplitude in the alpha frequency range is similar in all cases the H-response can be said to depend almost entirely on the amplitude of responses at 18-20 Hz.

CHAPTER 8 DISCUSSION

It should be noted that this was a volunteer study and therefore the subjects may not be representative of the general population of migraine sufferers for factors such as sex ratio, unilaterality of the headache and aura and various precipitating factors. I have studied a selected group of migraineurs in an attempt to understand some of the pathophysiological mechanisms of migraine.

The significance of the findings depends on differences between these migraine subjects and the matched control group, so it is important first to establish the conformity of results in the control group to those previously published for normal subjects.

8.1 Data from control subjects:

8.1.1 Electrophysiological tests

ERG

The latencies and the amplitudes of the alpha and beta waves of the pattern ERG found in normal subjects in this study are comparable to those reported by others (Adachi-Usami and Murayama 1985, Kakisu et al. 1986) using skin electrodes, and are also comparable to the normal values obtained with gold foil conjunctival electrodes (e.g Holder 1987), if account is taken of the longer latencies produced with a TV type stimulator as opposed to the mirror reversal method used by Holder (1987).

The normal values of the flash ERG are also comparable to

those reported by other workers (e.g Papakostopoulos 1982 and Winter 1985). Age and sex had no effect on either flash or pattern ERG. Wright et al. (1985) and Celesia et al. (1987) found increased latency of P-ERG latency with age, probably because their sample included older age groups. Celesia et al. (1987) found no sex differences in the pattern ERG, and there is no study known on sex differences in the flash ERG.

PRVEP

In the current study normative data for pattern-reversal VEP (PRVEP) are comparable to reported values using television display and a check size of 38 minutes (e.g Chiappa 1989).

The contralateral responses were variable, sometimes not well-formed and not even present all the time. This precluded their use for analysis in this study. The monocular response had a larger amplitude than the half-field response. The binocular response had a shorter latency than the monocular response, was smaller and less well formed, and sometimes showed a "W-shape" pattern. All these observations agree with the findings of previous authors (Barrett et al. 1976, Shagass et al. 1976, Kennard et al. 1978, Blumhardt et al. 1982, Onofrj et al. 1982).

The shorter latency in females (mean 2.7 msec) in this study was close to the one reported by Stockard et al. (1979) using a T.V stimulator and comparing 50 healthy women and 50 healthy age-matched men. Halliday et al. (1982), using a mirror projector, found female latencies to be shorter by 3.5 to 3.9 msec and mean P100 amplitude to be 4-5 uV greater. These differences have been attributed to a smaller head size and thinner skull in

women (Halliday et al. 1982), and also to a higher core temperature in women (Stockard et al. 1979). There was no sex difference in P100 amplitude in the present study. It is worth noting that recently Poole and Payne (1990) showed that a smaller head circumference correlates significantly with shorter latency but not with higher amplitude.

Age had no significant effect on P100 latency or amplitude in this study, which is in agreement with the literature (section 4.2.2).

SFVEP

The SFVEP has a different waveform (Fig 16) and greater interindividual variability among normal subjects than the pattern reversal VEP, as can be seen by the higher standard deviations obtained here (tables 9 and 10). For this reason several authors (e.g Halliday and Mushin 1980) have recommended the use of only the pattern VEP in clinical practice. Nevertheless the P1 and P2 waves can be clearly recorded in most subjects (Wright et al. 1985). The control values found in the current study are comparable to those in the literature for occipital flash responses (Cigánek 1961, Kooi and Bagchi 1964, Borda 1977, Wright et al. 1985) and for vertex flash reponses (Kooi and Bagchi 1964 and Borda 1977). The results did not vary with age or sex. Some workers (Dustman and Beck 1966, Wright et al. 1985) studying older age groups showed that P2 latency was prolonged with age. The observation of higher SFVEP amplitudes in females by Buchsbaum et al. (1974) was not confirmed.

RFVEP

Direct comparison of current results with those of other authors is not practicable for the amplitude of repetitive flash responses at various frequencies because individual responses vary widely and different authors have used different methods.

8.1.2 Psychophysical data:

Illusions

The average number of illusions seen by these normal subjects was slightly less than in those subjects with a low incidence of headache in the study by Wilkins et al. (1984).

The values for Arden CS were similar to those reported by other authors (e.g Arden 1978 and Marmor 1986) and they did not vary with age. There is no general agreement on an effect of age on the Arden CS. Arden himself (1978) found no effect in the age range 11 to 70 , grouped in decades. However, Skalka et al. (1980) found a progressive increase in the threshold scores for all plates irrespective of spatial frequency from the second to the 6th decade in subjects with "excellent" visual acuity. This was confirmed by Singh et al. (1981) using plates 6 and 7 only.

Hemifield CD was better in the right than the left hemisphere and central CS was better than peripheral. It is well known that the right hemisphere is more important for visual perceptual and spatial abilities (Kimura 1973, Kimura and Durnford 1974), and Kobayashi et al. (1985) have demonstrated that the Arden CS is much more affected by lesions involving the right parieto-occipital region than the left parieto-occipital region. Several

authors have shown that CS is better in the central field than in the peripheral field of vision (e.g Robson and Graham 1981, Wright and Johnston 1983).

Normal values in this study for temporal CS are comparable to those in the reported literature (De Lange 1958a, van der Tweel and Estèvez 1974, Wright and Drasdo 1985). No effect of age or sex was found. The age effect reported by Wright and Drasdo could not be detected within the age group involved in this study. No studies have mentioned the effect of sex on temporal CS.

8.2. Abnormalities found in migraine subjects: relation to previous studies.

8.2.1 ERG

There was no difference in flash ERG or pattern ERG between migraine and control subjects. There is no study in the literature on pattern ERG in migraine, but there are two studies on flash ERG. The first was by Winter (1985), the only previous migraine study to record ERGs simultaneously with VEPs, and he found both the flash ERG and the EOG to be normal under both photopic and scotopic conditions. In the present study a rather scotopic condition was used to record the ERG because this produces a larger b wave than photopic conditions. The second study, by Puca et al. (1985), found a reduction in the amplitude and/or frequency of oscillatory potentials in all 13 migraineurs tested. They attributed these changes to an effect on the retinal circulation as

part of the vascular changes in migraine. It was not possible to record the oscillatory potentials in the present study, as the EEG amplifier bandwidth was only 0.5 Hz to 150 Hz, and these recordings require a wider range e.g 0.5 to 10 KHz.

The importance of the normal ERG results obtained here is the implication that any changes found in VEP represent dysfunction central to the ganglion cell layer, in the visual pathways and/or the visual cortex.

8.2.2 Pattern VEP

P100 latency was significantly prolonged in both common and classical migraine. The delay averaged about 5 msec, and was similar when evoked by full-field or half-field stimulation. Only 17 subjects had a latency greater than mean+2SD of normal controls.

Prolongation of P100 latency has previously been reported in several studies. Kennard et al. (1978) found a mean latency increase of 5-6 msec in 28 classical migraineurs, and Winter (1985) found a mean increase of 5 msec in classical cases, which was significant only in females. Polich et al. (1986) reported a 2-4 msec delay in 20 subjects with classical migraine, which did not reach statistical significance. Mariani (1988) reported an increase of 4 msec in 20 subjects with common migraine, but again the difference was not significant. Surprisingly, Drake et al. (1990) found a delay of only 1 msec in 50 patients with common migraine using a similar method to the current study.

The total group of migraine subjects had slightly higher P100 amplitude (1.5 μV) than normal controls (Table 2). This

difference is not as significant as that for latency because the total migraine group contains classical migraineurs with a long duration of migraine who had a lower P100 amplitude than normal subjects (Table 32). However, when these were excluded the P100 amplitude was significantly higher (4 μV) both in patients with common migraine (Table 17) and in classical migraineurs with a short duration (Table 32).

Several other studies have also reported an increased P100 amplitude. Kennard et al. (1978) found the amplitude to be greater by 3-4 μV with binocular and monocular whole-field stimulation but only in patients with left sided headache (n=11), and the difference was of higher statistical significance with recording over the left hemisphere. Diener et al. (1984) also found also higher amplitudes of the order of 2-3 μV with both half-field and whole-field stimulation in 188 migraineurs. Drake et al. (1990) found that the mean P100 amplitude was only slightly higher (1 μV) in 50 patients with common migraine, and the difference was not significant.

Benna et al. (1985) claimed no abnormalities in either P100 latency or amplitude in 10 subjects suffering from common migraine. Comment can not be made since the patients were few in number and above all methods and values were not reported.

8.2.3. Single Flash VEP

The P1 and P2 latencies of the occipital flash reponses were prolonged in migraine sufferers of both types, while the amplitudes were normal. The latencies and amplitudes of the

vertex flash responses were normal.

The prolongation of P1 latency was not significant when only 51 migraineurs and 30 controls had been studied (Khalil and Legg 1989), but the difference became significant with larger numbers. Lehtonin (1974) reported normal latency in 33 subjects, and Winter (1985) in 45 subjects, but Richey et al. (1966) found prolongation in 50 subjects and Lehtonin et al. (1979) found it in 11 females.

No other study has found prolongation of P2 latency. Richey et al. (1966) found that the negative component of the secondary responses, which they called N95, was delayed, but they did not measure the second positive wave. By contrast Winter (1985) found a shorter N3 latency in young migraineurs (15-35 years) under photopic conditions. However, this wave is not consistently present, and since he used bipolar recording it is not clear whether this was a vertex or an occipital response.

There is no agreement on the SFVEP amplitude in migraine in the literature. Lehtonin (1974) found a high P1 amplitude in 33 patients and Lehtonin et al. (1979) found low P2 and N2 amplitudes in 11. Both Richey et al. (1966) and Winter (1985) found a low P2 amplitude. Conversely, Connolly et al. (1979) found a high amplitude of the "major positive wave" which they called P100, but they were recording from the temporal region.

The normal results found here for vertex SFVEP are in agreement with those of Richey et al. (1966) and Winter (1985). Only Connolly et al. (1982) found long latency and high amplitude of the vertex N120 wave, using very bright prolonged flashes.

Sex was not found to influence the responses, and the more

significant difference between female migraineurs and controls compared with male migraineurs and controls (Table 14) is due to the larger female population in this study. However some authors (Richey et al. 1966, Lehtonin 1974, Winter 1985) found that VEP changes were more prominent in females. It has been suggested that different stages of the menstrual cycle may influence the VEP changes in female migraineurs (Richey et al. 1966, Lehtonin 1974), but Lehtonin et al. (1979) found that this did not affect SFVEP components or RFVEP at 10 and 20 Hz in either controls or migraineurs.

Occipital and vertex flash responses are thought to represent two different physiological systems (see section 4.3.3), and their differential involvement in migraine is one more piece of evidence in favour of this. Furthermore, the present study has confirmed previous observations of differences in waveform morphology, latencies and amplitudes between the vertex and occipital flash responses. The new observation that these responses overlap at Pz (Fig 17) is additional evidence for that difference and supports the notion of two different systems.

8.2.4. Repetitive flash VEP

Direct comparison of responses at various frequencies showed that the responses at 6 Hz, 18 Hz and 20 Hz were increased, while the responses in the alpha frequency range were normal. The finding of a higher amplitude at 6 Hz is in line with that of Lehtonin (1974) who observed a higher amplitude at 7.7 Hz in 33 migraineurs, but this was not significantly different from 11 controls. In addition, Nyrke and Lang (1982) found that

amplitude in the alpha frequency range was normal in 30 patients with common migraine.

The differences between responses at individual frequencies are of limited value because the amplitude of the whole range of responses varies widely between individuals. This is why the criteria of the H-response were introduced by Golla and Winter (1956) for comparing results between migraine and control subjects.

The prevalence of an H-response test proved to be greater with eyes closed than with eyes open, confirming Winter's (1985) observation.

The hallmark of the H-response is enhanced photic driving, or an enhanced response to flicker, with a maximal difference from controls around 20 Hz. This original observation of Golla and Winter (1959) has been confirmed many times (see section 4.4.2) and the variable incidence of the the response in various studies is almost certainly due to different methods and different criteria.

The H-response is significantly more frequent in migraine sufferers than controls when tested with the eyes open. However, with eyes closed its frequency is greatly reduced in controls but only slightly in migraineurs, so that the difference between them is then even more significant. Eye closure produces reduced illumination and a shift of spectral content of the stimulus towards a longer wavelength, due to the blood in the eyelid. Therefore, the H-response observation might be explained by an increased sensitivity either to luminance or to red light in migraine. An increased sensitivity at lower illumination would

suggest involvement of M cells, but these are not sensitive to colour. Whatever the mechanism it is worth noting that spontaneous fast activity in the EEG is also enhanced with the eyes closed (Mundy-Castle 1951).

8.2.5 General discussion on VEP in migraine

The explanation of VEP changes in migraine is not easy. VEPs are usually used in clinical neuro ogy to detect abnormalities caused by structural lesions. However, they can also reveal changes in neurological function resulting from abnormalities in neurotransmitters, and this seems by far the most likely explanation for the migraine findings. Kennard et al. (1978) suggested that the prolonged latencies in migraine could have either a structural or a physiological basis. Structurally, they thought prolongation could be due to ischaemic damage suffered during the attacks, and inspection of their data does indeed show that their 31 patients had a relatively long history of migraine, mean duration 17.9 years. Physiologically, they suggested that long latencies might represent synaptic delay due to a neurotransmitter abnormality at the retinal, lateral geniculate or cortical level. They suggested that the structural explanation could be tested by examining patients with classical migraine of recent onset, and this has been done in the current study. The results showed that latency did not change with duration of migraine (Table 32), so ischaemia during attacks is not the explanation. Another possible cause could be ergotamine intake, either by producing ischaemia from vasoconstriction or by an

effect on neurotransmitters in the visual pathway. Heider et al. (1986) presented evidence of a toxic effect on the optic nerve by chronic ergotamine poisoning. They reported the case of an 18 year old man who developed reduction of visual acuity and central visual field after several years of ingestion of daily ergotamine for migraine, and whose P100 latency was found to be increased. This seems not to have been due to structural damage, since three years after stopping ergotamine there was a total recovery of visual acuity, visual field and P100 latency. Furthermore, it is of interest that a recent study has shown that the presence of MRI lesions in the brain of migraineurs bore no relation to the intake of ergotamine (Igarashi et al. 1989). In the current study many of the patients were taking ergotamine on an irregular basis to treat individual attacks, and none were taking it consistently, so the effect of ergotamine on VEP abnormalities cannot be tested. Hence, it seems most likely that the prolonged latencies are due to a neurotransmitter abnormality.

The transmitter which has been amply shown to be affected in migraine is serotonin (for reviews see Lance et al. 1989 and Fozard 1990). It is a highly important neurotransmitter in the central nervous system including the visual system. We do not know whether 5HT is abnormal in the visual system in migraine, but there are some very interesting observations relating VEP to serotonin level in the brain, which may be relevant. McKean (1972) found that the high level of phenylalanine in patients with phenylketonuria markedly reduced catecholamine and serotonin levels in brain tissue. Schafer and McKean (1975) then showed that the latencies of both flash and pattern VEPs were prolonged in four patients with phenylketonuria, and when the blood level of

phenylalanine was reduced by dietary restriction the VEP latencies were significantly shortened, suggesting a role of catecholamines and serotonin in the mediation of VEP. It is interesting that the latency and amplitude of flash and pattern ERG were normal in these patients, as in the current study of migraine patients. Thus, any search for a disturbance in serotonin metabolism should most probably be in neural elements central to the retina.

Another condition in which neurotransmitter dysfunction appears to underlie VEP delay is Parkinson's disease (Bodis-Wollner and Yahr 1978, Gawel et al. 1981, Hershanu et al. 1986). This delay can be corrected by treatment with L-dopa (Bodis-Wollner et al. 1982), suggesting that it is due to dopamine deficiency. In addition, Filip and Balik (1978) showed prolongation of a and b wave latencies and reduction in b wave amplitude of the flash ERG in Parkinson's disease, and Gottlob et al. (1987) found a reduction in the amplitudes of both flash and pattern ERGs, and prolongation of the pattern ERG latencies at high contrast. Dopamine receptors are certainly abundant in human retina (Borbe et al. 1987), and Gottlob et al. (1989) have shown that pattern ERG latency was reduced in normal subjects given L-dopa. Thus, ERG abnormalities in Parkinson's disease are probably part of a generalised dopamine dysfunction.

The amplitude of VEP with surface recording presumably reflects the number of cells excited with external stimuli. This means that in migraine there must be more cells available to fire, or the cells have a lower threshold for excitation. Leathards and Eccles (1986), by studying the effect of potassium chloride on

autopsy strips of human cerebral arteries and uterine veins of migraineurs, presented an idea that the lowering of threshold or hyperexcitability of neurones in the visual cortex and maybe other changes, including those in platelets and smooth muscle vasculature are all due to reduced transmembrane potassium conductance i.e all the target organs involved in the complex symptoms of migraine have a constitutional hyperexcitability due to low potassium conductance. Welch et al. (1990) have recently provided more direct evidence of central neuronal hyperexcitability by recording magnetoencephalography from migraineurs during the attack. They have identified three types of signal in patients suffering from migraine with aura, which they interpreted as manifestations of central neuronal hyperexcitability and spreading depression.

The high VEP amplitude may not necessarily reflect a primary hyperexcitability of the visual cortex or the retinocortical pathway. The site of dysfunction could be in structures influencing sensory inputs to the visual cortex, such as the reticular formation, as suggested by Smyth and Winter (1964) or the thalamus or hypothalamus, which have important structural and functional connections with the reticular formation, as shown by Dafny and Gilman (1973). This latter structure has of course been implicated in nearly all physiological functions, including arousal, sleep, and perception of pain and emotions as well as control of the rhythmic electrical activity of the brain. However, it seems inevitable to conclude that the enhanced P100 amplitude does reflect hyperexcitability of the visual cortex itself, by whatever mechanism.

The repetitive flash responses give rise to a number of other considerations. The response to luminance (flash) stimuli is different from that to contrast (pattern) stimuli as shown by the different morphology of the responses, and the complexity of responses to luminance stimuli suggests activation of several pathways to the visual cortex apart from the direct retino-striate pathway. For example the luminance-responsive cells of the thalamic-reticular formation may be involved as suggested by Sack et al. (1986).

The majority of normal subjects show prominent photic driving in the alpha frequency range, i.e the highest amplitude of repetitive flash responses is this range, presumably because the dominant rhythm is the alpha rhythm. In normal subjects, those who show prominent responses to higher frequencies are those who have a higher than normal amplitude of fast activity (beta rhythm) in their spontaneous EEG (Montagu 1967). In fact migraine is associated with increased fast activity (Boudin et al. 1962, Friedman and Pampiglione 1974). Thus enhanced responses to high frequency (20 Hz) photic stimulation, as in the H-response, may be a manifestation of increased fast wave activity in the EEG. This amounts to saying that in these subjects high frequency flash stimuli augment the already existing fast activity. So far no one has correlated these two in the same subjects.

Since anxiety is associated with enhanced response to flicker (Ulett and Gleser 1952, Ulett et al. 1953), Hockaday and Debney (1988) have suggested that the enhanced response to flicker in migraine is a manifestation of sympathetic overactivity. Evidence of overreaction of the sympathetic system

triggered by light stimuli in migraine is provided by the demonstration by Stoica and Enulescu (1988) of an abnormal catecholamine response to l'ght in 26 migraineurs, consisting of a rise in urinary excretion of epinephrine and fall in that of norepinephrine. These responses were abolished after propranolol administration.

Animal studies (Nakao et al. 1956) have shown that as flash stimulus frequency is increased new populations of neurones are activated. Furthermore intracerebral recordings by Smyth and Winter (1964) from patients with and without migraine showed that the responses at different flash frequencies involved participation of different brain regions. This may suggest participation of reticulo-thalamic structures rather than just the direct retino-cortical projection pathways.

The greatest difference between migraine and normals is around 20 Hz, suggesting that at this frequency there is the highest excess recruitment of neurones. This frequency is also the most epileptogenic, i.e the most likely to produce spike and wave activity in the EEG in epileptics, representing massive (synchronous) firing of neurones in the visual cortex. Kuhnt (1972) used cortical and extracellular electrodes to study VEP in cats, with flicker stimuli of various frequencies. He found that the VEP consisted of a series of excitatory and inhibitory postsynaptic potentials that reacted differently according to stimulus rate and intensity, and that disinhibition in the visual cortex occurred with higher frequency stimuli at 8-16 Hz. Such a mechanism may be relevant to the prominent response at 20 Hz in migraine.

The finding of VEP abnormalities (including P100 latency and amplitude, flash P1 and P2 latencies, and the H-response) in the headache-free period suggests an underlying abnormality in the visual system in migraine subjects, and supports a neural origin for migraine. The distribution of these "constitutional" abnormalities suggests involvement of both the geniculostriate (M- and P- pathways) and the extrageniculostriate systems.

The pattern VEP is mediated via the geniculostriate pathways and generated mainly in the primary visual cortex (Jeffreys 1971, Leserve and Joseph 1979). Flash stimuli activate all pathways to the visual cortex; the P1 component is probably generated in the primary visual cortex, but the P2 component has different characteristics and may be generated via a nongeniculostriate pathway ending in the secondary visual cortex (Kraut et al. 1985, Wright et al. 1987). The components of the H-response are thought to be processed in the secondary visual cortex (Reits 1975, Spekreijse et al. 1977, Winter 1985). Thus, the previous and the current observations suggest that disorders of visual function in migraine as shown by neurophysiological studies involve both the geniculostriate and nongeniculostriate pathways and both the striate and prestriate visual cortex.

8.2.6 Illusions/visual discomfort

Illusions were more frequent and varied in migraineurs and caused greater visual discomfort than in controls. They were more common in patients with frequent attacks and in patients whose attacks were triggered by visual stimuli. The more the

illusions the more the discomfort; some patients did not want to look at the patterns, especially the larger ones, for any length of time. One patient reported headache preceded by visual aura a few hours after the examination, and one might postulate that the pattern caused excessive cortical excitation, followed by spreading depression and leading to the aura/headache response.

Illusions were not affected by the duration of migraine, but they lessened when a patient received effective prophylactic treatment with propranolol, amitriptyline or pizotifen (see section 8.5).

The finding of more illusions agrees with that of Wilkins et al. (1984) who first drew attention to this observation in patients with tension headache as well as migraine subjects. The high visual discomfort agrees with the recent report of Marcus and Soso (1989).

The occurrence of asymmetry of illusions between the two hemifields suggests that the underlying mechanism of illusions lies behind the optic chiasm, presumably at a cortical level, rather than being related, for example, to eye movements. Their perception depends on the number of neurones activated, as indicated by their greater prominence with larger stimulus sizes as shown in the present study and by Wilkins et al. (1984), and with binocular rather than monocular perception (MacKay 1957). Wilkins et al. (1980,1984,1986) found that patterns which induced illusions also induced paroxysmal EEG activity in patients with photosensitive epilepsy, and concluded that the underlying neural mechanisms were the same for both. These observations, together with the finding in this study that illusions were more prevalent in patients whose migraine was triggered by visual

stimuli, suggest that illusions and visual discomfort may well be further manifestations of hyperexcitability of the visual cortex in migraine.

Illusions and visual discomfort could be due to a reduction in lateral inhibition between neurones of the visual cortex, as suggested by several authors (e.g Blakemore et al. 1970, Carpenter and Blakemore 1973, Klein et al. 1974, Tolhurst and Thompson 1975) who have attributed illusions to the phenomenon of lateral inhibition between neurones of the visual cortex. One might therefore propose the following synthesis. Patterns of high contrast and square-wave luminance profile, like the one used in this study, may be aversive/illusionary by producing excessive excitation and interactions of neurones in the visual cortex. This excitation may then exceed the inhibitory capacity of the GABA-ergic lateral inhibition system, which is thought to be important for sharpening the boundaries of spatial contrast. Overriding the process of lateral inhibition by a process of massive excitation could result in both alteration of form/contrast perception and the production of illusions of motion, due to excitation of nearby orientation-specific columns. Thus, illusions could be produced by a combination of hyperexcitability of cortical neurones and an insufficiency of the proper mechanism to check this excitation.

8.3 Effect of duration of migraine, or changes caused by the attacks

The spatial and temporal CS and the P100 amplitude in

classical migraine were all reduced in proportion to the duration of migraine. In patients with a consistently lateralised visual aura the hemifield CD and the P100 amplitude were reduced predominantly on the side of the visual aura. This suggests that repeated migraine attacks can themselves damage the visual system, and the lateralised changes suggest that this damage occurs at a cortical neuronal level.

Such damage seems to be selective. As mentioned previously (Section 3.3) the M-pathway is concerned with coarse perception and temporal analysis and the P-pathway is concerned with pattern details (Shapley et al. 1981, Derrington and Lennie 1984). In this study the reduction in Arden CS at all spatial frequencies, including the low and medium frequencies in the face of normal visual acuity, together with reduction of VER amplitude at the medium check size (38') suggest a predominant involvement of the M-pathway to the secondary visual cortex. The two systems can be differentially involved in disease but the M-pathway generally seems to be more vulnerable to pathology.

The findings are comparable to those of Regan and Maxner (1987) and Bulens et al. (1986) in Parkinson's disease, in which they demonstrated a selective involvement of the pathway from the magnocellular layer to the striate cortex, manifested as orientation-selective loss of CS at low and medium spatial frequencies. Furthermore, Hughes et al. (1987) found abnormal flash VEP in early optic neuritis but normal pattern VEP, and explained this on the basis of early affection of the retinal periphery, where M-cells predominate, before affection of the papillomacular bundle, predominantly P-cells. It has also been

demonstrated by Bodis-Wollner (1972, 1976) and Regan et al. (1977) that patients with blurred vision due to purely cerebral lesions or to multiple sclerosis, who had normal Snellen acuity, had abnormal CS in either the medium or low spatial frequencies, again suggesting preferential M-system involvement.

There are no previous studies on the effect of duration of migraine on CS. Indeed CS has only been examined, using a most unusual non-psychophysical test, by Orban and Orban (1987) who reported it to be reduced in both common and classical migraine.

VEP studies which looked at the effect of duration of migraine and the frequency of attacks did not show any effect on SFVEP or PRVEP (Lehtonin 1974, Jonkman and Lelieveld 1981, Winter 1985). However, the duration of migraine in all these studies was fairly short, and in the first two the number of classical migraine subjects was small, so the effect might easily have been missed.

Since the duration of migraine affects CS but not illusions one could argue that these have different underlying mechanisms. The stimuli used for eliciting CS are clearly different from those which produce visual discomfort and illusions. A sinusoidal pattern does not produce illusions and nor does a low contrast square wave pattern (Tolhurst and Thompson 1975). Thus, a stimulus with both a sinusoidal luminance profile and a low contrast, such as the one used for CS testing, would not be expected to produce illusions, presumably because it does not produce excessive cell excitation nor influence lateral inhibition.

In the present study a correlation was established between spatial CS and the P100 amplitude, but not the latency, in the PRVEP. Abnormalities in spatial contrast sensitivity in multiple

sclerosis patients have also been found to be related to VEP amplitude but not to latency (Bodis-Wollner et al. 1979, Neima and Regan 1984, Wright et al. 1987, Sanders et al. 1987). This close relationship suggests that P100 amplitude and spatial contrast perception are parameters of the same visual mechanism. The reduction in temporal CS at 10 and 20 Hz in chronic classical cases was not associated with any reduction in flicker responses at 10 and 20 Hz i.e there was no relationship between the perception of flicker and the electrophysiological responses it evoked. This coincides with previous results in normal subjects. It has been found that the amplitude of the VEP elicited by pattern stimuli and the objective contrast of the pattern have a logarithmic relationship similar to that between the stimulus contrast and the subjective perception of contrast (Campbell and Maffei 1970, Campbell and Kulikowski 1972, Fiorentini and Maffei 1972). The perception of flicker bears no relationship to the size and shape of the flicker responses in the low, medium and high frequency regions (Van der Tweel and Verdunyn Lunel 1965, Spekreijse 1966). The lack of correlation between electrophysiology and perception of flicker does not necessarily mean that they have different neural origins. But there is no doubt that the pattern VEP and spatial perception system and the flicker responses and flicker perception system represent different physiological functions.

It was originally reported (Khalil and Legg 1989) that the incidence of the H-response was reduced with increasing duration of migraine. However, re-examination of the data showed that although H-responses were indeed less frequent in chronic cases

this was because of a correlation with the frequency of attacks, and not because of the duration of migraine itself.

We do not know the underlying mechanism of reduced CS and P100 amplitude in classical migraine of long duration. It may well be due to repeated transient ischaemia suffered during the attacks, which has been also invoked as the cause of local and generalized atrophy found in some patients on computerised tomography (Hungerford et al. 1976, Dorfman et al. 1979, Jain and Ahuja 1986) and MRI scanning (Jacome and Leborgne 1990, Kuhn and Shekar 1990) and at necropsy. The neural damage suffered as a result of profound cerebral hypoxia is well known. However, less severe transient hypoxic episodes can lead to permanent damage if experienced over a long period of time (Brierley and Graham 1984).

Regional blood flow was reported to diminish by about 20% during attacks of classical migraine (Olesen et al. 1981a, Lauritzen et al. 1983). Although information about occipital cortex was not available from these intracarotid studies, the changes certainly start posteriorly and spread forward from one arterial territory to the other. Because the lowest blood flows were 40 to 50 ml/100gm/min, well above the threshold for producing neural damage by ischaemia, it was concluded that ischaemia is not the primary cause for aura symptoms in migraine. However, recalculation of the figures, allowing for the influence of scattered radiation in the ^{133}Xe technique, has shown that the flow actually dropped to 16-23 ml/100 gm/min in the least perfused areas in the majority of patients (Skyhøj Olsen et al. 1984, 1987). This degree of ischaemia is certainly sufficient

to explain transient neurological deficits in classical migraine and possibly persistent neurological deficits in complicated migraine. This evidence, together with one example of increased cerebral oxygen extraction (Herold et al. 1985), raises fresh doubts as to whether the primary event in migraine is vascular rather than neural, because if the reduction in blood flow is just a metabolic adjustment it should not drop to ischaemic levels. However, there are many points indicating that the changes in blood flow are the result of disturbed cortical function and not the cause of it. These are:

1. The reduction of blood flow does not conform to individual arterial territories.

2. The suppression of VEP during the attack occurs simultaneously in both occipital and parietal areas (Shoenen 1986), and this would seem to argue against a simple vasoconstrictor mechanism.

3. Evidence of disturbance of cellular brain function during an attack as shown by low brain magnesium level and normal pH using 31-phosphorus NMR spectroscopy (Welch et al. 1988, Ramadan et al. 1989).

4. The symptoms and signs in complicated migraine are not confined to the supply of one artery, and in some cases both hemispheres are affected with varying localisation during an attack (Heyck 1973).

5. Central scotomas are never seen in occlusion of the posterior cerebral artery, so combined central and peripheral scotomas imply involvement of more than one arterial territory.

Even if the reduction of blood flow was not enough to produce ischaemia, one should also remember that reduction in blood flow

is not the whole story of the vascular pathophysiology. Other factors which contribute to the development of ischaemic damage are the a-v shunting of blood, the formation of microemboli, stagnation and hypercoagulability of blood and vasoconstriction.

In summary there is considerable blood flow and biochemical evidence that vascular pathophysiology may be a secondary phenomenon but there is also evidence that cerebral ischaemia occurs during a classical migraine attack, and this could account for the reduction of CS and P100 amplitude, reported for the first time in this study, with increasing duration of migraine.

Finally it is now known that the excitatory amino acids, glutamate and possibly aspartate, can cause neuronal damage through prolonged activation of N-Methyl-D-Aspartate (NMDA) receptors (Rothman and Olney 1987). This process has been implicated in the pathophysiology of cell loss in ischaemia, but also in other situations, and thus might be relevant to impaired neuronal function in chronic classical migraine, even in the absence of ischaemia.

8.4 Effect of unilaterality of headache/aura on the visual tests

An important feature of migraine is the asymmetry or laterality of headache and of the neurological phenomena.

Unilaterality of headache or aura were not associated with asymmetry of the VEP recorded from the two sides of the head (R5 and L5 positions) for full-field PRVEP or SFVEP. Only the half-field PRVEP, the perception of illusions and the hemifield CD

showed asymmetry, reflecting asymmetrical involvement of the visual system. Asymmetry in the VEP of migraineurs has been reported by several authors, in the headache-free period, during attacks, and with serial recording, using PRVEP, SFVEP and RFVEP, but only a few studies have examined the relation of these asymmetries with the laterality of headache and aura.

Four studies looked at the relationship of PRVEP to headache/aura side. Winter (1985) found no effect of either headache side or aura side and Polich (1986) found no effect of headache side for either full-field or half-field stimulation. Kennard et al. (1978) found higher P100 amplitude over the left hemisphere in classical migraineurs with left-sided headache. This is an interesting observation as patients with left sided headache are more likely to have neurological symptoms on the right, and any change from repeated migraine attacks would therefore affect the left hemisphere, leaving the right hemisphere relatively intact, thus producing a higher amplitude on the left, because of the paradoxical lateralisation of PRVEP (section 4.2.1). In the present study no such asymmetry was found. However, with half-field stimulation, which is a more suitable measure for testing each hemisphere separately than the full field stimulation used by Kennard et al. , P100 amplitude was found to be asymmetrically reduced in the 17 migraineurs with a strictly unilateral aura, on the side corresponding to the aura, and this was associated with reduced hemifield CD. These patients had in general a low spatial CS, which may be because the spatial CS measured by Arden gratings covers the peripheral field as well as the central fields, and all had a long history of migraine.

Dalla-Volta and Anzola (1988) with pattern VEP hemifield binocular stimulation reported "asymmetry" in the ipsilateral P100 amplitudes of the two hemifields in 5 out of 9 patients with classical migraine, but no asymmetry in common migraine. However, it was not clear what were their criteria of asymmetry, as no figures were given, and the asymmetry was not correlated with the side of headache or aura.

Connolly et al. (1982) made a curious observation, in that they found the SFVEP in a group of common and classical migraineurs with right-sided headache had a higher amplitude at the left temporal site. They also made a curious comment, considering this to represent "a secondary phenomenon to repeated right-sided headaches affecting structures in the left hemisphere". If this were true, then we would expect to find low amplitude over the left hemisphere, because it has been confirmed by PET studies that the paradox i.e the recording of good responses over the bad hemisphere, which is a characteristic of pattern VEP, does not apply to flash VEP. Furthermore, higher amplitude over the left hemisphere may be seen in normals (Borda 1977).

Jonkman and Lelieveld (1981) using spectral EEG analysis with photic stimulation reported asymmetry of response in 55% of subjects with common and classical migraine (n=20) in the alpha peak frequency and in total alpha power, not related to the type or duration of migraine. Unfortunately they did not correlate this finding with the side of headache or aura, although all of their patients had one-sided headache.

Regan and Heron (1970) found a significant asymmetry in the amplitude of the RFVEP, which was accentuated during an attack,

in 3 out of 5 migraine subjects compared with controls. They made no mention of the type of migraine or the laterality of visual symptoms. MacLean et al. (1975) found a marked reduction in the amplitude of the early components of the SFVEP, during an attack of classical migraine, over the hemisphere contralateral to the field defect. Two patients also showed asymmetry while they were headache-free.

With serial recordings Lehtonin et al. (1979) found a transient asymmetry in the amplitude of flash VEP in some subjects with menstrual migraine but there was no relationship between the direction of VEP asymmetry and the side of visual symptoms. They suggested that "the phenomenon, being transient, is functional rather than pathoanatomical in origin". This was supported by Nyrke et al. (1990) in classical migraine using steady state VEP, usually with complete normalisation in the following session. The incidence of abnormality was relatively independent of the interval between the last attack and the recording. They did not relate these asymmetries to the side of headache and aura.

In the current study patients with bilateral headache tended to have a bilateral aura, and those with unilateral headache tended to have a unilateral aura. There was a tendency for the headache to be on the opposite side to the aura, but the relationship was not significant. Peatfield et al. (1981) reported a similar lack of relationship in a larger series. They found that aura symptoms were on the same side as the headache in 55 out of 111 patients and on the opposite side in 20. Similar findings were recently obtained in a prospective analysis of the same

patients (Peatfield and Clifford Rose 1990). This inconsistency is important considering that changes in rCBF are consistently related to the side of the aura but not to the side of the headache (Davies et al. 1990), and asymmetry of CS and illusions likewise. This finding has led Lance's group (e.g Lance 1988) to postulate two independent mechanisms for the production of aura and headache. However, Olesen et al. (1981a) studying rCBF during attacks, observed that the headache was always contralateral to the neurological symptoms. The data in table 27c suggest that a significant contralateral relation might be apparent with a larger sample, but nevertheless a significant number of patients do have headaches on the same side as their aura symptoms. An important factor in this issue is that patients may not always be accurate in recalling the side of either symptom.

The lateralisation of illusions suggests that the underlying mechanism of illusions lies behind the optic chiasm, probably at the cortical level, and the correlation between the side of illusions and the side of the visual aura suggests that the illusions and aura share a common anatomical substrate. There is certainly evidence to suggest that the mechanisms underlying the visual aura influence cortical function. For example:

1. The slow migration of the visual aura across the visual field suggests a process spreading through the cortex, perhaps "spreading depression", as pointed out by Lashley (1941).

2. The same can be said of the nonvisual aura (Fisher 1971).

3. Visual hallucinations associated with occipital lobe lesions are very similar to fortification spectra in migraine patients (Kölmel 1984, quoted by Olesen 1990).

4. The fortification spectra and scintillations often seen on the border of a scotoma can be accounted for by disordered functioning in orientation-specific columns of cells as described by Hubel and Wiesel (1968). Thus, the aura could be caused by a phase of excitation, associated with a shimmering zig-zag, followed by inhibition, associated with a scotoma passing across the visual cortex (e.g see Lance 1986).

5. Blood flow and electrophysiological studies have made it clear that the migraine aura is associated with physiological changes in the cerebral cortex.

The unilateral deterioration of CS indicates that damage to the visual system can occur unilaterally, behind the chiasm, and the correlation with the side of the aura indicates that the damage is most likely to occur in an area of existing abnormality of neural function. However, CS deteriorates with the duration of migraine while illusions remain unchanged, and there is no relationship between the side of the more prominent illusions and the reduction in CS, indicating important differences in their underlying mechanisms.

8.5 Effect of treatment

Drugs that successfully reduced the attacks also reduced illusions and H-responses. This suggests that the mechanisms producing the increased illusions and the H-responses are the same as those underlying migraine itself, and that the drugs are acting on these mechanisms, perhaps both cortical and brainstem, to reduce illusions and H-responses.

The effect of these drugs is clearly not just a direct

nonspecific action on VEP, since the response did not change in patients who did not improve. One patient retained an H-response after 3 months of unsuccessful treatment, with propranolol and 3 months of amitriptyline separately. Furthermore, propranolol had no effect in healthy controls. In addition, the only significant changes occurred in that particular variable, the responses at 18 and 20 Hz, which best differentiates between migraine subjects and controls.

These results are in agreement with Nyrke et al. (1984) who demonstrated that the increased amplitude of the fundamental response to repetitive flash stimuli around 20 Hz was significantly reduced with propranolol treatment, and this was correlated with clinical improvement. Furthermore Schoenen et al. (1986) showed that a high CNV amplitude (an event-related potential that is modulated by central catecholaminergic systems) in 33 patients with common migraine tended to normalise in all patients who showed clinical improvement after three months treatment with beta-blockers. Moreover, the larger the CNV, the better the clinical response to beta-blockers. Dalla-Volta and Anzola (1988), quoting no figures, found that "asymmetry" in the ipsilateral P100 amplitude in five patients with classical migraine disappeared in two and was reduced in one after six months of treatment with the calcium blocker nicardipine (20mg tds), in parallel with clinical improvement. Marsters et al. (1988) found that "fast wave act vity" of the late components of flash and pattern VEP was reduced, together with a reduction in headache frequency, in seven patients following prophylactic treatment, six with atenolol and one with pizotifen.

Somewhat different observations were made by Diener et al. (1989), who found that beta blockers reduced VEP amplitude to transient and steady state chequerboard stimulation by 3-4 μV in both responders and non-responders, whereas VEP latency remained unchanged. However, after a follow up period of 3 months off treatment the VEP amplitude returned to the initial baseline value in the non-responders, but stayed at lower values in the responders. They thought the lack of any relation between the VEP amplitude and the clinical outcome was due to lower plasma levels of metoprolol in non-responders, which were enough to influence VEP but too low to reduce the frequency of migraine attacks.

In general line with these findings is the observation that the abnormal responses to repetitive flash stimuli in patients with photosensitive epilepsy are corrected by anticonvulsant therapy (Lee et al. 1980).

The observation that treatment reduces illusions is very interesting, and may be related to the further finding that the number of illusions is proportional to the frequency of attacks. Both are consistent with the observation of Wilkins and colleagues (unpublished), that patients have more illusions around the time of a headache, so one would expect less illusions in patients with less frequent headaches.

8.6 Differences between classical and common migraine

Both illusions and H-responses were commoner in classical than in common migraine, and illusions were more prominent on

the side of a consistently unilateral aura.

Marsters et al. (1988) reported a higher amplitude of "fast wave activity" in the VEP in classical migraine, and suggested differentiating the two forms on that basis. Dalla-Volta and Anzola (1988) found VEP asymmetry to hemifield stimulation in five out of nine classical migraineurs only.

Such differences between common and classical migraine have led some investigators to suggest different pathogenetic mechanisms and a different degree of neural involvement (Wilkinson and Blau 1985, Olesen 1986). However, the fact that various changes are more prominent in classical migraine does not mean the two forms have different pathophysiological mechanisms. EEG data suggest that there is a cerebral disturbance in common migraine (Schoenen et al. 1987, Angoli et al. 1985). Using spectral analysis and EEG mapping, Schoenen et al. (1987) showed a unilateral suppression of alpha power in 17 out of 20 patients during an attack of common migraine, which was identical to the changes seen in classical migraine attacks. Such changes may outlast the attack by up to 72 hours. Depression of alpha activity is also an early feature of SD in animals (Leão 1944a). The EEG findings suggest that attacks of common migraine, as well as classical migraine, are accompanied by focal brain dysfunction, and that both may have common underlying pathophysiological cerebral mechanisms.

More recently, Nyrke et al. (1989) found that classical and common migraine showed opposite patterns of response to repetitive flash. The amplitude of the fundamental response was increased in common migraine (n=30), whereas the amplitudes of both the fundamental and the second harmonic response were

reduced in classical migraine (n=20). This was explained on the supposition that classical migraine is a cortical disturbance while common migraine is a thalamic/hypothalamic disturbance. However, these findings were not confirmed in the present study, which was considerably larger, and no differences in VEP changes were found between common and classical migraine in some other studies either (Lehtonin 1974, Richey et al. (1966).

Reduction of P100 amplitude and CS was found only in patients with classical migraine of long duration, and at an early stage these measurements were the same as in common migraine. These reductions may be caused by ischaemic damage, and be a consequence of the reduced cerebral blood flow which occurs only in classical but not in common migraine.

8.7 Can these tests be used to diagnose migraine?

It has been suggested that a neurophysiological test might be of value in the diagnosis of migraine. Examples include spectral analysis of the VEP (Nyrke and Lang 1982, Simon et al. 1982) and the use of CNV (Schoenen et al. 1985). More recently Marsters et al. (1988) and Mortimer et al. (1990) have described increased amplitude of fast wave activity in the late components of single flash responses, more than 250 msec after the stimulus, and claimed that this can be used to diagnose migraine and even to differentiate between common and classical migraine. However, the relation of all these tests to migraine has been validated solely on the basis of a clinical diagnosis of migraine, and it is therefore impossible for any test to be more accurate than the

clinical diagnosis. Furthermore the overlap is considerable; in the present study only 17 patients had a P100 latency exceeding mean+2SD of the control subjects, and for P2 latency there were only 7. Again, prevalence of the H-response with eyes closed was 77% in migraine subjects and 13% in controls. If the incidence of migraine in the general population is 15%, a simple calculation will show that 22.5% of an unselected population will have a positive H-response, and of these about half will have migraine and half will not. However, this does not diminish the interest of the tests or their potential for distinguishing between subgroups of patients. For example investigations are under way in this department to see if the H-response can predict the response of migraine patients to treatment with flickering light, delivered through goggles, which has been shown to relieve headache in a small series of migraine patients (Anderson 1988).

CHAPTER 9 CONCLUSIONS

Abnormalities of visual function in the headache free period suggest an underlying disturbance of visual function in migraine. These disturbances can be either "constitutional" or due to repeated migraine attacks. The "constitutional" disturbances are represented by the prolongation of pattern P100, flash P1 and P2 latencies, higher P100 amplitude, higher prevalence of H response and enhanced perception of illusions. These disturbances occur central to the retina since retinal function was normal as shown by the normal ERG, and illusions were lateralised in conjunction with asymmetry of the visual aura.

The prolongation of VEP latencies is most probably due to abnormalities in cerebral neurotransmission. Secondary structural damage has been excluded since latency was not affected by the duration of migraine. The high amplitude of VEP to pattern stimuli, in patients with common migraine and with classical migraine with a short history , indicate hyperactivity of the visual cortical neurones concerned with contrast detection. The prominent H-responses and the increased illusions, associated with greater visual discomfort, experienced by migraineurs may be further manifestations of such hyperactivity.

The occipital and vertex flash responses represent two separate physiological functions, and migraine differentially affects the occipital response to both single and repetitive flash stimuli. The main component of H responses is the response at 18 or 20 Hz, i.e the medium frequency subsystem of the RFVEP, which is thought to be processed in the prestriate cortex, together with

flash P2. The pattern VEP and flash P1 are thought to be functions of the primary visual cortex. Thus, these "constitutional" disturbances in visual function in migraine suggest a generalised involvement of both the geniculostriate (M- and P- pathways) and the extrageniculostriate systems, and probably the brainstem-thalamic reticular formation which influences activity of the cerebral cortex. Abnormalities producing symmetrical changes suggest generalised dysfunction of retino-cortical pathways and/or thalamic reticular formation, while lateralised abnormalities, like illusions, suggest cortical dysfunction.

In addition to the constitutional abnormality in the visual system, abnormalities apparently develop after repeated attacks of migraine. This was shown by the reduction in P100 amplitude and in spatial and temporal CS with increasing duration but only in classical migraine. This could be due to ischaemia or perhaps to neurotoxicity. In patients with a consistently lateralised visual aura the hemifield CD and half-field P100 amplitude were reduced predominantly on the side of the visual aura. This means that the damage is most likely to occur in an area of pre-existing neural abnormality in the visual cortex. The predominant involvement of the spatial and temporal CS at the medium and intermediate frequency ranges (10 and 20 Hz), and the reduction in the P100 amplitude at the medium check size (38') suggest that damage to the visual system in migraine predominantly involves the M-pathway to the prestriate cortex.

Patients with bilateral headache tended to have b'lateral aura, and those with one-sided headache tended to have asymmetrical aura, but not necessarily on the opposite side. A significant

number of patients had headaches on the same side as their aura symptoms. The only unequivocal conclusion from this is that the mechanisms for the production of aura and headache cannot invariably consist of a sequence of changes confined to the intracranial vessels on one side of the brain: clearly, the two mechanisms can operate independently on the two sides. Such separation is of course also indicated by the fact that patients may experience headache or aura symptoms in isolation, in sequence, or both at the same time.

Drugs that successfully reduced the attacks reduced both illusions and H responses. This did not occur in controls after a single dose of propranolol, and the response remained the same in patients who did not improve. Furthermore, illusions and H responses tended to be less common in patients with infrequent attacks. These observations suggest that some mechanisms producing the increased illusions and the H responses are the same as those underlying migraine itself, and that the drugs act on these mechanisms, perhaps in both cortex and brainstem, to reduce illusions and H responses respectively.

Both illusions and H-responses are commoner in classical than common migraine, suggesting greater involvement of the nervous system in classical cases, but also suggesting that the two forms share the same pathophysiological mechanisms.

These tests of visual function are not diagnostic tests for migraine, but they provide clues to certain underlying mechanisms, and may be useful in distinguishing subgroups of migraine which cannot be recognised clinically but which have important implications for management.

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APPENDIX HEADACHE QUESTIONNAIRE

Please tick and/or answer questionnaire where appropriate:

NAME

(Surname first).....(Mr/Mrs/Miss)

ADDRESS.....

.....

.....

TELEPHONE NO (Home).....

(Work).....

DATE OF BIRTH.....

Are you right handed.....left handed.....or both.....

What is (was) your main occupation?.....

When did you start having this type of headache?.....

Do you get any of the following problems 1-24 hours before migraine starts:

.....Fatigue.....Overactivity.....Yawning.....Emotional upset

.....Constipation.....Frequent motions.....Craving for certain food

Are there sometimes bright flickering lights or zigzags in front of your eyes just before the headache begins?

.....Yes

.....No

If so, do they appear on the Right....., Left.....or both sides.....

and how long do they last?.....

Have you noticed any change in your sight before or during the attack?

Please tick any that apply.

.....dimming or darkening of vision

.....blurring of vision

.....dark spots in the visual field which may gradually increase in size

.....loss of sight limited to the right side of the field

.....loss of sight limited to the left side of the field

.....total loss of sight

.....appearance of coloured spots, dots or stars or bright zigzags anywhere in the visual field.

.....fear or dislike of light

.....double vision

.....others

How often do you get the headache?

.....about once a year

.....several times a year

.....about once a month

.....several times a month

.....about once a week

.....several times a week

.....every day

.....every day, all day

How long does your headache usually last?

.....hours

.....all day

.....two days

.....three days

How do you describe the nature of your headache?

.....dull

.....tightening

.....throbbing

.....aching

.....sharp

.....other

How do you grade the severity of your headache?

.....Mild	does not interfere with sleep or daily activities
.....Moderate	prevents you from doing heavy duties
.....Severe	prevents you from sleep and performing daily activities

Site of the headache - please tick any that apply.

.....all over the head

.....usually one side only

.....usually right side

.....usually left side

.....always right side

.....always left side

.....around the eye socket

.....in the eye ball

.....in the temple

.....around the back of the head

History of migraine in the family:

.....children

.....brothers and sisters

.....mother

.....father

Have your headaches been brought on by any of the following?

.....flashing lights

.....fluorescent light

.....bright light

.....lights of different colours

.....specific patterns

.....loud noises

.....strong smells or perfumes

.....stress

.....physical exercise

.....lack of sleep

.....food (e.g cheese, chocolate)

.....a missed meal or eating insufficient food

.....alcoholic drinks

.....menstruation

.....contraceptive pills

.....heat, cold, or changes in weather

.....others. If so, what?.....

When did you last have a headache brought on by one of these?.....

What was it that brought that attack on?.....

Other problems may precede or accompany the headache -
Please tick any that apply

.....nausea

.....vomiting

.....dizziness

.....feel sleepy

.....loss of appetite

.....change in mood - e.g. depression

.....ringing in the ears

.....intolerance to light or fear of light or light hurts your eyes

.....intolerance to or dislike of loud noises

.....intolerance to or dislike of strong smells or perfumes

.....weakness in arms or legs

.....numbness or pins and needles in arms or legs

Have you ever seen a doctor about your
headaches?

.....Yes

.....No

If you have a headache apart from the one which you are seeking a help for, please describe it below:

What drugs have you had to relieve migraine, and have they worked?

.....Yes/No/Possibly

.....Yes/No/Possibly

.....Yes/No/Possibly

What drugs have you had, on a daily basis, to prevent migraine, and have they worked?

.....Yes/No/Possibly

.....Yes/No/Possibly

.....Yes/No/Possibly

What drugs are you taking at present for migraine?

Are you taking contraceptive pills (females only) or any other drugs?

When was your last period (females only)?

Past and present major illnesses:

.....Eye problems e.g Glaucoma

.....Diabetes

.....Thyroid problems

.....Colour blindness

.....Cyclical Vomiting

.....Epilepsy

.....Others

If you have further comments, please write in the space below:

This work was presented in part at an EEG Society meeting, London, 22 Jan. 1988, the first meeting of the European Neurological Society, Nice, France, 19-22 June 1988, the 7th Migraine Trust International Symposium, London, 5-8 Sept. 1988, and a meeting of the Association of British Neurologists, Glasgow, 6-8 April 1989.

A chapter from the Proceedings of the 7th Migraine Trust International Symposium (London 1988) entitled "Pathophysiology of migraine: a study using VEP and Contrast sensitivity", is enclosed.

10

Pathophysiology of migraine: a study using VEP and contrast sensitivity

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Introduction

The visual evoked potentials (VEPs) in people suffering from migraine are different from normal controls. This was originally reported by Golla and Winter[1], who showed that patients with episodic headache had an increased amplitude of cortical responses to repetitive flash, especially at 18 Hz, compared with normal controls, a phenomenon they called the H-response.

These studies have subsequently been expanded to included responses to pattern[2–4], single flash[4–9] and repetitive flash stimuli[1,4,6,8,10–16] as well as the recording of electroretinogram and electro-oculogram[4]. However, positive findings from these studies have been few, and there have been no reports on contrast sensitivity (CS) in migraine.

In this study we have explored different components of visual physiology by recording various visual evoked potentials to pattern and to single and repetitive flash stimuli, as well as by measuring spatial contrast sensitivity.

Methods

Fifty-one migraine subjects (35 females and 16 males), 33 suffering from classical and 19 from common migraine, and 30 normal controls (16 females and 14 males) with the same age range (17–58 years) were tested.

The pattern-reversal visual evoked potentials (PRVEPs) were elicited by monocular viewing using a checkerboard reversing at 2/s. At 1 m distance from the subject's eye the stimulus field subtends 30° × 25° of visual angle, and the individual squares 38'. The mean luminance of the screen was 90 cd/m^2 and the contrast was 95%. The recording electrodes were placed at Oz and Pz and at 5 and 10 cm lateral to Oz on both sides, and referred to a common reference placed at Fz. A total of 240 responses were averaged and displayed on an eight-channel EEG machine at various gain settings.

The single flash visual evoked potentials (SFVEPs) were elicited by binocular viewing using a xenon flash tube at a frequency of 2/s with a mean single flash luminance of 11 cd/m^2 and a duration of 65 μs. The recording electrodes were placed at Oz, Pz, Cz and Fz and at 5 cm lateral to Oz on both sides and connected to a common linked-ear reference. Two trials of 120 responses were averaged.

The repetitive flash visual evoked potentials (RFVPs) were recorded with the subject's eyes both closed and open, using a programme made and installed into the averager by Dr Horace R. A. Townsend. The rate of presentation starts at 4/s, increases stepwise by 1/s up to 12/s and thereafter by 2/s up to 24/s. Each presentation lasts 10 s and the averaged responses were recorded on to four channels representing R5, Oz, L5 and Cz with linked-ear reference.

Although recordings were made from several derivations, the data presented here were derived from measurements at Oz only.

Contrast sensitivity (CS) is a method of assessing an important visual function which is spatial contrast discrimination. It was determined using Arden type sinusoidal gratings[17], which consist of a series of six photographic plates in the range of 0.2 to 6.4 cycles per degree of visual angle at 57 cm from the observer's eye. The threshold scores at the sides of each plate range from zero at the top, low-contrast end, to 20 at the bottom, high-contrast end of the plate. The plates are encased in a pocket and exposed slowly until the subject is able to recognize the pattern on the plate. That point is the subject's threshold score for that plate. The presentation starts with plate 2 and progresses to plate 7. Each plate is presented four times and each eye is tested on each plate separately. The total contrast threshold for the eye is the sum of scores for individual plates.

Contrast sensitivity is the reciprocal of contrast threshold. In this chapter results will be presented as contrast threshold, so that the higher the score the poorer the contrast sensitivity.

Results and discussion

Pattern-reversal VEPs

The P100 latency of the PRVEPs was significantly longer in migraine sufferers than in normal controls following stimulation of the right and left eyes. The mean P100 amplitude was greater in the migraine group than controls but the difference was not significant (Table 1).

Table 1. P100 latency (ms) and amplitude (μV) for the pattern-reversal visual evoked potentials in migraine and controls groups.

Measurements	*Eye*	*Controls*	*Migraine*	*t-value*	*P-value*
P100 latency (ms)	OD	111 ± 8.3	118 ± 5.7	4.10	0.000
	OS	113 ± 7.9	119 ± 5.2	4.10	0.000
P100 amplitude (μV)	OD	15.2 ± 5.1	17.18 ± 6.1	1.43	0.16
	OS	51.4 ± 4.4	18.16 ± 7.3	1.80	0.800

Results are mean ± s.d.

Table 2. P100 latency (ms) and amplitude (μV) for the single flash visual evoked potentials in migraine and control subjects.

Measurements	*Wave*	*Controls*	*Migraine*	*t-value*	*P-value*
Latency (ms)	P1	75.4 ± 8.3	78.6 ± 9.3	1.55	0.126
	P2	123.4 ± 8.7	130.7 ± 11.3	3.05	0.003
Amplitude (μV)	P1	5.8 ± 2.7	7.2 ± 3.5	1.65	0.100
	P2	12.8 ± 4.9	15.3 ± 6.8	1.54	0.130

Results are mean ± s.d.

Single flash VEPs

The P1 latency of the SFVEPs was the same in migraineurs and normal controls, but the P2 latency was significantly longer (Table 2). The increase is comparable to the prolongation of P100 latency of the PR-VEPs.The amplitudes were normal.

Repetitive flash VEPs

The amplitude of responses at various flash frequencies were measured and then

analysed to determine the H-response, which is defined in terms of two ratios; first the ratio of the amplitude at 20 Hz to the peak amplitude in the alpha frequency range and second the ratio of the smallest amplitude between these two peaks to the amplitude at 20 Hz. It is positive when both the ratios are ≥ 0.5.

With eyes closed there was a significantly higher incidence of H-response in the migraine group (71%) than the control group (17%) as shown in Table 3. In the migraine group the incidence was somewhat greater with eyes open than with eyes closed (80% compared with 71%), but in controls the incidence was increased even more (63% compared with 17%). The difference between the two groups with the eyes open was not significant.

Table 3. Prevalence of the H-response of the repetitive flash visual evoked potentials in migraine and control subjects.

	Eyes closed					*Eyes open*				
	H	*n*	%	χ^2	*P*	*H*	*n*	%	χ^2	*P*
Controls	5	30	17			19	30	63		
				19.87	0.000				2.04	0.153
Migraine	36	51	71			41	51	80		

Table 4. Contrast sensitivity (Arden threshold scores) in migraine and control subjects.

Controls	*Migraine*	*t-value*	*P-value*
63.77 ± 5.6	69.11 ± 7.4	4.83	0.000

Results are mean ± s.d.

Contrast sensitivity (CS)

The contrast threshold in the migraine group as a whole was significantly higher than that of normal controls (Table 4), which means that their contrast sensitivity is lower.

The data were examined for any effect of the duration of migraine on those parameters which showed differences between normal and migraine subjects (Tables 5 and 6). Only the P100 amplitude, the H-response and CS showed any relationship. In patients with a long duration of migraine, the P100 amplitude, the incidence of the H-response and the CS were all reduced.

To illustrate this point, the migraine subjects were divided into two groups (Table 6) above and below the mode of contrast threshold (CT) of controls, which was 68. Group 1 includes 28 subjects, groups 2 includes 23 subjects. The subjects in group 1 have a mean CT of 63, the same as the controls (63). The mean P100 amplitude in this group (22 μV) is significantly greater than the mean P100 amplitude of normal controls (15 μV). In Group 2 the mean CT is 75 which is higher than the mean CT of normal controls (63). The mean P100 amplitude (12 μV) is significantly lower than the mean P100 amplitude (15 μV) of normal controls. The duration of migraine in group 2 (32 years) is significantly greater than in group 1 (12 years). Thus, patients with migraine of long duration had a lower P100 amplitude, lower contrast sensitivity and a lower incidence of H-response.

Discussion

The prolongation of P100 latency and the higher incidence of H-response in migraine subjects have been reported previously, and are confirmed in this study. We have also confirmed the previous observation[4] that this prolongation is not related to the

Table 5 Correlations of duration of migraine with visual evoked potentials and contrast sensitivity.

	Duration of migraine		
Measurements	*r*	*t*	*P*
P100 latency PRVEP)	0.14	0.70	0.50
P100 amplitude PRVEP	0 18	0.70	0.00
P2 latency SFVEP)	0 12	0.82	0.42
Co ntrast sensitivity	0.70	8.94	0.00

Table 6. The relationship between contrast sensitivity, P100 amplitude and H-response in patients with short and long duration of migraine (normal control figures between brackets).

	Group 1 (28 subjects)		*Group 2 (23 subjects)*
Duration of migraine (years)	11.86		32.29
		P<0.001	
Contrast sensitivity (Arden scores)	63.47 (63.77)		75.33 (63.77)
P100 amplitude (μV)	22.12 (15.29)		12.20 (15.29)
	P<0.001		*P*<0.002
%H-response	82		52

duration of migraine. The new observations are the prolongation of flash P2 latency, the reduction in spatial contrast sensitivity and, perhaps most importantly, the relationship of P100 amplitude, H-response and contrast sensitivity to the duration of migraine.

The pattern-reversal visual evoked potentials and contrast sensitivity are thought to be functions of the primary visual cortex[18,19]. The flash P2 and the components of the H-response are thought to be processed in the secondary visual cortex[4,19–21]. Thus, our observations suggest that the disorders of visual function in migraine involve both the geniculostriate and the visual association areas.

P100 amplitude is higher than normal in patients with migraine of short duration. This might therefore be a component of the underlying "migraine constitution", and this could also be true for the prolongation of P100 and P2 latencies. However, P100 amplitude declines in proportion to the duration of migraine, as does the contrast sensitivity, so that it appears probable that repeated migraine attacks damage the visual system. We do not know the mechanism for this. It might be due to repeated transient ischaemia, which has been invoked as the cause of the local and generalized atrophy found in some patients on CT and MRI scanning and at necropsy. However, the current view of the pathogenesis of the classical migraine attack is that the initiating event is neuronal depression in the occipital cortex, and that the fall in cerebral blood flow is secondary to this metabolic change. Thus, the ischaemic hypothesis is at present open to question.

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