The Optometric Correlates of Migraine

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Declaration

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Thesis Abstract

The role of the optometric factors in migraine headache is still controversial. The aim of this thesis was to investigate the optometric correlates of migraine. Following a detailed literature review a wide-ranging study of the optometric correlates of migraine is described.

This study showed that in people with migraine, pupil responses associated with both sympathetic and parasympathetic autonomic nervous system changes are altered in the interictal phase of migraine. This indicates an effect of migraine on the autonomic nervous system between migraine attacks. Low degrees of astigmatism were more common in people with migraine, and the most significant finding was the horizontal component. Subtle binocular vision anomalies and reduced stereoacuity were also detected in people with migraine.

It was shown that visual fields remain unaltered in migraine, increasing our understanding on how and where in the visual pathway deficits in migraine may occur. A second cohort of patients was recruited to investigate this area more fully. Using visual field and optical coherence tomography data this second, complimentary study, confirmed that visual fields measurements and retinal nerve fibre layer measurements are unaltered in relatively young people with migraine.

It was found that pattern glare is a correlate of migraine and that migraine is associated with visual triggers such as light sensitivity, aversive patterns and other visual stimuli. A factor analysis was used to investigate the interaction between these visual triggers. This revealed two aspects of pattern glare; the overall number of illusions seen in striped patterns was associated with visual triggers whilst pattern glare, use of coloured filters and interictal light sensitivity together formed a component interpreted as visual stress.

It is possible that some of the optometric correlates of migraine identified might play a causal role in some migraine episodes. This hypothesis was investigated using seven single subject double-masked placebo controlled trials. Spectacle lenses to correct astigmatic refractive error, prism spectacles to correct for subtle binocular vision anomalies and precision tinted lenses to reduce pattern glare were amongst the interventions assessed. In two individuals, prism spectacles relieved some migraine symptoms. However neither precision tinted spectacles nor the correction of refractive errors influenced migraine factors in those individuals assessed.

In conclusion, there are distinct optometric correlates of migraine and visual triggers of migraine are important. Relieving optometric conditions in people with migraine may reduce co-morbid ocular disorders but may not alter migraine head pains.

Section 1

Introduction

Chapter 1 Literature Review

1.1 Brief historical overview

From 3000 BC, vision has been linked to migraine headache (Pearce, 1986; Alvarez, 1945). Hippocrates himself alluded to the visual prodrome of migraine (Allory, 1859):

"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...vomiting, when it became possible, was able to divert the pain and render it more moderate"

Migraine has been described in other ancient writings, too numerous to review here. Particularly relevant to this overview, Celsus (AD30, cited by Thomas, 1887) listed sunlight among the triggers of migraine. The severity of migraine, and its association with photophobia, was highlighted by Aretaeus (AD81, translated by F Adams, 1856):

"For they flee the light; the darkness soothes the disease; nor can they bear readily to look upon or hear anything pleasant... The patients are weary of life and wish to die."

Figure 1

An 17th century image of Zeus (Atlanta Fugiens – M.Maier) complaining of such a headache that he forces Hephaestus to split his head with an axe, thus giving birth from his head to the goddess Athena (with permission from Glasgow University Library Dep. Special Collections)

Gowers (1886) referred to the two main theories of migraine: vascular and neural, an observation which is equally valid today. The 1920's saw allergic theories come and go, as did the psychosomatic theories of the 1950s (Pearce, 1986). Pearce (1986) concluded;

"...(nowadays) migraine headache can be considered to be a reaction or biological adaptation determined by a primary disorder of brain threshold in combination with a variety of external precipitating factors. Together, these lower this threshold to a point when a migraine attack will occur."

1.2 Pathophysiology, pathogenesis and treatment of Migraine

Goadsby *et al.* (2002) have reviewed migraine pathophysiology from a medical perspective, but in a broad sense, migraine can be thought of as a tendency to have headache that is characterised by certain associated symptoms. The basis of this predisposition has been attributed to a lack of stability in the control of pain, the control of sensory information coming from the pain producing intra-cranial structures and sensitivity to cyclic changes in the central nervous system (Lance and Goadsby 1998).

1.2.1 Genetic factors

The migraine brain has a reduced threshold to a variety of stimuli, and this has been described as cortical hyperexcitability. The factors that set this threshold are genetically determined (Ophoff *et al.,* 1996; Ducros *et al.,* 2001). A hereditary component to migraine has been shown by prevalence studies, particularly twin studies. One such example is familial hemiplegic migraine; a specific type of migraine characterised by attacks of transient hemiparesis followed by a migraine headache. It is classically divided into pure familial hemiplegic migraine (about 80% of sufferers) and familial hemiplegic migraine with permanent cerebellar signs (about 20% of sufferers). It is an autosomal dominant condition directly related to mis-sense mutations in the alpha-1 sub-unit of the P/Q calcium channels on chromosome 19 (Ophoff *et al.,* 1996). This mutation explains about 55% of cases with another 30% localised to another locus on chromosome 1 (Ducros *et al.,* 1997). The broad clinical spectrum of familial hemiplegic migraine can be directly related to mutations found in Ca^{2+} channel gene labelled "CACNA1A", which encodes these neuronal calcium channel (Ducros *et al.,* 2001). Neurological conditions that are due to abnormalities in channels are called channelopathies (Griggs and Nutt 1995). These often have episodic characteristics, and migraine characteristics are well known to be episodic.

1.2.2 Magnesium deficiency

Magnesium ion concentration has been shown to be lower during migraine headache (Ramadan *et al.,* 1989) Ramadan's group used a magnetic resonance imaging technique which measured the chemical shift properties of resonance signals of injected ^{31}P. Magnesium gates and blocks the N-methyl-D-aspartate (NMDA)-subtype glutamate receptor, so these results suggests a basis for cerebellar hyperactivity via increased activity at NMDA receptors (Welch and Ramadan 1995). Additionally, given that NMDA-mediated activation is essential for spreading depression (Lauritzen 1994) a relative reduction in magnesium may make the brain more susceptible to the triggering of spreading depression. Speading depression is discussed in more detail later.

1.2.3 Amino acid factors

D'Andrea et al (1989) showed that the platelet content of glutamate and aspartate was increased in patients suffering with migraine with aura during headache free periods when compared to migraine without aura patients and normals. These glutamate levels rose even further during a headache. Ferrari *et al.* (1990) measures the plasma level of amino-acids and found the level to be elevated in patients between attacks, more so in patients with migraine with aura than those without. Again these levels increased further during a headache. This suggests that the cortex might also become over excited leading to migraine symptoms if a rise in amino-acid levels could be shown to exists at the cortex in migraine sufferers.

1.2.4 The Hypothalamus and the role of Dopaminergic Transmission

Many migraine patients can report symptoms of mood changes before they have a migraine headache such as elation, irritability, depression, hunger, thirst or drowsiness. Many of these symptoms can be attributed to the hypothalamus (Kupfermann 1985). A substantial number of patients report yawning (Russell *et al.,* 1996), which is distinctly doperminergic. Dopermine-2 receptor activation will activate yawning, and yawning is blocked by dopermine-1 receptor blockers (Sera *et al.,* 1986, 1987).

Prolactin is suppressed by doperminergic agents in migraine women (Nappi and Savoldi 1985) and the control of prolactin secretion varies between normals and migraine sufferers during the menstrual cycle (Murialdo *et al.,* 1986). Glover *et al.* (1996) reported that the administration of fenfluramine, which releases 5-HT caused a significantly higher level or prolactin in migraine patients compared to controls suggesting a supersensitivity of hypothalamic 5-HT receptors.

The thyrotropin response hormone to TRH (thyrotropin releasing hormone) is also diminished in some migraine patients (Daras *et al.,* 1987) and patients with headache including migraine are more responsive to drugs such as LSD and psilocybin (Fanciullacci *et al.,* 1974).

1.2.5 Vascular Reactivity

The cerebral vasodilator response to carbon dioxide is greater in migraine patients than in normal controls (Sakai and Meyer 1979). Also, the reaction of extracranial arteries to exercise is greater on the side of their usual migraine headache (Drummond and Lance 1981, Drummond 1982). This suggests some greater vascular reactivity in migraine patients compared to normals.

It was once thought that migraine was a vascular headache, determined by changes in cranial vascular diameter. Howver May *et al.* (2001) examined neural influences on the cranial circulation by studying healthy volunteers' responses to injection of the pain-producing compound "capsaicin" by measuring the calibre of the internal carotid artery. The study was conducted using magnetic resonance angiographic techniques. Injection of capsaicin into the skin innervated by the ophthalmic (first) division of the trigeminal nerve elicited a mean increase of 40% (+/- 27% standard deviation) in vascular cross-sectional area in the ipsilateral internal carotid artery. Injection of capsaicin into the skin of the chin to stimulate the mandibular (third) division of the trigeminal nerve and into the leg led to a similar pain perception but did not produce any significant change in vessel calibre. May *et al.* stated that this data "suggested a highly functionally organized, somatotopically congruent trigeminal innervation of the cranial vessels, with a potent vasodilator effect of the ophthalmic division on the large intracranial vessels". They concluded that their data was consistent with the notion that pain drives changes in vessel calibre in migraine, not vice versa. Migraine might therefore be regarded as primary neuro-vascular headaches not as vascular headaches.

1.2.6 Reduced Habituation

Migraine sufferers show a variation in their response to visual evoked potentials. This has been shown not to reflect the severity or duration of a migraine attack but rather to reflect a general predisposition to migraine headache (Winter 1987). Schoenen *et al.* (1995) showed that migraineurs do not show the same habituation of visual evoked potentials over time as normals, and the intensity dependency of auditory cortical evoked potentials is increased in migraine sufferers (Wang *et al.,* 1996).

1.2.7 Migraine attack initiation, spreading depression and pain

Migraines can be initiated by "triggers". Such triggers can be divided into internal and external. One example of an internal trigger might be hormonal factors, whilst external triggers could be flickering lights, certain patterns or strong smells. External triggers have the potential to cause, and therefore to prevent, migraine and will be outlined in more detail later. Once triggered, a migraine has two main consequences: pain and spreading depression (which may or not be perceived as aura).

1.2.7.1 Trigeminal pain in migraine

The trigeminovascular system contains the cerebral and intracranial vessels and the meninges. The ophthalmic division of the trigeminal nerve innervates the area in which most migraine patients report head pain. Two trigeminal neurotransmitters have had role in the development of recent highly effective medications for migraine: serotonin (5HT) and Calcitonin Gene-Related Peptide (CGRP). 5HT can abort headache in migraine patients and 5HT agonist drugs have been shown to be very effective anti-migraine drugs because oftheir ability to block trigeminal nerve activation and cranial vessel dilation.

CGRP is a potent vasodilatory neuropeptide and sensory neurotransmitter, which is synthesised in the trigeminal ganglion cell body. When the trigeminal nerve is stimulated CGRP is released and this causes the vessel to dilate. In migraine patients CGRP increases in the jugular blood during the headache and its release can be blocked by 5HT agonists and CGRP antagonists.

Many anti-migraine drugs are 5HT (specifically, 5HT1B/1D) agonists specific to cranial vessel and trigeminal nerve sites. 5HT1D receptors have their central location on the trigeminal neuron apposing the cranial vessel. But 5HT1D receptors also exist at the peripheral end of the trigeminal neurone in the spinal cord, so it may be possible that the anti-migraine effect of 5HT1B/1D agonists also works at this peripheral site.

1.2.7.2 Spreading depression and aura

Leão (1944) described "spreading depression" as a progressive shut down of cortical function. Waves of cortical inhibition, sometimes preceded by transient excitation, move slowly over the cortex (2 to 3 mm per minute), suppressing normal activity, and take 5 to 60 minutes before recovery takes place. Spreading depression is associated with vascular changes (Lauritzen *et al.*, 1982; Goadsby, 1992; Piper *et al.*, 1991). One such vascular change that has been suggested in patients with migraine with aura is a "spreading oligaemia" (Olesen *et al.*, 1981; Dreier *et al.*, 2001). Dreier *et al*, (2002) has

suggested that the link between the vascular oligaemia and the neurological spreading depression may be that endothelial irritation triggers cortical spreading depression. Hadjikhani *et al.*, (2001) showed vasoconstriction and then vasodilation followed the cortical spreading depression using an imaging study. The oligaemic waves of reduced blood flow progress over the cortex at the same rate of 2 to 3 mm per minute as cortical spreading depression. They start in the visual cortex and advance forward without respecting arteriolar territories. These vascular changes can last several hours and are followed by delayed hyperaemia (Andersen *et al.*, 1988). As the spreading oligaemia reaches the sensory and motor areas of the brain, the patient experiences the focal neurological aura symptoms. The neurological changes during aura parallel that seen if the brain is directly stimulated (Brindley and Lewin, 1968; Penfield and Perot, 1963) and are similar to the changes that would be predicted if ocular dominance columns (Hubel and Weisel, 1968) in the cortex were serially activated.

Woods *et al.* (1994) demonstrated a spreading oligaemia directly with a positron emission (PET) study. Interestingly, the patient in this study did not perceive aura in any traditional sense, suggesting that the oligaemia can traverse the whole cortex without the patient experiencing symptoms. Indeed, Lance and Anthony (1966) claimed that only 10% of migraine patients perceive the fortification spectra but 25% of patients perceive less specific symptoms of "spots before the eyes" or "shimmering vision" covering the entire visual field.

Other neuro-vascular interactions can occur with migraine. Kruit *et al.* (2004) found that some patients with migraine were at risk of sub-clinical lesions in certain brain areas and suggested that the cerebellar region was an area where migraine sufferers had a greater number of infarcts than controls. Lipton and Pan (2004) considered that this might be evidence that migraine is a progressive brain disease as this area had been previously implicated in persons with both stroke and migraine (De Benedittis *et al.*,1995; Hoekstra-van Dalen *et al.*, 1996).

There is some pathophysiological evidence linking the aura phase of migraine and the pain phase of migraine. Moskowitz (1984) considered that the spreading depression of the cortex might depolarise trigeminal nerve fibres and initiate pain. However, if this hypothesis were true then the headache would always develop on the side of the head responsible for the aura symptoms (e.g., a left sided headache would arise from a right field aura). Olesen *et al.* (1990) showed that in 38 patients with migraine with aura, three experienced headache on the "wrong" side and Jensen *et al.* (1986) showed that aura symptoms were ipsilateral to the headache in 19 patients and contralateral in 18 patients. Thus, there must be some "central link" which can trigger pain on either side of the head

for one sided aura symptoms. Bolay *et al.* (2002) have suggested that cortical spreading depression activates trigeminal vascular afferents to evoke meningeal and brainstem events that potentially lead to the development of headache.

1.3 Migraine Prevalence, Classification and Diagnostic Criteria

In the UK there are up to 5.85 million people aged 16 to 65 experiencing 190000 migraine attacks every day (Steiner et al 2003) and in North America, more than 2.5 million people have at least one day of migraine per week (Goadsby et al 2002). Headache is an extremely common symptom presenting to primary health care professionals, and an accurate diagnosis is essential to ensure both the correct management of benign conditions and to ensure that when headache presents as a symptom of serious disease then it is dealt with appropriately. The International Headache Society (IHS) published the second edition of The International Classification of Headache Disorders recently (Headache classification committee of the IHS, 2004). The IHS classification is lengthy and is summarised in Table 1. The first edition has been summarised from a clinical optometric viewpoint, by Patel *et al.* (2003) but the migraine classification of the IHS can also be summarised as follows:

1 Migraine
1.1 Migraine without aura
1.2 Migraine with aura
1.2.1 Typical aura with migraine
1.2.2 Typical aura with non-migraine headache
1.2.3 Typical aura without headache
1.2.4 Familial hemiplegic migraine
1.2.5 Sporadic hemiplegic migraine
1.2.6 Basilar-type migraine
1.3 Retinal migraine
1.4 Childhood periodic syndromes that may be precursors to or associated with migraine
1.4.1 Benign paroxymal vertigo of childhood
1.4.2 Abdominal migraine
1.5 Complications of migraine
1.5.1 Status migrainosus
1.5.2 Chronic migraine
1.5.3 Persistant aura without infarction
1.5.4 Migrainous infarction
1.5.5 Migraine triggered seizure

1.6 Probable Migraine

1.6.1 Probable migraine without aura

1.6.2 Probable migraine with aura

1.6.3 Probable chronic migraine

In this migraine section, optometric factors are not mentioned. However, some diagnostic criteria within this section mention vision and / or ophthalmic conditions as part of the aura phase. Additionally some optometric factors are noted in the section relating to "Headache or facial pain associated with disorders of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cranial structures" and the "eyes" section is subdivided as eyes, acute glaucoma, refractive errors and heterophoria or heterotropia. Acute glaucoma is the only ocular pathology mentioned and there is no place for any other ophthalmic pathology that may cause headache in the classification. Headache associated with refractive errors has an IHS diagnostic criteria of:

A Uncorrected refractive errors eg hypermetropia, astigmatism, presbyopia, wearing of incorrect glasses

B Mild headache in the frontal region and in the eyes themselves

C Pain absent on awakening, and aggravated by prolonged visual tasks at the distance or angle where vision is impaired.

Weaknesses in these criteria might be that there is no place for any headache of greater severity than "mild" and this pain must be located both in the eyes and to the frontal region. In addition the pain must be aggravated by visual tasks at the distance for which vision is impaired. As such an uncorrected moderate hyperope who has 6/6 vision but needs to exert considerable accommodative effort to do so, would not be able to be classified as having a refractive error headache since the vision is not impaired.

Headache associated with Heterophoria or heterotropia (latent or manifest squint) has an IHS diagnostic criteria of:

A Hetrophoria or heterotropia is demonstrated

B Mild to moderate constant headache in the frontal region

C At least one of the following:

1: Headache occurs or worsens during a visual task especially when tired

2: Intermittent blurred vision or diplopia

3: Difficulty adjusting focus from near to distant objects or vica versa

D Relief or improvement of symptoms by closing one eye

Weaknesses in these criteria might be that there is no mention of the sensory factors associated with heterophorias such as compensation, aligning prism and foveal suppression and no mention of the motor factors such as size and direction. There is equally no mention of the sensory and motor factors associated with hetrotropia. The headache must be constant, and must be located to the frontal region. Headaches that are not constant or are not located to the frontal region cannot be diagnosed as a heterophoric or heterotropic headache. Finally, the symptoms must be relieved or improved by closing one eye but no time scale is given on how long this diagnostic test should be applied.

This IHS classification section concludes with a comment:

> "Uncorrected refractive errors and heterophorias may cause headaches but their importance is widely overestimated"

Despite the weaknesses of the classification criteria, the IHS criteria are widely used. Leone *et al.* (1994) have stated that the diagnostic criteria are satisfactorily applicable to high quality medical records abstracted by experienced neurologists. Cady and Dodick (2002) were more pragmatic and suggest that the guidelines are invaluable in organizing headache research but that clinicians may prefer assessment tools more applicable to clinical practice. Ryan (1999) suggested that for effective management headache need only be classified into three main classes, migraine, cluster headache and tension headache.

Table 1.

A summary of the classification of migraine

Migraine without aura						
Migraine with aura	Typical aura with migraine headache	Typical aura with non-migraine headache	Typical aura without headache	Family hemiplegic migraine	Sporadic hemiplegic migraine	Basilar-type migraine
Retinal migraine						
Childhood periodic syndromes that are commonly precursors of migraine	Benign paroxysmal vertigo of childhood	Abdominal migraine	Cyclical vomiting			
Complications of migraine	Chronic migraine	Status migrainosus	Persistent aura without infarction	Migrainous infarction	Migraine-triggered seizure	
Probable Migraine	Probable migraine without aura	Probable migraine with aura	Probable chronic migraine			

1.4 The Visual Aura of Migraine

The cornerstone to visual aura in migraine are fortification spectra or "teichopsia", though this may present in only 10% of migraine patients (Lance and Anthony 1966). Originally described by Airy, the term teichopsia was coined from the Greek terms "teichos" meaning wall and "opsis" meaning seeing, alluding to the zig-zag design of early Italian military fortifications with which Airy was familiar (Airy 1870). The symptoms of scintillating scotoma and a marching fortification figure that gradually expands and then breaks-up is characteristic of migraine with aura. Wilkinson (2004) and Celesia (2005,2006) have reviewed migraine visual aura in the context of other visual hallucinations and suggested how these might relate to the neural mechanism of aura.

Queiroz *et al.* (1997) showed that visual aura accompanied the patient's first headache in 39% of patients but only 19% had visual aura with every attack. The free period between visual aura and head pain was less than 30 minutes in 75% of cases. The symptoms were described as "small bright dots" (42%), "flashes of light" (39%), "blind spots" (32%) and "foggy vision" (27%). Fortification spectra were reported by only 20%.

Usually migraine aura is binocular but rarely migraine can affect the pre-chiasmal visual pathway and produce monocular symptoms. These retinal migraines produce monocular scotomas, and are caused if any of the circulation of the anterior visual pathway becomes involved in the angio-spastic disturbances of migraine. Often the visual loss is described as a blackout or grey-out which can last from seconds to hours, the vast majority lasting less than 30 minutes (Hupp *et al.* 1989).

Migraine aura can occur without headache. The Framingham Study (Wijman *et al.*1998) demonstrated that these migrainous visual accompaniments occur in just over 1% of the population aged between 30 and 62 years. This study showed that the mean age of onset of these symptoms was 56 years and in 58% of subjects no headache was reported. Indeed, 42% had no headache history at all. A variety of ophthalmic conditions may produce visual aura like symptoms and need to be differentially diagnosed. Table 2 contrasts the signs and symptoms of these conditions.

Most migraine sufferers avoid bright light during headache (Selby and Lance, 1960). Wolff (1963) argued that true photophobia is pain induced and exacerbated by bright light, for example in corneal disease or anterior uveitis, and is derived from stimulation of the trigeminal nerve. He argued that glare or dazzle on the other hand is uncomfortable but not painful. Glare can be caused by stray light scattering into the eye from ocular structures (such as cataract) or environmental factors (such as a poorly placed lamp). Glare might also be caused by a general excitability of the senses in migraine sufferers and migraine sufferers have been shown to be more susceptible to glare than controls (Drummond, 1986).

Table 2.

A variety of ophthalmic conditions may produce visual aura-like symptoms and need to be differentially diagnosed. This table contrasts the signs and symptoms of these conditions.

Diagnosis	**Monocular or Binocular Disturbance**	**Onset of Symptoms**	**Usual Duration of Symptoms**	**Scotoma**	**Photopsiae**	**Build up of scotoma**	**Migration of scotoma**
Migraine with Aura	Binocular	Gradual	15 to 30 minutes	Yes	Yes	Yes	Yes
Retinal Migraine	Monocular	Gradual	15 to 30 minutes	Yes	No	No	No
Amaurosis Fugax	Monocular	Sudden	minutes	Yes	No	No	No
Occipital Transient Ischaemic Attack	Binocular	Sudden	minutes	Yes	Yes	No	No
Posterior Vitreous Detachment	Monocular	Sudden	One Month	No	Yes	No	No
Retinal Break or Detachment	Monocular	Sudden	One Month to Continuous	Yes	Yes	Yes	No

Stimulation of the trigeminal nerve during a migraine attack probably accounts for photophobia. Drummond and Woodhouse (1993) stimulated the trigeminal nerve with ice on the forehead and measured discomfort thresholds for migraine sufferers and controls. They showed that trigeminal discharge contributes to photophobia in migraine sufferers and that this trigeminal discharge continued during headache free periods. Later, Drummond (1997) showed that it is glare, rather than true photophobia that probably accounts for the light sensitivity experienced by migraine suffers between attacks. This heightened sensitivity to light is consistent with the heightened sensitivity found to other visual stimuli in migraine sufferers, such as pattern glare, which is reviewed in section 1.10.

1.5 Visual Migraine Triggers

Migraine triggers are the internal or external factors that excite the migraine brain above its genetically reduced threshold and in doing so, precipitate the chain of neuro-vascular events that produce a migraine headache. It has been suggested that common triggers include certain foods, stress, smells, hormonal changes, irregular meals, changes in sleep pattern and environmental factors such as excessive heat, light or noise (Peatfield and Olesen, 1993). It should be noted that some authors suggest that migraines occur spontaneously and that the triggers that patients associate with their migraine headache are actually due to the fact that in the "prodrome" phase of a migraine attack some migraine sufferers have a craving for certain foods or drinks (Dowson and Cady, 2002). These then may be blamed for the attack when in fact they are a consequence. Nevertheless, it is generally considered that by making lifestyle changes, the frequency and severity of migraine headache can be reduced (NHS Direct 2006).

Migraine patients are sensitive to light during and between headaches (Drummond, 1986). It has also been stated that migraine, as compared with other headaches, is worse during midnight-sun summer than during the polar night (Salvesen and Bekkelund, 2000). Visual stimuli that can trigger migraine do not have to be strong. Jacome (1998) described a patient who, on multiple occasions, could trigger his typical headache within thirty minutes just by rubbing his eyes gently and inducing bilateral photopsias. Liveing (1873) described falling snow as a migraine trigger. Debney (1984) produced a thorough review of the literature relating to visual stimuli as migraine trigger factors. She showed that visual stimuli were quoted by at least ten other authors and ranked visual triggers as of similar importance to other more obvious triggers such as stress and hormonal factors.

Debney (1984) reviewed the medical notes of 344 migraine patients and showed that 62% had "glare" as a precipitating factor, 53% had "flicker" as a precipitating factor and 1% had "colour" as a precipitating factor. Debney analysed these findings further and sought to correlate non-visual precipitating factors to those patients who claimed their migraines were induced by visual stimuli. She found significance only with two factors 1: "other sensory and environmental factors" 2: "dietary factors". Debney (1984) suggested;

> "... that it would be interesting if the aberrant biochemistry underlying dietary triggers of migraine also affected the sensitivity of the sufferer to visual triggers and to other sensory and environmental triggers."

Debney (1984) then analysed her data further and split them into two groups, one detailing visual tasks quoted to have induced migraine because of glare, and one

detailing visual tasks quoted to have induced migraine because they involve flicker. In the glare group, she found that the following situations had all been implicated in precipitating migraine: sun reflections; rippling water or sea; at the beach; snow; paper; chrome trim on a car; microscopy; facing bright windows; fluorescent lighting. In the flicker group, she found that the following situations had all been implicated in precipitating migraine: television; cinema; faulty fluorescent lighting; lighting in vehicular tunnels; flashlights; headlights; stroboscope; travelling past railings, telegraph poles and fences (by train).

Debney (1984) listed many visual stimuli reported to induce migraine. This list was lengthy but can be summarised by splitting visual triggers into four simple groups; glare, flicker, patterns and colours. Glare could be explained by the trigeminal nerve sensitivity demonstrated by migraine sufferers (Drummond, 1986) or, with flicker, patterns and colour, by cortical hypersensitivity theories (Wilkins, 1995). Both these aspects will be discussed later.

Traditional clinical advice is to avoid trigger factors. Interestingly however, Martin (2000) showed that in patients with visually triggered headaches, there is a desensitisation period such that the visual triggers become less likely to produce headache symptoms with continued exposure. This finding could conceivably alter the way headaches are managed, with exposure to triggers to produce desensitisation as a possible approach, rather than trigger avoidance. However, such a provocative approach would require further research before it could be advocated.

In conclusion, visual stimuli are common and potent migraine triggers. This is emphasised by the fact that some experimenters have used an alternating red and green checkerboard as a strong visual stimulus to cause migraine headache for experimental purposes (Cao *et al.*, 1999).

1.6 Refractive Errors and Migraine

In the early 1900s, uncontrolled studies by Gould (1904) and Snell (1904) argued that low refractive errors, particularly astigmatism, are associated with migraine.

Turville (1934) claimed that uncorrected errors of refraction were a major cause, or at least an important precipitating factor, in cases of migraine. He also claimed that the conventional methods of the time used to provide correction for refractive errors were inadequate. In his opinion, the investigation of refractive errors must include both manifest and latent errors. He defined a latent error not just as latent hyperopia but also

as heterophorias, accommodative anomalies "and in fact any departure from normal visual activity, physiologically, optically, functionally, mentally and psychologically."

Turville stated that even an inequality of refractive error of 0.25 dioptres was important in many cases and noted that the difference was rarely more than 0.75 dioptres. Turville's study lacked a control group and lacked any form of statistical analysis. It is unclear whether it was the correction of refractive errors, the correction of any decompensated phorias, or placebo effects that were relieving symptoms.

Wilmut (1956), although mostly concerned with effect of binocular vision on migraine (described below), did look at the refractive errors of 116 cases of migraine and compared them to a non-migraine group. He found a similar prevalence of refractive errors in migraine and a non-migraine control group.

Several other authors have argued that headaches or migraine are associated with uncorrected refractive errors, but these studies will not be described in detail because there were no control groups or statistical analyses (Lanche, 1966; Gordon, 1966; Vaithilingham and Khare, 1967; Cameron, 1976; Hedges, 1979; Worthen, 1980).

Waters (1970) identified by a questionnaire, in a random sample of a general population, groups of individuals with; headache, unilateral headache, migraine, and a fourth group who had not had a headache for a year. A masked assessment of the visual acuity and ocularmotorbalance was then performed on each group. Visual acuity was measured unaided and aided if spectacles were worn. Waters found that there was no significant difference between the unaided vision, or visual acuity with spectacles if normally used, of the four groups in either men or women. In addition, he found no significant difference between groups in the number of individuals wearing spectacles for either distance or near vision. He concluded by suggesting that these data showed that in the general population headaches are seldom caused by a visual defect. However, Waters did not assess refractive error at all and so doubt must be raised over his conclusions.

Vincent *et al.* (1989) determined the prevalence of visual symptoms and eyestrain factors in a group of chronic headache sufferers compared with age and sex matched controls and found near visual tasks to be one of the many visual triggers for chronic headache. However, this questionnaire survey did not take account of whether the near visual tasks were carried out with corrected or uncorrected refractive errors. Nevertheless, some authors (Gordon *et al.,* 2001) have suggested that Vincent's data could suggest a relationship between headache, refractive error, accommodation and convergence.

Gordon *et al.* (2001) reviewed the experimental and clinical evidence on possible links between refractive errors and headaches and listed several issues that were still to be resolved. This review did not relate specifically to migraine, so will not be described in detail. Evans *et al.* (2002), in a study described in the next section, found no significant difference between a group of migraine and a group of control patients in the subjective refractive error or the proportion of participants who wore spectacles.

To conclude, the association between uncorrected refractive errors and migraine seems to be equivocal. Early studies have shown much anecdotal evidence but the few modern studies, which included masked control groups and statistical analyses, have found little evidence. Often researchers have failed to accurately classify headaches and so data relating specifically to migraine is rare. In addition, little or no evidence appears to relate to any possible pathogenic link between refractive errors and migraine.

1.7 Binocular Vision (orthoptic) Anomalies and Migraine

Snell (1904) argued that heterophoria is a cause of headache, especially esophoria when found in conjunction with myopia. Turville (1934) suggested that low convergent and divergent fusional reserves are correlates of migraine and that base in prisms are an effective treatment for many cases of severe classical migraine. Turville describes his first successful case of relief of migraine with base in prisms and it is interesting to note that this patient was esophoric rather than exophoric as might have been expected. The prism power was determined in an unconventional way: as one third of the recovery point from the measurement of the *divergent* fusional reserves. He described a migraine sample of 123 cases, but there was no control group or placebo treatment. As recently as 2000, this use of base in prism to relieve migraine headache was still being advocated (Patterson, 2000; Bush, 2000).

The Turville Infinity Balance test (Turville, 1946) is a distance vision binocular vision test consisting of a 3cm wide vertical septum placed half way between the patient and a 6m optotype acuity chart. It is used for refractive binocular balancing, assessing heterophoria, and suppression associated with binocular vision disorders (Morgan, 1949). Wilmut (1956), using a polarised version of the Turville Infinity Balance, found that 91% of patients with migraine had "excessive exophoria" and had previously argued that 56% of his cases were cured with base in prism (Wilmut, 1951). Wilmut's 1956 study was of a clinical sample and may have suffered from referral bias, and does not appear to have been a randomised control trial. However the results were compared to an unspecified control group in which exophoria occurred in only 25%.

Waters' (1970) questionnaire regarding headache and migraine sufferers, discussed in the previous section, not only looked at visual acuity but also ocularmotorbalance. The ocularmotor balance was assessed by the cover-test and a Maddox hand frame with habitual spectacle correction, if worn. Thus, the total dissociated strabismus or phoria was assessed. Waters stated that there was no evidence that the proportion of subjects with esophoria or exophoria for either distance or near vision differed in the four groups in either sex. Unfortunately, the data for esophoria and exophoria was combined and so data on this aspect are not meaningful. He concluded by suggesting that these data showed that in the general population headaches are seldom caused by a visual defect. He also noted that the beneficial effect of any treatment, if applied in an uncontrolled manner, could not be considered as evidence relevant to the aetiology of headache.

Worthen (1980) studied the effects of stimulating extra-ocular muscles in patients on whom operations for strabismus were performed under local anaesthesia. The muscles were exposed under light anaesthesia and then stimulated in various ways. Pinching, pricking or cutting the recti muscles caused no sensations, but traction produced prompt exclamations of pain. The pain was always described as an aching sensation localised deep in the eye/orbit on the side of the stimulated muscle. Worthen went on to describe two case studies where the reproduction of extra-ocular muscle imbalances produced consistent results of headache and aesthenopic symptoms. Electromyographic recording of these patients suggested that the symptoms arose from increased tension in the muscles of the head and neck. Nevertheless, Worthen claimed that the headaches caused by muscle imbalance (heterophoria) could be eliminated by proper alignment of the visual axes and stated that prisms, orthoptic training, or even surgery may be necessary. He suggested that occlusion could be used to diagnose headaches associated with binocular anomalies. Although Worthen (1980) used an interesting approach, his small number of subjects limits the strength of his conclusions.

Sucher (1994) related the symptoms of headache to the "monocular blur effect": a consistent blur of one eye when viewing the 6/18 letters on a letter chart during the Turville infinity balance test, whilst the patient raises and lowers their chin. Sucher found a statistical relationship between this monocular blur effect and patients who have three or more headaches a month. He also found that the monocular blur occurred on the same side of literalised headaches in 94%, and then in 93%, of two cohorts of patients tested. Sucher speculated that the monocular blur effect could be corrected by prisms, and that this correction would then relieve tension on the ocular motor system and so remove a source of headache. However, Sucher's study did not look at the effect of treatment.

Evans *et al.* (2002) compared 21 migraine sufferers to 11 controls and found no difference between the groups in relation to strabismus or hyperphoria. The main purpose of this study was to investigate the effect of coloured filters (Wilkins *et al.*, 2002), so the migraine sufferers were selected as those who found a coloured filter to be helpful. They therefore did not represent a "normal" group of migraine sufferers. Evans *et al.* (2002) did find, using one test method, that the migraine group tended to have a marginally decompensated exophoria at near, however other test methods suggested that the migraine group were as able to compensate for their exophoria as the control group.

Wilkinson et al (2006) measured eye movements in patients with migraine with and without aura and in found no difference in the eye movements of people in these two groups using a variety of experimental techniques. They concluded that visual abnormalities in migraine have their origin in the visual pathways and not in the ocular motor system.

Decompensated heterophoria, the diagnosis of which is discussed by Evans (2002), has been linked to headaches by many authors (e.g., Jenkins *et al.*, 1989; Yekta *et al.*, 1989; Evans, 2002). However, these authors do not specifically discuss migraine.

In summary, the association between optometric anomalies of binocular vision and migraine seems to be equivocal. Early studies have suggested anecdotal evidence but the few modern studies, which have been more statistically and methodologically robust, have either found little or no evidence, or have generally related to headache or aesthenopic symptoms, rather than specifically to migraine.

1.8 Visual Fields and Migraine

The central visual pathway can be investigated in a number of ways. Psychophysical testing of visual processing can shed light on perceptual issues in migraine as discussed by Coleston *et al.* (1994), McKendrick *et al.* (1998) and others. These studies do not involve clinical optometric approaches and will not be discussed in detail here, but are reviewed by Chronicle and Mulleners (1996). Electrophysiology can directly measure cortical activation but is not an optometric procedure and is extensively reviewed elsewhere (Aurora *et al.* (1998); Áfra *et al.* (1998); Áfra *et al.* (2000); Cao *et al.* (1999)).

Several studies have assessed visual fields in migraine. McKendrick *et al.* (1998) showed in a single migraine sufferer deficits to tasks involving 16 Hz flicker using a Medmont 6000 perimeter auto flicker paradigm. Later, McKendrick *et al.* (2000) performed similar temporally modulated perimetry in sixteen migraine sufferers and sixteen controls and

suggested that migraine sufferers have selective visual dysfunction for temporally modulated targets of a temporal frequency greater than 9 Hz.

Other visual field anomalies have been found in migraine patients. McKendrick *et al.* (2002) performed Short-Wavelength Automated Perimetry (SWAP) and Standard Automated Perimetry (SAP) using a Humphrey Visual Field Analyser. Although they did not find a significant difference in mean deviation and pattern standard deviation between migraine sufferers and controls using SAP, both these parameters were significantly worse in the migraine group using SWAP. The authors suggested that people with migraine should not be included in visual field normative databases.

Visual field loss is a key diagnostic test in glaucoma. Klein *et al.* (1993) reported results from the Beaver Dam Eye Study that showed no relationship between open-angle glaucoma and migraine headache. They used diagnostic criteria based on visual fields, intra-ocular eye pressure, cup/disc ratio and history. Usia *et al.* (1991) found no greater prevalence of migraine in a glaucoma population compared to a normal population and Pradalier *et al.* (1998) commented that migraine prevalence was not significantly different between normal and high tension glaucoma sufferers.

In contrast, other authors have found that there is a relationship between normal tension glaucoma and migraine headache (Cursiefen *et al.,* 2000). In particular, migraine has been considered a risk factor for glaucomatous visual field progression (Drance *et al.,* 2001). Comoglu *et al.* (2003) found glaucomatous-like visual field defects in patients with migraine in the absence of raised intra-ocular pressures and suggested that there might be a relationship between the pathophysiology of normal tension glaucoma and migraine. McKendrick agreed with this viewpoint (McKendrick *et al.,*2000; McKendrick *at al.*, 2002) and concluded that the similarity of SWAP defects and temporally modulated perimetry defects in migraine sufferers and glaucoma sufferers might raise the possibility of a common pre-cortical vascular involvement in these two conditions.

Interestingly, McKendrick and Badcock (2003) have shown that migraine sufferers with visual field loss to temporally modulated targets but not to standard automated perimetry exhibit dysfunction of both the parvocellular and magnocellular pathways. How this might relate to the mechanism of visual field dysfunction in migraine is yet to be investigated. Coleston *et al.* (1994) also found evidence suggesting both magno- and parvocellular deficits in migraine. These authors suggested that the deficit was pre-cortical, and they noted that this could reflect either intrinsic abnormalities or a consequence of attacks. Since considerably more nerve fibres run from the cortex back to the lateral geniculate nucleus than the ascending geniculostriate pathway, they hypothesised that recurrent

migraine episodes might cause cortical damage which in turn causes pre-cortical deficits. Chronicle and Mulleners (1994) suggested that cerebral ischaemia occurs in migraine and that this results in long-term damage to GABA-ergic cells in the visual cortex, which are especially sensitive to hypoxia.

1.9 Pupil Anomalies and Migraine

The iris sphincter pupillae muscle is innervated by the parasympathetic autonomic nervous system and the iris dilator pupillae sympathetic autonomic nervous system. Autonomic nervous system dysfunction in migraine has long been investigated (Olesen and Diener 2000) and Lance (1993) has suggested that migraine could be viewed as a derangement of autonomic monoaminergic function. If this is so, then pupil dysfunction should be a feature of the migraine headache. However, the issue is confused by Rubin *et al.* (1985) who found that any difference in pupil responses between migraine sufferers and controls can be attributed, at least in part, to differences in personality. They claim that the migraine personality is more neurotic and depressive, and so responds emotionally in a different way to non-migraine controls. This, they claim, can affect the pupil responses since emotional factors are related to the autonomic nervous system.

Whilst the pupil abnormalities associated with migraine headache are often sub-clinical, there is some good evidence that such pupil anomalies can be unmasked by experimental procedures.

1.9.1 Sympathetic Hypofunction

Herman (1983) has shown that anisocoria exists in both migraine and cluster headache sufferers but by only a mean of 0.8mm. Gotoh *et al.* (1984) found sympathetic hypofunction in migraine sufferers during headache free periods with a variety of neurological tests. Rubin *et al.* (1985) have shown that 70% of migraine sufferers in the interictal phase have deficient sympathetic innervation of the dilator pupillae as compared to controls if challenged by a cold compress. Drummond (1987) compared the pupil diameter of the headache side and non-headache side in migraine sufferers, tension headache sufferers and non-headache controls. He showed that pupil diameter was smaller on the side of the headache both during headache and during headache free periods in patients who habitually had headache on the same side of the head. Drummond (1990) has shown that facial temperature and pupil responses show a sympathetic deficit in migraine sufferers. The facial temperature was asymmetric and associated with the side of headache during a headache attack but not between attacks.

In contrast, pupil diameter was smaller on the usual side of headache both during the headache and during the headache free interval.

De Marinis (1994) stated that the evidence was so strong that pharmacological tests of the pupils could be used to differentially diagnose different forms of idiopathic headache. De Marinis *et al.* (1998) used pharmacological pupillary tests to investigate the oculosympathetic system in patients diagnosed as having migraine without aura. In contrast to the findings of Drummond (Drummond 1987; Drummond 1990) De Marinis *et al.* claimed that the oculosympathetic hypofunction was not related to headache side and was temporally related to the migraine attack, being absent after 15 days. Battistella *et al.* (1989) showed that this sympathetic hypofunction existed in children with migraine but to a lesser extent, which suggests a progression of the sympathetic hypofunction from childhood into adulthood.

1.9.2 Parasympathetic Deficits

Mylius et al (2003) showed that not only sympathetic deficits but also parasympathetic deficits could be shown in the pupil responses of people with migraine. This group demonstated sympathetic dysfunction in terms of baseline anisocoria but also reduced velocity and amplitude of pupil constrction using pupillometry methods suggesting parasympathetic dysfunction. However, these parasympathetic deficits were only recorded within two days of a migraine event.

Purvin (1995) described a case of a 46 year-old woman who had suffered migraine headaches for the previous twenty years. Following one attack, she developed Adie's tonic pupil in one eye. He stated this could be caused by an unusually prolonged migrainous vasospasm leading to local ischaemia of the posterior lateral ciliary artery supplying the ciliary ganglion.

1.9.3 Overall considerations of the pupil and migraine

The evidence for a sympathetic hypofunction in migraine is strong although different authors disagree on whether it persists in the headache free period and if it is related to the side of the habitual headache.

The evidence of Adie's tonic pupil relates to one case study which although detailed is not good evidence and may represent a unique patient event rather than a general trend for migraine sufferers. Mylius et al (2003) do however present further evidence that parasympathic dysfunction may also occur in migraine but only with a few days of an

attack. Evans and Jacobson (2003) recently presented a case study of transient anisocoria in a migraineur and suggested that migraine headache can exaggerate physiological anisocoria and that in their case there were no sympathetic or parasympathetic deficits.

1.10 Pattern Glare/Visual Stress and its Relief with Colour

Some people will report visual perceptual distortions (illusions), eyestrain, and headaches when viewing patterned stimuli. This has been termed "patterned glare" (Wilkins and Nimmo-Smith, 1984) and more recently "pattern glare" (Evans and Drasdo, 1991). Table 3 summarises the features of patterns that are most likely to produce an epileptic response and these are the same characteristics of patterns that cause pattern glare (Wilkins et al 1984).

When the symptoms of pattern glare are present in everyday life then this is called visual discomfort or visual stress. The early literature included several references to the anomalous visual effects to such patterns (e.g., Purkinje, 1823; Brewster, 1832) and by the 1960s and 1970s these effects were being used in the art world, in a movement called "Optical Art" or "Op Art".

Wade (1978) listed the visual phenomena exploited in op-art and included afterimages, Hermann grid effects, Gestalt grouping principles, blurring and movement due to astigmatic fluctuations in accommodation, scintillation and streaming, possibly due to eye movements, and visual persistence. Symptoms produced from such visual phenomena can range from "unpleasantness" to producing epileptic fits in susceptible individuals.

Wilkins (1995) summarised the various effects that normal subjects perceive when viewing a striped pattern as follows: red, green, blue, yellow, blurring, bending of the lines, shadowy shapes amongst the lines, shimmering of the lines, flickering of the lines, nausea, dizziness and pain. Wilkins (1995) suggested that if a person suffered from two or more of these illusions when looking at a striped pattern then they were more sensitive than average, should avoid looking at such a pattern for a long time, and could be diagnosed with visual stress. Conlon *et al.* (2001) showed that her patients with visual stress reported most perceptual distortions with a grating of 4 cycles per degree but that patients with little or no visual stress still had perceptual distortion but at a much higher spatial frequency of 12 cycles per degree. A test (Wilkins and Evans, 2001) is now available for pattern glare/visual stress, which takes advantage of this (IOO Sales Ltd, 56-62 Newington Causeway, London. SE1 6DS)

Table 3.

Certain features make geometric patterns most likely to produce an epileptic response. These same features can cause pattern glare.

Feature	**Reference**
Contrast energy concentrated within one orientation	(Wilkins *et al.* 1979)
the length of line is long	(Wilkins *et al.* 1979)
high luminance, high contrast	(Wilkins 1995, p. 17)
square wave grating	(Soso *et al.* 1980)
increased size of pattern	(Wilkins *et al.*, 1979)
spatial frequencies between 2 and 4 cycles per degree	(Wilkins *et al.*, 1979)
pattern direction is reversed ten to twenty times a second	(Wilkins 1995, pp. 31-34).
Binocular rather than monocular viewing	(Jeavons and Harding 1975; Chatrain *et al.*, 1970; Wilkins *et al.*, 1979,1980).
Pattern presented in the visual hemifield that corresponds to the side of the patients cortex that is most easily excited	Wilkins *et al.*, (1981); Soso *et al.*, (1980); Binnie *et al.*, (1981).

1.10.1 Mechanism of Visual Stress

Wade (1977) had earlier suggested three mechanisms that could explain some of these illusions: (the physiological fixation instability, accommodative changes and the chromatic aberrations of the eye). Zanker (2002) agreed from a computational viewpoint, and claimed that the illusions could have an almost trivial solution in terms of small involuntary eye movements leading to image shifts that are picked up by motion detectors in the early motion system. However, recent evidence that eye movements are not abnormal in migraine would make this conclusion unlikely (Wilkinson et al 2006). Wilkins (1995) suggested that explanations such as Wade's were not adequate to explain the illusions and agreed with Georgeson (1976, 1980) that the illusions had a structure that could be more readily be attributed to inhibitory connections in the visual cortex.

A detailed paper by Wilkins *et al.* (1984) is the seminal work in establishing a neurological basis for visual stress. These authors demonstrated in a number of experiments that the illusions were produced by pattern glare, showed that if the number of illusions was more

than two then the patients was more likely to have visual stress, that the illusions produced were lateralized with other symptoms and that the same stimuli that produced pattern glare also produced epileptiform EEG activity in susceptible individuals. Unlike the epileptic response to patterns, the illusion response to patterns does not spread widely across a hemisphere probably because the processing is more focal. This focal (localised) response does not spread widely because the cortex is not sufficiently hyper-excitable (Wilkins, 1995).

It should be noted that this visual stress is conceptually different to the sensory visual deficits discussed in Section 1.8 (e.g., Coleston *et al.*, 1994; McKendrick and Badcock, 2003). Visual stress seems to be a manifestation of cortical hyperexcitability resulting in a visual trigger for migraine (Wray *et al.*, 1995), eyestrain, and visual perceptual distortions. It can be thought of as a visual component to the brain's over-sensitivity to environmental triggers (Welch, 2003). In contrast, the sensory visual deficits (discussed in Section 1.8) seem more likely to be a consequence of neural damage caused by migraine over a number of years.

1.10.2 Pattern Glare, Visual Stress and Headache

Interestingly, this illusion response to patterns has a relationship to headache frequency. Wilkins *et al.,* (1984) showed that there is a direct correlation between the number of headaches reported and the number of illusions seen whilst viewing a striped pattern of about 4 cycles per degree. Unfortunately, several of the experiments cited in this paper excluded migraine sufferers. However, experiment seven in this paper did show that migraine sufferers perceive more illusions with a pattern glare stimulus than tension headache sufferers. The correlation between migraine headache and pattern glare only held when the pattern design was within the epileptogenic range and did not hold when other symptoms such as back pain were discussed. For these reasons Wilkins and his team suggested that the finding could not be attributed to response bias.

People are more susceptible to illusions on days when they have headaches (Nulty *et al.,* 1987). In addition, people show more aversion to striped patterns if they are headache sufferers, particularly if the headaches are migraines. Marcus and Soso (1989) showed that when viewing epileptogenic striped patterns, 82% of migraine suffers demonstrated aversion whist only 18% of a control group did so. There was no difference between migraine with and without aura. If the illusions appear more pronounced on one side of a pattern then that patient is more likely than others to experience head-pain that is consistently lateralized (Wilkins *et al.,* 1984).

Aurora *et al.* (1998, 1999) used transcranial magnetic stimulation to demonstrate that the visual cortex is indeed hyperexcitable in people who suffer from migraine. Huang *et al.* (2003) used functional MRI in patients who had migraine with aura to show that square-wave gratings that produced pattern glare did induce a hyperneuronal response in the visual cortex.

1.10.3 The Relief of Pattern Glare and Visual Stress with Colour

Colour preference can be related to psychology (red for danger and excitement or blue being a calming colour) or to ocular pathological conditions such as the brunescence of nuclear sclerotic cataract producing yellowing vision. Some individuals may wear tinted lenses due to neuroses (Howard and Valori, 1989). Other people with certain disorders, such as dyslexia, migraine or epilepsy can be helped by using individually prescribed coloured filters (Lightstone, 2000), most likely through their effect on pattern glare/visual stress (Wilkins, 2003). Griffiths (2001) stated that measuring colour preference should be part of a routine optometric examination and produced a six colour system to do this. However, the randomised controlled trials of Wilkins *et al.* (1994; 2002) and Robinson and Foreman (1999) suggest that a greater degree of precision is required and this is supported by recent data (Wilkins at al 2005a,b). The Intuitive Colorimeter (Wilkins and Sihra, 2000) is commonly used for this purpose in the UK.

The use of individually prescribed coloured filters for children with reading difficulties has been described as Meares-Irlen syndrome, which is likely to be a manifestation of visual stress. This subject has recently been reviewed by Evans (2001) and Wilkins (2003). The benefit from coloured filters is not solely attributable to: placebo effects (Wilkins *et al.*, 1994; Robinson and Foreman, 1999), conventional optometric or orthoptic anomalies (Evans *et al.*, 1995, 1996b; Scott *et al.*, 2002), spatio-temporal contrast sensitivity functions (Simmers *et al.*, 2001), or a magnocellular deficit (Evans *et al.*, 1995, 1996a; Simmers *et al.*, 2001). Instead, the benefit from coloured filters is most likely attributable to pattern glare (Wilkins and Neary, 1991; Evans *et al.*, 1995, 1996a) which can be caused by lines of text (Wilkins and Nimmo-Smith, 1984). Deficits of visual attention in some people with reading difficulties might make them particularly sensitive to pattern glare (Evans, 2001). Since people with migraine are particularly sensitive to pattern glare, it is not surprising that migraine-like headaches are prevalent in children with reading difficulties who benefit from precision tinted lenses (Evans *et al.*, 1996b).

It is argued that coloured filters change the distribution of the firing pattern within the visual cortex and, since cortical hyperexcitability may vary locally within the visual cortex,

individually prescribed coloured filters are an effective treatment (Wilkins, 1995; Wilkins *et al.*, 2003). This hypothesis has been supported by recent work showing that the representation of colour in the visual cortex follows topographic maps (Xiao *et al.*, 2003).

Chronicle and Wilkins (1991) found that people with migraine tend to avoid red illumination. In contrast, Good *et al.* (1991) showed that migraine frequency was reduced in children who wore rose tinted spectacles compared to a blue tint. If the tint is prescribed precisely and individually, then the reduction in symptoms with colour is not due to alterations in binocular function or refraction (Evans *et al.* 1996 a,b, 2002).

Wilkins *et al.,* (2002), in a double-masked randomised controlled study, compared the effectiveness of precision tinted ophthalmic lenses in the prevention of headache in migraine sufferers. They showed with headache diaries that headache frequency was significantly lower when a precise optimal tint was worn when compared to a sub-optimal tint used as a control. The participants were a selected group of migraine sufferers who found colour helpful and their optometric characteristics were described by Evans *et al.,* (2002). Evans *et al.,* (2002) showed that pattern glare symptoms of visual stress were reduced with a precisely selected colour of tinted spectacles. However, this reduction in visual stress was not significantly different from that produced by only a slightly different tint that was used as a control.

To conclude, certain visual stimuli produce visual stress. Migraine sufferers are particularly susceptible to visual stress and visual stress can be reduced with precision tinted spectacles. By reducing visual stress in migraine sufferers, migraine frequency may be reduced.

1.11 Summary of literature review

Migraine is a common, chronic, multi-factorial, neuro-vascular disorder typically characterised by recurrent attacks of unilateral, pulsating headache and autonomic nervous system dysfunction. Migraine may additionally be associated with aura; those focal neurological symptoms that may precede or sometimes accompany the headache (Headache classification committee of the IHS, 2004). Headache is a common symptom reported by patients who consult optometrists (Barnard and Edgar, 1996). Since migraine accounts for as many as 54% of all headaches (Leone *et al.*, 1994) this suggests that optometrists are likely to encounter patients with migraine very commonly. This chapter, which formed the majority of a manuscript published in Ophthalmic and Physiological Optics in 2004 (Harle and Evans 2004), describes the optometric aspects of migraine headache.

Some authors have argued that optometric anomalies are a trigger for migraine (Snell 1904; Turville 1934; Wilmut 1956; Waters 1970; Griffin, 1996; McKendrick *et al.,* 1998). In contrast, other authors have been more sceptical about the role of visual factors in headaches and migraine (Lyle, 1968; Headache classification committee of the International Headache Society, 2004). There have been claims of a relationship between migraine headaches and errors of refraction, binocular vision anomalies, pupil anomalies, visual field changes and pattern glare. The quality of the evidence for a relationship between errors of refraction and binocular vision anomalies and migraine is poor but there is stronger evidence for a relationship between migraine headache and pupil anomalies, visual field defects and pattern glare. In particular the link between migraine headache and pattern glare is striking. The therapeutic use of precision tinted spectacles to reduce pattern glare (visual stress) and to help some migraine sufferers is described later in this thesis.

In the current climate of clinical governance, there is a need for evidence-based research to guide optometrists as to the role they can play, if any, in managing some cases of migraine. This chapter has critically examined the evidence of a correlation between migraine headache and optometric factors. Each optometric correlate of migraine can be classified into either a visual sensory or visual motor factor, and Table 4 summarises the evidence. In this table the Centre for Evidence Based Medicine level of evidence tool has been used (Centre for Evidence Based Medicine, 1999). This tool grades evidence from grade 1 which includes randomly controlled trials, grade two which include outcomes and cohort studies, grade 3 which includes case-controlled studies, grade 4 including case series and grade 5 which included epert opinions without critical appraisals.

With the exception of the sensory visual factor of visual stress / pattern glare, and sympathetic hypofunction, the evidence correlating optometric factors with migraine is generally poor.

Thus, it appears that there is acceptable evidence in the literature to suggest that both cortical hyperexcitability (as demonstrated by pattern glare) and peripheral neurological defects (as demonstrated by the sympathetic hypofunction with pupil responses in migraine sufferers) are associated with migraine headache. The cortical and peripheral theories are not incompatible. It is possible that cortical hyperexcitability is an interictal status that leads to pattern glare and that this sensory visual factor is a trigger for migraine. This is consistent with many other authors who have found that migraine can be triggered by certain visual stimuli. It seems that precision tinted lenses might be one method of minimising the impact of visual triggers for migraine headache sufferers.

Additionally, pre-cortical changes to the visual system (such as the pupil changes and some of the visual field anomalies found) may be a long-term consequence of the neuro-vascular interactions of migraine headache.

Table 4. Summary of visual correlates of migraine.

The visual correlates have been divided into sensory and motor correlates. Levels of evidence based on the Centre for Evidence Based Medicine recommendations (Centre for Evidence Based Medicine, 1999) have been assigned (where 1 is high evidence and 5 is low evidence), as interpreted by Harle and Evans, 2004.

Visual Sensory Factors			
Factor	**Assessment (clinical or research)**	**Evidence (Levels 1 to 5)**	**Relevance (Correlate, Cause) (Treatable?)**
Pupil (sympathetic hypofunction)	Research tests routine clinical tests	Level 1b	Correlate
Pupil (parasympathetic hyperfunction)	Research tests	Level 4	Correlate
Flicker	Routine clinical tests	Level 2b	Correlate
Visual Stress / Pattern Glare	Routine clinical tests	Level 1b	Correlate Cause? Treatable

Visual Motor Factors & Refractive Error			
Factor	**Assessment (clinical or research)**	**Evidence (Level 1 to 5)**	**Relevance (Correlate, Cause) (Treatable?)**
Exophoria	Routine clinical tests	Level 4	Correlate Cause? Treatable
Hyperphoria	Routine clinical tests	Level 4	Correlate Cause? Treatable
Refractive error	Routine clinical tests	Level 4	Correlate Cause? Treatable

Section Two

Chapter 2 General Methods

2.1 Subjects and Recruitment

2.1.1 Sections 2 and 3

Participants were recruited to as a part of collaboration with local general medical practitioners and with a Charing Cross Hospital Neurology Unit specialising in Migraine Headache. The Charing Cross Hospital Neurology Unit gave access to its electronic database of patients with a formal diagnosis of migraine, from which names and addresses were printed. A letter of invitation (Appendix 1) to participate in the study was sent to each person on this database.

Care was taken to avoid referral bias: at no time were the details of the study, its association to vision, or words associated with vision, the eyes, or eye-care mentioned to participants during the initial stages of recruitment. The visual nature of the research was only revealed when participants arrived at the clinic, when full informed consent was obtained. This ensured a balance between recruitment that did not bias towards those people with migraine who may have already considered that they had an eye condition, whilst meeting research standards ensuring that those recruited had the required information.

Of the 250 names supplied by the hospital neurological unit, 54 replied to the initial contact. At this stage (before the first appointment) written correspondence was sent out to request that each participant attend together with a friend (non-migraineur) of appropriate age and gender as a control. This correspondence explained and stressed the importance of the masked controlled design. From this group 20 migraineurs eventually attended the research clinic. In addition to these 20, a further 5 migraine patients were recruited from local GPs, and these participants were similarly requested to attend with a friend as a control. A letter (Appendix 1) was written to local GPs telling them about the study:

A secretary telephoned all those participants who responded and arranged an appointment. This secretary also instructed, over the telephone, each participant on the completetion of a six-week headache diary. These were sent to the participant together with a letter (Appendix 1) that confirmed the appointment.

All participants for the migraine group were recruited as not being younger than 10 years nor older than 50 years, with a frequency of migraine headaches of at least one per month. People with systemic health problems, pregnancy, or ocular disease were excluded from the study. Each participant was asked to complete a headache diary (Appendix 2) indicating, for six-weeks, every day whether or not they had head pain, and on the days with pain to complete a sheet describing that pain (Appendix 3).

All but three of the 25 migraine participants brought with them a person of the same gender and of a similar age, but who did not experience migraine or frequent headaches or have any health problems as listed above. These people undertook the same battery of tests as the migraine sufferers and were used to constitute a control group. All participants completed a consent form on attending the clinic (Appendix 4). Three members of the staff of the Institute of Optometry were used to complete the control group and were paired with the three migraine sufferers who did not bring a friend.

Participants were asked to cancel their appointment and re-book if they had a migraine headache on or around the day of the appointment for the experimental investigation. On attending the clinic, all participants were asked to complete a short questionnaire (Appendix 5) detailing their symptoms and history, including questions relating to headaches. This ensured that the migraine group met all the IHS criteria for migraine headache (IHS, 2004) and ensured that the control group were truly migraine free. The responses to this questionnaire were not revealed to the research optometrist until the end of the tests of both the migraineur and the control participant and were analysed in Chapter 6.

To ensure that the researcher was masked as to whether the participant was from the migraine or control group: they were seen in random order, were asked not to reveal their identity, and the contents of the questionnaire were not revealed to the research optometrist until the end of the tests of both the migraine sufferer and the control participant. All participants were headache free at the time of testing. From the headache diary sheets the descriptive data for the headache parameters could be determined (Table 5).

Table 5. *The descriptive data for the headache parameters of the migraine group*

	Number of migraine headaches per year	Duration of worst migraine headache (hours)	Severity of worst migraine headache (1=mild, 2=mod, 3=severe)	Time since last migraine headache (days)
Median	24	25	3	14
first quartile	20	7	3	11
third quartile	43	53	3	20
Minimum	8	2	1	4
Maximum	200	120	3	45

2.1.2 Sample size calcuations

A power or sample size calculation is a statistical technique that is used to predict the number of subjects that are necessary to detect a certain result (Armitage and Berry 1987). To do this the most important outcome of the research must be determined. The most important variables were felt to be those that met the following criteria:

- identified by a literature review as possible causes or correlates of migraine
- detectable in clinical eye examinations
- potentially treatable

On this basis, four variables were felt to be most important, and of these two were selected and two discarded as the data was unlikely to be normally distributed. These variables were:

- Exophoria
- Aligning prism - *not used as not likely to be normally distributed*
- Dissociated vertical phoria - *not used as not likely to be normally distributed*
- Pattern glare

The required number of subjects (n) was calculated from the following formula:

$$n > 2\left\{\frac{(z_{2\alpha} + z_{2\beta})\sigma}{\delta_0}\right\}^2$$

The value $z_{2\alpha}$ represents the level of result that will be taken as being statistically significant. This was (as is typical) a two-tailed p=0.05, giving $z_{2\alpha}$ =1.65. $z_{2\beta}$ represents the desired statistical power. Again a typical value of 0.90 was taken, giving $z_{2\beta}$ =1.28. σ represents the standard deviation and δ_0 the clinically signifianct difference between groups.

2.1.2.1 Exophoria

Several authors, reviewed by Harle and Evans (2004), have argued that an exophoria is a common feature in migraine. Most of these authors have used the Turville infinity balance, which is not directly comparable with the methods used in this research. Evans et al (2002) found a migraine group to be more exophoric than a control group by 1^{Δ} (mean 3.5^{Δ} exophoria in migraineurs, 2.5^{Δ} exophoria in controls), but 1^{Δ} would not be considered to be clinically significant and the sample size was modest (21 migraineurs & 11 controls). Goss (1977, p. 63) cited norms for near exophoria as 5^{Δ} exophoria with a standard deviation of 5^{Δ},which are similar to those of Morgan (3^{Δ} exophoria, SD 5^{Δ}; Morgan, 1944). Therefore, it was assumed that a difference between the migraine and control groups of 5^{Δ} or more would be likely to be clinically significant. So δ_0 is 5.

From the data of Evans et al. (2002), the standard deviation of near dissociated heterophoria in their control group was 3.04, and in the migraine group 5.15. The standard deviations of the two populations were different, so the square root of the mean of the variances was taken as the estimate of standard deviation; this was 5.98 (=σ), which is only slightly larger than Morgan's (1944) figure of 5^{Δ}.

Substituting all these values into the above formula:

$$n > 2\left\{\frac{(1.65+1.28)5.98}{5}\right\}^2 = 24.56$$

Hence, this calculation suggests that a minimum of 25 subjects were required in each group, or 50 subjects in total.

2.1.2.2 Pattern glare

Evans et al. (2002) found the mean pattern glare score (experimental grating) for the migraine group to be 4.35, compared with 1.46 for controls. So δ_0 is 2.89.

From the data of Evans et al. (2002), the standard deviation of pattern glare in their control group was 1.81, and in the migraine group 2.98. The standard deviations of the two populations were different, so again the square root of the mean of the variances was taken as the estimate of standard deviation; this was 3.49 (=σ).

Substituting all these values into the above formula:

$$n > 2\left\{\frac{(1.65+1.28)3.49}{2.89}\right\}^2 = 25.04$$

Hence, this calculation again suggested a minimum of 25 subjects were required in each group, or 50 subjects in total.

2.1.2.3 Conclusion

From the above data, it was concluded that 25 partipants for the migraine group and 25 for the control group should be recruited. This exceeds the numbers seen by Evans et al (2002). It should be noted that these authors did detect some statistically significant differences between the control and migraine populations, although their sample had been pre-selected as reporting visual symptoms.

The data from these participants in the migraine and control groups will be described in the next chapters. In each chapter, the results relating to a visual factor or group of related visual factors will be described.

2.1.3 Age, gender and spectacle use

Of the subjects recruited, the mean age of the migraine group was 37.5 years (33.2-41.8), which did not differ significantly (t-test, p=0.77) from the mean age of the control

group of 36.8 years (33.3-40.2). The age ranges were 14 years to 50 years for the migraine group and 25 years to 49 years for the control group. Only two subjects (one in each group) were under the age of 25 years. Each group contained 21 females and 4 males. Similar numbers wore spectacles in each group (X^2 test, p=0.77). In the migraine group 14 used spectacles and in the control group 12 wore spectacles.

2.1.4 Overview of optometric testing

A detailed optometric examination was carried out on all participants. The precise methodological details are specified in subsequent chapters, which deal with the specific groups of optometric factors. The testing typically took approximately a total of 2 hours per participant and patients were given regular breaks as often as required and were provided with refreshments. The usual clinical care was taken with subjective testing to double-check responses and reiterate instructions to ensure consistent results.

2.2 **Pupillometry subjects**

Pupillometry testing (Chapter 3) was not possible on all subjects. Results were obtainable for a migraine group containing 3 males and 17 females and a control group contained 2 males and 14 females. There was no significant difference (t-test, p=0.79) between the mean age of the migraine group (37.3 years, 32.2 – 42.4) and the control group (36.4 years, 31.7 – 41.0).

2.3 **Subjects, recruitment and overview; a complimentary study**

For a second complimentary study evaluating retinal nerve fibre layer changes in people with migraine a new cohort of subjects were recruited. Participants (those with migraine and those without migraine) were recruited from the School of Psychology volunteer database at Birkbeck College, University of London. Written informed consent was obtained and the Institute of Optometry research and ethical committee approved the study, which followed the Tenets of the Declaration of Helsinki. All the people with migraine had a formal medical diagnosis. Participants with systemic health problems (including epilepsy), pregnancy and known ocular disease were excluded from the trial, as were those who anticipated changing any medication for migraine in the four weeks before the study. Participants were asked to cancel their appointment and re-book if they had a migraine headache on or around the day of the appointment for the experimental investingation. In the migraine group, the median number of days since the last migraine headache was 8 (95% CI 2-30) and all participants were headache free at the time of testing. The participants were divided into two groups: a migraine group, and a control group matched to the migraine group by gender and age. Both the grouping and the

clinical testing were independently blind until after the results were analysed; one investigator recruited the participants into the groups and a second investigator performed the clinical tests. This investigator did not know which groups contained people with migraine and which groups contained people without migraine.

2.3.1 Age, gender and spectacle use

There were 19 participants in the migraine group (8 with aura and 11 without), mean age 39.2 years (33.1-45.3) and 16 participants in the control group, mean age 40.2 years (33.5-46.8). The migraine groups contained 12 females and 7 males whilst the control group contained 10 females and 6 males.

2.4 **Statistical Analyses**

When analysing the results of all the experiments conducted, distributions were tested for normality by inspecting frequency distributions and carrying out the Kolmogorov-Smirnov and Shapiro-Wilk tests of normality. Statistical calculations were performed using v1.71 Analyse-it for Excel, based on two-tailed tests, except for the anaysis for colour vision. For colour vision a one-tailed test was used because although there is some limited evidence for supra-normal colour vision (Jordan and Mollon 1993) the experimental colour vision test that was used only assessed a one-way deviation from normality.

Parametric and non-parametric statistical tests were used as appropriate and when group means are quoted the 95% confidence limits are given in parentheses. When comparing proportions, the Chi-square test was used, unless the number in any cell was less than 5, in which case the Fisher Exact test was used. Where the same hypothesis was tested more than once, Bonferroni corrections were made.

The statistical analysis of multi-eye data in ophthalmic research is discussed in the literature (Ray and O'Day, 1985; Murdoch et al., 1998). The inclusion of data from each eye of each participant, especially where the data from each eye are highly correlated (as in the much of the present data), is deprecated because it overestimates the statistical significance of the data. One acceptable solution (Ray and O'Day, 1985; Murdoch et al., 1998) is to average the data from right and left eyes for each participant, and this was the approach that was followed in section 2 with the obvious exception of data such as anisometropia, when the difference between the test results of each eye are investigated. Here, scatter plots were inspected to ensure there were broadly similar for each eye. In section four an alternative but equally acceptable approach (Ray and O'Day, 1985; Murdoch et al., 1998) was taken and the data from one eye were randomly discarded.

2.5 **The Effect of Medication**

Medication use can produce ocular adverse reaction that may confound optometric experimental results in migraine research for example in theories relating to a putative transient headache-episode-related intraocular pressure (IOP) elevation in migraine patients (Gupta 2006).

Just four of the 25 people with migraine in the study took prophylactic medication; one used the selective serotonin re-uptake inhibitor Paroxetine and three used beta-adrenoreceptor blocking drugs; one took Propanolol (Inderal) and two took Atenolol. The only other medication taken by any of the migraine group was that one subject took the lipid-lowering medication Pravastatin. In the non-migraine group just one subject took regular medication and this was the combined contraceptive Ethinylestradiol (Minulet).

A commercially available drugs database (Thomson and Lawrenson 2003) was used to assess any reported ocular adverse reactions to these medications. These were listed as follows:

- Paroxetine

hallucinations

- Propanolol

reduced acuity

- Atenolol

non-specific visual disturbances
hallucinations
diplopia
reduced intraocular pressure
conjuctival erythema
lid erythema
decreased lacrimation
lid ptosis
reduced acuity
paresis
retinal haemorrhages
sub-conjuctival haemorrhages

- Pravastatin

no reported ocular adverse reactions

- Ethinylestradiol

reduced acuity
retinal vascular changes
diplopia
optic neuritis
retrobulbar neuritis
papilloedema
decrease contact lens tolerance
uveitis
coloured haloes around lights
blue tinge to objects
colour vision defects
conjuctival allergic reaction
lid oedema
conjuctival oedema

Systemic health problems, pregnancy, and ocular disease were part of the exclusion criteria for these studies. No subjects were excluded for this reason and no subjects exhibited any of the ocular disease reactions listed.

Those subjects that took medications that might reduce acuity did not in fact have different acuity from others in their group [Migraine group; three subjects using beta-blocking medications had a mean (right and left eyes) aided VAR 99.5, 100 and 103 respectively; which was very similar to the mean VAR score for the migraine group of 101.3 (99.4-103.3)]. In the non-migraine group, the one subject taking Minulet had a mean (right and left eyes) aided VAR acuity 100; compared to a mean VAR score for the non-migraine group of 101.1 (99.5-102.7).

Those migraine subjects that took medication that might reduce intra-ocular pressure did not have an intra-ocular pressure that was significantly different from the rest of the subjects in the migraine group. [Migraine group; two subjects taking Atenolol medication both with a mean IOP of 13 mmHg; compared to a mean IOP for the migraine group of 14 mmHg (13-15).

Those subjects that took medications that might cause hallucinations or other visual disturbances were not significantly different from others in their group in reporting illusions or visual disturbances on pattern glare testing [Migraine group; one subject using Paroxetine and two using Atenolol pattern glare score (3-12) of 0,2,2; compared to a mean pattern glare score for the migraine group of 1.5 (0.5-2.6)] [Non –migraine group;

one subject taking Minulet pattern glare score 0; compared to a mean (3-12) pattern glare score for the non-migraine group of –0.3 (-0.9-0.3)].

The one non-migraine subject that took medication that might alter colour vision did not in fact not have corrected colour vision index (CCI) that was significantly different from the rest of the subjects in the non-migraine group. [Non -migraine group; one subject taking Minulet CCI 1.00; compared to a mean CCI for the non-migraine group of 1.03 (0.99 to1.06).

From these findings it was concluded that no subjects had ocular adverse reactions to their medications to confound the data presented in this thesis.

Chapter 3 The pupillary light reflex in migraine

3.1 Introduction

In section 1.9 the association of pupil changes and migraine was discussed. Controversy still exists as to whether migraine is a chronic sympathetic nervous system disorder (Peroutka, 2004 a,b) or whether there are possible parasympathetic contributions (Yarnitsky et al., 2003; Yarnitsky and Burstein 2004). If migraine is either a sympathetic or parasympathetic disorder, it would be expected that pupil dysfunction should be a feature of the migraine headache. Some clinically significant pupil abnormalities have been reported in migraine sufferers (Hodge and Friedrich, 2004; Evans and Jacobson, 2003; Purvin, 1995; Miller et al., 1986; Woods et al., 1984), but generally the pupil abnormalities associated with migraine headache can be considered to be sub-clinical. There is however, some evidence that these subtle pupil anomalies in migraine can be unmasked by experimental procedures (section1.9.1) with some authors (De Marinis; 1994; 1998) stating that the evidence was so strong that pharmacological tests of the pupils could be used to differentially diagnose different forms of idiopathic headache.

This chapter was published in Ophthalmic and Physiological Optics in 2005 (Harle et al 2005). The aim of this part of the study was to compare the magnitude and latency of the pupil light response in migraine sufferers with age and gender matched controls to establish if pupil changes persisted in the interictal phase of migraine. If pupil changes occur in this non-headache phase then this would support theories of sustained autonomic imbalance in migraine sufferers.

3.2 Method

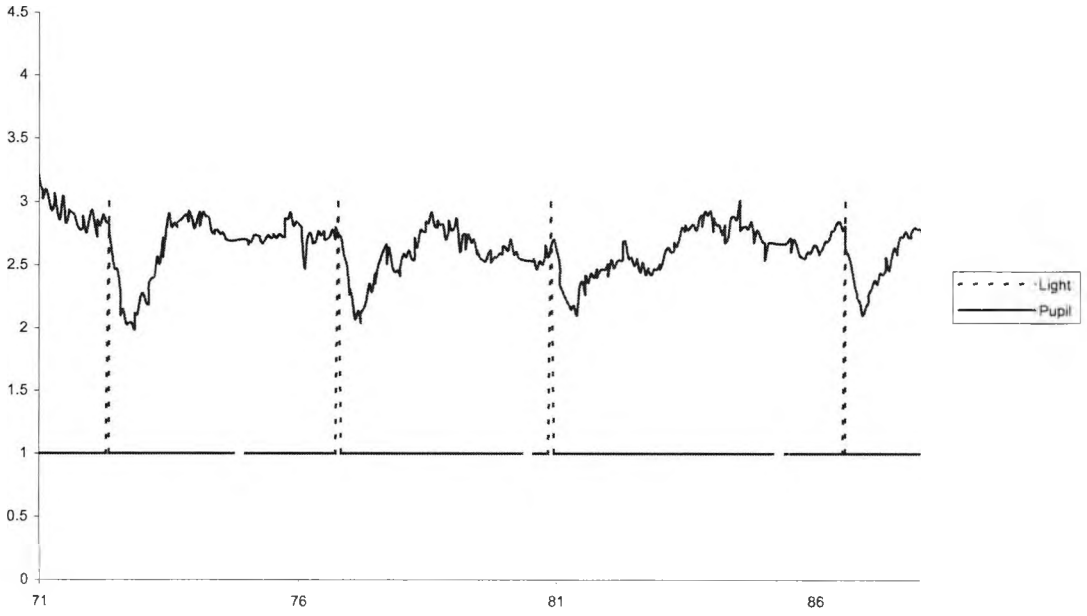
The pupil recording apparatus was constructed specifically for this experiment (by Dr James Wolffsohn) but was conceptually similar to that described in a previous technical note (Wolffsohn *et. al.* 2004). The patient viewed a fixation spot at 20cm from a 15" cathode ray tube monitor on which was mounted an infra-red sensitive camera surrounded by six infra-red light emitting diodes (area covered $20cm^2$). The camera was linked to a National Instruments PCI-1407 image acquisition card in a Pentium III 700MHz PC via the BNC connector. Thresholding image analysis using purpose-written program in LabView and Vision software (National Instruments, Austin, Texas, USA) allowed the pupil size to be detected in real-time at up to 60Hz. Although the NTSC (National Television Systems Committee) signal is completely refreshed at a frequency of

30Hz, by analysing the non-interlaced signal a frequency of 60Hz can be achieved on a half-height image. Conventional image analysis for edge detection is limited to a resolution of 1 pixel for a given intensity threshold criterion. However in a real image, an 'edge' is contained within a pixel 'staircase' of changing intensity. By fitting the 'staircase' with a quadratic profile, a given intensity threshold criterion (to detect the edge of the pupil) was extrapolated to determine the horizontal pupil diameter at an accuracy of $1/1000^{th}$ of a pixel, allowing a system resolution of <0.01mm. The intensity of the monitor surrounding the camera was increased (from 2.6 cd/m^2 to 128cd/m^2 for a duration of 0.25s) to produce a screen "flash" four times at random intervals (to avoid adaptive or prediction effects) to stimulate a time-synchronised change in pupil size. Each screen flash was not repeated until baseline pupil diameter had been re-established. Testing was carried out under room illumination of approximately 100 cd/m^2. Results were obtained for 20 of the migraine group and 16 of the control group.

The data were saved into a Microsoft Excel spreadsheet for each subject and graphed. The mean of the horizontal pupil size for 0.5 seconds before each flash of light was taken as the baseline pupil size. Blinks or eye movement artefacts (defined as any value outside ±3 S.D. of the mean) were excluded. The time taken for the horizontal pupil to reach maximum constriction from the flash presentation and the minimum pupil size at this point was recorded (see Figure 2). This was averaged over the four repeated measures for each eye individually.

Figure 2.

A pupil light response trace was produced for each eye. The latency was taken as the time from stimulus to minimum pupil size. The base line pupil diameter was taken as the mean diameter 0.5 seconds before the stimulus. A blink artefact is shown at 76 seconds.



3.3 Results

Pre-stimulus pupil size

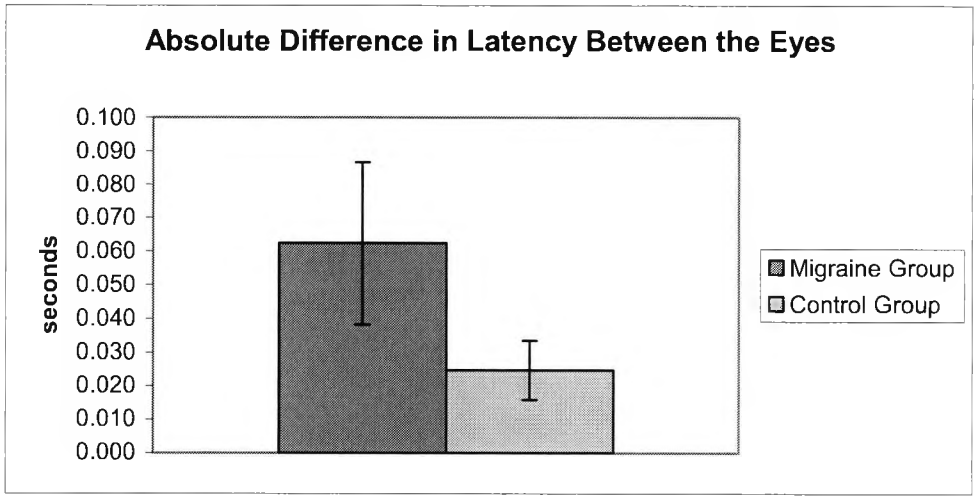
There was no significant difference (t-test, p=0.74) between the mean pre-stimulus pupil size of the migraine group (3.062mm, 2.803 – 3.322) and the control group (3.003mm, 2.735 – 3.271). Nor was there a significant difference (t-test, p=0.26) between the pre-stimulus anisocoria between the migraine group (mean, 0.197mm, 0.110 – 0.284) and the control group (mean, 0.264mm, 0.179 – 0.349).

Amplitude of pupillary light response

The amplitude of the pupillary light response was calculated as the change in pupil size of each eye following the light stimulus. The amplitude of pupillary light response did not differ significantly in the migraine group and the control group for either eye (Mann-Whitney test, p>0.36). Nor was there a significant difference between the absolute inter-eye difference in pupillary light response between the migraine group and the control group (Mann-Whitney test, p=0.52).

Figure 3.

The absolute inter-eye difference in latency of the pupil light response is greater in migraine sufferers compared to controls. Error bars show 95% confidence limits.



Latency to the maximum pupillary light response

The latency to the pupil light response was that time recorded from the light flash until maximum constriction. There was no significant difference (t-test, p=0.78) between the latency of the mean (right and left) pupil light response of the migraine group (mean, 0.638s, 0.605 – 0.671) and the control group (mean, 0.631s, 0.591 – 0.671). There was however a significant difference, (t-test, p=0.014) in the mean absolute inter-eye difference in latency between the migraine group (0.062s, 0.037 – 0.088) and the control group (0.025s, 0.014 – 0.035). This is shown in Figure 3. This inter-eye difference in latency was not strongly related to anisocoria ($r<0.30$) for either signed or absolute data.

Correlation between migraine characteristics and pupil responses to light

For the migraine participants for whom pupil data were available, descriptive data for the number of days since the last migraine headache, the severity of the worst headache, the duration of the worst headache and the number of headaches per year was calculated (Table 6).

Table 6

The descriptive data for the headache parameters of the migraine group for which pupil response results could be obtained.

	Number of migraine headaches per year	Duration of worst migraine headache (hours)	Severity of worst migraine headache (1=mild, 2=mod, 3=severe)	Time since last migraine headache (days)
Median	24	25	3	14
first quartile	20	7	3	11
third quartile	43	53	3	20
Minimum	8	2	1	4
Maximum	200	120	3	45

Using the Spearman non-parametric correlation, there were no significant correlations (r_s<0.43, p>0.08) between these variables and baseline anisocoria, and the two amplitude and two latency pupillary variables described above.

There was however a significant correlation between anisocoria at baseline and lateralisation of headache (r_s=0.59, p=0.006). Interestingly, when the signed difference between the pupil sizes at baseline was compared to lateralization of the headache, the correlation lost significance (r_z=-0.42, p=0.066). To investigate this further, the migraine group was split into those who had a habitual head pain side (n=10) and those who did not have a habitual head pain side (n=10). The mean anisocoria of the group with a habitual head pain side was 0.281mm (0.138 – 0.424) and the mean anisocoria of the group without a habitual head pain side was 0.113mm (0.018 – 0.208). This difference was statistically significant (t-test, p=0.015). Of those with a habitual head pain side, there were those with habitual left-sided head pain (n=4) and those with habitual right-sided head pain (n=6). The mean pupil size on the affected side was 2.881mm (2.51 - 3.24) and 3.012mm (2.70 - 3.32) on the un-effected side and these results were not statistically different (t-test, p>0.38). The mean anisocoria of the group with left-sided habitual head pain was 0.109mm (-0.107 – 0.326) and the mean anisocoria of the group with right-sided

habitual head pain was 0.396mm (0.242 – 0.549). This difference was statistically significant (t-test, p=0.0075).

3.4 Discussion

Barbur (2004) has discussed the pupil response to a variety of stimuli and reached tentative conclusions regarding components of the sympathetic pupil pathway. The evidence presented in that work suggests a pathway involving inhibitory projections from the visual cortex to the Edinger-Wesphal nucleus and both a sustained and a transient projection from the retina to the olivary pretectal nucleus. This differs from previous suggestions that the pupil light response is a single sub-cortical neural pathway (Snell and Lemp, 1989). If it is true that migrainous cortical hyperexcitability (Wilkins et al., 1984; Wilkins, 1995; Welch, 2003) is linked to a failure of cortical inhibition (Palmer et al., 2000) then a possible hypothesis could be that migraine sufferers may have reduced inhibition of the cortical projections to the Edinger-Westphal nucleus that contributes to the pupil responses seen in migraine sufferers and may be the link between these two well known correlates of migraine (Chronicle and Mulleners, 1996).

In this chapter, using an infra-red pupillometer to measure dynamic pupil responses to light in 20 migraine sufferers (during non-headache periods) and 16 non-migraine age and gender matched controls, the data has shown a significant increase in the absolute inter-ocular difference of the latency of the pupil light response in the migraine group compared to the controls (0.062s vs 0.025s, p=0.014). There was also a significant correlation between anisocoria and lateralisation of headache such that migraine sufferers with a habitual head pain side have more anisocoria ($r=0.59$, $p<0.01$), but this was not related to headache laterality. The pupil changes were not correlated with the interval since the last migraine headache, the severity of migraine headache or the number of migraine headaches per annum.

Our data suggest that between headache events, migraine sufferers do not differ significantly from controls in their pupil diameters or degree of anisocoria under room illumination, nor in the latency of the pupillary light reaction. For the two of these three variables that were normally distributed, the effect size that this study would have been able to have detected was calculated, given the sample size, a p-value of 0.05, and power of 80% (Jones et al., 2003). This study would have been able to detect a difference between the mean pupil size of the two groups of 0.509 mm and a difference in mean latency of 0.071 seconds.

Migraine sufferers who have a habitual head pain side demonstrated significantly more anisocoria than migraine sufferers who do not have a habitual head pain side. However, overall there is no significant relationship between the pupil size or laterality of the anisocoric pupil and the side of the habitual head pain. This can be explained because for these data it was the migraine sufferers with right-sided habitual head pain that had more anisocoria that those with left-sided head pain. Therefore migraine sufferers with a typical head pain side have more interictal anisocoria, but not necessarily on the side of the head pain. This might suggest that the sympathetic hypofunction found in previous studies during or shortly after migraine events may persist into the non-headache phase for those migraine sufferers who have a habitual head pain side, but does not persist for those migraine sufferers who do not have a habitual head pain side. It may also add further weight to experimental evidence of autonomic asymmetry in unilateral migraine sufferers (Avnon et al., 2004). Alternatively, perhaps those migraine sufferers who do not have a habitual head pain side have more symmetrical sympathetic hypofunction in the non-headache phase than migraine sufferers who do have a habitual head pain side.

Although the latency to the maximum pupil light response was not significantly different between migraine sufferers and controls, the absolute inter-eye difference in this latency was significantly different between the two groups. This suggests that migraine sufferers do, on average, have one eye whose pupillary light response is slower relative to the other. This could be considered to be some evidence of a mild parasympathetic dysfunction (Micieli et al., 1995). Previous studies in this area have also found parasympathetic dysfunction, but only within a few days of a migraine attack (Mylius et al., 2003). These data suggest that subtle inter-eye differences in pupil light response latency occur in migraine sufferers, and are not correlated to the number of days since the last migraine headache.

Our findings lend weight to the argument that migraine sufferers do indeed have subtle autonomic disturbances in the interictal phase and that both sympathetic and parasympathetic deficits can be demonstrated. Although too small to be considered clinically important, the subtle abnormalities of pupillary light responses do demonstrate that migraine sufferers have a different autonomic nervous system response and that in migraine sufferers with a habitual head pain side, this different response may be asymmetrical.

Chapter 4 The correlation between migraine headache and refractive errors

4.1 Introduction

In section 1.6 the review of the association between refractive errors and migraine shows the literature to be equivocal. Early studies provide anecdotal evidence but the few modern studies, which included control groups and masked experimental designs, have found little evidence of an association. The early uncontrolled studies argued that migraine is associated with low refractive errors, notably astigmatism (Gould 1904; Snell 1904) or latent errors particularly low anisometropia (Turville 1934). A slightly later study found little difference in refractive error in people with migraine and controls (Wilmut 1956).

Chronicle and Mulleners (1996) suggested that there was a lack of conclusive evidence concerning the involvement of refractive error in the aetiology of migraine. In a more recent study (Evans et al 2002), no significant difference between a group of migraine and a group of control patients was found in the subjective refractive error or the proportion of participants who wore spectacles. Yet there is evidence that the public remain convinced that there is an association between their eyesight and headaches (Thomas et al 2004) with 21% of people with headache having consulted an eyecare practitioner for advice, second only to a visit to a general medical practitioner (28%) and far more commonly than a visit to a pharmacist (8%).

This chapter was published in Ophthalmic and Physiological Optics in 2006 (Harle and Evans 2006a). In this part, the migraine and control groups were compared with respect to the four aspects of refractive error historically suggested to be linked to migraine; spherical refractive error, astigmatic refractive error, anisometropia (the inter-eye difference in the spherical equivalent) and uncorrected ametropia (the difference in the mean spherical equivalent between the spectacle refractive correction and the final subjective refractive error found). Scalar calculations were performed to compare total refractive error and inter-eye difference in total refractive error together with the recorded aided and unaided visual acuity and habitual spectacle use. The correlations between the key migraine headache variables and the key refractive variables were then investigated.

4.2 Method

Participants' own spectacles were analysed using a Shin-Nippon LM-15C lensometer (focimeter) to establish their own habitual spectacle refractive error. Aided and unaided visual acuities were taken monocularly using a National Vision Research Institute of Australia Bailey-Lovie Chart (Bailey and Lovie 1976) and were rated using the VAR score and counting per letter correctly identified (Ruamviboonsuk et al 2003). To ensure full optical correction of all the participants, standard optometric refraction tests were performed. The test methods are detailed below and are described in more detail in Rabbetts (1998).

In a 3m optometric refraction cubicle, the subjects underwent objective retinoscopic refractive assessment, at a working distance of 66cm, using a Keeler spot retinoscope, with 6m fixation towards a spot of light. This was followed by subjective refractive assessment. Assessment of spherical error was first assessed subjectively comparing the clarity of optotypes at 6m using +0.25 / -0.25 dioptre spherical twirled lenses and confirmed using the duochrome test. With the appropriate best spherical correction in place, crossed cylinder evaluation of astigmatism corrected with negative cylindrical lenses was then undertaken, firstly establishing the axis of astigmatic correction required and subsequently the power of astigmatic correction required with the subject viewing Verhoff circle targets (Rabbetts 1998). Then a binocular balancing technique (Rabbetts 1998) was completed if appropriate, fogging first one eye with a +0.75 dioptre lens whilst subjectively offering a +0.25 dioptre lens to the other eye, and then repeating this for the second eye, whilst the subject viewed the smallest size of optotypes distinguishable. This ensured a maximally positive (minimally negative) subjective refractive correction. Following measures of accommodation, near refractive additions were found if required, using near subjective refractive testing with positive spherical lenses whilst the subject viewed N5 text at their habitual reading distance.

Refractive errors were analysed using both the raw data and the components of astigmatic decompensation calculations (Thibos et al 1997). Humphrey's principle of astigmatic decompensation represents the cylindrical power C, as a combination of two obliquely crossed cylinders, C_0 at axis 0° and C_{45} at axis 45° and has been suggested as a good method to statistically analyse ophthalmic prescriptions (Rabbetts 1998), since all cylinders are put on a common basis.

A given prescription of sphere S, cylinder C and axis θ can be used to calculate;

C_o = C cos 2 θ

C_{45} = C sin 2 θ

and it follows that:

C= $\sqrt{C_0^2 + C_{45}^2}$

The spherical equivalent power M, is the algebraic mean of the two principle powers S and (S+C) such that:

M= S +(C/2)

As such, for any given prescription, the total sphero-cylindrical power can be represented by a single scalar quantity (Rabbetts 1996; Harris 1996) as:

u= $\sqrt{C_0^2 + C_{45}^2 + M^2}$

where u is given the same sign as M.

It is well known that refractive error is not, strictly speaking, normally distributed with the distribution of spherical refractive error showing leptokurtosis (Mallen et al 2005; Thorn 2005). However, refractive errors seem reasonably well described by parametric descriptive statistics and, as is usual practice, (Mallen et al 2005; Thorn 2005; Logan 2005; Goldschmidt and Fledelius 2005; Kee et al 2005) the variables were described in this way. When group means are quoted, the 95% confidence limits are given in parentheses. When carrying out comparative statistics, a conservative approach was taken and used the non-parametric Mann-Whitney U test. Spearman correlations were carried out to compare spherical refractive error, astigmatic refractive error, anisometropia and uncorrected errors with migraine variables of severity of worst headache, duration of worst headache, the number of headaches in the last 12 months and the number of days since the last migraine headache.

The key variables found to be statistically different in the migraine group were re-analysed with outliers (values greater than 3 inter-quartile ranges (IQRs) from the upper or lower inter quartile range) removed to determine the contribution of these few subjects compared to the entire sample.

4.3 Results

Visual Acuity

The mean VAR score for unaided visual acuity was 82.6 (73.1-92.0) for the migraine group and 79.8 (68.8-90.9) for the control group. The groups were not significantly different (Mann-Whitney U-test, p=0.96). The LogMAR (and Snellen) equivalents for the mean unaided visual acuities are 0.35 ($6/12^{-2}$) for the migraine group and 0.4 (6/18) for the control group. The mean VAR score for aided visual acuity was 101.3 (99.4-103.3) for the migraine group and 101.1 (99.5-102.7) for the control group. The two groups did not differ significantly. The LogMAR (and Snellen) equivalents for the mean aided visual acuities are –0.02 ($6/6^{+1}$) for the migraine group and –0.02 ($6/6^{+1}$) for the control group.

Total and Spherical Refractive Error

The mean of the spherical refractive error S, from the right and left eyes was calculated and then compared in the two groups. The true (signed) rather than absolute values were taken so that bias towards myopia or hyperopia could be distinguished. This mean subjective spherical refractive error S_r, was –0.540 DS (-1.581-0.501) for the migraine group and –1.080 DS (-1.926-0.234) for the control group and the groups were not significantly different (Mann-Whitney U-test, p=0.10).

The mean scalar value u_s, of the absolute value of u from the right and left eyes of the subjective refraction (a representation of the total spectacle prescription found) was 2.037 (1.143-2.931) for the migraine group and 1.482 (0.660-2.304) for the control group and the groups were not significantly different (Mann-Whitney U-test, p=0.11).

Astigmatic Refractive Error

The average of the absolute astigmatic refractive error C, from the right and left eyes was calculated and then compared in the two groups. The mean objective (retinoscopy) astigmatic refractive error C_{ob} was also calculated in the same way to ascertain if these results held for both objective and subjective data. To establish if these astigmatic results were influenced by axis, the C_0 and the C_{45} components of the Humphrey decompensation were analysed for both objective and subjective data. The average of the absolute value for C_0 and C_{45}, from the right and left eyes were calculated and then analysed between the groups. The astigmatic data are shown in Figures 4,5, and 6.

Figure 4.

A box plot showing the distribution of mean subjective astigmatic power C (y axis) for people with migraine and controls (x axis). The diamond and line shows parametric statistics. The centre of the diamond shows the mean and the height of the diamond shows the 95% confidence interval. The notched box and whiskers show non-parametric statistics. The centre line of the box is the median, the notch is the confidence interval of the median, whilst the overall size of the box is the inter-quartile range. The dotted line connects the nearest observations within 1.5 IQRs of the lower and upper quartiles. "+" markers indicate near outliers between 1.5 and 3.0 IQRs away, whilst "o" markers indicate outliers over 3.0 IQR away.

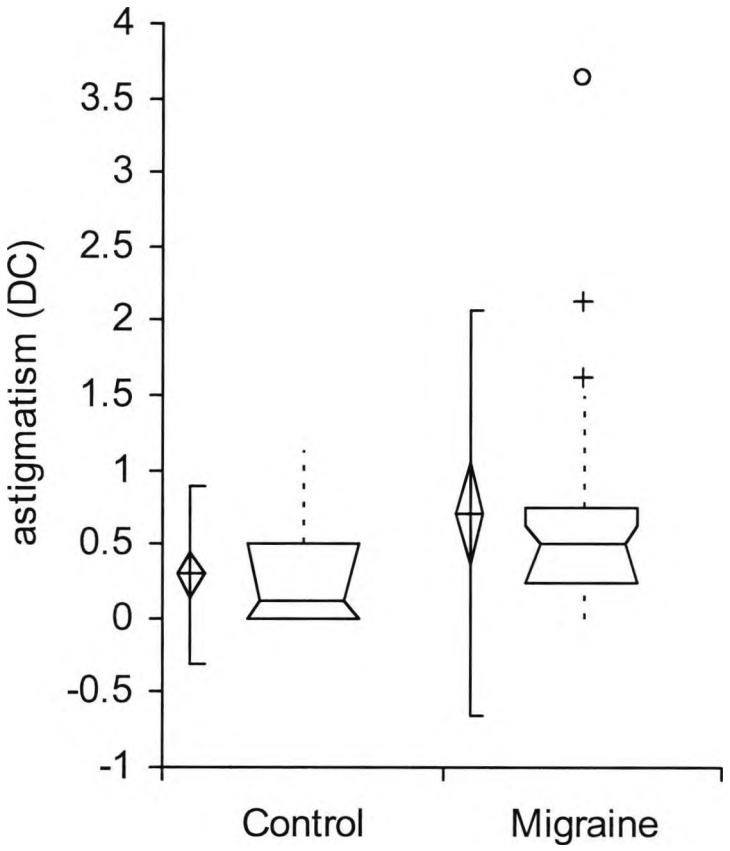


Figure 5.

A box plot showing the distribution of mean objective astigmatic power by its C_0 and C_{45} components (y axis) for people with migraine and controls (x axis). For Figure description see Figure 4.

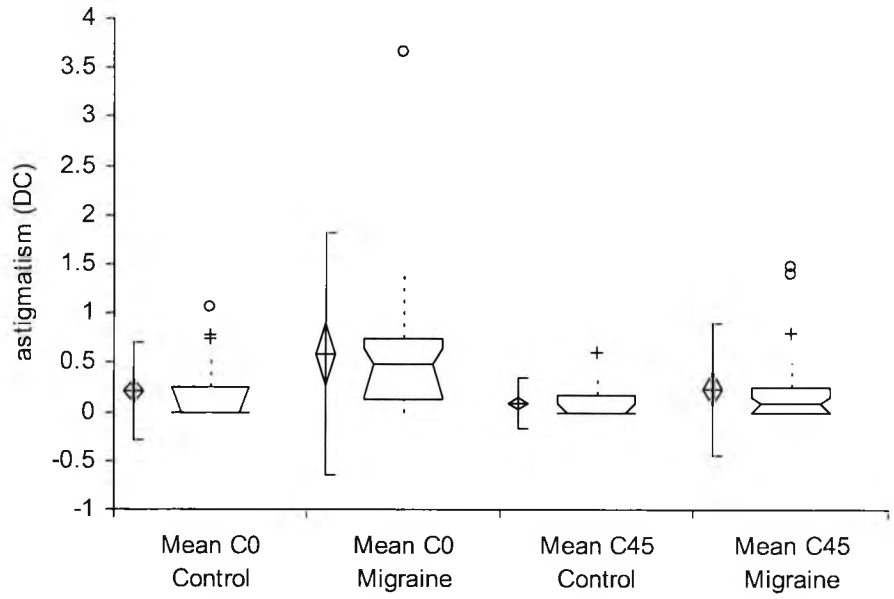
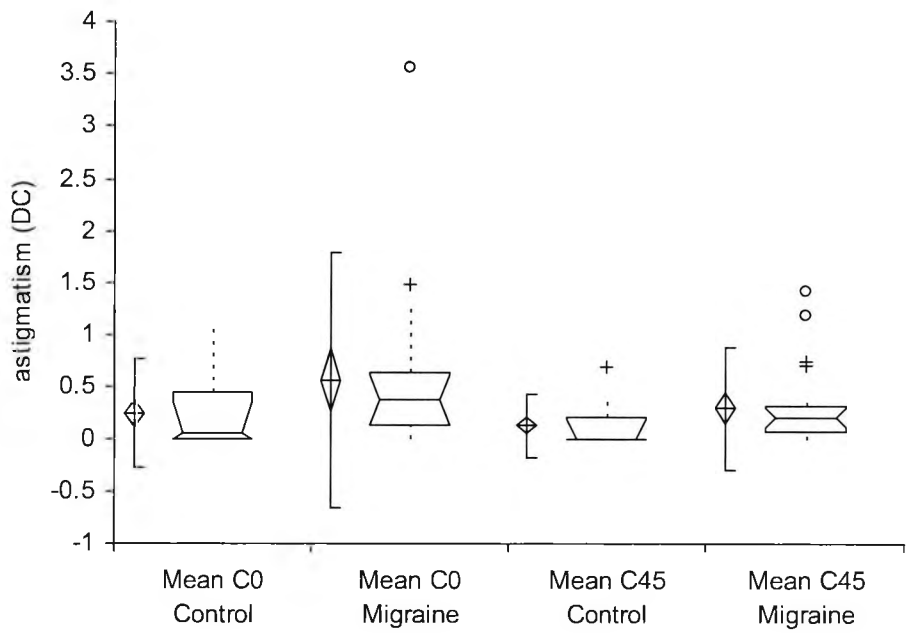


Figure 6

A box plot showing the distribution of mean subjective astigmatic power by its C_0 and C_{45} components (y axis) for people with migraine and controls (x axis). For Figure description see Figure 4.



To compare the data Mann Whitney U-tests were performed. Outliers (those data points further than 3 IQRs) were removed and the Mann Whitney U-tests re-performed on the amended dataset to establish the influence of the outliers on the group as a whole. These results are in Table 7.

Table 7

The astigmatic refractive components of total mean astigmatism (C) and the decompensated astigmatic components (C_0, C_{45}) for the migraine and the control group were compared for both subjective and objective refractive data. The mean results are shown with the 95% confidence limits in parentheses. Mann-Whitney U-tests were performed to compare these results and the statistical significance of the differences found between the groups is shown as the p-value in the table. Finally, outliers were removed from the data and the Mann-Whitney U-tests comparisons repeated, these are shown in square brackets in the p-value column.

	Subjective Refractive Results (DC)			Objective Refractive Results (DC)		
	Migraine	Control	p-value	Migraine	Control	p-value
C	0.705 (0.363-1.047)	0.295 (0.143-0.447)	p=0.03 [p=0.04]	0.710 (0.359-1.061)	0.245 (0.106-0.384)	p=0.01 [p=0.01]
C_0	0.565 (0.257-0.874)	0.247 (0.115-0.380)	p=0.03 [p=0.05]	0.588 (0.279-0.898)	0.205 (0.082-0.329)	p=0.01 [p=0.01]
C_{45}	0.295 (0.145-0.445)	0.131 (0.055-0.208)	p=0.05 [p=0.11]	0.235 (0.065-0.404)	0.088 (0.023-0.153)	p=0.05 [p=0.12]

Anisometropia

Anisometropia was considered as a continuous variable and was calculated as the absolute inter-ocular difference in M, the spherical equivalent of each eye. The mean degree of anisometropia was 0.515 DS (0.297-0.733) for the migraine group and 0.295DS (0.145-0.445) for the control group. This difference approached significance (Mann-Whitney U-test, p=0.06). The inter eye difference in u (a representation of total anisometropia) was 0.623 (0.356-0.890) in the migraine group and 0.332 (0.182-0.482) and this difference was not statistically significant (Mann-Whitney U-test, p=0.09).

Uncorrected Ametropia

The spherical equivalents of the lensometry results of the participants' own spectacles M_s were calculated and then averaged for the lenses of the two eyes. The absolute difference between this mean spectacle spherical equivalent M_s and the mean subjective refraction spherical equivalent M_r was calculated to give a value of uncorrected ametropia. The mean uncorrected ametropia in the migraine group was 0.339D (0.214-0.463) and was 0.221D (0.118-0.325) in the control group and these results were not significantly different (Mann-Whitney U-test, p=0.13).

The u value lensometry results of the participants' own spectacles u_s was calculated and then averaged for the lenses of the two eyes. The difference between this mean u_s and the mean subjective refraction spherical equivalent u_r was calculated to give a value of uncorrected scalar u. The mean uncorrected u in the migraine group was 0.715 (0.123-1.306) and was 0.558 (-0.073-1.190) in the control group and the difference between the two groups was not significant (Mann-Whitney U-test, p=0.09). To assess whether these results were influenced by the astigmatic component, the uncorrected decompensated astigmatic component was assessed, i.e. the absolute difference between the mean C_{0s}, C_{45s} of the participant's own spectacles and the C_{0r}, C_{45r} of the participants subjective refraction was calculated. The mean uncorrected C_0 in the migraine group was 0.279DC (0.144-0.413) and was 0.126DC (0.044-0.209) in the control group. The difference between the two groups was statistically significant (Mann-Whitney U-test, p=0.02). The mean uncorrected C_{45} in the migraine group was 0.116 DC (0.068-0.165) and was 0.075 DC (0.025-0.125) in the control group. The difference between the two groups was statistically significant (Mann-Whitney U-test, p=0.04).

Correlations

The Spearman correlations between severity of worst headache ($r_s< 0.33$, $p>0.11$), duration of worst headache ($r_s< 0.17$, $p>0.42$) and the days since last migraine headache ($r_s< 0.32$, $p>0.18$) and each of the refractive variables of mean sphere, mean astigmatic power, anisometropia and uncorrected error, were all low and not significant. The number

of headaches in the last 12 months did show a statistically significant correlation with anisometropia such that the fewer the headaches the more the anisometropia (r_s =-0.42, p=0.04). The number of headaches in the last 12 months was not significantly correlated with each refractive variable (r_s< 0.27, p>0.21).

4.4 Discussion

There are historical references to an association between migraine headache and refractive errors, but a lack of scientific evidence relating to these claims. It is not uncommon for optometrists to encounter patients who believe that migraine is triggered by a refractive error or that the headache might be ameliorated by a refractive intervention. Since the level of evidence in the literature for any association between migraine and refractive error is, by modern standards, weak, it is not surprising that the IHS classification system (IHS 2004) classifies headache attributed to refractive errors separately from those of migraine, and no mention of refractive error is made in the migraine section of the classification.

This lack of evidence-based research led Gordon et al (2001) to conclude that the whole issue of headache and refractive error has been dominated "by clinical anecdote throughout the 20th century". They asked that future research in this area addressed (i) the scale of the problem, (ii) whether people with migraine are optometrically unusual, (iii) if they are optometrically unusual, what is the mechanism generating the headache and (iv) whether correction ameliorates the headache.

Whilst only large epidemiological studies can hope to address the scale of the problem, it is known that migraine is a very common condition, with more than 2.5 million persons in North America having at least one day of migraine per week (Goadsby et al 2002).

The range of low degrees of refractive errors in both groups was fairly typical of the age group in a UK population (Rabbetts 1998). This masked case-controlled study provides some evidence that astigmatic refractive error and possibly anisometropia are greater in people with migraine than controls, as suggested in the historical texts. For astigmatism the difference was driven in part by a few people with migraine who were particularly optometrically unusual but still held for the group as a whole (when the outliers were removed) for C and C_0 components. Objective, subjective and uncorrected astigmatic refractive components were all significant findings.

The differences between the two groups were not large and, due to the large number of statistical comparisons made, it is possible that some of the

statistically significant findings resulted by chance. In any event, it seems unlikely that the degree of uncorrected astigmatism that was found is a direct cause of migraine, but a subtler path may exist. One hypothesis might be that astigmatic errors of refraction cause changes to visual perception that alter the hyperexcitability in the visual cortex of the brain of some migraine sufferers (Wilkins et al 1984; Wilkins 1995; Welch 2003) perhaps because astigmatic blur may exacerbate the perception of striped patterns thought to be important in the visual triggers of migraine (Wilkins et al 1984; Wilkins 1995). An alternative hypothesis could be that neurotic personality traits that are associated with migraine (Breslau and Andreski 1995; Breslau et al 1996; Cao et al 2002) result in a greater likelihood of people with migraine demanding small cylindrical corrections during a subjective refraction, particularly since more of the controls than the migraineurs had zero astigmatism. However greater astigmatic power was found in the migraine group for both objective (retinoscopy) and subjective testing and so this would seem unlikely.

Compared with the control group, the migraine group had higher degrees of astigmatic components of refractive error assessed both objectively (C, $p=0.01$; C_0, $p=0.01$; C_{45}, $p=0.05$) and subjectively (C, $p=0.03$; C_0, $p=0.03$; C_{45}, $p=0.05$), uncorrected astigmatic components of refractive error (C_0, $p=0.02$; C_{45}, $p=0.04$) and anisometropia ($p=0.06$). The higher levels of astigmatism in the migraine group reached statistical significance and an inspection of Figure 4 indicates that there were more cases in the migraine than the control group where the degree of astigmatism was of a level that would be considered by many practitioners to be clinically significant (O'Leary and Evans 2003). Uncorrected astigmatic refractive errors were significantly greater in people with migraine than controls. A theoretical causative effect is weakened by a lack of significant correlations between the headache characteristics and refractive error, although it is possible that refractive error could have an association with being a migraine sufferer, whilst having no impact on the severity or frequency of headaches. Whether correcting refractive errors does, or does not, have an impact on migraine severity or frequency is a matter for future research, but this study does suggest that migraine sufferers have a slight predisposition to manifest significant degrees of astigmatism. Quite apart from any hypothetical effect of astigmatism on migraine, it would be sensible for these people to have routine eye examinations as should any patient with significant refractive errors.

Chapter 5 Subtle binocular vision anomalies in migraine

5.1 Introduction

Section 1.7 reveals historical papers suggesting that binocular vision anomalies are correlates or causes of headache or migraine (Snell, 1904; Turville, 1934). It has been suggested that exophoria (Wilmut 1956) and its correction with base-in prisms (Turville, 1934;Wilmut, 1951) or vision therapy (Friedman, 1977) is associated with migraine. However these studies either fid not include a control group or were only case descriptionsy. A study (Waters, 1970) which suggested that migraine is not correlated with horizontal heterophoria but may be correlated with hyperphoria was also poorly executed in that the study failed to differentiate between esophoria and exophoria.

Electromyographic case studies have demonstrated that migraine-type pain can be reproduced by stimulating the extra-ocular muscles directly (Worthen, 1980). These findings led to claims that the headaches caused by muscle imbalance (heterophoria) could be eliminated by proper alignment of the visual axes and that prisms, orthoptic training, or even surgery may be necessary, diagnosis being made with a trial period of monocular occlusion (Worthen, 1980).

Several authors have linked decompensated heterophoria or convergence insufficiency with headache (Jenkins *et al.*, 1989; Yekta *et al.*, 1989; Rouse et al., 2004; Karania and Evans, 2006) or as part of general asthenopia (Sheedy et al., 2003). However, these authors do not specifically discuss migraine. In the only modern optometric controlled trial that could be found that did specifically address migraine, Evans *et al.* (2002) compared 21 migraine sufferers to 11 controls and found no difference between the groups in relation to strabismus or hyperphoria. The main purpose of this particular study was to investigate the effect of coloured filters (Wilkins *et al.*, 2002), so the migraine sufferers were selected as those who found a coloured filter to be helpful. They therefore did not represent a "normal" group of migraine sufferers. Evans *et al.* (2002) did find that the migraine group tended to have a marginally decompensated exophoria at near, but this result was equivocal depending on the precise criteria that were used to diagnose decompensated heterophoria.

Ocular motor paresis (De Silva and Siow 2005; Celebisoy et al 2005; Weiss and Phillips 2004; Levin and Ward 2004; Lee 2003; Carlow 2002; Daroff 2001,2000) and eye movement disorders associated with vertigo (Marano et al 2005; von Brevern et al 2005; Liao and Young 2004; Harno et al 2003; Dieterich and Brandt 1999) and their link to

migraine are well documented and there is recent evidence suggesting no difference in the eye movement measurements (pursuit, saccades, and fixation stability) in people with migraine (Wilkinson et al 2006). However, the literature on the association between the more subtle anomalies of binocular vision and migraine seems to be equivocal. To investigate these optometric binocular vision correlates of migraine, migraine and control groups were compared with respect to clinical optometric measures of binocular vision. The correlations between the key migraine headache variables and the key binocular vision variables were then investigated. This chapter was published in Ophthalmic and Physiological Optics in 2006 (Harle and Evans 2006c).

5.2 Methods

Clinical tests were undertaken in the following order: cover-uncover test, alternate cover test, aligning prism and foveal suppression on the Mallett Unit, Randot stereopsis, Maddox Rod, Maddox Wing, convergence tests, fusional reserves and finally ocular motility. Clinical optometric tests including the Mallett Unit and Randot stereopsis test were supplied by IOO Sales Ltd, London. The test methods are detailed below and are described in more detail in Evans (2002, 2005).

Clinical Tests

For all binocular vision tests except ocular motility, the patient wore a refractive correction if it was habitually worn for more than 50% of the time at the appropriate test distance. Ocular motility was assessed by observing the eye movements whilst the patient fixated a point light source at a distance of 50cm which was moved into the cardinal positions of gaze. The corneal reflections of the light source were observed and if either eye lost fixation then the incomitant deviation was investigated with cover testing in peripheral gaze.

Ocular alignment was assessed at distance (6m) and then near (40cm) by the cover-uncover test with an opaque occluder, followed by an alternate cover test. A clinically experienced optometrist estimated the magnitude of heterophoria (in prism diopters, $^{\Delta}$) for both distance and near, in the horizontal and vertical plane. The type (heterophoria or heterotropia) and direction of movement was recorded. For example, in heterophoria the direction of movement was recorded as exophoria (XOP), esophoria (SOP), right hyperphoria, or left hyperphoria. Esophoria and right hyperphoria were recorded as positive values and exophoria and left hyperphoria were recorded as negative values. Separate data were obtained for both the cover-uncover test and the alternate cover test,

which is associated with greater dissociation and is therefore likely to reveal a larger deviation.

If heterophoria was detected on cover testing, then the quality of the recovery was subjectively graded by the optometrist on a scale of 1-5, one being an excellent recovery and 5 being a very poor recovery breaking down to strabismus (Evans, 2005).

The Maddox Rod Test was used to measure horizontal and vertical dissociated deviations at distance. A red Maddox Rod was place before the right eye and the patient was instructed to view a bright spot light at a 6m distance. Trial lens prisms were used to align the Maddox streak with the spot light first in the horizontal and then in the vertical plane. As for the cover test results, eso-deviations and right hyper-deviations were recorded as positive values.

The Maddox Wing Test was used to measure horizontal and vertical dissociated deviations at near. The horizontal and vertical values were recorded as the number read from the scale by the patient. The variability in the horizontal reading was recorded as a measure of vergence instability by asking the patient to report the range of numbers over which the reading varied.

The presence of fixation disparity and degree of aligning prism found by the distance Mallett Unit at 6m and the near Mallett Unit at 40cm were recorded. Polarised visors were placed in front of the refractive correction and any aligning prism (the minimum amount of prism required to cause alignment) was recorded as the base direction (In or Out / Up or Down), and the eye to which the prism needed to be applied. As for the other measurements of eye alignment, eso-deviations and right hyper-deviations were recorded as positive values. The precise test instructions with the Mallett Fixation Disparity Test are important (Karania and Evans, 2006) and the instructions recommended by Evans (2002) were used, which have been shown to be best at predicting symptoms (Karania and Evans, 2006). Using the near Mallett Unit, foveal suppression was recorded as the difference between the monocular and binocular acuity (in minutes of arc) with the polarised visor always in place (Evans, 2002).

The Randot shapes and circles tests (Stereo Optical Co Inc., 1988) were used to assess random dot stereopsis and contoured stereopsis. Each test was terminated when one error was made and stereo-acuity was recorded as the stereo-disparity of the last target correctly identified.

Near point of convergence, measured with the RAF rule (IOO Sales Ltd, London), was recorded as the nearest distance to which the patient could converge without experiencing subjective diplopia of the line target. Eye movements were observed and the objective break point was recorded if there was no subjective break point. Vergence facility was measured by the number of cycles of convergence and divergence that the patient could perform whilst viewing a near N5 print target through prism "flippers" that alternated the vergence stimulus between 1.5^{Δ} base in each eye (3^{Δ} total) and 6^{Δ} base out each eye (12^{Δ} total). The prisms were "flipped" when the subject reported verbally that no blur or diplopia was present.

Fusional reserves were measured with a Variable Prism Stereoscope which uses linked rotary prisms in front of each eye with an accommodative target. Distance divergent (base in) followed by (see Discussion) convergent (base out) reserves were recorded as three values, the blur point, the break point and the recovery point with a prism rate change of ~1^{Δ} /s. Near base in and base out fusional reserves were recorded in the same way. At both distance and near, the fusional amplitudes were calculated as the differences between the convergent and divergent blur points, or if there was no blur point then break point.

Sheard's criterion assesses whether the fusional reserve that opposes the heterophoria is adequate to overcome the heterophoria, stating that the fusional reserve (blur point, or if no blur point then break point) that opposes the heterophoria should be at least twice the heterophoria (Sheard, 1931). Percival's criterion states that the working fixation point should lie in the middle third of the total fusional amplitude, that is to say, the complementary fusional reserves should be balanced within the limits that one should not be less than half the other (Percival, 1928). For both distance and near vision, the proportion of participants passing Sheard's criterion and the proportion passing Percival's criterion was calculated. Variables called here Sheard's value and Percival's value, which graded on a continuous scale the degree to which each participant passed or failed Sheard's and Percival's criteria at each distance were also calculated.

Clinically, the diagnosis of decompensated heterophoria is usually based on a combination of several test results. This led Evans (2002) to develop an algorithm that combines relevant test results to give a score indicating the likelihood of decompensated heterophoria. The algorithm was amended (Table 8) and the results were calculated separately for horizontal heterophoria at distance and near and produced both a score for compensation and a pass / fail criterion, which was then compared between the groups.

Table 8

An algorithm (Evans, 2002) for indicating if a patient has a decompensated binocular vision was adapted. The standard algorithm uses a score of +3 for the presence or absence of headache. As this would bias towards the migraine group this question was removed. The distance algorithm also removed questions (5 and 8) that related to near vision results. The pass criteria of the standard algorithm was a score of 5/16. As the maximum score for this adapted algorithm was 10 for distance and 13 for near a pass criteria of ((5/16)x10) for distance and ((5/16)x13) for near was used.

	score
1. Is the patient orthophoric on cover testing? Yes ☐ or No ☐ *If no, score +1*	
2. Is the cover test recovery rapid and smooth? Yes ☐ or No ☐ *If no, score +2 (+1 if borderline)*	
3. Is the Mallett H aligning prism: <1Δ for patients under 40, or <2Δ for pxs over 40? Yes ☐ or No ☐ *If no, score +2* ***ALL THE FOLLOWING QUESTIONS APPLY TO HORIZONTAL RESULTS***	
4. Is the Mallett aligning prism stable (Nonius strips stationary with any required prism)? Yes ☐ or No ☐ *If no, score +1*	
5. Using the polarised letters binocular status test, is any foveal suppression < 4'? Yes ☐ or No ☐ *If no, score +2*	
6. Sheard's criterion: (a) measure the dissociated phoria (e.g., Maddox wing, prism cover test); record size & stability (b) measure the fusional reserve opposing the heterophoria (i.e., convergent, or base out, in exophoria). Record as blur/break/recovery in Δ. Is the blur point, or if no blur point the break point, [in (b)] at least twice the phoria [in (a)]? Yes ☐ or No ☐ *If no, score +2*	
7. Percival's criterion: measure the other fusional reserve and compare the two break points. Is the larger break point less than twice the smaller break point? Yes ☐ or No ☐ *If no, score +1*	
8. When you measured the dissociated heterophoria, was the result stable, or unstable (varying over a range of ±2Δ or more). (e.g., during Maddox wing test, if the Hz phoria was 4Δ XOP and the arrow was moving from 2 to 6, then result unstable) Stable ☐ or Unstable ☐ *If unstable, score +1*	
9. Using the fusional reserve measurements, add the divergent break point to the convergent break point. Is the total (=fusional amplitude) at least 20Δ? Yes ☐ or No ☐ *If no, score +1*	

5.3 Results

Ocular motility and cover testing

No cases of incomitancy were apparent on motility testing. The cover-uncover test revealed no cases of strabismus in either group. Seven of the 25 people with migraine demonstrated a heterophoria at 6m by cover-uncover testing but only three of the control group did so. This increased to 11 of the migraine group and 5 of the control group on alternating cover testing. At near, ten of the migraine group and nine of the control group demonstrated a heterophoria by cover-uncover testing. This increased to 16 of the migraine group and 11 of the control group on near alternating cover testing. These differences between the two groups were not statistically significant (X^2 test; $p>0.13$). The magnitude of horizontal heterophoria by both methods of cover testing in the two groups are shown in Figures 7a and 7b. The results were not significantly different between the groups (Mann-Whitney U-test; $p>0.25$). It is clear from Figure 7 that hardly any subjects had a vertical heterophoria and the two groups were similar in this respect.

Figure 7a

Distance cover test (CT) and alternating cover test (ACT) results both horizontal (H) and vertical (V) readings in migraine and control groups. The y axis shows heterophoria in prism dioptres.

The diamond and line shows parametric statistics. The centre of the diamond shows the mean and the height of the diamond shows the 95% confidence interval. The notched box and whiskers show non-parametric statistics. The centre line of the box is the median, a notch is the confidence interval of the median, whilst the overall size of the box is the inter-quartile range (IQR). In some cases the inter-quartile values are zero, so there is just a line and no box. The dotted line connects the nearest observations within 1.5 IQRs of the lower and upper quartiles. "+" markers indicate near outliers between 1.5 and 3.0 IQRs away, whilst "o" markers indicate far outliers over 3.0 IQR away.

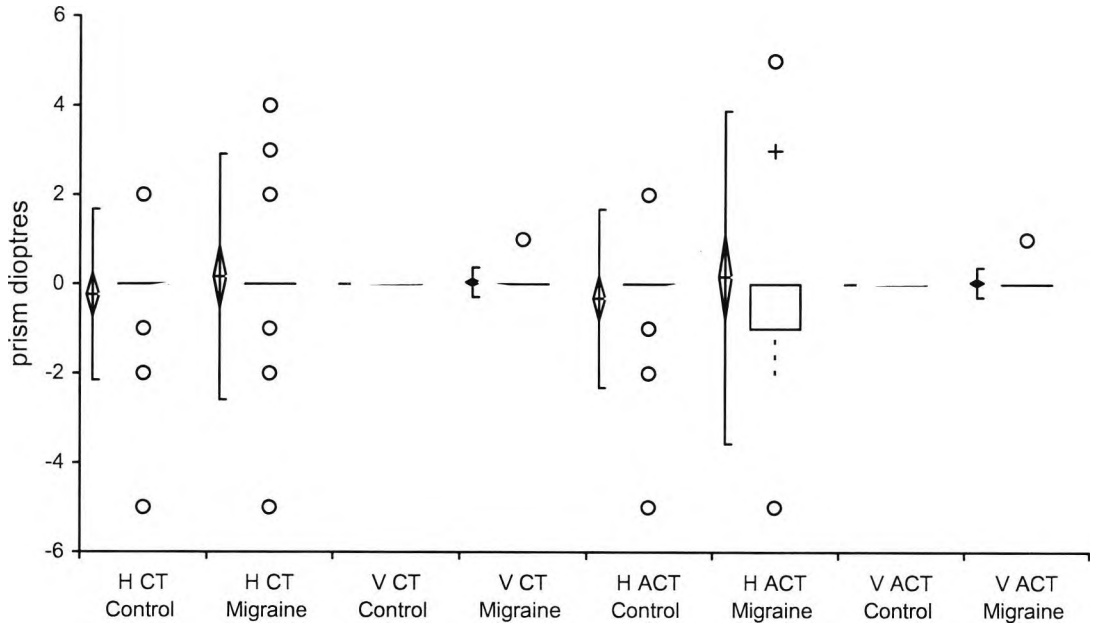
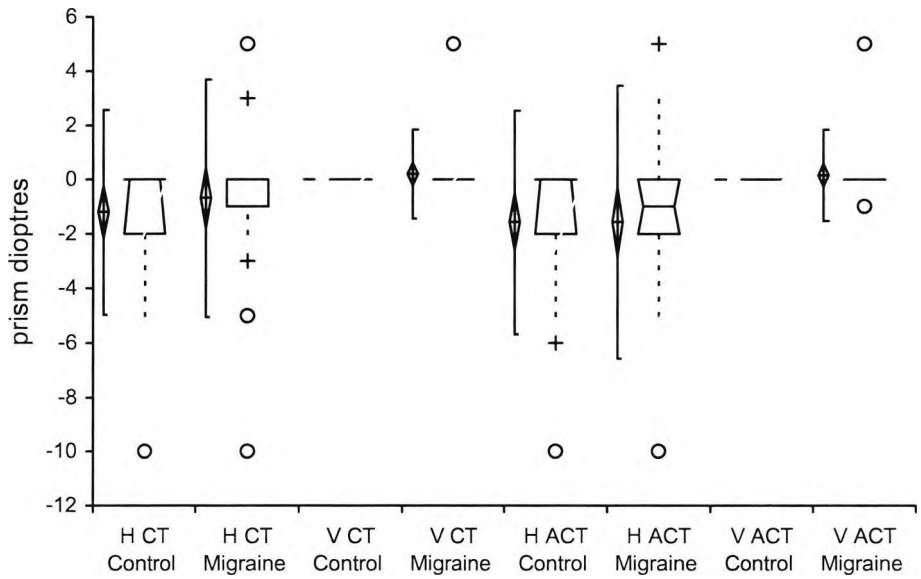


Figure 7b

Near cover test (CT) and alternating cover test (ACT) results both horizontal (H) and vertical (V) by migraine and control. The y axis shows heterophoria in prism dioptres.

For Figure description see Figure 7a.



Maddox Rod and Maddox Wing

One person with migraine could not be tested with the Maddox Rod test as the streak produced by the Maddox Rod was not perceived. 19 out of 24 people with migraine demonstrated a heterophoria at 6m by Maddox Rod but only 8 of the 25 in the control group did so. This difference was statistically significant (X^2 test; p=0.0024). 19 out of 25 people with migraine demonstrated a heterophoria at near by Maddox Wing but only 12 of the 25 in the control group did so. This difference was not statistically significant (X^2 test; p=0.080).

The magnitude of dissociated heterophoria determined by the Maddox Rod and Wing tests are shown in Figures 8a and 8b. These results were not significantly different between the groups, and nor was the difference in the variability of the Maddox Wing

result (Mann-Whitney U-test; p>0.080). Figure 8a indicates a greater spread of results for the horizontal distance heterophoria in the migraine group than in the control group. Therefore the Mann-Whitney U-test was repeated but using unsigned horizontal heterophoria to investigate whether the two groups differed in terms of the unsigned magnitude of horizontal heterophoria regardless of the presence of esophoria or exophoria. This revealed a significantly greater horizontal distance heterophoria in the migraine group than in the control group (unsigned data, Mann-Whitney U-test, p=0.001). No such effect was apparent at near (Maddox Wing test, unsigned data, Mann-Whitney U-test, p=0.22).

Figure 8a

Maddox Rod at 6m results both horizontal (H) and vertical (V) by migraine and control. The y axis shows heterophoria in prism dioptres.

For Figure description see Figure 7a

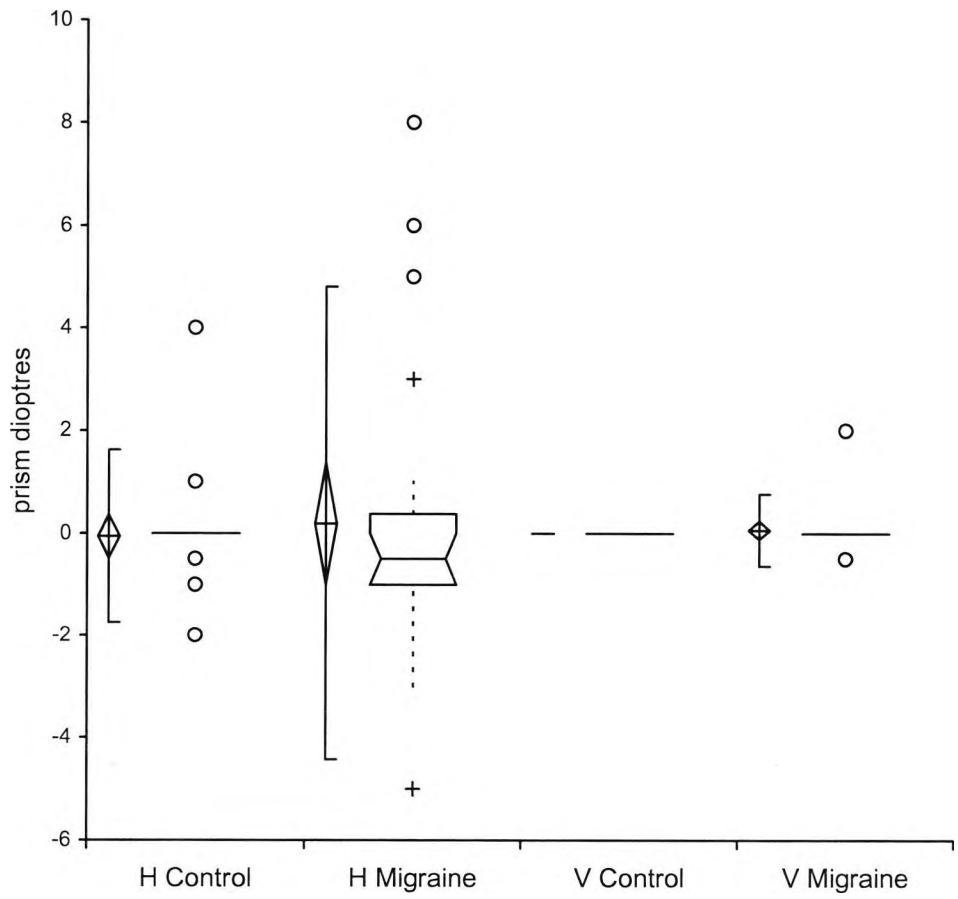
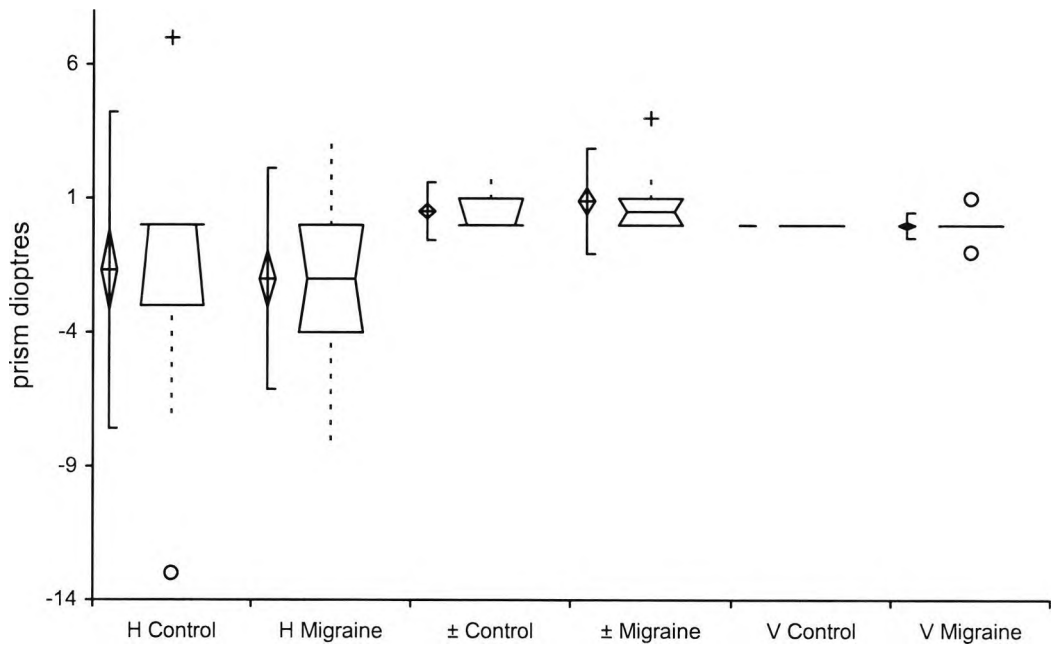


Figure 8b

Maddox Wing results for horizontal (H) horizontal variability (+/-) and vertical (V) by migraine and control. The y axis shows heterophoria in prism dioptres.

For Figure description see Figure 7a



Fixation disparity, aligning prism, and foveal suppression

Seven of the 25 people with migraine demonstrated some degree of fixation disparity (at either distance) but only one of the 25 controls did so. This difference was statistically significant (Fisher exact test; p=0.049). At distance (6m) three of the 25 people with migraine had horizontal fixation disparity and one had vertical fixation disparity but no control did so (Fisher exact test; p=0.11). At near three of the 25 people with migraine had horizontal fixation disparity and one had vertical fixation disparity and one control had horizontal fixation disparity (Fisher exact test; p=0.35). This one control subject also demonstrated 3 seconds of foveal suppression in the eye that required an aligning prism. No other subjects demonstrated any foveal suppression. The magnitude of aligning prism in the two groups are compared in Figures 9a and 9b. The results were not significantly different between the groups for signed and unsigned data (Mann-Whitney U-test; p>0.077).

Figure 9a

Distance aligning prism results both horizontal (H) and vertical (V) by migraine and control. The y axis shows aligning prism in prism dioptres.

For Figure description see Figure 7a

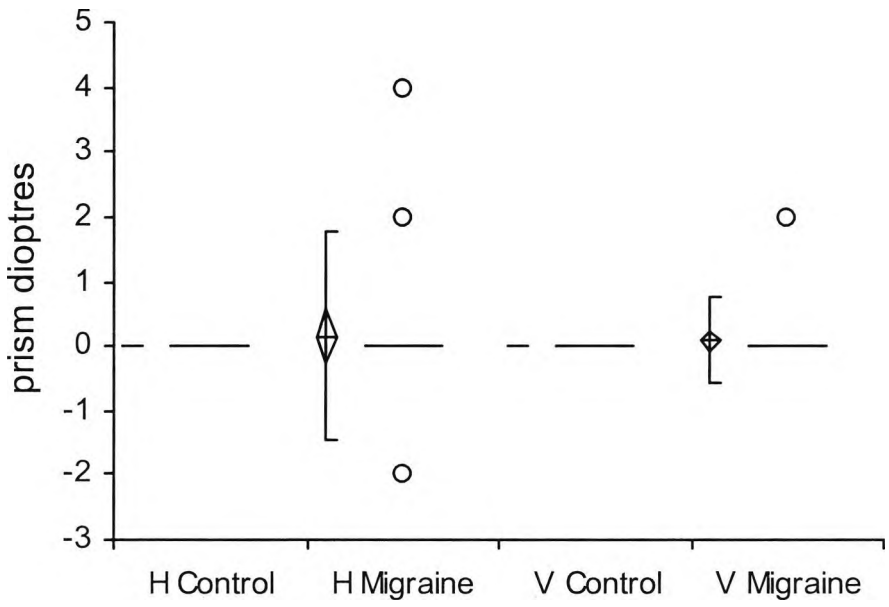
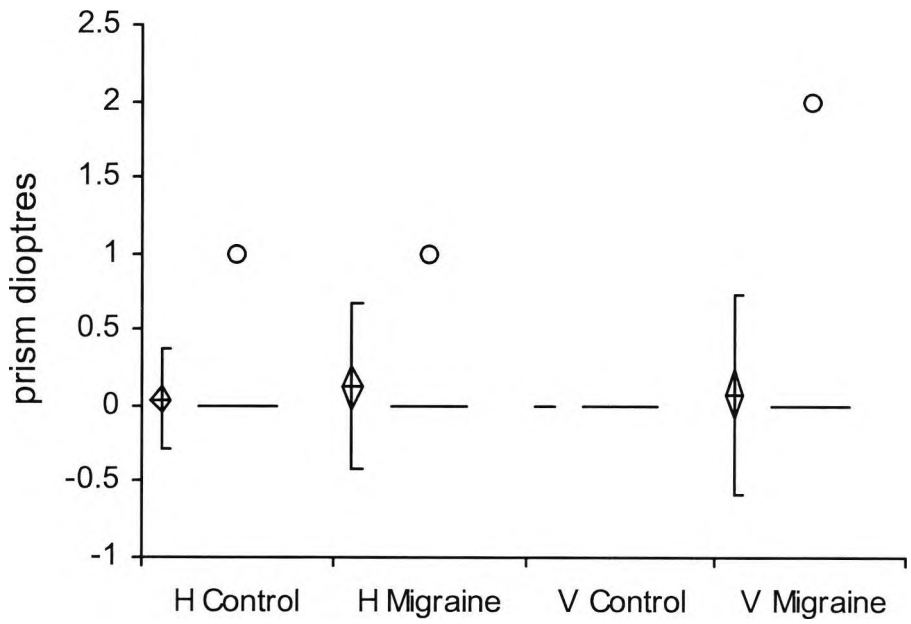


Figure 9b

Near aligning prism results both horizontal (H) and vertical (V) by migraine and control. The y axis shows aligning prism in prism dioptres.

For Figure description see Figure 7a



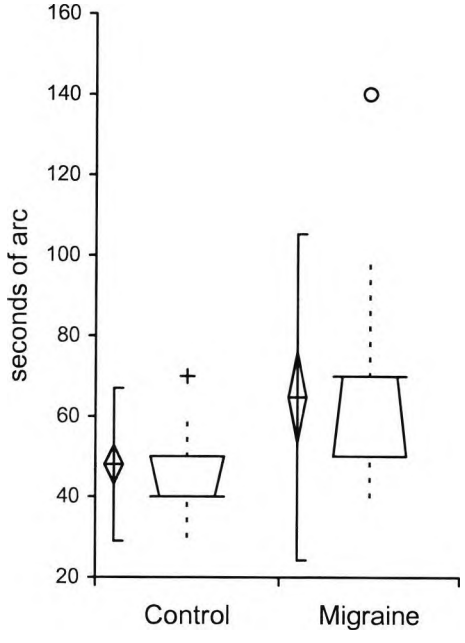
Stereopsis

On the Randot shapes test, three people with migraine had stereopsis less than 500 seconds and one had stereopsis of 500 seconds. The remaining 21 people with migraine and all 25 controls had at least 250 seconds of stereopsis by Randot shape testing (Fisher exact test; p=0.11). On the Randot circles test, the median stereopsis was 50.0 seconds (50.0-70.0) in the migraine group and 40.0 seconds (40.0-50.0) in the control group. These results were significantly different (Mann-Whitney U-test; p=0.0045) (Figure 10).

Figure 10

Randot stereopsis results for migraine and control.

For Figure description see Figure 7a



Near Point of Convergence and Convergence Facility

The mean near point of convergence in the migraine group was 5.1cm (3.9-6.4) and was 4.9cm (3.9-5.9) in the control group. Convergence facility was 11.5 cycles per minute (9.7-13.3) in the migraine group and 13.0 cycles per minute (11.6-14.4) in the control group. These results were not significantly different between the groups (Mann-Whitney U-test; $p>0.15$).

Fusional reserves, Sheard's and Percival's Criteria

The fusional amplitudes were calculated as a measure of total fusion in reserve. At distance the mean fusion amplitude was 30.4^{Δ} (26.4-43.4) in the migraine group and 31.5^{Δ} (25.9-37.1) in the control group. At near the mean fusion amplitude was 24.7^{Δ} (19.9-29.5) in the migraine group and 23.6^{Δ} (19.0-28.3) in the control group. The fusional amplitudes of the two groups did not differ significantly at distance (t-test; $p=0.74$) or at near (t-test; $p=0.74$).

Sheard's Criterion was passed by 24 of the control group and 22 of the migraine group at distance (Fisher exact test, $p=0.61$), and 21 of the control group and 23 of the migraine group at near (Fisher exact test, $p=0.67$). Sheard's Value indicated reduced ability to overcome Sheard's Criterion in the migraine group compared with the control group at distance (Mann-Whitney U-test, $p=0.038$). However since the null hypothesis for this variable, that Sheard's criterion was not significantly different in the migraine and control groups, was essentially tested in two ways then a Bonferroni correction is required. This lowers the p-value for statistical significance to $p=0.025$, suggesting that the two groups were not significantly different. There was no significant difference between the groups in Sheard's value at near (Mann-Whitney U-test, $p=0.34$).

Percival's Criterion was passed by 17 of the control group and 19 of the migraine group at distance (χ^2, $p=0.75$), and 20 in both groups at near. Percival's Value indicated a similar ability to overcome Percival's Criterion in the migraine group compared with the control group at distance and near (Mann-Whitney U-test, $p>0.08$).

Algorithm for diagnosing decompensated heterophoria

The decompensation algorithm was passed by 21 of the migraine group and 24 of the control group at distance (Fisher exact test, $p=0.35$) and 24 in both groups at near. The mean algorithm score at distance was 1.9 (1.1-2.8) in the migraine group and 1.4 (0.9-1.9) in the control group and these results were not significantly different (t-test, $p=0.28$). The mean algorithm score at near was 1.6 (1.1-2.1) in the migraine group and 1.5 (0.8-2.1) in the control group and these results were not significantly different (t-test, $p=0.77$).

Correlations

Since fixation disparity, dissociated heterophoria at distance (Maddox Rod), fusional amplitude measures and stereopsis were found to be different in the migraine group, Spearman correlations were calculated for the migraine group between these variables and the headache variables of lateralization of headache, severity of worst headache, duration of worst headache, the number of headaches in the last 12 months and the number of days since the last migraine headache.

Lateralization of headache was correlated with near horizontal fixation disparity (r_s = -0.43, p=0.031). The signing of these variables meant that right sided headaches are more likely to be associated with exophoria. Lateralization of headache was not correlated to any other of the binocular vision variables that were found to be different in the migraine group. ($r_s \leq$ 0.35, $p \geq 0.086$).

The severity of worst headache was not significantly correlated to any binocular vision variable ($r_s \leq$ 0.38, $p \geq 0.060$) but the duration of worst headache was quite strongly correlated with Randot circle stereopsis (r_s=0.59, n=21, p=0.0053), such that the longer the worst headache the poorer the stereopsis. To evaluate the clinical significance of this correlation, a duration of worst headache of 12 hours was chosen as significant, and a stereopsis less than or equal to 50 seconds as normal, which led to a calculation of the odds ratio of 33.2 (0.2-105.7). The duration of worst headache was not correlated to any other binocular vision variable ($r_s \leq 0.36$, $p \geq 0.096$).

The number of headaches in the last 12 months was not correlated with any of the binocular vision variables that were found to be different in the migraine group ($r_s \leq 0.39$, $p \geq 0.069$).

The number of days since the last migraine headache was correlated with near fusional amplitude (r_s=0.56, n=18, p=0.017). To investigate the clinical significance of this, a period of 7 days since the last headache was taken as significant, and calculated the odds ratio for the presence of a near fusional amplitude greater than 20 prism dioptres as 3.9 (0.1-24.3). The days since last migraine headache was not correlated with any other binocular vision variable ($r_s \leq 0.37$, $p \geq 0.15$).

5.4 Discussion

The evidence in the literature for any association between migraine and the more subtle binocular vision anomalies is weak, yet it is not uncommon for optometrists to encounter patients who believe that migraine might be ameliorated by an optometric or orthoptic intervention. Incomitant deviations and strabismus, although part of the migraine spectrum, can be serious signs of underlying neurological disease, and it is reassuring that these conditions were not present in any of the migraine (or control) participants. Objective recording of eye movements was not undertaken and so subtle abnormalities in eye movements might not have been detected.

By both methods of simple cover testing, people in the migraine group were not more likely to have a heterophoria than controls and have, on average, a size of heterophoria within normal limits. An advantage of the cover-uncover test is that it provides an insight into the immediate effect of covering before the eyes are dissociated for prolonged periods. The disadvantage is that the precision of an estimated cover test reading might not be as great as that obtained with a dissociation test (e.g., Maddox Rod or Maddox Wing test). This is why both approaches were used.

When distance heterophoria was assessed under completely dissociated conditions using the Maddox Rod, people with migraine were statistically significantly more likely to demonstrate a heterophoria than controls, but did not have a statistically different amount of heterophoria than the control group. There was no correlation between the heterophoria measured by Maddox rod and any of the headache variables.

The presence and degree of heterophoria are poor predictors of symptoms: the key question is whether the person can compensate for their heterophoria. Two key methods of assessing this are to determine whether the person has a fixation disparity/aligning prism under natural and fused viewing conditions and to assess the adequacy of their fusional reserves to overcome the heterophoria (Evans, 2002). The test order can influence the test results in patients with a history of unstable binocular vision (Brautaset and Jennings 1999) and so aligning prism measurements on the Mallett Unit were undertaken before the dissociating measures of Maddox rod, wing and fusional reserves. People with migraine are slightly more likely to have a fixation disparity on the Mallett Unit, but overall the degree of aligning prism was not significantly different in the two groups. The near aligning prism was correlated to lateralization of headache such that left sided headaches are associated with base in aligning prisms and right sided headaches associated with base out aligning prisms. This correlation only just reached statistical significance and would seem difficult to explain. In fact, the signing of positive or negative

values to base in / base out aligning prisms was arbitrary and so such a correlation is unlikely to be clinically relavent.

The near point of convergence was no different in the two groups and within normal limits (Hayes et al 1998) for both people with migraine and the controls. When testing fusional reserves, the divergent reserve was always measured before the convergent reserve. This conflicts with the recommendation of Rosenfield et al. (1995) and these results could therefore be confounded by prism adaptation effects. However, this is unlikely to have influenced the conclusions concerning differences between the migraine and control groups because the type of heterophoria did not differ significantly in the two groups.

Percival's value was not different between the groups and the migraine group only showed a slightly reduced ability to overcome Sheard's criterion at distance. However, this was only apparent for one method of analysing the results and lost significance when a Bonferroni correction was applied. Interestingly, Evans et al. (2002) found an increased tendency for people with migraine to fail Sheard's criterion at near, but as noted above the migraine group in this study were selected as reporting a benefit from coloured filters so do not represent a normal cross-section of migraine sufferers.

Near fusional reserves were correlated to the number of days since the last migraine headache and this is some temporal evidence for causation (since the more days since a migraine attack, the bigger the near fusional reserves) with an odds ratio that suggests over a three times relative risk (but with broad confidence intervals).

Stereo-acuity was reduced in the migraine group but was within normal limits in the control group. Stereo-acuity was correlated to the duration of worst headache such that the longer the worst migraine headache the lower the stereopsis. The odds ratio indicated a 33 times increase in risk but the lower confidence limit of this odds ratio was less than one, reducing the confidence that this correlation is causal. Again, the fact that several correlations were investigated was highlighted so that chance findings of statistical significance are possible.

This data suggests that people with migraine are predisposed to have subtle deficits in their binocular co-ordination that slightly increase the risk of decompensated heterophoria and reduced stereopsis. Although more of the sample of people with migraine met usual clinical criteria for decompensated heterophoria at distance, this did not reach statistical significance, and was not the case at near. Therefore, it unlikely that binocular vision anomalies were causally related to the headaches in the majority of cases. However, headache is a recognised symptom of decompensated heterophoria (IHS, 2004) and in

view of these findings it is suggested that patients with migraine or suspected migraine ought to have an eye examination in case orthoptic problems are a contributory factor.

Chapter 6 Visual stimuli that trigger migraine

6.1 Introduction

Section 1.5 described that visual triggers of migraine are common (Chapter 1 published as Harle and Evans 2004) and include visual environmental stimuli (Kesari 2004; Alstaghaug et al 2005) and self-induced photopsiae (Jacome 1998). People with migraine, both during and between headaches (Drummond 1986; Drummond 1997; Drummond and Woodhouse 1993) are particularly prone to glare (Harle and Evans 2004) and to after-images following light exposure (deSilva 2001). A review of the literature relating to visual stimuli as migraine trigger factors suggested that visual stimuli are of similar importance to other non-visual triggers such as stress and hormonal factors (Debney 1984) and that review is discussed more fully in section 1.5.

Simple striped patterns have also been implicated as stimuli that can trigger migraine (Shepherd 2000) and such patterns are easily found in the environment. (Figure 11)

Figure 11

The view from Platform One, London Bridge Station. The modern built environment often includes architecture that has repetitive structures of spatial frequencies implicated in visual stress and associated with triggering migraine.

Migraine sufferers find striped patterns of 2-4 cpd particularly aversive (Wilkins et al 1984; Shepherd 2000) and this had lead to the development of a clinical test, the "pattern glare test" to investigate visual stress responses (Wilkins and Evans 2001; Stevenson and Evans 2006). Mulleners et al (2001) found that interictal photophobia was more common in migraine groups than control groups in both a North American and a European cohort, and that people with migraine had lower thresholds for visual stress. However, Mulleners et al did not link their data to the visual triggers of migraine.

This chapter was published in Headache in 2006 (Harle et al 2006). In this part, the links between pattern glare, visual stress and visual triggers of migraine, in between migraine episodes, using questionnaire data collected prior to participation in two separate experiments was investigated. The association between the questionnaire data and the optometric variables of pattern glare, use of coloured filters and colour vision was also reported. Pattern glare was assessed with the pattern glare test (Wilkins and Evans 2001), which gives a score for the number of visual illusions reported on viewing square-wave gratings of spatial frequencies 0.5 cycles per degree (cpd), 3 cpd and 12 cpd. Since there is some evidence that coloured filters are an effective intervention for people who are prone to pattern glare (Evans et al 1994; Evans et al 1995) or visually precipitated migraine (Evans et al 2002), the participants' colour vision, preferences for coloured filters (Wilkins 1994) and the effects of these coloured filters on visual performance using the Wilkins Rate of Reading Test (Wilkins at al 1996) were also investigated.

To explore the relationships between headache triggers, a principal component analysis was performed to determine general clusterings between the variables. Principle component analysis is a mathematical linear transformation such that the greatest varience by any projection of the data lies on the first coordinate (the principle component), the second greatest varience on the second coordinate and so on. This statistical factor analysis allows a large data set to be described by a series of components, each accounting for a proportion of the variance. Each components "eigenvalue" is the amount of variance that component explains. A second analysis was also conducted to determine how the choice of coloured filter, or the illusions seen in striped patterns in the pattern glare test, related to these triggers.

6.2 Methods

Participants were asked to complete a questionnaire (see Chapter 2 and appendix), which confirmed that those in the migraine group had a migraine diagnosis that conformed to IHS criteria (IHS 2004) or confirmed that those in the control group did not experience migraine. The questionnaire detailed the subjects' symptoms and history,

including questions relating to headache severity, frequency, and duration. Part of the questionnaire listed potential triggers and participants were asked to record if that trigger commonly, occasionally, or never triggered a headache. Potential triggers were given a score of 2 if the factor precipitated headaches "commonly", 1 for "occasionally" and zero for "never".

The pattern glare test was administered binocularly as described in the test instructions (Wilkins and Evans 2001). Printed square wave gratings were presented together with a list of visual perceptual distortions (illusions) that may be perceived whilst viewing the grating (Figure 12). Participants of study one viewed each of the three test patterns (0.5 cpd; 3 cpd; 12 cpd) of the pattern glare test and were asked to report if they noticed any of the following illusions or visual perception distortions; colours, bending of lines, blurring of lines, shimmer / flicker, fading and shadowy shapes.

Figure 12

A circular target square wave grating

Three square wave gratings were used with spatial frequencies of 0.5 cpd, 3 cpd and 12 cpd. To increase sensitivity, participants were asked to grade each visual perceptual distortion as not present, mild or severe; scored as 0, 1, or 2, respectively. The total score for each grating was then summed for each participant as previous research has shown the sum is a good measure of pattern glare (Stevenson and Evans 2006, in preparation). An alternative scoring method in the test instructions (Wilkins and Evans 2001): the difference between the illusion score for the 3 cpd and the 12 cpd, was also investigated.

The Intuitive Overlay Test uses a range of transparent plastic filters (overlays) that are of colours designed to systematically sample colour space (Wilkins 1994). Participants viewed (binocularly) the standard test pattern of text that is included in the test, which is

designed so that the pattern that the lines of text form can trigger pattern glare. Any visual perceptual distortions that were perceived were reported and recorded on the standard recording sheet supplied with the test. Participants then viewed the text through the coloured filters, presented in the same standard way, to determine the coloured filter (or combination), if any, which most improved their perception of the text. The Wilkins Rate of Reading Test (Wilkins et al 1996) is a simple test that is used to quantify the benefit from coloured filters and has been used in a variety of studies (Wilkins 2002). After selecting an individual's optimum filter, the Wilkins Rate of Reading Test was then completed (binocularly) to compare the rate of reading with and without that filter. Rate of reading (recorded as the number of words read in one minute using this test) was recorded four times, twice with the selected coloured filter in place and twice without and the mean rate of reading for both situations was recorded.

Colour vision was assessed binocularly using the Farnsworth saturated D15 test under a MacBeth solsource desk lamp. Scores were analysed using the Optical Diagnostics Color Vision Recorder computer programme (version 2.3) which generates a Colour Confusion Index (CCI) for each participant. The colour vision test comprises 15 coloured Munsell papers set in black caps. The participants were asked to order the 15 coloured caps so as to form a smooth colour sequence from a single fixed reference cap. There was no time constraint.

In section three, prior to the series of optometric tests (which did not include pattern glare and the use of coloured filters) questionnaire data were also collected. Here, this questionnaire data were combined with those from the first cohort of subjects to increase the number of respondents.

6.3 Results

Colour vision data

No subjects had a clinically demonstrable diagnosis of a colour vision defect on the Farnsworth D-15 test. However, the mean Color Confusion Index was significantly higher in the migraine group at 1.0696 (1.0251-1.1142) compared to 1.0301 (0.9972-1.0630) in the control group (Mann Whitney U-test, one-tailed p=0.034). This is consistent with previous work (Sherherd 2005).

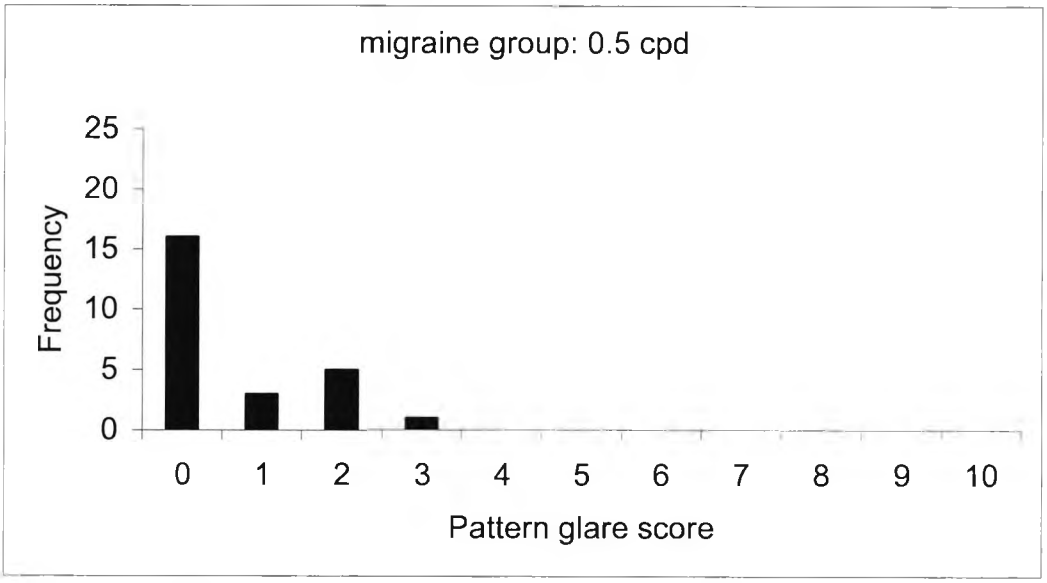
Pattern glare data

The Pattern Glare Test provides two indices of the severity of pattern glare: the number of illusions with the 3 cpd grating and the difference between the number of illusions on viewing the 3 cpd grating and the 12 cpd grating (Wilkins and Evans 2001; Stevenson and Evans 2006). Specifically, patients with pattern glare or visual stress should report

more visual perceptual distortions on viewing the 3 cpd pattern than the 12 cpd pattern, whereas control participants should exhibit the opposite tendency. Figures 13 and 14 shows that the migraine group saw significantly more illusions than the control group on viewing the 3 cpd grating (Mann Whitney U test, $p<0.0001$) and the difference between the number of illusion with the 3 and 12 cpd gratings was significantly greater in the migraine group than the control group (t-test, $p=0.0036$). These findings were still significant when a Bonferroni correction was applied. As expected, there was a significant positive correlation between the two scoring methods (Spearman $r_s=0.53$, $p<0.01$).

Figure 13a

Frequency distributions of pattern glare test results in the control and migraine groups for a 0.5 cpd pattern. People with migraine tend to have a higher score to all test patterns compared to a control group, but especially to the 3 cpd test pattern.



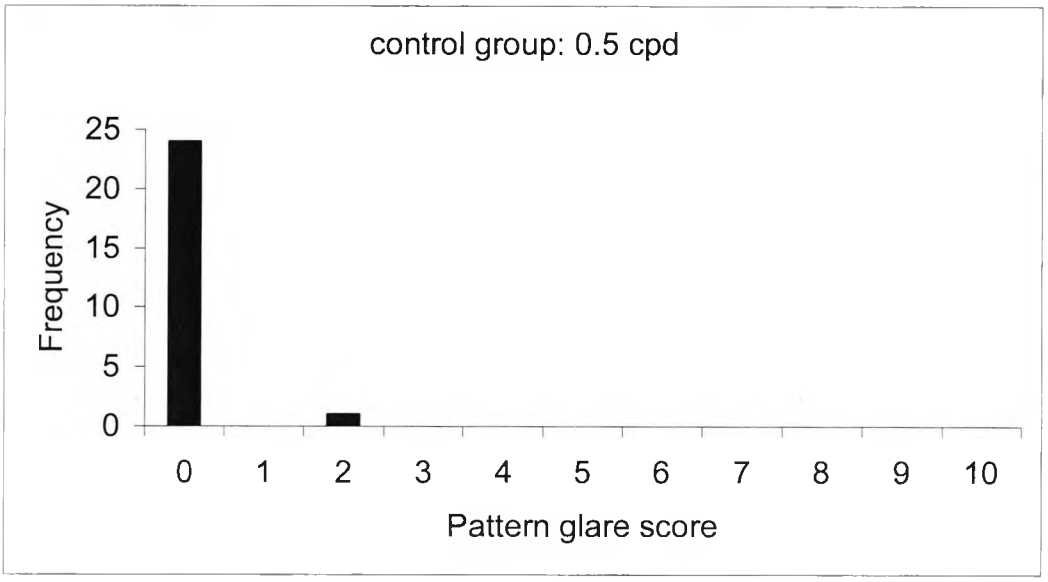
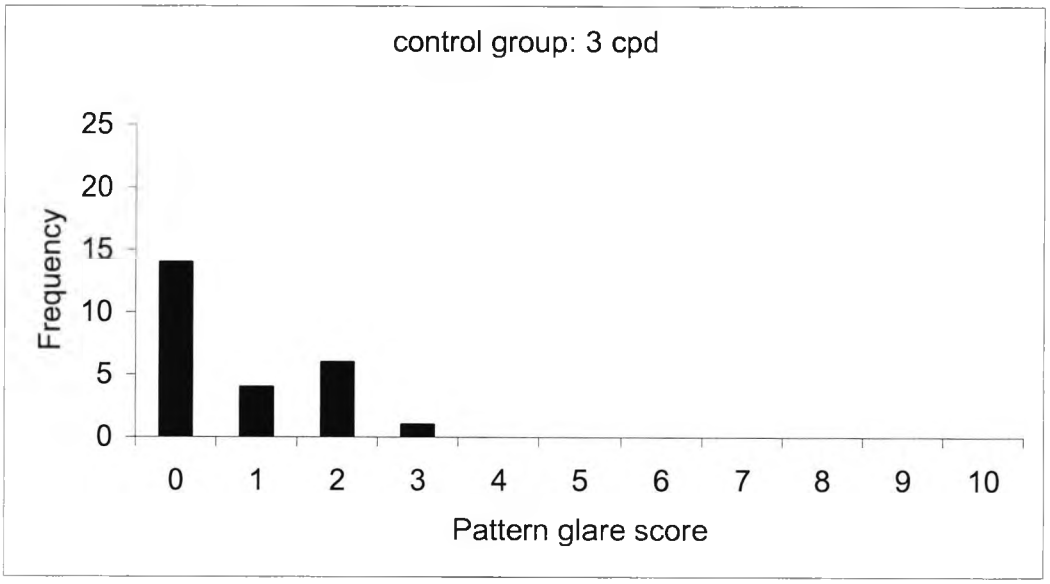


Figure 13b

Frequency distributions of pattern glare test results in the control and migraine groups for a 3 cpd pattern. People with migraine tend to have a higher score to all test patterns compared to a control group, but especially to the 3 cpd test pattern.



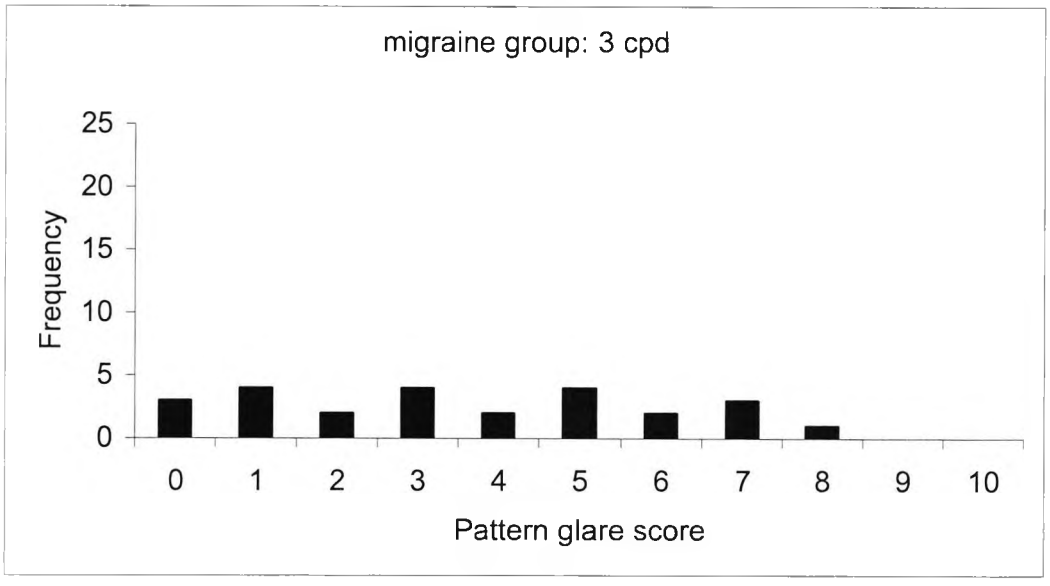
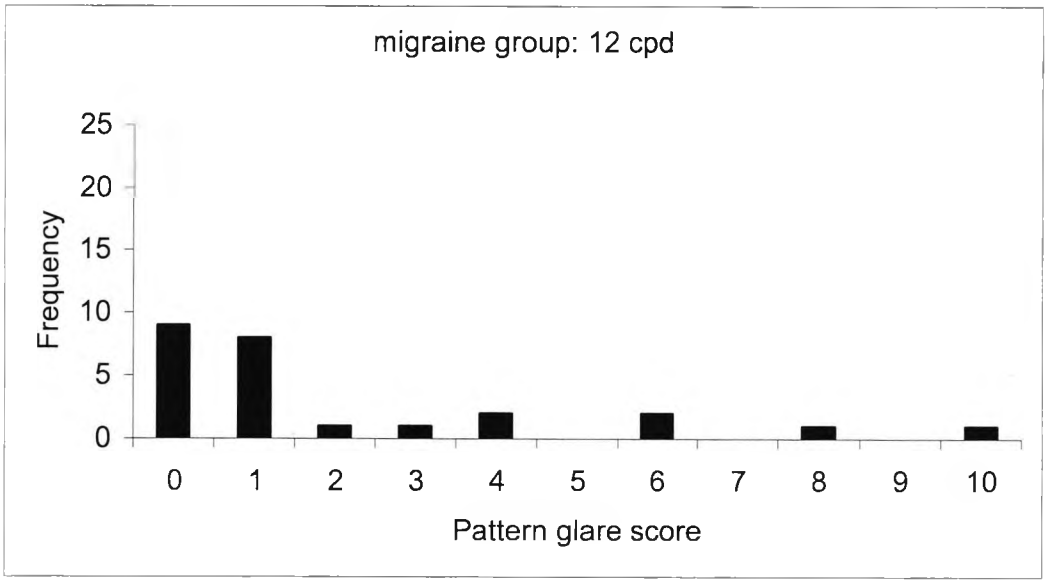


Figure 13c

Frequency distributions of pattern glare test results in the control and migraine groups for a 12 cpd pattern. People with migraine tend to have a higher score to all test patterns compared to a control group, but especially to the 3 cpd test pattern.



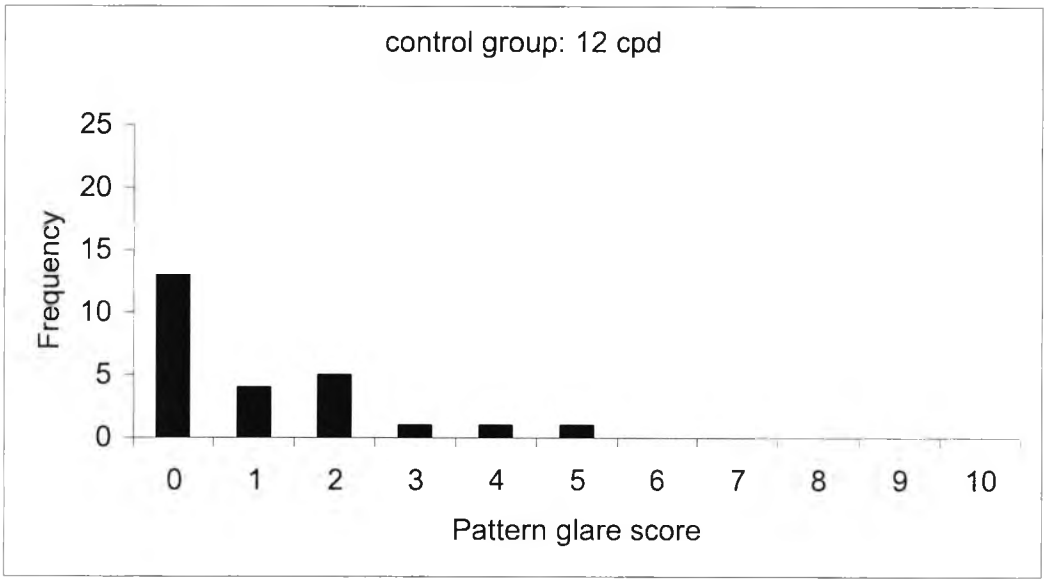


Figure 14a

The number of reported illusions to square wave patterned gratings of 0.5 cpd, 3 cpd and 12 cpd for people with migraine. Error bars give the 95% confidence interval.

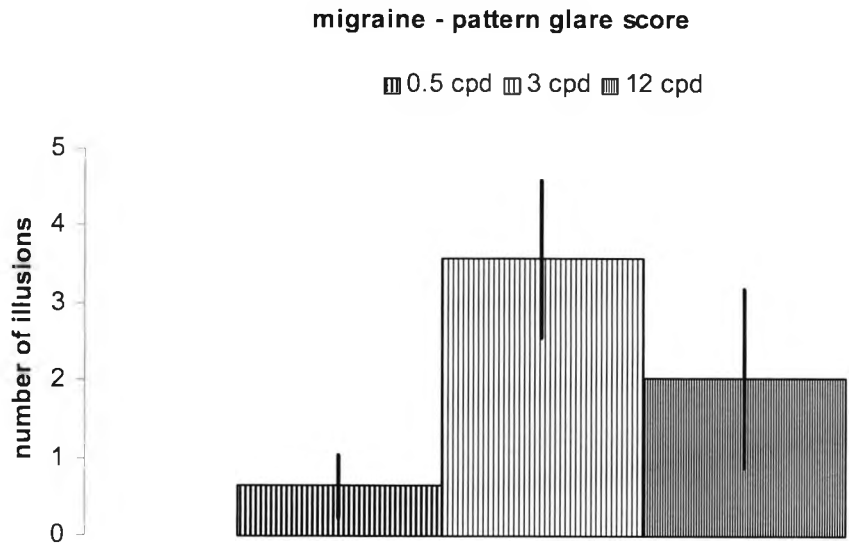
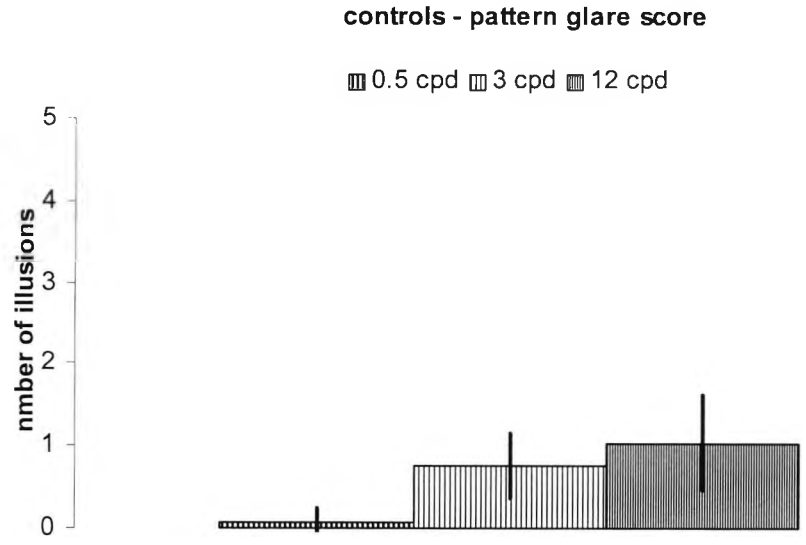


Figure 14b

The number of reported illusions to square wave patterned gratings of 0.5 cpd, 3 cpd and 12 cpd for the control group. Error bars give the 95% confidence interval.

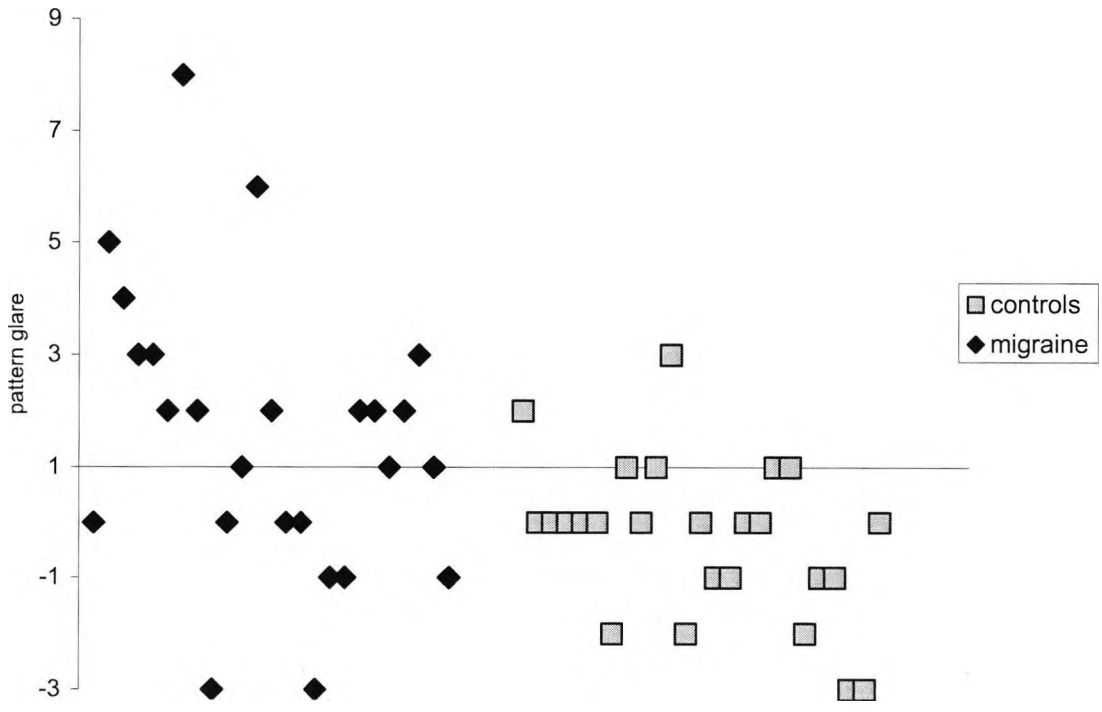


Pattern glare can be diagnosed by a score on the 3 cpd grating of at least 1.0 greater than the score on the 12 cpd pattern (Wilkins and Evans 2001) Using this criterion, it can be seen in Figure 15 that of the 25 participants in the migraine group, 16 had pattern glare whilst only 6 of the 25 controls had pattern glare.

Using these findings in a 2x2 contingency table, the performance of the pattern glare test as a diagnostic test for migraine (see Section 7.4) can be illustrated in terms of the number of non-migraine and migraine cases correctly identified by pattern glare. In these subjects the pattern glare test had a sensitivity of 64% and a specificity of 76% for diagnosing migraine (positive predictor value 73%, negative predictor value 68%).

Figure 15

For each subject (x axis) the difference between the number of illusions seen in the 3 cpd and 12 cpd patterns was calculated (y axis). A value of one or greater can be considered to be indicative of pattern glare. Migraine subjects are recorded as black diamonds and control subjects as light grey squares. As can be seen, the control data tend to lie below 1 whereas the migraine data tend to lie on or above 1.



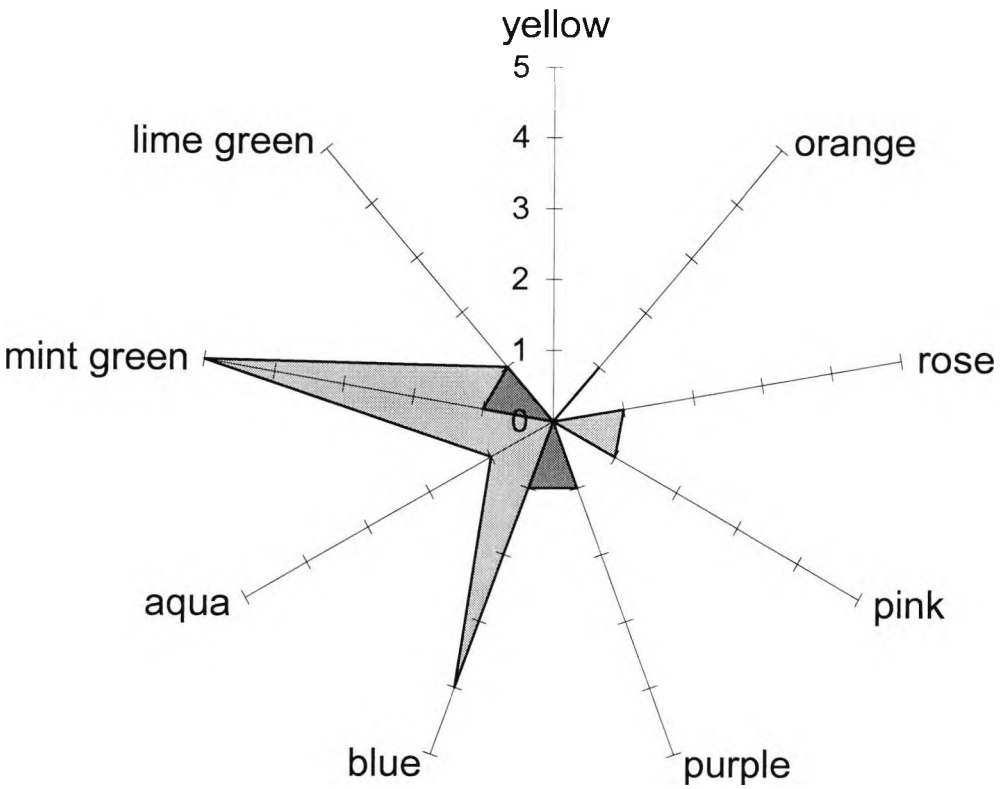
Coloured filters and rate of reading data

In the migraine group, 8 subjects did not find any filter improved their perception of text , 13 selected a coloured filter and 4 selected a grey filter. In the control group 19 subjects did not select a filter, 5 selected a coloured filter and 1 selected a grey filter (Figure 16).

There was a significant association between group (migraine or control) and the likelihood of subjects selecting a filter to reduce symptoms of visual perceptual distortions or increase the comfort of the text (χ^2, p=0.0073). Rate of reading using the Wilkins Rate of Reading Test was recorded for those participants who selected a coloured filter. Clinically, a rate of reading increase of 5% is considered significant (Kriss and Evans 2005). The mean rate of reading in words per minute with the filter (control group: 130.2 (101.1-159.3) migraine group: 156.7 (144.7-168.7) and without it (control group: 134.0 (113.7-154.3) migraine group 157.5 (142.4-172.6)) was similar and there was no association between group (migraine or control) and the number in each group who manifested at least a 5% increase in reading rate (χ^2, p=0.557).

Figure 16

For those participants that selected a coloured filter, the colour was recorded. Each spoke represents a colour of filter (those that chose a non-coloured (grey) filter are not shown). People with migraine (recorded in light grey) compared to people in the control group (recorded in darker grey) were more likely to select a coloured filter and the colours tended to be green to blue.



Symptom data

The symptom data in study one revealed the characteristic features of migraine. For example, a high proportion of the migraine groups reported nausea with headache (88%), pulsating quality (72%), phonophobia (68%), photophobia (68%), unilaterality of headache (56%), and aggravation by routine physical activity (48%).

Not surprisingly, people with migraine in study 1 had significantly more headaches (t-test, $p=0.0019$) in the last 12 months (mean 56.2 days / year) compared to controls (mean 3.8 days / year) and these headaches lasted longer (t-test, $p<0.0001$) in people with migraine (mean 37.0 hours) compared to controls (3.6 hours).

Principal components analyses: migraine triggers

Participants in both studies were asked about triggers for their migraines (Table 9).

Table 9

Subjects were presented with a list of possible headache triggers and were asked to record whether each of these triggered their headaches either "commonly" (scored as 2), "occasionally" (scored as 1), or "never" (scored as 0). The correlations between each variable and the component to which it contributes are shown from the rotated principal component analysis.

Triggers	General Food	Visual Triggers	Alcohol	Stress and Tiredness	The Environment
Chocolate	0.79				
Cheese	0.71				
Other food	0.81				
Caffeine	0.59				
Flickering lights		0.56			0.60
Certain patterns		0.78			
Other visual stimuli		0.81			
Red wine			0.74		
Other alcohol			0.92		
Stress				0.82	
Tiredness				0.86	
Noise				0.43	0.41
Smells					0.73
Light sensitivity					0.57

To explore the relationships between the headache trigger data, an exploratory principal components analysis was conducted. The data from both studies were combined and five components were extracted with eigenvalues greater than 1, which accounted for 70% of the variance in the original variables. The rotated solution (varimax rotation) lead to an interpretation of these components as (1) general food; (2) visual triggers; (3) alcohol; (4) stress and tiredness; (5) the environment (Table 11). Although listed in order, the amount of variance that was explained by each component was broadly similar. These components accounted for 18%, 14%, 13%, 13% and 12% of the variance, respectively. A cut-off correlation was selected (0.5) that resulted in all but two variables (flicker and noise) loading on only one component (allowing an oblique rotation did not alter this pattern). The correlations between each variable and the component to which it contributes are shown in Table 9. Flicker correlated moderately with both the visual trigger and environment components.

The first study included data on the illusions seen in striped patterns, and the number of people who found coloured filters beneficial when reading. A second analysis on the data from just Experiment 1, which also included the pattern glare and filter data, was conducted to determine how the choice of coloured filter, or the illusions seen in striped patterns related to the clusters of visual triggers. The second analysis produced six components with eigenvalues greater than 1, and these accounted for 72% of the variance in the original variables. The rotated solution (varimax rotation) lead to similar interpretations for four components: (1) general food; (2) visual triggers; (3) stress/tiredness; (4) alcohol. The scope of the environment component was reduced (smells and flicker) and an extra component emerged as a visual stress component. These 6 components accounted for 17%, 13%, 12%, 10%, 10% and 11% of the variance in the variables, respectively. Each variable correlated strongly with only one component. The correlations between each variable and the component to which it contributes are shown in Table 10.

Flicker again correlated moderately with both the visual trigger (0.37) and environment components (0.59) but reached the cut-off correlation only for the environment.

Table 10

Results of a second analysis to determine how the choice of coloured filter, and the illusions seen in striped patterns, related to the clustering of the triggers. The pattern glare test was scored using both methods: Pattern Glare Score 1 (as the total illusion score for the 3cpd pattern) and Pattern Glare Score 2 (as the difference in the illusions score between the 3cpd and 12 cpd square wave grating.

Triggers	General Food	Visual Triggers	Stress and Tiredness	Visual Stress	Alcohol	The Environment
Chocolate	0.76					
Cheese	0.68					
Other food	0.90					
Caffeine	0.85					
Certain patterns		0.79				
Other visual stimuli		0.80				
Pattern glare score 1		0.63				
Stress			0.83			
Tiredness			0.71			
Noise			0.57			
Light sensitivity				0.60		
Pattern glare score 2				0.79		
Coloured filter chosen				0.73		
Red wine					0.73	
Other alcohol					0.91	
Smells						0.86
Flickering lights						0.59

6.4 Discussion

Three measures, colour vision, pattern glare, and the selection of coloured filters to reduce pattern glare, each differed between the migraine and control groups. The questionnaire data revealed visual stimuli to be relevant as triggers for migraine, whereas in the principal components analysis a measure of visual stress emerged as a separate component that was not strongly associated with visual triggers. The significance of these results, and interactions between them, will now be discussed in more detail.

Colour vision scored as the colour confusion index (CCI) on standard D15 testing was subtly, but significantly, different between the groups. Other recent work (Shepherd 2005) has suggested subtle alterations in colour perception in people with migraine, using both psychophysical tests and the Farnsworth-Munsell 100-hue test. In that study, Farnsworth-Munsell partial error scores along the blue-yellow axis were found to be elevated in migraine. Whilst type three (blue-yellow) defects are reminiscent of congenital tritan anomalies, it is the chromatic mechanism rather than the blue cones that appear dysfunctional in migraine (Hart 1987) as is typical in acquired colour defects with preserved acuity. Further evidence of normal overall retinal function in migraine (Kahil 1991) supports this view. Subtle colour perception dysfunction has also been used as an argument to explain (Harle and Evans 2006b) blue on yellow visual field changes in people with migraine (Yenice et al 2005).

As described in the introduction, some people report headaches during or after viewing patterned stimuli (Wilkins et al 1984). This is a component of "patterned glare" (Wilkins and Nimmo-Smilth 1984) or more commonly "pattern glare" (Evans and Drasdo 1991). A correlation between the number of headaches reported and the illusions seen whilst viewing a striped pattern has been reported previously (Wilkins et al 1984) and many more people with migraine report aversion to these patterns compared to people without migraine (Marcus and Soso 1989). In the data reported here, the pattern of 3 cpd had a markedly increased likelihood of producing visual perceptual distortions in people with migraine compared to the control group.

The questionnaire data revealed that migraine groups, not surprisingly, had the characteristic features of migraine (IHS 2004). Visual stimuli that trigger migraine headache are commonly reported (Jacome 1998; Harle and Evans 2004; Kesari 2004; Alstaghaug et al 2005), and in the main analysis, general visual stimuli and certain patterns formed a cluster of triggers with flickering lights. Flicker also correlated with other environmental triggers (noise, smells and sensitivity to bright lights). Flicker has been implicated in the past as a significant migraine trigger (Debney 1984) with some authors

reporting a direct relationship to flicker frequency (Kowacs et al 2004) and others noting abnormal flicker thresholds in people with migraine with a variety of experimental procedures (Coleston et al 1994; Coleston and Kennard 1995; McKendrick and Badcock 2004a; McKendrick and Badcock 2004b; Kowacs et al 2005).

In the second analysis on the data from Experiment 1 only, the overall number of illusions for the 3 cpd grating clustered with the visual triggers, suggesting that this grating is a potent visual trigger to migraine. Pattern glare (calculated as the difference between the number of illusions seen in the 3 cpd and 12 cpd gratings) clustered separately with light sensitivity and with whether a coloured filter was chosen. These data may suggest visual triggers and visual stress are separable, though this requires replication before further conclusions can be drawn.

It has been suggested that in migraine, hyperexcitability of the visual cortex may manifest as pattern glare (Wilkins 1995). Furthermore, this hyperexcitability has been proposed to explain increased pattern glare in three conditions: (Wilkins 1995) specific learning difficulties (Wilkins et al 1994), migraine (Wilkins et al 2002), and epilepsy (Marcus and Soso 1989). The Wilkins Rate of Reading Test is commonly used to evaluate the effect of coloured filters on pattern glare in people with specific learning difficulties (Wilkins 2002), but the data reported here do not support this use of the test in people with migraine. Specifically, there was not a significant association between the diagnosis of migraine and reaching the test criterion of at least a 5% increase in reading speed with that filter.

Nonetheless, there was a preponderance of people with migraine who selected a colour to improve text clarity and there was a relationship between the pattern glare score and the selection of colour. The distribution of the colour selection was not random and was dissimilar to that found in studies that have looked at the colour selection to benefit reading (Wilkins et al 2001). One hypothesis is that the number of symptomatic neurological conditions, including migraine, that are associated with visual stress, may relate to one another on a continuum of cortical hyperexcitability, possibly affecting different areas or extent within the visual cortex. The precision of colour choice for any alleviating filter may reduce as the extent of the area of cortical hyperexcitability increases. An alternative hypothesis would be that the blue-green preference in this study supports the previously discussed colour vision studies (Shepherd 2005) showing S-cone deficits in migraine.

In migraine, visual triggers are important because they are relatively easy to alleviate. It is suggested that the investigation by healthcare professionals of people with migraine should include questions about visual triggers and visual stress. The pattern glare or pattern glare difference score, rather than the Wilkins Rate of Reading Test, might be

useful as a screening tool for this purpose. Those that report visual triggers such as flicker or patterns, or those who give a positive response to the pattern glare test, may benefit from consulting eye care practitioners to investigate the potential for optometric intervention (Wilkins 2002; and Evans 2006a; Harle and Evans 2006c)

Chapter 7 Frequency Doubling Technology Perimetry, Standard Automated Perimetry and Intraocular Pressures in Migraine

7.1 Introduction

People who suffer from migraine headaches have been found to perform less well than non-headache controls when undergoing psychophysical tests designed to try to isolate the magnocellular pathway. For example, it has been shown (Coleston *et al.,* 1994; Coleston and Kennard, 1995; McKendrick *et al.,* 1998; McKendrick *et al.,* 2001) that migraine sufferers have a reduced ability to detect some temporal visual stimuli in the range of 10 to 20 Hz and that migraine sufferers also have impaired perception of spatial frequency stimuli around 4 to 5 cycles per degree (Coleston *et al.,* 1994).

In chapter 1.8 it was discussed that some perimetric studies found similar deficits in people in migraine: McKendrick et al. (1998) found deficits involving 16 Hz flicker, however, these results are of one migraine sufferer only. Temporally modulated perimetry showed that migraine sufferers have selective visual dysfunction for temporally modulated targets of a temporal frequency greater than 9 Hz (McKendrick *et al.*, 2000) or general visual field deficits when comparing short-wavelength automated perimetry (SWAP) and standard automated perimetry using a Humphrey Visual Field Analyser (McKendrick *et al.*, 2002) but not when using frequency doubling stimulus (McKendrick and Badcock; 2004a).

These visual field findings have raised questions about whether migraine might be associated with glaucoma (McKendrick *et al.*, 2000,2002), although this is controversial (the literature on this subject is summarised in Section 7.4). One explanation of the conflicting views regarding migraine and glaucoma is that migraine headache might be associated with visual field changes unrelated to glaucoma. Such an interpretation would predict that intra-ocular pressures should remain unaffected, which would account for the fact that some studies have suggested a link with normal tension glaucoma. In this part of the study, published in Ophthalmic and Physiological Optics in 2005 (Harle and Evans 2005), visual fields in migraine using both frequency doubling technology (FDT) perimetry and Humphrey SITA visual fields were investigated.

7.2 Methods

The first examination procedure was an assessment of intra-ocular pressure with an American Optical Non-Contact II Tonometer. Subjects were seated and, following a demonstration of the technique to ensure they were relaxed and comfortable with the procedure three readings for each eye were taken and the mean of these three readings recorded.

N30 FDT (Frequency Doubling Technology) Humphrey Visual Fields were performed with the patients' own habitual far refractive correction. The procedure was explained and demonstrated to the participant. Then subjects were seated, and the right eye was assessed first, followed by the left eye. Subjects were instructed to press a trigger button, when a flickering grating was seen which varied in contrast whilst maintaining central fixation.

30:2 SITA (Swedish Interactive Threshold Algorithm) Humphrey Visual Fields were performed with the patients' own habitual near refractive correction. The procedure was explained and demonstrated to the participant, and the right eye was again assessed first, followed by the left eye. Subjects were instructed to press a trigger button, when a small white light was seen which varied in luminance whilst maintaining central fixation. SITA 30:2 and FDT N30 perimetry both give an assessment of the central 30 degrees of visual field. Mean deviation (MD, an indication of any general depression across the visual field compared with the internal normative database of the perimeter) and pattern standard deviation (PSD, an indication of any local abnormalities in a individual's visual field relative to the remainder of their visual field) are calculated and reported by both instruments. Reliability indices are also reported so that any unreliable visual fields could be rejected. For SITA, an unreliable field was classified as one that had greater than 20% false positive errors or greater than 20% false negative errors. For FDT fields, an unreliable field was classified as one that had greater than 1/8 false positives or greater than 1/5 false negatives.

7.3 Results

Global indices

The reliability criteria for all field results were met and so none were rejected. The reliability indices for false positives and false negatives for each instrument were not significantly different in the two groups for both tests (Mann-Whitney U test, $p \geq 0.30$).

Clinically, MD and PSD data are analysed by comparison with normative databases. However, migraine sufferers are included in the instruments' normative databases thus weakening the validity of comparing a migraine group with the instrument norms. Therefore, the MD and PSD in the migraine group with equivalent variables in the control group were compared. The statistical analysis of multi-eye data in ophthalmic research is discussed in the literature (Ray and O'Day, 1985; Murdoch et al., 1998).

Figures 11-14 show the frequency distributions for the MD and PSD for the SITA and FDT results. The distributions of both SITA variables appeared skewed and a Kolmogorov-Smirnov test confirmed that these data were not normally distributed ($p<0.05$), whereas the distributions of the FDT variables were normally distributed ($p>0.10$). Therefore, non-parametric statistical tests were used for the SITA variables and parametric tests for the FDT variables. Appropriate descriptive statistics are given in Tables 9 and 10 which, for completeness, also include the data for each eye individually.

Table 11

Descriptive statistics for the MD and PSD results for the SITA visual field test. IQR, inter-quartile range; (R+L), mean of right and left eye data.

	group	Median RE	IQR RE	Median LE	IQR LE	Median (R+L)	IQR (R+L)
MD	control	-1.32	-2.63 to -0.40	-0.98	-1.88 to -0.41	-1.39	-1.81 to -0.57
	migraine	-1.88	-3.79 to -0.47	-1.63	-3.36 to -0.74	-2.14	-2.98 to -0.66
PSD	control	1.48	1.34 to 2.02	1.60	1.28 to 1.99	1.62	1.35 to 1.91
	migraine	1.72	1.33 to 2.73	1.53	1.33 to 2.17	1.57	1.35 to 2.37

Table 12

Descriptive statistics for the MD and PSD results for the FDT visual field test. SD, standard deviation; (R+L), mean of right and left eye data

	group	mean RE	SD RE	Mean LE	SD LE	Mean (R+L)	SD (R+L)
MD	control	-1.14	1.90	-1.30	2.03	-1.22	1.91
	migraine	-1.13	2.37	-1.23	2.74	-1.18	2.33
PSD	control	3.84	0.63	3.82	0.82	3.83	0.61
	migraine	3.85	0.66	4.65	2.27	4.25	1.26

Figures 17-20 are suggestive of a "tail" of worse performance in the migraine group, but using the Mann-Whitney U test this did not reach statistical significance with the SITA test for either the MD (p=0.20) or PSD (p=0.71) variables. Similarly, using an unpaired t-test the performance of the two groups at the FDT test did not differ significantly for either the MD (p=0.95) or PSD (p=0.14) variables.

Figure 17

Histogram of the mean deviation (MD) for the Humphrey SITA visual field test.

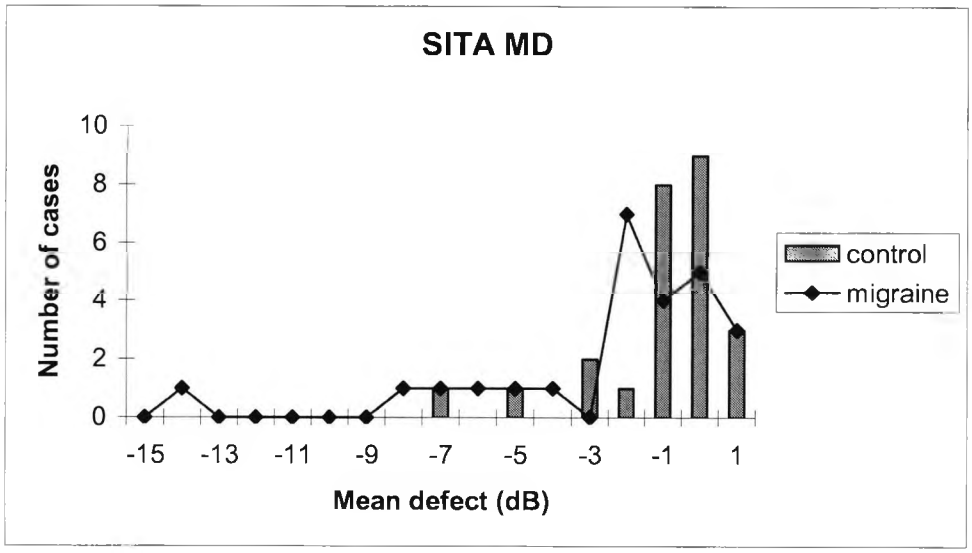


Figure 18

Histogram of the pattern standard deviation (PSD) for the Humphrey SITA visual field test.

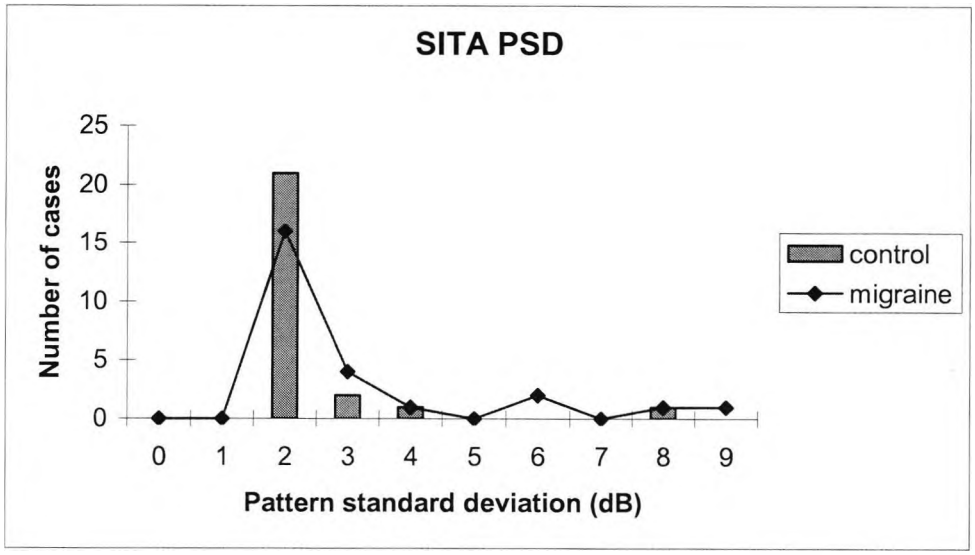


Figure 19

Histogram of the mean deviation (MD) for the Humphrey FDT visual field test.

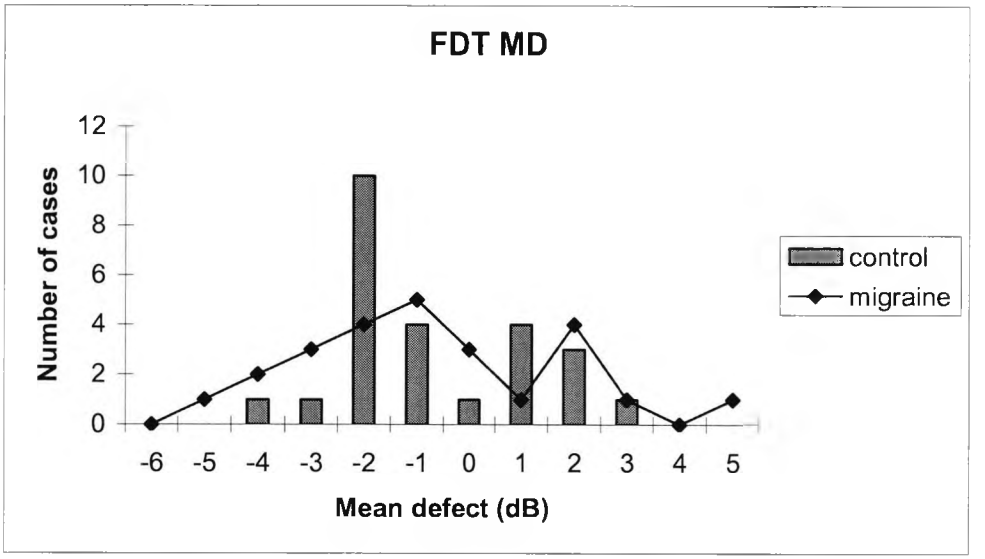
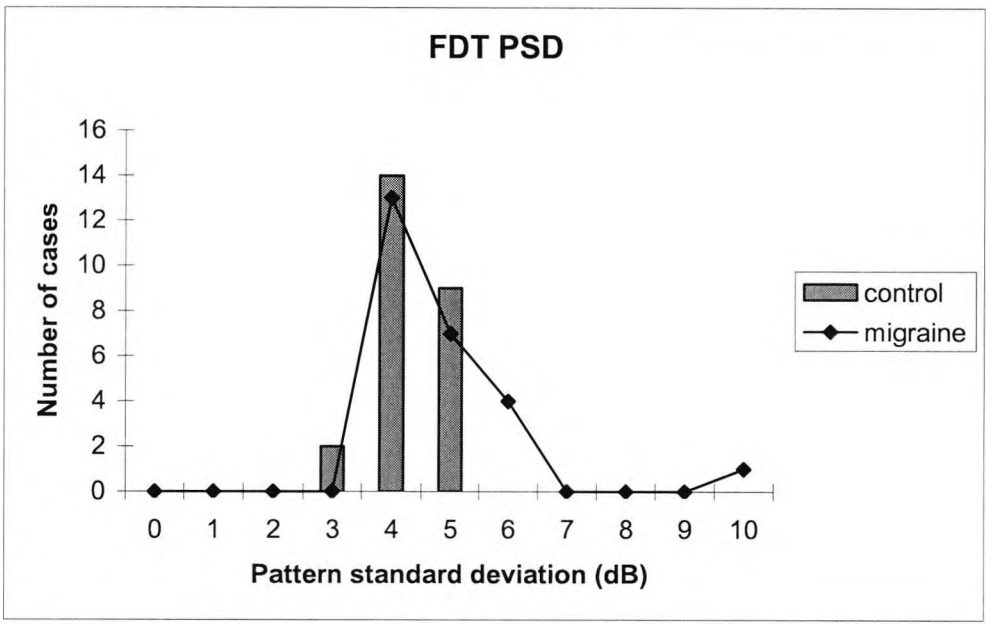


Figure 20

Histogram of the pattern standard deviation (PSD) for the Humphrey FDT visual field test.



To evaluate inter-ocular asymmetries, for each participant, the absolute value of the difference between the right and left eye data was calculated. Inspection of the frequency distributions of this inter-ocular difference for the MD and PSD variables for each instrument showed that these data are not normally distributed, and this was confirmed by Kolmogorov-Smirnov tests ($p<0.04$). These four variables did not differ significantly in the two groups (Mann-Whitney U test, $p>0.12$).

To evaluate inter-hemifield asymmetries, thresholds for each hemifield were averaged. The mean of the right hemifield and the mean of the left hemifield were calculated and then the difference between the right and left hemifield was obtained by finding the absolute difference between these two mean values. There were no significant differences in hemifield data in the migraine group when compared to the control group for both SITA visual fields (Mann-Whitney U test, $p=0.99$) and FDT visual fields (unpaired t-test, $p=0.39$).

Correlation between results from the two visual field instruments

To ascertain whether the participants who performed poorly on the SITA task were the same as those who performed poorly on FDT and to note if there was there significant correlation between the global indices for SITA and FDT when compared for individual participants, a correlation analysis was performed. The Spearman correlation coefficients for the total study population of 50 participants were low for each eye MD ($r_s<0.29$) and PSD ($r_s<0.22$) and for the signed (right eye minus left eye) inter-ocular difference for MD ($r_s<0.14$) and PSD ($r_s<0.14$).

Intra-ocular pressure

The mean IOP for the migraine sufferers was 14 mmHg in each eye and the mean IOP for the control group was 15 mmHg in each eye. These values did not differ significantly in the two groups ($p\geq0.14$), and neither did the difference between the eyes ($p=0.14$).

Correlations between headache variables and visual field results

The Spearman correlation coefficients between visual field data (averaged right and left eye values) and headache variables were calculated. The correlations for both PSD and MD for SITA visual fields and the number of headaches per year, number of days since last migraine, and severity of worst headache were all low ($r_s<0.37$) and non-significant ($p>0.05$). There were significant correlations between the duration of worst headache and SITA MD ($r_s=-0.42$, $p=0.04$) and PSD ($r_s=0.45$, $p=0.03$). The correlation coefficients between both PSD and MD for FDT visual fields and the number of migraine headaches per year, duration of worst headache, and severity of worst headache were all low ($r_s<0.30$) and non-significant ($p>0.05$). The correlation between the FDT MD and the

number of days since last migraine approached significance (r_s=-0.46, p=0.05), but the correlation between FDT PSD and number of days since last migraine was not significant (r_s=0.15, p=0.56).

Finally, whether the inter-ocular visual field differences were related to whether the headaches were typically unilateral was investigated. Migraine participants were divided into those whose headaches were usually unilateral (N=13) and those whose headaches were not typically unilateral (N=12). For each visual field parameter with each instrument, the absolute inter-ocular difference of the participants with unilateral headaches did not differ significantly from those with non-unilateral headaches (Mann-Whitney U test, p>0.15).

7.4 Discussion

Several authors have evaluated test-retest repeatability of perimetry, for both methods that were used (e.g., Artes et al., 2002; Horani et al., 2002) and concerns over repeatability have led many researchers to repeat visual field testing to confirm the presence of any defects. However, in migraine research it is possible that visual field defects might vary with the interval since the last headache (McKendrick and Badcock, 2004c) and this raises serious doubts over the usefulness of repeat testing in this population. In other words, the interval since the last headache may be a confounding variable influencing visual field reproducibility. The validity of these data was evaluated using the intra-test reliability data. The reliability indices were good and showed that the results were of similar reliability in each group. Since the reliability indices of the visual fields were within acceptable limits, the fact that participants were not trained in perimetry would seem not to be an issue. The participants wore their habitual refractive correction, rather than their optimal refractive correction and all participants completed all the visual field tests. An advantage of using the habitual refractive correction is that the data were gathered under conditions reflecting participants' everyday visual status.

Our results suggest that migraine sufferers are no more likely to have abnormal visual fields than controls. No more inter-eye differences or inter-hemifield differences in migraine sufferers than controls were found. As these results were found for both FDT and SITA, these data do not support a magnocellular specific dysfunction in migraine. This conflicts with some of the literature that suggests visual field defects in migraine (McKendrick and Badcock 2004b, 2004c; McKendrick et al., 1998, 2001) and it is doubtful that this is an effect of statistical power since the subject numbers in this thesis exceeded those in most of these studies (McKendrick and Badcock, 2004c; McKendrick et al., 1998, 2001). McKendrick and Badcock (2004b) compared 24 controls with 28 migraine

with aura and 25 migraine without aura participants. They found significantly lower general sensitivity across the visual field and a higher prevalence of localised defects in their migraine group. The discrepancy between their findings and the data presented in this thesis might be explained by the fact that they used different flickering stimuli, although the FDT method did involve flickering stimuli. Another possible explanation is that McKendrick and Badcock (2004b) pooled the data from right and left eyes. This approach has been criticised, especially when the right and left eyes' data are strongly correlated as McKendrick and Badcock demonstrated, as being likely to "give a greater measure of statistical significance than the data warrant" (Ray and O'Day, 1985).

McKendrick and Badcock (2004a) used a computer driven display with custom software to produce an FDT stimulus and compared these results to motion coherence thresholds. The object of this study was to evaluate motion coherence and frequency doubling at the same points in the visual field and so MD and PSD findings were not reported. Nevertheless these authors did not find differences in their migraine participants compared to controls with their custom software FDT method and this study agrees with these findings.

As noted in the introduction, any link between glaucoma and migraine needs to be carefully considered. The literature suggests that people with glaucoma are not especially likely to have had a migraine (Usui *et al.*, 1991) and migraine prevalence is not significantly different between normal tension and high tension glaucoma sufferers (Pradalier *et al.*, 1998). The Beaver Dam Eye Study also showed no relationship between open-angle glaucoma and migraine headache (Klein *et al.*, 1993), using diagnostic criteria based on visual fields, intra-ocular eye pressure, cup/disc ratio and history. Other authors have found that there is a relationship between normal tension glaucoma and migraine headache (Cursiefen *et al.*, 2000). In particular, migraine has been considered a risk factor for glaucomatous visual field progression (Drance *et al.*, 2001). Recently, glaucomatous-like visual field defects have been found in patients with migraine in the absence of raised intra-ocular pressures and this has led to the suggestion that there might be a relationship between the pathophysiology of normal tension glaucoma and migraine (Comoglu *et al.*, 2003). This relationship was also the conclusion of the perimetric studies that suggested a possibility of a common pre-cortical vascular involvement in these two conditions (McKendrick *et al.*, 2000,2002). In the data presented here, no significant differences between the migraine and control group in visual fields or intra-ocular pressure were found. This suggests that in this young (up to age 50 years) sample of participants, migraine sufferers do not have changes that might be considered to be clinically associated with glaucoma in an older popupation. However, it would be interesting to investigate whether the subgroup of individuals with migraine that some

studies suggest might show periodic visual field deficits when they are younger, are more likely to be diagnosed with glaucoma when they are older.

All migraine sufferers were headache-free at the time of testing and nearly all had been headache free for a week. The relationship between severity of visual field defect and duration of worst migraine could be explained if the visual field loss results from neural damage occurring during prolonged migraine attacks. There is some support in the literature for a hypothesized chronic damage to the visual system from migraine (Chronicle and Mulleners, 1994). The presented results in this study were however equivocal on this issue, since the relationship was found only by SITA field analysis and not by FDT field analysis. Nevertheless a relationship between both length of migraine history and frequency of migraine occurrence and lower general sensitivity to flickering visual field stimuli have been recently reported to add weight to this argument (McKendrick and Badcock, 2004c).

To conclude, these data do not reveal visual field abnormalities in migraine headache sufferers, and any visual field deficits in migraine are likely to be subtle and are highly unlikely to be clinically significant.

Section Three

Further Investigation into the retinal nerve fibre layer in migraine

Chapter 8 Perimetry and optical coherence tomography measurements in people with migraine.

8.1 Introduction

Chapter 1 described that migraine and vision have been linked throughout history (Pearce 1986), but until recently, visual changes were considered only as part of the spectrum of migraine aura. Recent evidence is growing (Chapter 1 published as Harle and Evans 2004) that some changes in the visual system do occur in the interictal phase in people with migraine in the higher visual pathways (Chronicle and Mulleners 1996; Shepherd 2001). Research into the early stages of visual processing is more limited, but although Chapter 7 found little association, some other studies have added weight to the argument that deficits, demonstrable by certain visual field analyses, do exist early in the visual system in migraine in-between headache events (McKendrick et al 2002; McKendrick and Badcock 2004a; Yenice et al 2005). The similarities of these migraine visual deficits to those that occur in glaucoma have added to the debate regarding a common link between these conditions (Usui et al 1991; Klein et a l993; Wang 1997; Pradalier et al 1998; Drance et al 2001; McKendrick et al 2002; Comoglu et al 2003; Yenice et al 2005). A common neurovascular mechanism for these two very different conditions is an intriguing possibility; for example migraine has been implicated as a risk factor for ischaemic optic neuropathy (King 1979; Weinstein and Feman 1982) and a migrainous ischaemic mechanism has been suggested for normal tension glaucoma (Corbett et al 1985; Phelps and Corbett 1985), perhaps related to vasospastic actions at the optic disc (Flammer 1992; Nicolela 1996; Nizankowska 1997; Broadway and Drance 1998). Indeed migraine may be a risk factor for optic disc haemorrhage (Healey et al 1998).

The evidence of subtle visual field changes in a minority of people with migraine has only been obtained using a computerized visual field simulation (McKendrick and Badcock 2004b) and short wavelength automated perimetry SWAP (McKendrick 2002, Yenice et al 2005) but not when standard clinical white on white Humphrey SITA visual fields or Humphrey FDT visual fields were used (Chapter 7). Recent evidence regarding colour vision changes in people with migraine (Shepherd 2005) and concerns (Harle and Evans 2006b) with the statistical pooling of the data in some previous studies has challenged the concept that SWAP is altered in migraine.

Tan et al (2005) found no retinal alterations in migraine. To establish the relationship between visual field alterations and retinal changes, this section sought to further

investigate retinal nerve fibre layer and visual fields in migraine using a masked case control study. A battery of tests in a group of people with migraine seen during the non-headache phase and age- and sex-matched controls was undertaken. Optical coherence tomography (Zeiss Stratus OCT) measurements of retinal nerve fibre thickness and optic nerve head volume were assessed to establish if the retinal structure was or was not unchanged in people with migraine. If structural differences did occur then these may have been detectable by standard automated perimetry or by frequency doubling perimetry and so these were also undertaken. SWAP was not included because of the challenges associated with subtle colour vision alterations in people with migraine previously discussed. Intra-ocular pressure measurements were also taken to aid differential diagnosis should optic disc and visual field changes be found.

8.2 Methods

The recruitment and participants of this completely separate study are described in Chapter 2.3. Subsequent to the test session, all participants completed a short questionnaire detailing their symptoms and history, including questions relating to headaches. This was used to check that the migraine group met all the International Headache Society (IHS) criteria for migraine headache with aura or migraine headache without aura (Headache Classification Sub-Committee of the International Headache Society 2004), ensured that the control group were truly migraine free, and for the migraine group gave a time in days since the last migraine headache. The contents of this questionnaire were not revealed to the researcher performing the clinical tests and a third investigator collected these data.

The test examinations were near visual acuity (VA) using the Lighthouse Near Visual Acuity Test 2nd Edition (Lighthouse Low Vision Products), Humphrey frequency doubling technology (FDT) N30 threshold visual fields (Carl Zeiss Humphrey FDT perimeter), Humphrey Swedish interactive threshold algorithm (SITA) 30:2 standard threshold visual fields (Carl Zeiss Humphrey VFA II 720 perimeter), Pulsair non-contact tonometry (NCT).(Keeler) and Optical Coherence Tomography (OCT)(Carl Zeiss Stratus OCT 3000) Methods of applying visual field and non-contact tonometry tests were as described in the methods section of Chapter 7.

OCT is a computer-assisted optical instrument that generates cross sectional images (tomograms) of the retina with approximately 10 microns axial resolution. It uses low-coherence interferometry which, in a similar way to ultrasound, uses the echo time delay of light reflected and backscattered from different retinal structures on the ≤ 10 micron

scale (Carl Zeiss OCT User Manual 2002). For OCT testing the subject was given a fixation target and then the computerised display was used to align tomographic recording grahics with real time retinal features. Results from both eyes were recorded using the standard method (Carl Zeiss OCT User Manual 2002) and then manally tranfered to a Microsoft Excel spread sheet for analysis.

The application of each test is described in Table 13 and the order of the test examinations was counterbalanced within each group. For the visual field testing, FDT was performed for each eye twice with the first set of data treated as training and discarded.

8.3 Results

The Humphrey visual field examinations (SITA 30:2 and FDT N30 perimetry) reliability criteria for all field results were met (Table 20) and so none were rejected.

Table 13

The test order was randomised & counterbalanced for each participant according to a predetermined Latin square by a researcher who was blind to the experimental procedure to balance the test order in each group. Although data was collected for both eyes, the data from one eye (randomly selected) was discarded prior to analysis.

Number	Test	Description
1	*Visual Acuity*	*The binocular visual acuity at 58cm using a reduced logMAR test, recorded as number of letters correctly identified*
2	*Humphrey FDT*	*N30 Threshold Fields, the right eye tested first. The habitual far refraction was worn and test results were rejected with greater than 1/8 false positive or 1/5 false negative.*
3	*Humphrey VFA II*	*SITA 30:2 Standard Fields the right eye tested first. The habitual near refraction was worn and test results were rejected with greater than 20% false positives or negatives*
4	*Pulsair NCT*	*The average of four results for each eye, the right eye tested first and time of day recorded*
5	*Zeiss Stratus OCT*	*The right eye tested first. Scans performed were "fast optic disc" and "RNFL thickness"*

Clinically, MD and PSD (see page 83) data are analysed by comparison with normative databases. However, people with migraine are included in the instruments' normative databases thus weakening the validity of comparing a migraine group with the instrument norms. Therefore, the MD and PSD in the migraine group with equivalent variables in the control group were compared. Figures 21-24 show the frequency distributions for the MD and PSD for the SITA and FDT results.

Figure 21

The frequency distributions for the mean deviation of the Humphrey SITA 30:2 visual field results.

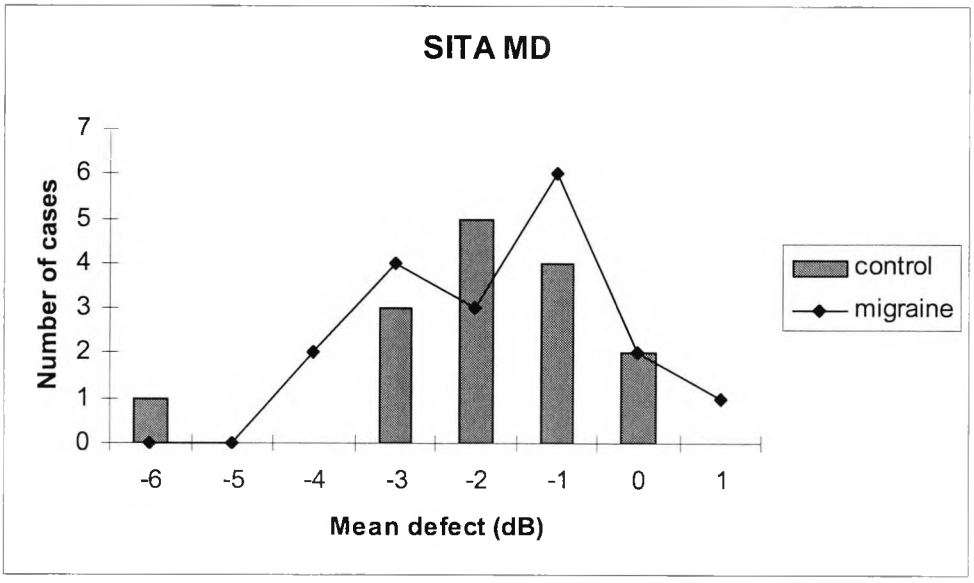


Figure 22

The frequency distributions for the pattern standard deviation of the Humphrey SITA 30:2 visual field results.

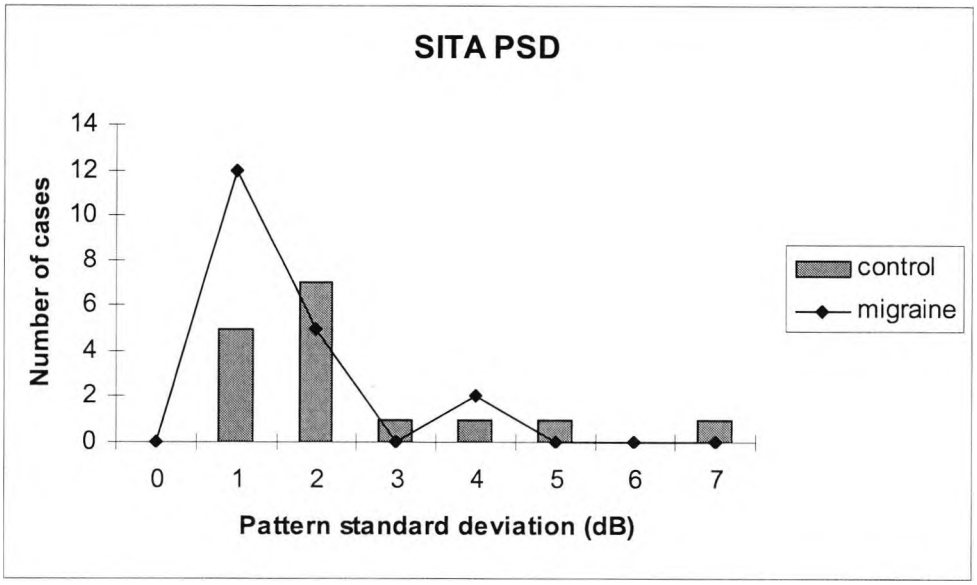


Figure 23

The frequency distributions for the mean deviation of the Humphrey FDT N 30 visual field results

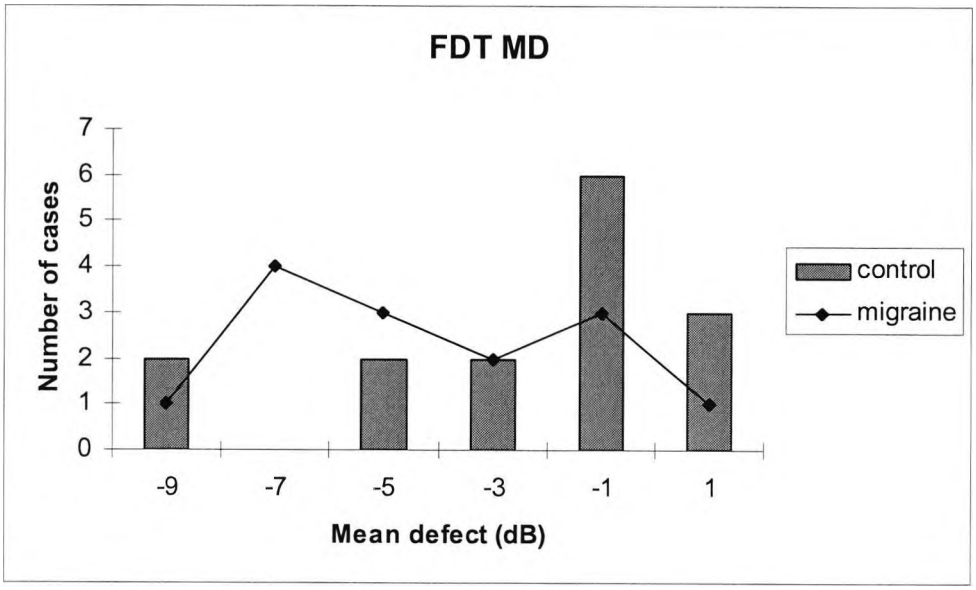
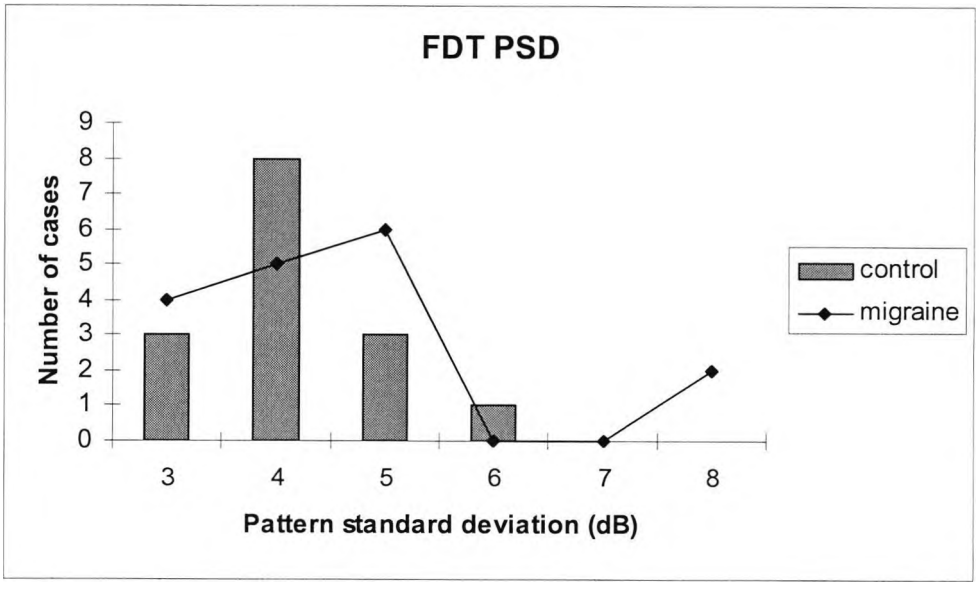


Figure 24

The frequency distributions for the pattern standard deviation of the Humphrey FDT N 30 visual field results



The data from the two groups were not significantly different (Mann Whitney U-tests p>0.07). For FDT perimetry these data had a power of 0.8 to detect a 1.69 difference in MD and 1.44 difference in PSD between the groups. For SITA perimetry these data had a 0.8 power to detect a 1.46 difference in MD and a 1.49 difference in PSD between the groups.

The mean IOP in the migraine group was 18.8 mmHg (95% CI 17.0 - 20.7), which was slightly higher than the control group 16.5 mmHg (95% CI 14.6 – 18.4) but this difference was not statistically significant (t-test; p=0.07). These data had a power of 0.8 to detect a 3mmHg difference in IOP between the groups.

The mean binocular visual acuity (VA) at 58cm, recorded as number of letters read on the Lighthouse Near Visual Acuity test, was 46.1 (95% CI 41.2 – 50.4) in the control group and 49.4 (95% CI 47.8 – 51.0) in the migraine group and did not differ significantly between the groups (t-test, p=0.11). These results are approximately equivalent to 95% of participants achieving a near acuity equivalent to 6/9 or better. These data had a 0.8 power to detect a six letter difference in VA (about one line) between the groups.

For OCT readings an a priori decision was made to concentrate on the optic nerve analysis report (the rim volume) and the retinal nerve fibre layer (RNFL) thickness average in each quadrant. No significant difference was found in optic nerve volume (t-test, p=0.68) or RNFL thickness in any quadrant (t-test, p>0.37) between the groups (Table 21).

It was calculated that this experiment had a 0.8 power to detect a 0.48 mm^3 difference in mean rim volume, a 31.6 micron difference in inferior RNFL thickness, a 22.0 micron difference in superior RNFL thickness, a 22.0 micron difference in nasal RNFL thickness and a 19.6 micron difference in temporal RNFL thickness.

Table 14

Using OCT, the Retinal Nerve Fibre Layer (RNFL) in microns in each scanned quadrant and the vertical integrated rim area volume (mm^3) was found for participants in each group. Group means are shown with 95%CI in parentheses. No results were significantly different (p>0.37) between the groups.

	RNFL Inferior	RNFL Superior	RNFL Nasal	RNFL Temporal	Rim Area Volume
Migraine	104.8 (87.3-122.4)	98.1 (86.6-109.3)	43.8 (32.7-54.8)	67.7 (58.9-76.4)	0.54 (0.27-0.81)
Control	94.6 (79.6-109.6)	95.7 (84.2-107.2)	47.0 (35.3-58.7)	62.0 (50.7-73.3)	0.46 (0.23-0.70)

8.4 Discussion

Migraine is a common neuro-vascular condition, which can sometimes affect the circulation of the anterior visual pathway, can have short lasting retinal effects as retinal migraine, and is known to have ophthalmic associations (Headache Classification Sub-Committee of the International Headache Society 2004; Friedman 2004). Nonetheless the literature linking migraine to retinal or visual field changes remains equivocal. To investigate any possible link between migraine and changes to the early visual pathway, consideration needs to be given to the retinal nerve fibre measurements and visual fields. Intra-ocular pressure measurements may also be useful if differences were found between the groups for differential diagnostic purposes.

As noted in Chapter 7.4, several authors have evaluated test-retest repeatability of perimetry, for both methods that were used (Artes et al 2002; Horani et al 2002) leading many researchers to repeat visual field testing to confirm the presence of any defects. In migraine research it is possible that visual field defects might vary with the interval since the last headache (McKendrick and Badcock 2004c) and this raises doubts over the usefulness of repeat testing in this population because the interval since the last headache may be a confounding variable influencing visual field reproducibility. Therefore in this study two paths; firstly to evaluate the validity of the data using the intra-test reliability data, an approach which has been employed in similar studies (Harle and

Evans 2005) and described in Chapter 2. Secondly, several visual field tests in the same clinic session were performed, discarded the first FDT data to minimize learning effects and counter balanced the test order to minimise fatigue effects. All the visual field tests performed had reliability indices that were good and similar in each group. The participants wore their habitual refractive correction, which gave good near visual acuity, and all participants completed all the visual field tests.

Our results suggest that people with migraine are no more likely to have abnormal visual fields than people without. This agrees with the previous data (Chapter 7 published as Harle and Evans 2005) but not with other work (McKendrick and Badcock 2004b; McKendrick et al 1998; McKendrick et al 2001; Yenice et al 2005). Although in this study the sample size was comparatively small, it was similar to those used in other studies and the effect size analysis suggests that this study had a reasonable statistical power to detect differences between the groups. In fact a closer look at the literature suggests that data pooling may well have over emphasised the statistical significance in previous work in this area (see Chapter 7 and Harle and Evans 2005; Harle and Evans 2006b).

No significant difference in the retinal nerve fibre layer of the migraine group compared to the control group in any of the measured OCT variables were found. This agrees with another recent study suggesting that the retinal nerve fibre layer is unaffected in migraine (Tan et al 2005) and adds weight to the argument that no detectable changes are found in people with migraine that could contribute to visual field defects in this group. Tan et al (2005) used the GDx (Nerve Fiber Analyzer, GDx VCC:5.3.3; Laser Diagnostic Technologies) instrument to establish retinal nerve fibre layer thickness in people with and without migraine and found no differences. Using OCT, these similar findings to that study suggests that this similarity of retinal nerve fibre layer measurements between the groups is repeatable and that people with migraine do not have detectable changes to the retinal nerve fibre layer.

As no difference in visual fields or retinal nerve fibre layer parameters was found between the migraine and control groups, the intra-ocular pressure measurements (IOP) that were obtained were not needed for differential diagnostic purposes in the migraine group. It is however reassuring that IOP results showed values that were within normal limits and similar in the migraine and control groups. The pharmacological implications of the migraine / IOP relationship in normal tension glaucoma have been debated (Gupta 2006; Harle and Evans 2006d) but these data again establishes no comparable changes to IOP in the interictal phase in people with migraine, although the age range of the participants (Chapter 2.3.1) is worth noting.

This small sample size study did not find any significant difference between migraine and control groups in OCT data, intra-ocular pressures, and several visual field parameters. Failure to find a significant relationship in a study may be because there is no relationship or because the study lacks the statistical power for any relationships to reach statistical significance. In a study with modest sample sizes, such as ours, this possibility must be addressed. This is done throughout the results section by calculating not just whether the groups were statistically different, but for each result what minimum effect size would have been detected as being significantly different. This reveals that with the presented sample size this study had a 0.8 power to detect a difference between the groups of 3mmHg for IOP; a difference of about 1.5 in both MD and PSD for FDT and SITA visual fields; a near acuity difference of six letters read at 58cm; and a difference of between 20 and 30 microns in retinal nerve fibre layer thickness. Although larger sample sizes would have led to narrower confidence limits, these effect sizes indicate that these data would have detected clinically important differences between the groups.

To conclude, in this study, no significant differences between the migraine and control groups in visual fields, OCT or intra-ocular pressures in between headache events were found. This suggests that in this small sample of participants, people with migraine do not have retinal or visual field changes in the non-headache phase using the methods assessed.

Section Four

Optometric Interventions in Migraine

Chapter 9 A collection of seven single-subject double cross over studies.

9.1 Introduction

Following reviews (Chronicle and Mulleners, 1996; Harle and Evans, 2004) and experimental papers (Drummond 1987; Drummond 1990; De Marinis, 1994; De Marinis et al. 1998; McKendrick et al 1998; McKendrick et al, 2000; McKendrick et al, 2002; Evans et al, 2002; Wilkins et al 2002; McKendrick and Badcock, 2003; Shepherd 2005; Tan et al 2005; Harle et al, 2005; Harle and Evans, 2005; Yenice et al 2005; Yucel et al, 2005; Harle and Evans 2006a,c; Harle et al, 2006) evidence is accumulating that certain optometric factors are correlated to migraine. These are described througout this thesis. Some of these factors may be consequences of migraine. For example it has already been commented that migraine can, in common with other central nervous system disorders (Shepherd, 2005), affect visual processing pathways. This may be linked to alterations in motion perception (McKendrick and Badcock 2004a) and perceptual colour vision alterations (Shepherd, 2005) in people with migraine. Reports of visual field defects in migraine (McKendrick et al 2002; McKendrick and Badcock 2004b; Yenice et al 2005) and of a link with glaucoma (McKendrick et al 2002; Yenice at al 2005) have proved controversial (Harle and Evans, 2005, 2006b) in the light of evidence of an unaltered retinal structure in migraine (Tan et al, 2005). Chapter 3 described pupil changes in people with migraine, in line with previous work (Drummond 1987; Drummond 1990; De Marinis, 1994; De Marinis et al. 1998) and both parasympathetic and sympathetic alterations have been experimentally implicated (Chapter 3, published as Harle et al 2005) following debate on the involvement of both autonomic nervous systems (Yarnitsky et al., 2003; Peroutka, 2004 a, b Yarnitsky and Burstein 2004).

To the optometrist, these possibly consequential correlates are important for differential diagnostic purposes but not for intervention. Perhaps of interest to the practising optometrist is the experimental evidence from Chapters 4 and 5 that subtle refractive (Chapter 4 published as Harle and Evans 2006a) and orthoptic deficits (Chapter 5 published as Harle and Evans 2006c) are more common in people with migraine than non-migraine controls. Additionally in Chapter 6 (published as Harle et al 2006), the link between visual symptoms, pattern glare (visual stress), interictal light sensitivity, coloured filters and migraine (Marcus and Soso 1989; Wilkins 1995; Mulleners et al 2001; Wilkins et al 2002) was established.

However there is little evidence to suggest that these correlative findings are causes of migraine. In the only randomized controlled study of an optometric intervention for migraine, tinted lenses for visually precipitated migraine (Wilkins et al 2002), the subjects were selected using a behavioural index of benefit such that they were only admitted to the study if they had reported a benefit from using coloured filters (Wilkins 1994) when reading for at least a month.

Single subject research design

Optometric interventions are, by their very nature, individually prescribed. The optometric decision of whether to prescribe spectacles is usually based not just on clinical findings but also on the presenting symptoms (O'Leary and Evans 2003). Case control studies of spectacle interventions for subtle optometric anomalies are problematic, since the precise optometric characteristics of each participant are likely to differ. An alternative experimental approach that has been proposed for medical (Janosky 2005) and optometric (Collins et al 1985) research is the "single subject design". This design has been used in other disciplines (e.g. Cadenhead et al 2002; Doepke et al 2003; Leon et al 2005) and explored in the past for behavioural and biofeedback optometric interventions (Gallaway et al, 1987; Leung 1988). The single subject design uses each subject as his or her own control. Keeping all other factors constant during the experiment, an active intervention "A" is prescribed for a period of time whilst symptom factors are monitored. Following a "wash out" period with neither intervention, a control intervention "B" is prescribed for the same period of time. Following a second wash out period the process is repeated. This ABAB design is known as a double crossover study and can provide good evidence of the effectiveness of an intervention in an individual. In this section, an ABAB design was used for seven individuals with migraine to assess the effect that refractive, orthoptic and precision tinted interventions had on migraine variables. A goal of the research was to identify, from the main study participants, which optometric correlates were most likely to be causally related to migraine. These correlates would then candidates for future randomised controlled trials.

9.2 Methods

During the study (described in Chapters 4,5, and 6), the participants were examined by an optometrist who performed a full eye examination that included assessment for the refractive error (Chapter 4 published as Harle and Evans 2006a), the binocular vision status (Chapter 5 published as Harle and Evans 2006c), and the effect of pattern glare (visual stress) (Chapter 6 published as Harle et al 2006) and precision tinted lenses (Wilkins and Sihra, 2000). New spectacles were advised in some cases, and the recommendations fell into three categories; 1) a change in refractive correction based on

the final subjective refraction found (Rabbetts, 1998), 2) the new prescribing of a prism, based on the aligning prism found on the Mallett unit (Evans 2002; 2005), 3) the new prescribing of a precision tinted lens based on the hue, saturation and attenuation found on colorimetry (Wilkins et al 1992; Wilkins & Sihra, 2000). Of those that were recommended a spectacle intervention, eight agreed to further investigation using a single-subject design.

For each of these eight people with migraine, a control and an intervention pair of spectacles were made. Both pairs used the same frame type, style, and colour; and the same lens type, optical centres, and dispensing characteristics. For those that required a refractive intervention, two pairs of spectacles were made; one pair contained the same refractive correction as in the spectacles that the patient wore to the appointment and the other pair had the new refractive correction exactly as found during the subjective refraction at the appointment (Chapter 4.2).

For those that required a binocular vision intervention; two pairs of spectacles were made; one to correct the subject's refractive error but with no prism and one to correct the same refractive error but incorporating the prescribed prism (Chapter 5.2).

For those that required a precision tinted lens; again two pairs of spectacles were made, one to correct the subject's current refractive error and including a control tint, and one to correct the same refractive error but with the true precision tint. Participants viewed text at 0.4 m illuminated with coloured light in the Intuitive Colorimeter (Wilkins and Sihra, 2000) that permits continuous and separate variation of hue and saturation. Hue and saturation values were then converted to tints having the same spectral transmission and chromaticities under fluorescent lightling CIE illuminant F3 as provided by the MRC system for Precision Ophthalmic tinting (Wilkins et al 1992). The control tint was calculated based on CIE 1976 UCS to have the same saturation as the experimental tint, but to have a different hue angle such that the CIE LUV colour difference was 100 (based on the data of Wilkins et al., 2005 (Wilkins 2005)). For each experimental tint there are two candidate control tints of equal saturation: one that is selected by moving clockwise and one anti-clockwise in CIE 1976 UCS colour space. To help maintain a masked design, the control tint that was most likely to give the same colour name or similar colour name to the experimental tint was selected.

A researcher who was masked as to which spectacles were the active intervention pair and which the control intervention, issued (in random order) one pair of spectacles (intervention A) to the patient for six weeks use, together with a six week headache diary to be completed. Following six weeks of use, this first pair was returned and after two

weeks the second pair of spectacles (intervention B) was issued to the patient for a further six weeks with another six-week headache diary. After this six-week period these spectacles were returned and following a two-week wait the process was repeated. This gave the ABAB double cross over design; six weeks with each intervention, two weeks between each intervention.

During both second six-week periods with both intervention A and intervention B, a telephone survey (Appendix 6) was undertaken, and in most cases completed, to monitor the use of the spectacles. At the end of the final six week period, each subject completed a final questionnaire (Appendix 7) again assessing the use of each pair, and chose which pair of spectacles they would like to keep and were asked which pair they thought most helped their migraine headaches. The study questionnaires (chapter 2 and appendix) asked participants to rank the amount of time that they had used each intervention using continuous performance scales 0 to 7 for the telephone survey and 0 to 70 for the final questionnaire. The data from these scales were combined to give a score indicating the amount of time that each intervention was used.

Following the completion of each single-subject study, results were analysed and compared using Analyse-it (version 1.71) for Excel software. One participant had improved migraine headache symptoms during the entire study period and the questionnaires revealed that he had very rarely used either pair of spectacles. This participant's data were excluded and are not described below. Four variables were returned from the headache diaries (Chapter 2 and appendix) for each period. Firstly the number of migraine headaches was simply recorded and were used to calculate the proportion of days that were headache-free with each intervention. Secondly, the severity of the headache was recorded as mild, moderate or severe. This was re-coded as a score of 1,2, or 3 respectively, and the product of this score and the length of the migraine headache in hours were used to give a "Pain rating"; larger values represent greater pain. Although severity and duration are clearly different aspects of headache, it was decided that a combined score is of interest since it intuitively seems to reflect the degree of suffering experienced.

The number of aura symptoms from the questionnaire (Chapter 2 and appendix) was used to give an "Aura rating" from 0 to 16; larger values represent more marked aura. Finally, to ensure medication use did not confound the findings, a "Palliation rating" was scored. This scored the first and second medication taken as 1 for an analgesic containing no codeine, 2 for medication containing codeine and 3 for a migraine abortive medication. Summing these scores for up to two medication types gave a rating scale for palliation from 0 to 6 for each headache event.

9.3 Results

Subject SG: Refractive intervention

Subject SG is a female who was aged 26 at the start of the trial. SG used one pair of spectacles for both distance and near visual tasks. She had no history of orthoptic or ophthalmological treatment but had noticed that her distance vision had gradually become slightly blurred. She had no other visual symptoms, was fit and well and took no medication other than that for migraine. Optometric examination results are in the Table 15.

SG was orthoptically normal (Evans 2002), had no pattern glare (Wilkins and Evans 2001), did not require a coloured filter but did have a change in refractive error. For the study she compared two different spectacle refractions: her previous and updated refractive correction. Figure 25 describes the migraine events and shows the headache variables during the study for SG. From the questionnaire, the score ranked from 0 to 70 of how much each intervention was used was not significantly different ($p=0.69$, Wilcoxon signed rank test) for the control intervention (median 65, IQR 2) or the active intervention (median 65, IQR 1) and from the descriptive statistics of the proportion of migraine headache free diary days, it is clear that the active intervention spectacles were not having a therapeutic effect on the frequency of migraines. The median palliation score during headache events was not significantly different to that with the control (Mann Whitney U-test; $p=0.50$) and so does not confound the headache diary results. The pain rating (Mann Whitney U-test; $p=0.20$) and the aura score (Mann Whitney U test; $p=0.94$) with the active intervention were not significantly different to that with the control.

Subject SG chose to keep the active intervention spectacles and indicated that these spectacles improved her migraine headaches.

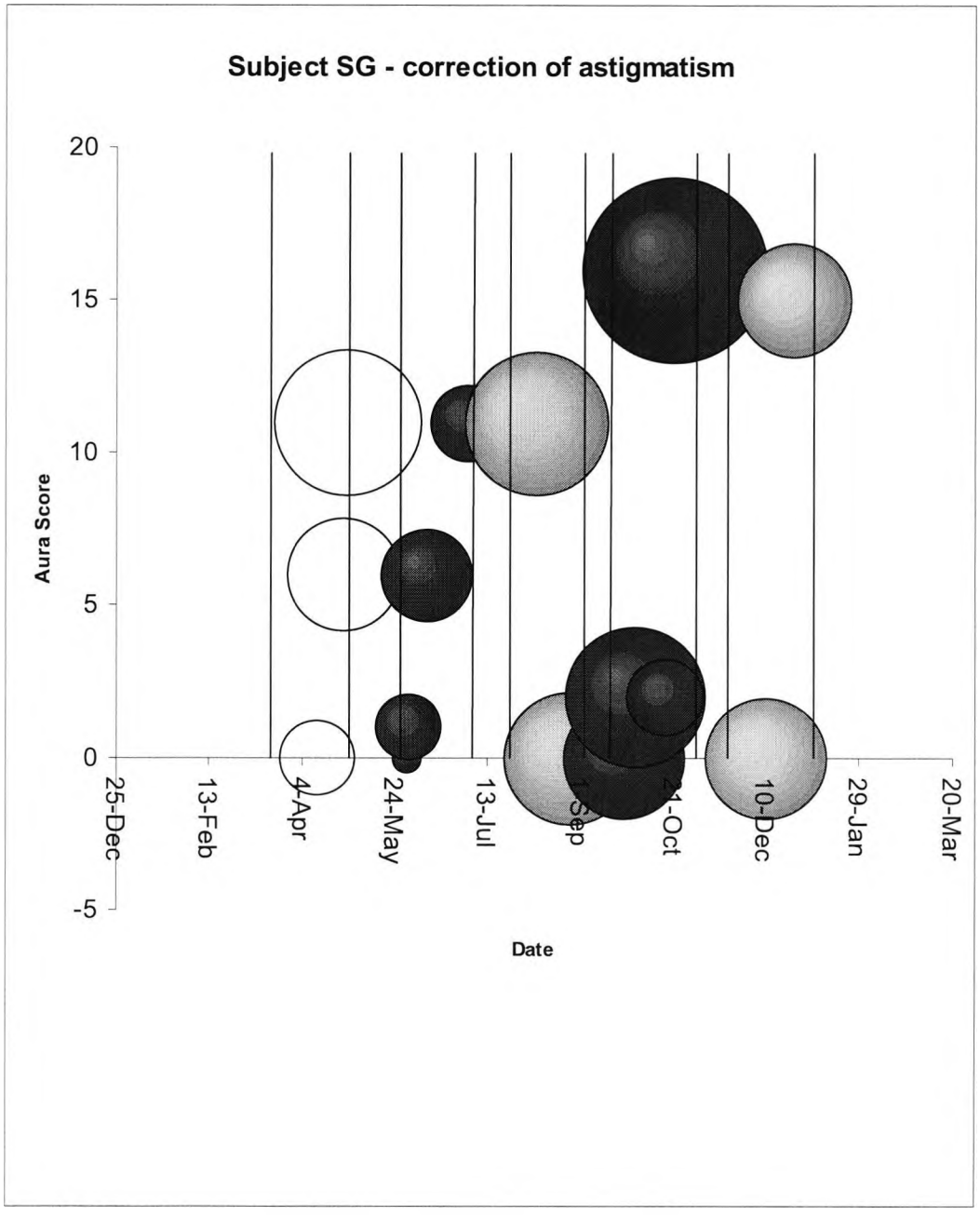
Table 15

Relevant Optometric Results. Normality of binocular vision tests were based on Evans 2002 and normality of pattern glare tests on Wilkins and Evans 2001. Visual acuities were measured on a Bailey-Lovie LogMAR chart and converted to Snellen equivalents. Palliation, Pain and Aura scores are given as the median with the inter-quartile range in parenthesis.

Initials	SG		
Age	26		
Gender	FEMALE		
Binocular Vision tests			
Ocular motor balance at 6m	Orthophoric		
Ocular motor balance at near	2 Prism Dioptres Exophoria		
Aligning prism at 6m	None		
Aligning prism at near	None		
Fusional Reserves	Normal		
Convergence	Normal		
Accommodation	Normal		
Pattern Glare and Visual Stress tests			
Coloured filter selected	Grey		
Pattern glare	None		
Rate of reading with coloured filter	140 words per minute		
Rate of reading without coloured filter	178 words per minute		
	Baseline	Active	Control
Refractive tests			
Refraction Right Eye	-0.50 / -2.50 x 15	-0.75 / -2.50 x 7	-0.50 / -2.50 x 15
Refraction Left Eye	+0.75 / -3.50 x 178	+0.75 / -4.75 x 175	+0.75 / -3.50 x 178
Visual Acuity Right Eye	6/9	6/6	6/9
Visual Acuity Left Eye	6/9	6/6	6/9
Results			
Intervention Use	N/A	65 (IQR 2)	65 (IQR 1)
Migraine Headache Free Days	39/42 (93%)	75/84 (89%)	80/84 (95%)
Palliation Score	3 (IQR 1)	1 (IQR 1)	2.5 (IQR 1.5)
Pain Rating Score During Migraine Headaches	216 (IQR 132)	96 (IQR 168)	264 (IQR 99)
Aura Score During Migraine Headaches	6 (IQR 6)	2 (IQR 5)	5.5 (IQR 14)

Figure 25

Figure 25 describes the migraine events and shows the headache variables during the study for SG. Each bubble represents a migraine event. White bubbles are those migraine events during the baseline period, black bubbles during the period with the control spectacles and grey bubbles during the period with the intervention spectacles. The larger the bubble the greater the pain factor (a product of pain rating and length of pain). The higher the bubble the greater the number of aura symptoms were experienced. Vertical lines delineate the six-week periods during which interventions were used.



Subject LH: Hyperphoria intervention

Subject LH is female and was aged 44 at the start of the trial. LH was an office worker and used one pair of spectacles for both distance and near visual tasks. She had no history of orthoptic or ophthalmological treatment but had noticed for as long as she could remember that she had to tilt her head when reading and tired easily. She had no other visual symptoms, was fit and well and took no medication other than that for migraine. Optometric examination results are in Table 16.

LH had a right hyperphoria. The difference between the Maddox Rod/Wing tests and the cover tests may be explained by the different positions of gaze with the different tests. Her ocular motility showed a normal range of eye movements: in particular, no superior oblique palsy was apparent on motility testing and no cyclo-deviation was reported on the Maddox wing test. LH had near horizontal fusional reserves, convergence facility and range and amplitudes of accommodation all within normal limits (Evans 2002; 2005). For the study, LH compared two different spectacle corrections, both with varifocal lenses that were of identical design and alignment. The control intervention included the same refractive correction as in the patient's existing spectacles, which was similar to that found in the subjective refraction during the research. The active intervention had the same refractive correction but incorporating the prism indicated by the Mallett Fixation Disparity Test (see Discussion). The goal with this case was therefore to investigate whether correction of the hyperphoria with prism in varifocal spectacles had a significant effect on the migraine headaches. Figure 26 describes the migraine events and shows the headache variables during the study for LH.

From the questionnaire, the score ranked from 0 to 70 of how much each intervention was used by LH was not significantly different ($p=0.94$, Wilcoxon signed rank test). The telephone questionnaire showed that both spectacles were used for 7 days a week during the intervention periods and, ranked on a scale of 0 to 7,the use was again not significantly different ($p=1.0$, Wilcoxon signed rank test). From the descriptive statistics of headache free days it is clear that the active intervention spectacles were not having a therapeutic effect on the frequency of migraines. The median palliation score was always 3 (IQR 0) during the baseline period, the period with the active intervention and the period with the control intervention. It is therefore also clear from these descriptive statistics that the medication use did not confound the headache diary results.

There was no statistically significant difference on pain rating (Mann Whitney U test; $p=0.08$) or in aura score (Mann Whitney U- test; $p=0.12$) between the active intervention and the control intervention. Subject LH chose to keep the active intervention spectacles and indicated that these spectacles improved her migraine headaches

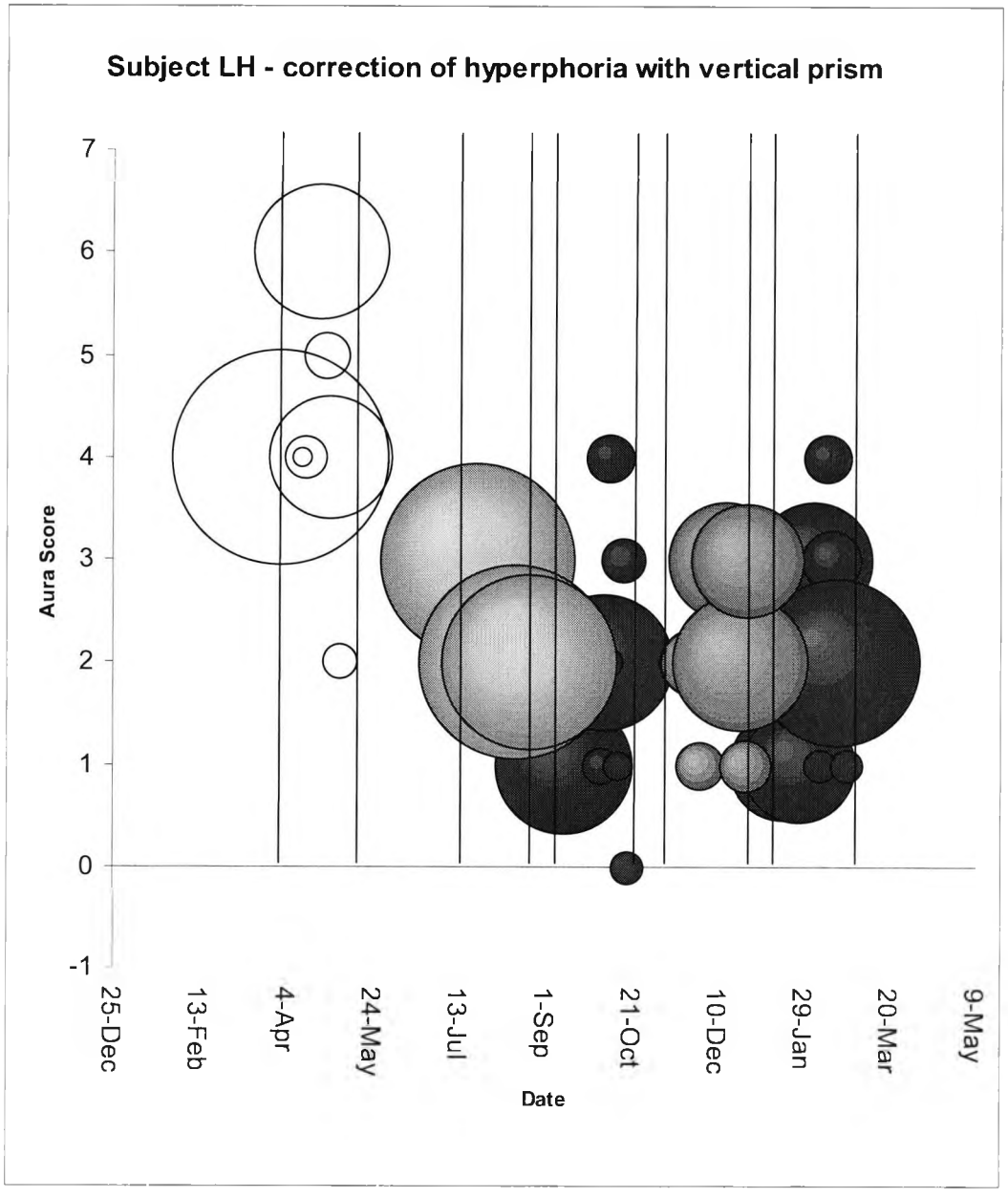
Table 16

Relevant Optometric Results. Normality of binocular vision tests were based on Evans 2002 and normality of pattern glare tests on Wilkins and Evans 2001. Visual acuities were measured on a Bailey-Lovie LogMAR chart and converted to Snellen equivalents. Palliation, Pain and Aura scores are given as the median with the inter-quartile range in parenthesis.

Initials	LH		
Age	44		
Gender	FEMALE		
Binocular Vision tests			
Cover Test at 6m	1^{Δ} Right Hyperphoria		
Cover Test at near	5^{Δ} Right Hyperphoria		
Maddox Rod at 6m	2^{Δ} Right Hyperphoria		
Maddox Wing	1^{Δ} Right Hyperphoria		
Aligning prism at 6m	2^{Δ} base up aligning prism to the left eye		
Aligning prism at near	2^{Δ} base up aligning prism to the left eye		
Fusional Reserves	Normal		
Convergence	Normal		
Accommodation	Normal		
Pattern Glare and Visual Stress tests			
Coloured filter selected	Pink		
Pattern glare	None		
Rate of reading with coloured filter	137 words per minute		
Rate of reading without coloured filter	142 words per minute		
Refractive tests			
Refraction Right Eye	+0.25 / -0.50 x 175		Add +1.75
Refraction Left Eye	+0.50 / -0.75 x 180		Add +1.75
Visual Acuity Right Eye	6/6 N5		
Visual Acuity Left Eye	6/6 N5		
Intervention	Baseline Refraction as above	Active Refraction as aboveplus 2^{Δ} Base Up in the left eye	Control Refraction was above
Results			
Questionnaire Intervention Use	N/A	60 (IQR 2)	61 (IQR 3)
Telephone Survey Intervention Use	N/A	3 (IQR 1)	4 (IQR 0)
Migraine Headache Free Days	34/42 (83%)	61/84 (73%)	65/84 (77%)
Palliation Score	3 (IQR 0)	3 (IQR 0)	3 (IQR 0)
Pain Rating Score During Migraine Headaches	18 (IQR 120)	18 (IQR 85)	24 (IQR 84)
Aura Score During Migraine Headaches	4 (IQR 0.5)	2 (IQR 1)	2 (IQR 1)

Figure 26

Figure 26 describes the migraine events and shows the headache variables during the study for LH. Each bubble represents a migraine event. White bubbles are those migraine events during the baseline period, black bubbles during the period with the control spectacles and grey bubbles during the period with the intervention spectacles. The larger the bubble the greater the pain factor (a product of pain rating and length of pain). The higher the bubble the greater the number of aura symptoms were experienced. Vertical lines delineate the six-week periods during which interventions were used.



Subject ID: Esophoria intervention

Subject ID is male and was aged 45 at the start of the trial. ID was a computer consultant, used a computer for many hours a day and used spectacles constantly. He had no history of orthoptic or ophthalmological treatment but had noticed that he sometimes experienced sore and tired eyes. ID had no other visual symptoms, was fit and well and took no medication other than that for migraine. Optometric examination results are in Table 17.

ID had a divergence weakness esophoria. His horizontal fusional reserves were BO 32 /-/- [suggesting that he suppressed to avoid a diplopia point] BI 8/12/4 at distance and BO 32/-/- BI 24/28/24 at near, his convergence facility and range and amplitudes of accommodation were all within normal limits (Evans 2002; 2005). For the study, ID compared two different spectacle corrections both with single vision lenses that were of identical design. The goal in this case was to assess if correcting the esophoria aligning prism had a significant effect on the migraine headaches. Figure 27 describes the migraine events and shows the headache variables during the study for ID.

From the questionnaire, the score ranked from 0 to 70 of how much each intervention was used was not significantly different ($p=0.84$, Wilcoxon signed rank test) and from the descriptive statistics in Table 17 it is clear that the active intervention spectacles were not having a therapeutic effect on the frequency of migraines. The median palliation score was always 3.0 during all periods and so did not confound the headache diary results.

The pain rating with the active intervention was significantly less than that during the control intervention (Mann Whitney U test; $p=0.01$). A post-hoc analysis was undertaken to establish which component of the pain rating (the product of the grade of severity and the length of pain) was affected. The severity of the pain was significantly less with the active intervention than during the control intervention periods (Mann Whitney U test; $p<0.001$) but the duration of the pain was no different (Mann Whitney U test; $p=0.14$).

The median aura score was 0 (IQR 0) during the baseline period, the periods with the active spectacles and during the periods with the control spectacles. The aura score with the active intervention was not significantly different to that with the control intervention (Mann Whitney U test; $p=0.08$). Subject ID chose to keep the active intervention and indicated that these spectacles improved his migraine headaches.

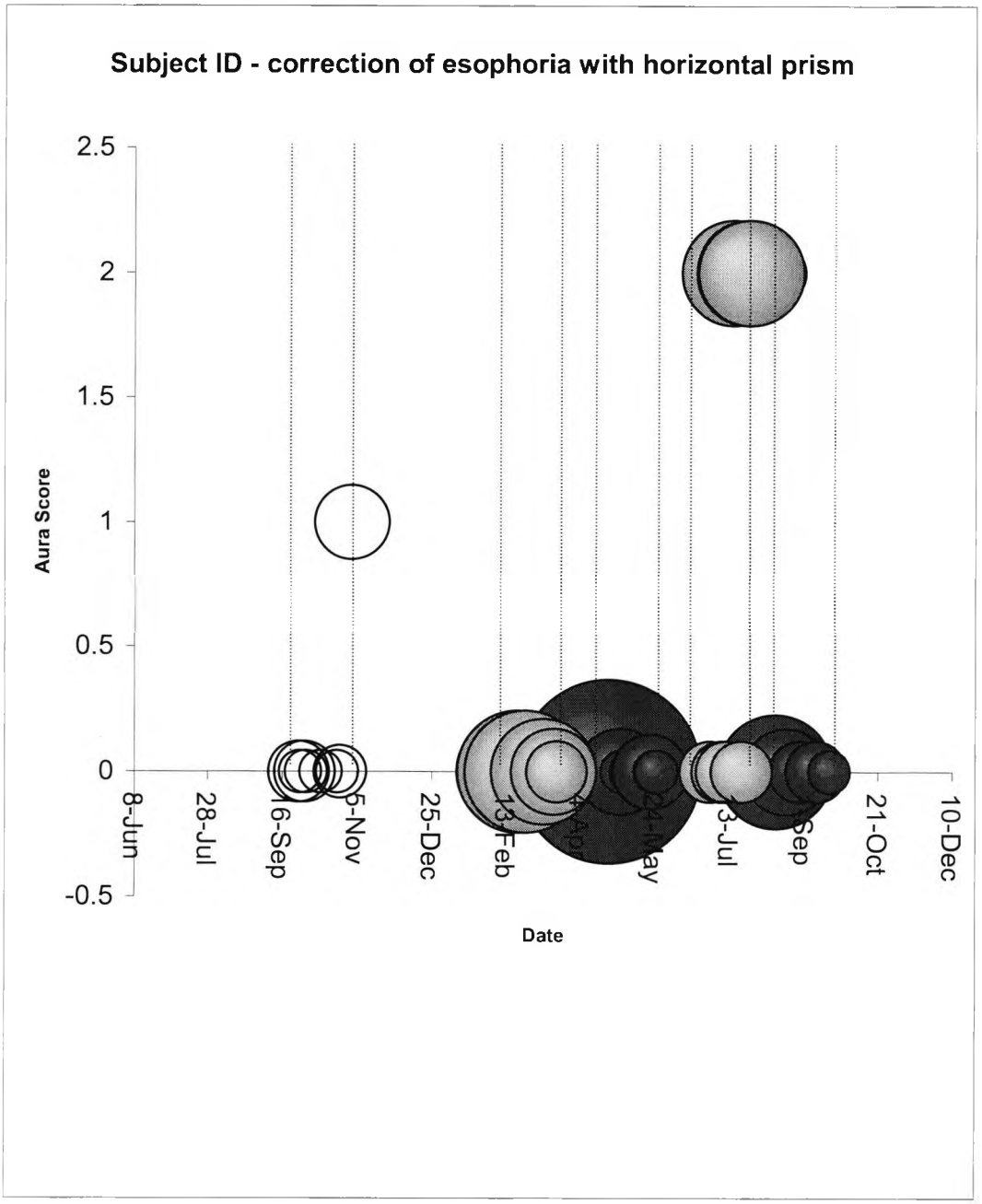
Table 17

Relevant Optometric Results. Normality of binocular vision tests were based on Evans 2002 and normality of pattern glare tests on Wilkins and Evans 2001. Visual acuities were measured on a Bailey-Lovie LogMAR chart and converted to Snellen equivalents. Palliation, Pain and Aura scores are given as the median with the inter-quartile range in parenthesis.

Initials	ID		
Age	45		
Gender	MALE		
Binocular Vision tests			
Cover Test at 6m	5^{Δ} Esophoria		
Cover Test at near	2^{Δ} Esophoria		
Maddox Rod at 6m	5^{Δ} Esophoria		
Maddox Wing	2^{Δ} Esophoria		
Aligning prism at 6m	2^{Δ} base out aligning prism to the left eye		
Aligning prism at near	2^{Δ} base out aligning prism to the left eye		
Fusional Reserves	suppressed to avoid a diplopia point?		
Convergence	Normal		
Accommodation	Normal		
Pattern Glare and Visual Stress tests			
Coloured filter selected	Blue		
Pattern glare	None		
Rate of reading with coloured filter	182 words per minute		
Rate of reading without coloured filter	189 words per minute		
Refractive tests			
Refraction Right Eye	-5.00 / -0.25 x 75		
Refraction Left Eye	-5.00 / -0.25 x 50		
Visual Acuity Right Eye	6/5		
Visual Acuity Left Eye	6/5		
Intervention	Baseline Refraction as above	Active Refraction as above plus 2^{Δ} Base Out in the left eye	Control Refraction as above
Results			
Questionnaire Intervention Use	N/A	67 (IQR 1)	67 (IQR 2)
Migraine Headache Free Days	34/42 (81%)	60/84 (71%)	60/84 (71%)
Palliation Score	3 (IQR 0)	3 (IQR 0)	3 (IQR 0)
Pain Rating Score During Migraine Headaches	1 (IQR 1)	1 (IQR 1)	2 (IQR 4)
Aura Score During Migraine Headaches	0 (IQR 0)	0 (IQR 0)	0 (IQR 0)

Figure 27

Figure 27 describes the migraine events and shows the headache variables during the study for ID. Each bubble represents a migraine event. White bubbles are those migraine events during the baseline period, black bubbles during the period with the control spectacles and grey bubbles during the period with the intervention spectacles. The larger the bubble the greater the pain factor (a product of pain rating and length of pain). The higher the bubble the greater the number of aura symptoms were experienced. Vertical lines delineate the six-week periods during which interventions were used.



Subject KG: Exophoria Intervention

Subject KG is female and was aged 39 at the start of the trial. KG was a housewife and used spectacles for distance and near visual tasks but had noticed a slight blur at distance and sore tired eyes when reading. When reading she often rubbed her eyes, confused letters or words, skipped lines of print and read slowly. KG had no history of orthoptic or ophthalmological treatment, had no other visual symptoms, was fit and well and took no medication other than for migraine. Optometric examination results are in Table 18.

KG had a decompensated exophoria and for this study, KG compared two different spectacle corrections both with single vision lenses that were of identical design. The goal in this case was to assess if correcting the exophoria aligning prism had a significant effect on the migraine headaches. Figure 28 describes the migraine events and shows the headache variables during the study for KG. From the questionnaire, the score ranked from 0 to 70 of how much each intervention was used was not significantly different ($p=0.94$, Wilcoxon signed rank test) but the proportion of migraine headache free diary days for KG did show a slight improvement with the active intervention. This data for the active and control interventions was entered in a 2x2 table so that the relative risk of having a headache free day could be compared with the two interventions. There was a 1.1 times greater risk of having a headache free day with the active than with the control intervention, but the 95% confidence limits of this relative risk (0.86 to 1.41) include 1.0, indicating that the small change in relative risk with the active intervention was not statistically significant.

The median palliation score during headache events was 1 (IQR 0.5) during the baseline period, 1 (IQR 0) during the periods with the intervention spectacles and 2 (IQR 1) during the periods with the control spectacles. These results were again significantly different (Mann Whitney U test; $p<0.01$) and showed that there was a greater medication use during the periods when the control spectacles were used. A review of the results showed that KG used non-codeine containing analgesic medication only. During the periods with the control spectacles she took a primary analgesic during 33 headache events and a second additional analgesic during 14 events but during the periods with the intervention spectacles she took a primary analgesic during 30 headache events and an additional second analgesic during just 4 events. Neither the pain rating, (Mann Whitney U test; $p=0.35$) nor the aura score (Mann Whitney U- test; $p=0.36$) were significantly different with the active intervention compared to the control but subject KG chose to keep the active intervention spectacles and indicated that these spectacles improved her migraine headaches.

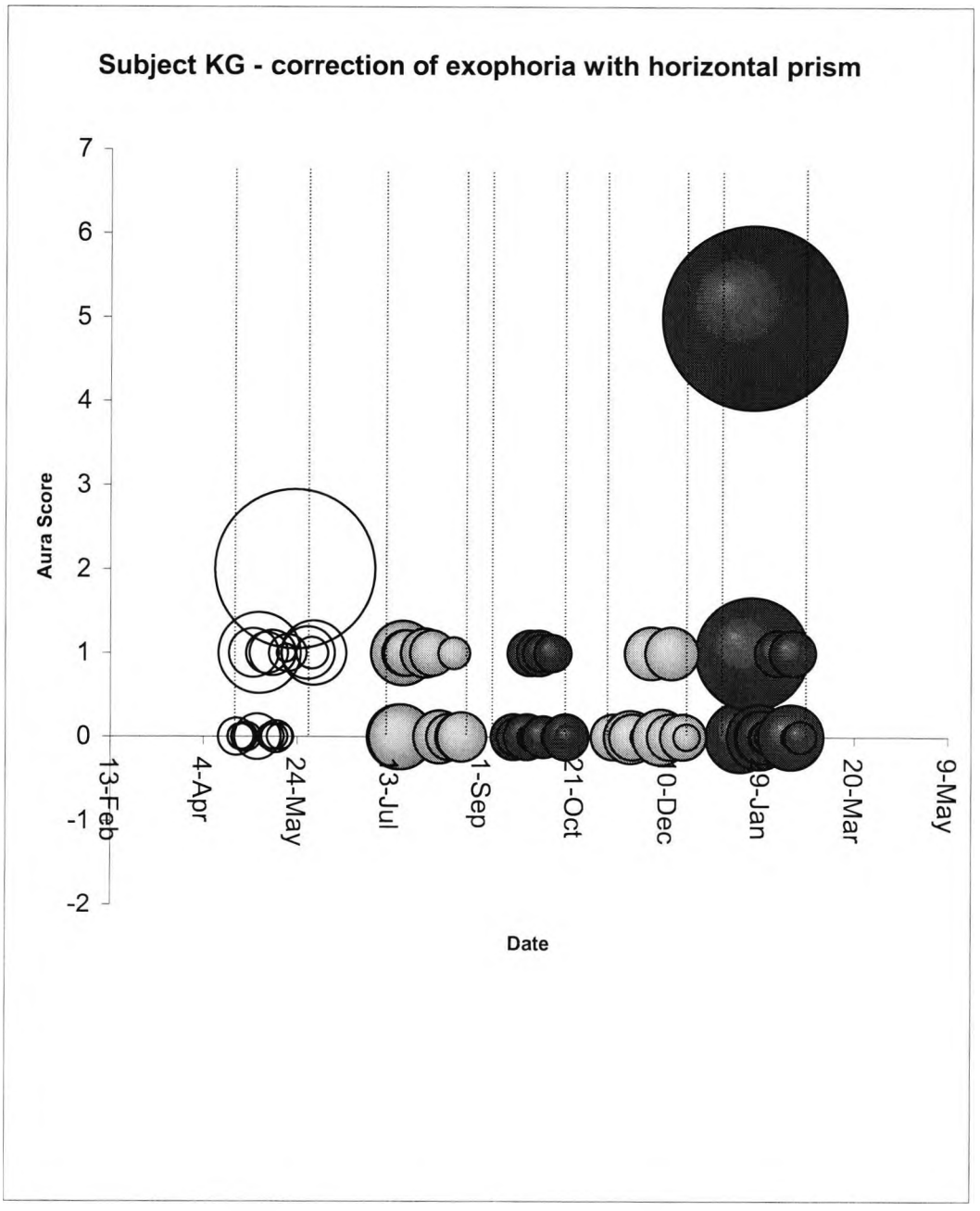
Table 18

Relevant Optometric Results. Normality of binocular vision tests were based on Evans 2002 and normality of pattern glare tests on Wilkins and Evans 2001. Visual acuities were measured on a Bailey-Lovie LogMAR chart and converted to Snellen equivalents. Palliation, Pain and Aura scores are given as the median with the inter-quartile range in parenthesis.

Initials	KG		
Age	39		
Gender	FEMALE		
Binocular Vision tests			
Cover Test at 6m	2^{Δ} Exophoria		
Cover Test at near	3^{Δ} Exophoria		
Maddox Rod at 6m	2^{Δ} Exophoria		
Maddox Wing	3^{Δ} Exophoria		
Aligning prism at 6m	2^{Δ} base in aligning prism to the right eye		
Aligning prism at near	2^{Δ} base in aligning prism to the right eye		
Fusional Reserves	Normal		
Convergence	Normal		
Accommodation	Normal		
Pattern Glare and Visual Stress tests			
Coloured filter selected	Mint Green		
Pattern glare	None		
Rate of reading with coloured filter	142 words per minute		
Rate of reading without coloured filter	144 words per minute		
Refractive tests			
Refraction Right Eye	+0.25 / -1.75 x 165		
Refraction Left Eye	-0.25 / -1.50 x 45		
Visual Acuity Right Eye	6/6		
Visual Acuity Left Eye	6/6		
	Baseline	Active	Control
Intervention	Refraction as above	Refraction as above plus 2^{Δ} Base In in the right eye	Refraction as above
Results			
Questionnaire Intervention Use	N/A	54 (IQR 52)	55 (IQR 63)
Telephone Survey Intervention Use	N/A	2 (IQR 2)	3 (IQR 2)
Migraine Headache Free Days	23/42 (55%)	53/84 (63%)	48/84 (57%)
Palliation Score	1 (IQR 0.5)	1 (IQR 0)	2 (IQR 1)
Pain Rating Score During Migraine Headaches	8 (IQR 9)	12 (IQR 10)	12 (IQR 18)
Aura Score During Migraine Headaches	1 (IQR 1)	0 (IQR 1)	0 (IQR 1)

Figure 28

Figure 28 describes the migraine events and shows the headache variables during the study for KG. Each bubble represents a migraine event. White bubbles are those migraine events during the baseline period, black bubbles during the period with the control spectacles and grey bubbles during the period with the intervention spectacles. The larger the bubble the greater the pain factor (a product of pain rating and length of pain). The higher the bubble the greater the number of aura symptoms were experienced. Vertical lines delineate the six-week periods during which interventions were used.



Subject LP: Refractive Constant use Precision Tinted Lens intervention

Subject LP is female and was aged 32 at the start of the trial. She was a teacher, and wore spectacles for constant use. She had no history of orthoptic or ophthalmological treatment but had noticed that her distance vision sometimes blurred and stated that she was light sensitive. She had no other visual symptoms, was fit and well and took no medication other than that for migraine. Optometric examination results are in the Table 19.

Examination showed that she was orthoptically normal and did not have a significant (O'Leary and Evans 2003) change in refractive error but did have visual stress as measured by the Pattern Glare Test (Evans and Wilkins 2001) and although she had a similar reading performance (Wilkins et al 1996) when reading using her chosen overlay (Wilkins 1994) colour she said it was subjectively much easier. Because of this response a colorimetry assessment was undertaken. Without colour LP reported that the target wobbled, shimmered and faded in and out. With her chosen colour these symptoms were relieved.

For the study LP compared two different spectacle corrections both with single vision lenses that were of identical design. The control intervention contained her current refractive correction with a control precision tint (Wilkins 2005) and the active intervention her current refractive correction containing a true precision tint. This was used to assess if using a true precision tint had a significant effect on migraine headaches over a control tint. Figure 29 describes the migraine events and shows the headache variables during the study for LP.

From the questionnaire, the score ranked from 0 to 70 of how much each intervention was used was significantly different ($p=0.04$, Wilcoxon signed rank test) for the control intervention compared to the active intervention. This suggested that the active intervention was used more often, however the telephone questionnaire showed that both spectacles were used for 7 days a week during the intervention periods and the use was this time not significantly different ($p=0.44$, Wilcoxon signed rank test). This perhaps suggests that this subject "remembered" a greater use with the active intervention spectacles as recorded with the end of experiment questionnaire than was actually reported at the time with the telephone survey.

The proportion of migraine headache free diary days for LP were very similar for both the baseline, control and active periods making it clear that the active spectacles were not having a therapeutic effect on the frequency of migraines. The median palliation score

was not different (Mann Whitney U test; p=0.70) during each period and so did not confound the headache diary results.

The median pain rating score (Mann Whitney U test; p=0.70) and aura score (Mann Whitney U test; p=1.0) were not different with the active intervention to that with the control intervention but Subject LP chose to keep the active intervention spectacles and indicated that these spectacles improved her migraine headaches.

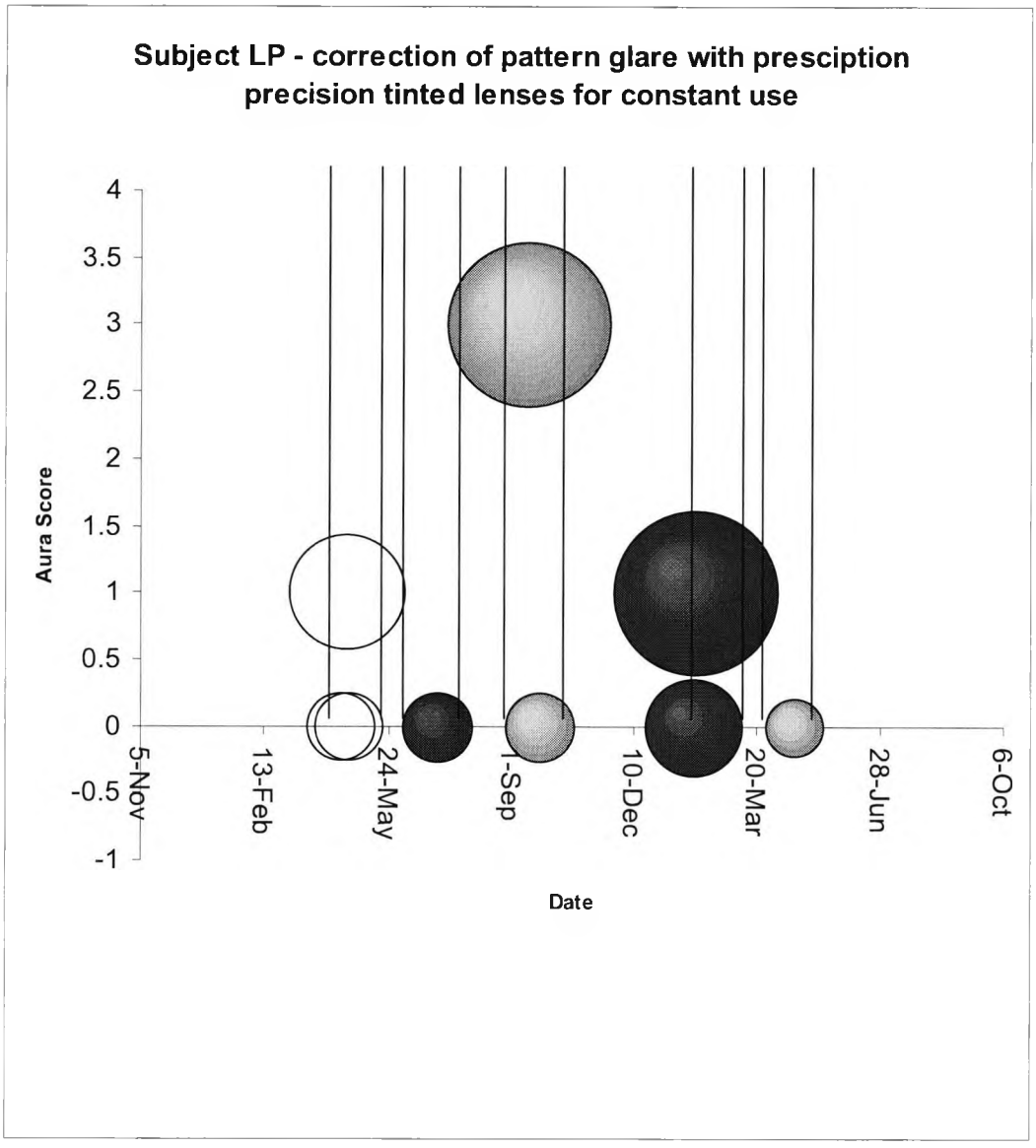
Table 19

Relevant Optometric Results. Normality of binocular vision tests were based on Evans 2002 and normality of pattern glare tests on Wilkins and Evans 2001. Visual acuities were measured on a Bailey-Lovie LogMAR chart and converted to Snellen equivalents. Palliation, Pain and Aura scores are given as the median with the inter-quartile range in parenthesis.

Initials	LP		
Age	32		
Gender	FEMALE		
Binocular Vision tests			
Ocular Motor Balance at 6m	Orthophoria		
Ocular Motor Balance at near	5^{Δ} Exophoria		
Aligning prism at 6m	None		
Aligning prism at near	None		
Fusional Reserves	Normal		
Convergence	Normal		
Accommodation	Normal		
Pattern Glare and Visual Stress tests			
Coloured filter selected	Purple		
Pattern glare	Yes		
Rate of reading with coloured filter	172 words per minute		
Rate of reading without coloured filter	170 words per minute		
Colorimetry preference	Rose C4+B5; Orange D2+A5		
Refractive tests			
Refraction Right Eye	-3.50 / -0.75 x 165		
Refraction Left Eye	-3.25 / -0.75 x 14		
Visual Acuity Right Eye	6/6		
Visual Acuity Left Eye	6/6		
	Baseline	Active	Control
Intervention	Refraction as above	Refraction as above plus Rose C4+B5; Orange D2+A5	Refraction as above tinted as Purple A6+B5+C4+D3; Rose B5
Results			
Questionnaire Intervention Use	N/A	53 (IQR 17)	48 (IQR 22)
Telephone Survey Intervention Use	N/A	3 (IQR 1)	4 (IQR 0)
Migraine Headache Free Days	39/42 (93%)	81/84 (96%)	81/84 (96%)
Palliation Score	2 (IQR 1)	1 (IQR 0.5)	2 (IQR 0.5)
Pain Rating Score During Migraine Headaches	4 (IQR 4)	4 (IQR 11)	8 (IQR 10)
Aura Score During Migraine Headaches	0 (IQR 0.5)	0 (IQR 1.5)	0 (IQR 0.5)

Figure 29

Figure 29 describes the migraine events and shows the headache variables during the study for LP. Each bubble represents a migraine event. White bubbles are those migraine events during the baseline period, black bubbles during the period with the control spectacles and grey bubbles during the period with the intervention spectacles. The larger the bubble the greater the pain factor (a product of pain rating and length of pain). The higher the bubble the greater the number of aura symptoms were experienced. Vertical lines delineate the six-week periods during which interventions were used.



Subject KB: Plano Constant use Precision Tinted Lens intervention

Subject KB is female and was aged 35 at the start of the trial. KB was a sign manufacturer and bookkeeper, and although she had been prescribed spectacles in the past she did not use them. She had no history of orthoptic treatment but had a cyst surgically removed from her eyelid in the past. She noticed that she rubbed her eyes frequently, used her finger as a marker when reading, read slowly, tired easily and was light sensitive, stating that she always has to use sunglasses when outside. She had no other visual symptoms, was fit and well and took no medication other than that for migraine. Optometric examination results are in the Table 20.

Examination showed that she was orthoptically normal and did not have a significant (O'Leary and Evans 2003) refractive error. KB did have visual stress as measured by the Pattern Glare Test (Evans and Wilkins 2001) and had a 10% faster reading performance (Wilkins et al 1996) when reading using her chosen overlay (Wilkins 1994) colour (Blue chosen). Because of these findings an assessment with the Intuitive Colorimeter (Wilkins & Sihra, 2000) was undertaken. Without the colour KB reported that the target was blurred. With her chosen colour these symptoms were relieved.

For the study KB compared two different spectacles corrections both with plano lenses that were of identical design. The control intervention contained plano lenses with a control precision tint and the active intervention plano lenses containing the true precision tint. This was used to assess if using a true precision tint had a significant effect on migraine headaches over a control tint. Figure 30 describes the migraine events and shows the headache variables during the study for KB.

From the questionnaire, the score ranked from 0 to 70 of how much each intervention was used was not significantly different ($p=0.69$, Wilcoxon signed rank test) for the control intervention or the active intervention. The headache variables were not different with either intervention (pain rating (Mann Whitney U test; $p=0.12$); aura rating (Mann Whitney U test; $p=1.0$)) and the palliation ratings were also similar (Mann Whitney U test; $p=0.84$) and so did not confound the results.

Subject KB chose to keep the active intervention spectacles and indicated that these spectacles improved her migraine headaches.

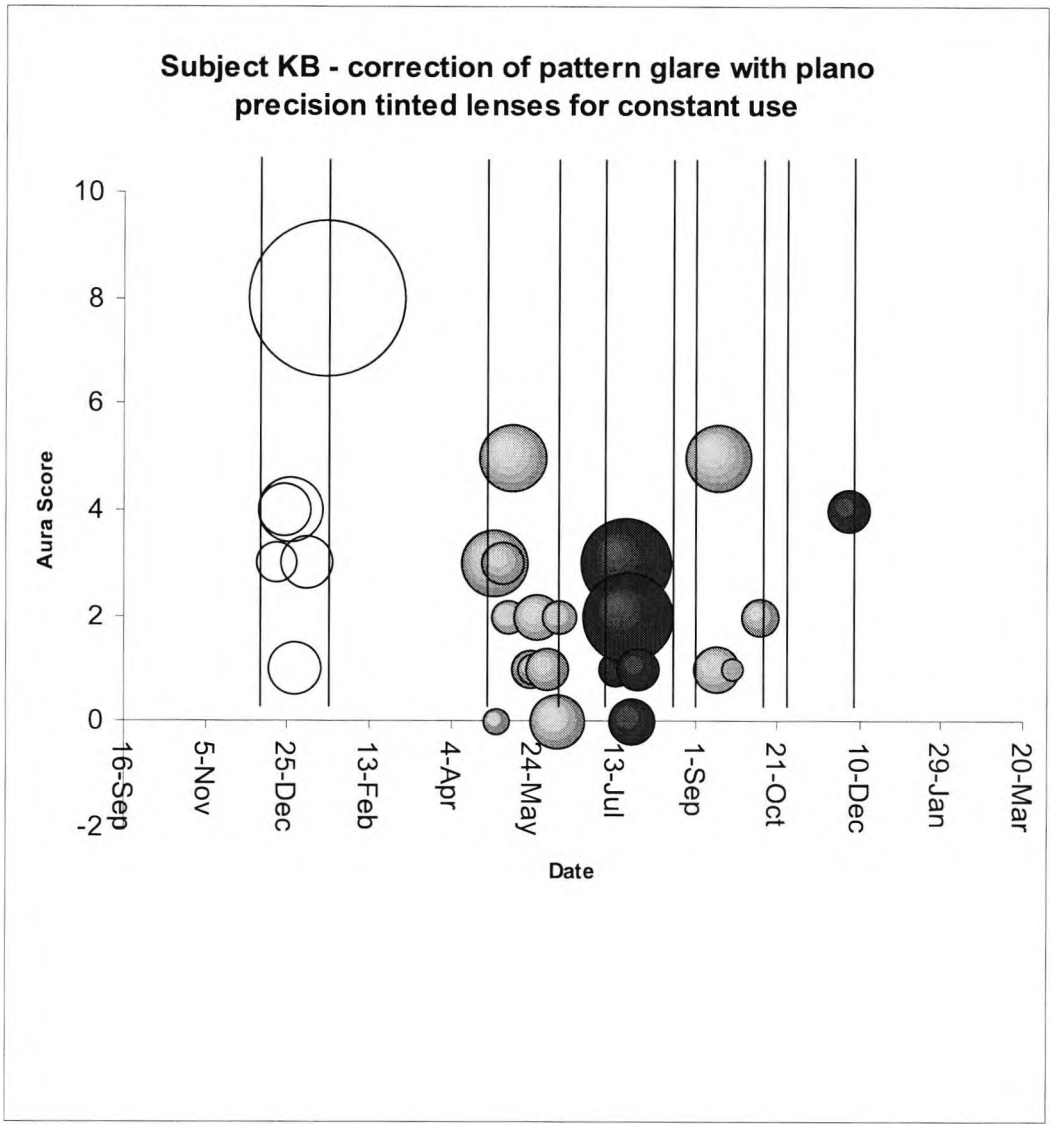
Table 20

Relevant Optometric Results. Normality of binocular vision tests were based on Evans 2002 and normality of pattern glare tests on Wilkins and Evans 2001. Visual acuities were measured on a Bailey-Lovie LogMAR chart and converted to Snellen equivalents. Palliation, Pain and Aura scores are given as the median with the inter-quartile range in parenthesis.

Initials	KB		
Age	35		
Gender	FEMALE		
Binocular Vision tests			
Ocular Motor Balance at 6m	Orthophoria		
Ocular Motor Balance at near	Orthophoria		
Aligning prism at 6m	None		
Aligning prism at near	None		
Fusional Reserves	Normal		
Convergence	Normal		
Accommodation	Normal		
Pattern Glare and Visual Stress tests			
Coloured filter selected	Blue		
Pattern glare	Yes		
Rate of reading with coloured filter	136 words per minute		
Rate of reading without coloured filter	123 words per minute		
Colorimetry preference	Turquoise E1+C3		
Refractive tests			
Refraction Right Eye	plano		
Refraction Left Eye	plano		
Visual Acuity Right Eye	6/6		
Visual Acuity Left Eye	6/6		
	Baseline	Active	Control
Intervention	No correction	Plano lenses tinted as Turquoise E1+C3	Plano lenses tinted Yellow E1+D2+C3+B4; Green D2+C3+B4
Results			
Questionnaire Intervention Use	N/A	60 (IQR 4)	57 (IQR 13)
Migraine Headache Free Days	36/42 (86%)	69/84 (82%)	77/84 (92%)
Palliation Score	2 (IQR 0)	1 (IQR1)	1 (IQR 1)
Pain Rating Score During Migraine Headaches	24 (IQR 3)	16 (IQR 13)	20 (IQR 57)
Aura Score During Migraine Headaches	3.5 (IQR 1)	2 (IQR 2)	2 (IQR 2)

Figure 30

Figure 30 describes the migraine events and shows the headache variables during the study for KB. Each bubble represents a migraine event. White bubbles are those migraine events during the baseline period, black bubbles during the period with the control spectacles and grey bubbles during the period with the intervention spectacles. The larger the bubble the greater the pain factor (a product of pain rating and length of pain). The higher the bubble the greater the number of aura symptoms were experienced. Vertical lines delineate the six-week periods during which interventions were used.



Subject AR: Refractive Near vision only Precision Tinted Lens intervention

Subject AR is female and was aged 49 at the start of the trial. AR was a care homes manager, used a computer for a few hours a day used spectacles for near vision. She had no history of orthoptic or ophthalmological treatment but had noticed that words in a book sometimes go blurred and that she experienced sore and tired eyes. She had no other visual symptoms, was fit and well and took no medication other than that for migraine. Optometric examination results are in Table 21.

Examination showed that AR was orthoptically normal (Evans 2002; 2005) and did not have a significant (O'Leary and Evans 2003) change in refractive error. AR did have visual stress as measured by the Pattern Glare Test (Evans and Wilkins 2001) and read 12% faster (Wilkins et al 1996) with her chosen overlay (Wilkins 1994). Because of these results a colorimetry assessment was undertaken.

As AR was only symptomatic at near, she compared two different spectacles for use only when reading, both with single vision lenses that were of identical design. The control intervention contained her current near vision refraction with a control precision tint and the active intervention her current near vision refraction containing a true precision tint. This was used to assess if using a true precision tint had a significant effect on migraine headaches over a control tint when used for near vision only. Figure 31 describes the migraine events and shows the headache variables during the study for AR.

From the questionnaire, the score ranked from 0 to 70 of how much each intervention was used was not significantly different ($p=0.11$, Wilcoxon signed rank test) and the telephone questionnaire showed that both spectacles were used for 7 days a week during both intervention periods and the same task time ($p=1.0$, Wilcoxon signed rank test).

The proportion of migraine headache free diary days for AR was similar for both intervention periods and the baseline period during which time the median palliation score were not significantly different (Mann Whitney U test; $p=0.09$) and so did not confound the headache diary results. The median pain rating score (Mann Whitney U test; $p=0.94$) and aura scores (Mann Whitney U test; $p=0.59$) were also not different with the active compared to the control spectacles.

Subject AR chose to keep the active intervention spectacles and indicated that these spectacles improved her migraine headaches.

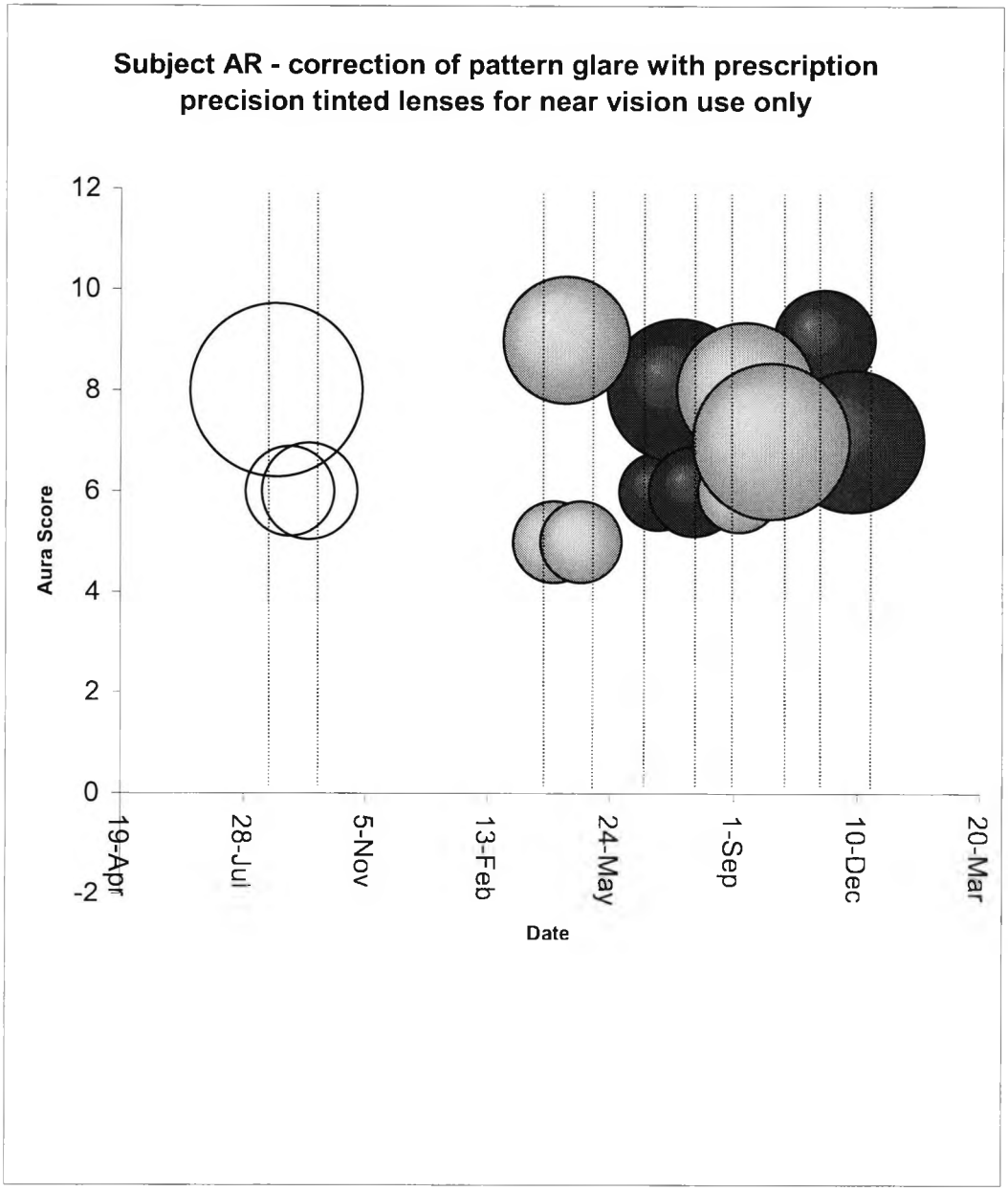
Table 21

Relevant Optometric Results. Normality of binocular vision tests were based on Evans 2002 and normality of pattern glare tests on Wilkins and Evans 2001. Visual acuities were measured on a Bailey-Lovie LogMAR chart and converted to Snellen equivalents. Palliation, Pain and Aura scores are given as the median with the inter-quartile range in parenthesis.

Initials	AR		
Age	49		
Gender	FEMALE		
Binocular Vision tests			
Ocular Motor Balance at 6m	1^{Δ} Exophoria		
Ocular Motor Balance at near	8^{Δ} Exophoria		
Aligning prism at 6m	None		
Aligning prism at near	None		
Fusional Reserves	Normal		
Convergence	Normal		
Accommodation	Normal		
Pattern Glare and Visual Stress tests			
Coloured filter selected	Mint Green		
Pattern glare	Yes		
Rate of reading with coloured filter	146 words per minute		
Rate of reading without coloured filter	130 words per minute		
Colorimetry preference	Purple D3; Blue D2		
Refractive tests			
Near Refraction Right Eye	+2.00 / -0.25 x 105		
Near Refraction Left Eye	+1.75 DS		
Visual Acuity Right Eye	N5		
Visual Acuity Left Eye	N5		
	Baseline	Active	Control
Intervention	Near refraction as above	Near refraction as above tinted as Purple D3; Blue D2	Near refraction as above tinted as Blue B4+C3; Turq D2+C3+A5
Results			
Questionnaire Intervention Use	N/A	53 (IQR 25)	35 (IQR 47)
Telephone Survey Intervention Use	N/A	3 (IQR 4)	3 (IQR 4)
Migraine Headache Free Days	36/42 (86%)	78/84 (93%)	80/84 (95%)
Palliation Score	3 (IQR 0.5)	3 (IQR1.5)	0.5 (IQR 1.3)
Pain Rating Score During Migraine Headaches	84 (IQR 98)	102 (IQR 89)	81 (IQR 50)
Aura Score During Migraine Headaches	1 (IQR 0)	7 (IQR 2)	7 (IQR 1)

Figure 31

Figure 31 describes the migraine events and shows the headache variables during the study for AR. Each bubble represents a migraine event. White bubbles are those migraine events during the baseline period, black bubbles during the period with the control spectacles and grey bubbles during the period with the intervention spectacles. The larger the bubble the greater the pain factor (a product of pain rating and length of pain). The higher the bubble the greater the number of aura symptoms were experienced. Vertical lines delineate the six-week periods during which interventions were used.



9.4 Discussion

As discussed in the previous chapters, there is evidence (Drummond 1987; Drummond 1990; De Marinis, 1994; De Marinis et al. 1998; McKendrick et al 1998; McKendrick et al, 2000; McKendrick et al, 2002; Evans et al, 2002; Wilkins et al 2002; McKendrick and Badcock, 2003; Shepherd 2005; Tan et al 2005; Harle et al, 2005; Harle and Evans, 2005; Yenice et al 2005; Yucel et al, 2005; Harle and Evans 2006a,c; Harle et al, 2006) that some optometric findings are correlated with migraine headache, but correlative evidence is not necessarily evidence of causation. Optometric interventions aimed at alleviating migraine have been suggested in both the historical and modern literature (Chapter 1, published as Harle and Evans, 2004). In most cases the suggestion that optometric findings are correlated with migraine headache have been the basis on which an intervention has been suggested, yet evidence of optometric factors causing migraine or of an optometric intervention alleviating migraine have been lacking (Chronicle and Mulleners 1996). To the author's knowledge the research described here is the first evaluation of a variety of optometric interventions on the frequency and severity of migraine headaches.

This chapter describes a collection of randomized controlled single subject trials with multiple crossovers. This is a valid research study design that can provide a valuable insight into individualised treatment approaches (Backman and Harris, 1999; Johannessen et al., 1991; Elder, 1997; Zhan, 2001; Janosky, 2005). The results of these seven cases cannot be taken as a single experimental group finding, but do clearly describe the effect of each intervention on an individual. If a clear benefit in migraine symptoms from an optometric intervention was demonstrated in a single subject trial, then this would support the case for larger group randomised controlled trials.

Refractive correlates of migraine have been suggested historically (Snell 1904; Gould 1904; Turville 1934), refuted (Chronicle and Mulleners 1996), and recently supported (Chapter 4 published as Harle and Evans 2006a). This most recent finding is that people with migraine have, on average, a small but significantly different degree of astigmatism in both the C_0 and C_{45} components (Chapter 4 published as Harle and Evans 2006a) compared to people without migraine. Subject SG had a current refractive error of: R -0.50 / -2.50 x 15; L +0.75 / -3.50 x 178 and a new refractive error of: R -0.75 / -2.50 x 7; L +0.75 / -4.75 x 175. Using the same astigmatic decompensation calculations as in the literature (Harle and Evans 2006a) the C_0 and C_{45} of the current (C_0; 2.83, C_{45}; 0.75) and new refractive errors (C_0; 3.67, C_{45}; 0.75) can be calculated for subject SG and the difference (C_0; 0.84, C_{45} 0.00) shown to be greater in the C_0 component than that suggested to be significant in that paper. This suggests that SG was a good candidate to

investigate refractive error, being an astigmat whose astigmatism could be further corrected by a degree considered significant in the literature. This ideal candidate showed no benefit to her migraine headaches when this astigmatism was corrected.

Tinted spectacles have also been suggested as a relief for migraine and people with migraine in general, do tend to use tinted spectacles more than those without migraine (Mulleners et al 2001). Recently, precision tinted spectacles have been prescribed for people with migraine (Wilkins 2002) using a system of individualised precision tinting (Wilkins at al 1992). The participants in that research had all indicated a benefit for coloured filters by first using coloured overlays, and it is not known what proportion of people with migraine this is likely to be. Whilst the theoretical benefit of precision tinted spectacles has been assigned to a reduction in cortical hyperexcitability in migraine (Wilkins 1995), imaging techniques have only been used to demonstrate this in one individual so far (Wilkins et al., 2003). Cortical hyperexcitability is believed to be linked to a positive response at the pattern glare test (Evans and Wilkins, 2001), which indicates increased susceptibility to illusions when viewing square wave gratings of 3 cycles per degree compared to gratings of 12 cycles per degree. In each case LP, KP and AR all had a positive response to the pattern glare test. Additionally they reported a benefit to colour using simple coloured filters (Wilkins 1994), albeit in a more short-term test than that used in previous research (Wilkins et al 2002). Nevertheless, no benefit to the migraine variables was recorded in any of these three individuals. It should be noted that for these cases the control intervention was unlikely to be an inert control, since the colour of the control filter was chosen to be similar to that of the active intervention. In other words, the control intervention was likely to be less active than the active intervention, not inactive. This was necessary to ensure a double-masked design, but may have reduced the chance of finding a significant benefit from the active intervention relative to the control. It should also be acknowledged that, in the research of Wilkins et al. (2002), not all participants benefited from precision tinted lenses.

Subtle binocular vision anomalies may also be correlates of migraine, both according to historical reports (Snell 1904; Turville 1934; Wilmut 1951; 1956) and recent experimental data (Chapter 5 published as Harle and Evans 2006c). This is described in chapter 5 where subtle deficits in binocular co-ordination that slightly increase the risk of decompensated heterophoria, and reduce stereopsis, were found to be more common in a group of people with migraine compared to a group that were free of head pain. Both horizontal (Turville 1934; Wilmut 1951,1956; Evans et al 2002) and vertical (Waters 1970) orthoptic anomalies have been suggested to be associated with migraine. Subjects LH, ID and KG represent hyperphoric, esophoric, and exophoric corrections respectively. The Mallett Fixation Disparity Test results were key in the diagnosis of decompensated

heterophoria in these three cases since this test has been shown, relative to other orthoptic tests, to be a good predictor of symptomatic heterophoria (Yekta and Pickwell, 1986; Yekta et al., 1989; Jenkins et al., 1989; Pickwell et al., 1991). The precise instructions were used, which have been shown to best predict symptoms (Karania and Evans, 2006). A small randomised controlled trial supported the use of prisms prescribed with the Mallett Fixation Disparity Test (Payne et al., 1974), indicating that the test may be a more useful prescribing tool than Sheard's criterion (Sheard, 1931), which fared less well in a recent randomized controlled trial of prisms to treat convergence weakness exophoria (Scheiman et al 2005) Subject ID had significantly less pain at headache events during periods when using intervention spectacles containing prism to control his esophoria compared to periods when using a control intervention. Subject KG had no change to her headache variables when using intervention spectacles containing prism to control her exophoria compared to periods when using a control intervention but needed to use significantly less analgesic medication during the intervention periods to maintain the same pain rating. This is some evidence to suggest that prism spectacles prescribed with the Mallett Fixation Disparity Test for patients with migraine and co-morbid horizontal decompensated heterophoria may improve headache factors in some individuals.

In all seven cases presented here, despite most having no migraine benefit to the measured migraine variables and with the mask fully maintained, every subject identified the true intervention spectacles over the control as the true pair of spectacles that helped their migraine headaches and the pair they would like to keep. Since the mask was kept during this choice, then either the spectacles were relieving optometric conditions that were perceived by the subjects as beneficial, or the spectacles were reliving a migraine variable that was not measured in this study. Subject LP was the only subject to record a different amount of use with each pair of spectacles; she recorded at the end of the experiment that she used the intervention precision tinted lenses pair more than the control, however the telephone survey suggested that this was not in fact the case. It might be that at the end of the experiment subject LP perceived some benefit from the active intervention spectacles over the control intervention pair.

Previous research (Wilkins 2002) has suggested that some people with migraine, selected from a group who showed benefit from coloured filters, have less headache days with precision tinted spectacles compared to non-optimum tinted spectacles. These results suggest that at least some people with migraine may feel a benefit when optometric correlates of migraine are corrected, despite having no effect on migraine variables. Perhaps, in some migraine sufferers, refractive and precision tint interventions treat the eye problems correlated with the migraine, not the migraine headaches per se,

but in some individuals with orthoptic anomalies, prism spectacles may have a subtle beneficial effect on some migraine factors.

Section 5

Ideas for Further Research and Final Summary

Chapter 10 Ideas for Further Research and Final Summary

10.1 Relationships Between Optometric Correlates of Migraine

The approach of hypothesis testing that has been used throughout this thesis means that it is possible that, in this extensive investigation of many diverse functions, an inter-relationship between two of these functions might have been missed. Although 'data trawling' is generally deprecated and has been avoided in the thesis, it was felt that it might be useful to carry out a cross-correlation between the individual results to establish any areas of interest for future research and to discover any unexpected relationships that would indicate the need for further work. To explore the relationships between the optometric correlates of migraine, multiple statistical relationship tests were conducted. The statistical relationships between the variables are shown in Table 22. This final table demonstrates that some of the optometric correlates of migraine are statistically related. Hypothetical suggestions as to why these relationships may exist are posed below. It should be noted that in these experiments the only one of these correlates that when relieved, acted on migraine variables, was decompensated binocular vision.

The presence of heterophoria by Maddox Rod testing (labelled heterophoria in Table 22) was associated with both corrected and uncorrected astigmastim. There is a refractive element to the Maddox Rod test (a Maddox Rod is, in effect, a series of high cylindrical lenses) but the author is not aware of any published previous research that has documented such a relationship in normal populations. Near heterophoria (eg Maddox Wing testing) was not statistically associated with migraine, differences between the two tests being the near proximity of the target and the need to accommodate, converge, and depress the gaze in Maddox Wing testing. However another major difference beween the tests is that in Maddox wing testing the targets are real, but in Maddox Rod testing the targets are "virtual", in otherwords the streak caused by the Maddox Rod lens requires an element of "perception". Perhaps those people with migraine associate more movement with the Maddox Rod test because of their pattern glare and susceptibility to illusions. This might explain the relationship between the presence of heterophoria found by Maddox Rod testing and pattern glare scores that are also shown in table 22.

The presence or absence of heterophoria by Maddox Rod testing was also associated with parasympathetic defects noted by pupil response latency. Maddox Rod testing involves placing the Rod lens in front of the right eye whilst viewing a light at 6m. It would

be surprising if these sub-clinical pupil response changes in migraine could influence Maddox Rod testing, but not inconceivable. Perhaps the subtle anisocoria that also exists in migraine alters inter-eye retinal luminance levels that interacts with this test.

Table 22 shows that reduced stereopsis was association with pattern glare in people with migraine. Interestingly, reduced stereopsis was also associated with the duration of worse headache. This poses an interesting hypothesis as to whether chronic migraine cause cortical damage with longer duration of headpain leading to reduced stereopsis and increased pattern glare.

Of interest, Table 22 shows that both refractive and binocular vision correlates of migraine were also associated with pattern glare when taken as the score for the 3 cpd pattern but not when scored as the difference in the number if illusions seen in the 3 cpd pattern and the 12 cpd pattern. This suggests that in people with migraine, an optical component is responsible for some of the glare illusions seen in both gratings, but that this component is removed when scoring the pattern glare as 3-12. One reason for this could be that the optical component is not dependant on the spatial frequency of the pattern, whilst the glare illusions are. This optical component may well have astigmatic factors and binocular vision factors. The data presented in this thesis might now suggest that the 3-12 score method would be the most appropriate in people with migraine when assessing pattern glare. Further research might investigate and differentiate any optical component of pattern glare from the cortical component and how these relate to visual triggers of migraine. The use of a coloured filter was only associated with pattern glare when taken as the 3-12 score in people with migraine. This adds wieght to the argument that colour is selected by people with migraine to relieves glare illusions not associated with an optical cause.

Table 22

How the optometric correlates of migraine relate to each other. This table includes the p values of statistical comparisons (as appropriate for the data) between the optometric correlates of migraine in addition to the Spearman (Rs) [when comparing continuous datasets], Chi squared statistic (X^2)[when comparing ordinal datasets] and Mann Whitney U statistic of the first sample (U) [when comparing continous data sets with ordinal datasets] themselves. Statistically significant relationships are in heavy delineated cells.

	Migraine or Control	Stereopsis	Heterophoria	Colourful filter selected	Illusions seen on a 3cpd grating	Pattern glare 3cpd minus 12 cpd score	Absolute Difference in pupil reaction latency	Symptoms of light sensitivity	Uncorrected astigmatism
Migraine or Control									
Stereopsis	p=0.0045 U=386								
Heterophoria	p=0.0024 X^2=9.19	p=0.48 U=282							
Colourful filter selected	p=0.039 X^2=4.25	p=0.027 U=346	p=0.73 X^2=0.12						
Illusions seen on a 3 cpd grating	p=0.0001 U=525	p=0.0001 Rs=0.53	p=0.0009 U=458	p=0.25 U=343					
Pattern glare 3cpd minus 12 cpd score	p=0.0045 U=457	p=0.19 Rs=0.20	p=0.13 U=371	p=0.039 U=389	p=0.0001 Rs=0.53				
Absolute Difference in pupil reaction latency	p=0.019 U=234	p=0.29 Rs=0.19	p=0.0012 U=244	p=0.41 U=169	p=0.23 Rs=0.21	p=0.35 Rs=0.16			
Symptoms of light sensitivity	p=0.0045 X^2=8.05	p=0.37 U=299	p=0.17 X^2=1.88	p=0.90 X^2=0.02	p=0.62 U=335	p=0.81 U=323	p=0.17 U=205		
Uncorrected astigmatism	p=0.016 U=434	p=0.10 Rs=0.25	p=0.0029 U=442	p=0.38 U=246	p=0.030 Rs=0.31	p=0.19 Rs=0.19	p=0.67 Rs=0.07	p=0.76 U=326	
Corrected astigmatism	p=0.010 U=442	p=0.12 Rs=0.23	p=0.010 U=421	p=0.26 U=234	p=0.0054 Rs=0.39	p=0.073 Rs=0.26	p=0.51 Rs=0.11	p=0.67 U=332	p=0.0001 Rs=0.73

10.2 Ideas and Suggestions for Further Research

The experimental results of this thesis raise interesting questions that could be further investigated. Changes in visual field data (Chapter 7) were not statistical significant in people with migraine. The pooling of data (e.g. Yenice et al 2005; McKendrick and Badcock 2004b) in other work might be an explanation as to why these studies did find a difference whilst the data in this thesis did not. The study (Chapter 8) that undertook similar experimental tests but included tests of retinal nerve fibre layer data also found no difference in people with migraine but the experimental design in this thesis was only able to detect larger clinically significant changes. A further larger study without pooled data might give more definitive results. These ideas are however speculative.

The findings of a correlation between uncorrected and corrected refractive errors, notably astigmastim, and migraine was a surprise. A larger study might be useful to establish if this hold true. Portable autorefractors are now commonplace and perhaps a study that assessed refraction in this way in a busy migraine clinic and then compared to a non-migraine population might add data on such an association. Current understanding would suggest that the data on refraction and migraine are correlative only, without any implication on cause or effect. Prospective clinical trials could be used to investigate the effect of correcting astigmatism on migraine.

Stereopsis was associated with duration of worst headache and pattern glare such that people with migreaine has reduced stereopsis and increased pattern glare. If this finding is replicated in other research, then establishing if there is in fact some true visual cortex pathology in people with migreaine leading to these findings would be interesting.

Hetrophoria by Maddox Rod testing was assocated with a number of other optometric correlates of migraine. It would be interesting to construct an experiment to tease out these components, taking into account inter-eye retinal luminance levels, differences in refraction and differences in pattern glare. Further experimentation that accounted for these possible confounding variables might establish if heterophoria by Maddox Rod testing is a true correlate of migraine or, an artefact of other optometric correlates.

10.3 Final Summary

Chapter 1 described the optometric aspects of migraine headache (Harle and Evans 2004) and discussed the claims of a relationship between migraine headaches and pupil anomalies, errors of refraction, binocular vision anomalies, visual field changes and pattern glare. This chapter noted that the quality of the evidence for a relationship

between errors of refraction and binocular vision and migraine was poor but that the quality of the evidence to suggest a relationship between migraine headache and pupil anomalies, visual field defects and pattern glare was stronger, particularly noting the link between migraine headache and pattern glare and the therapeutic use of precision tinted spectacles to reduce pattern glare (visual stress) in some people with migraine. Each claimed relationship was further investigated and described over subsequent chapters.

The literature suggested that there might be pupil size and response abnormalities in migraine headache sufferers. Chapter 3 described how, using an infra-red pupillometer (Harle et al 2005), dynamic pupil responses to light in 20 migraine sufferers (during non-headache periods) and 16 non-migraine age and gender matched controls were measured. There was a significant increase in the absolute inter-ocular difference of the latency of the pupil light response in the migraine group compared to the controls (0.062s vs 0.025s, $p=0.014$). There was also a significant correlation between anisocoria and lateralisation of headache such that migraine sufferers with a habitual head pain side have more anisocoria ($r=0.59$, $p<0.01$), but this was not related to headache laterality. The pupil changes were not correlated with the interval since the last migraine headache, the severity of migraine headache or the number of migraine headaches per annum. It was concluded that subtle sympathetic and parasympathetic pupil abnormalities persist in the interictal phase of migraine.

The literature review (Chapter 1 published as Harle and Evans 2004) also revealed historical references to an association between migraine headache and refractive errors, but found lack of scientific evidence relating to these claims. In Chapter 4 (Harle and Evans 2006a) the four aspects of refractive errors that have been implicated in the literature as correlated with migraine: spherical refractive error, astigmatic refractive error, anisometropia and uncorrected ametropia were investigated. The calculated scalar value of refractive error, aided and unaided visual acuity and spectacle use in migraine and control groups was also compared. An investigation into the relationship between refractive components and key migraine headache variables was then undertaken. It was found that compared with the control group, the migraine group had higher degrees of astigmatic components of refractive error assessed both objectively (C, $p=0.01$; C_0, $p=0.01$; C_{45}, $p=0.05$) and subjectively (C, $p=0.03$; C_0, $p=0.03$; C_{45}, $p=0.05$), uncorrected astigmatic components of refractive error (C_0, $p=0.02$; C_{45}, $p=0.04$) and anisometropia ($p=0.06$). This suggests that perhaps the historical literature was indeed correct in that low degrees of astigmatism and anisometropia are relevant in migraine. The most significant finding was of higher degrees of astigmatism in the migraine group, suggesting that people with migraine should attend their optometrist regularly to ensure that their refractive errors are appropriately corrected.

The literature review (Chapter 1, published as Harle and Evans 2004) revealed old references to an association between migraine headache and binocular vision anomalies, but again a lack of scientific evidence evaluating these claims. In chapter 5, binocular vision was investigated using standard clinical tests, in people with migraine and in controls (Harle and Evans 2006c). Some test results suggested that heterophoria and fixation disparity were more common in the migraine group. The migraine group also had slightly reduced stereopsis. Significant correlations between some migraine variables and some binocular vision variables (e.g., duration of worst headache and impaired stereopsis) were found, but the analyses did not suggest that a causal relationship is likely. In conclusion, people with migraine have on average a slightly higher prevalence of heterophoria and aligning prism and reduced stereopsis compared with controls. However the differences are subtle and the data do not support the use of binocular vision interventions prescribed solely on the basis of the presence of migraine.

Chapter 1 described the literature that suggests that visual field defects may be more common in people who experience migraine. Chapter 7 compared Humphrey FDT and Humphrey SITA fields of 25 migraine sufferers with 25 age- and gender-matched controls (Harle and Evans 2005). Although both mean deviation and pattern standard deviation were a little worse in the migraine group, these differences did not reach statistical significance. There were no inter-eye visual field differences in the migraine group compared to controls. Comparing the mean of all the contrast thresholds in each hemisphere, there were not more inter-hemifield visual field differences in the migraine group compared to controls. There was no significant difference between the migraine and control groups in intra-ocular pressures. The visual field parameters were not correlated with the interval since the last migraine headache, the severity of migraine headache, the duration of migraine headache or the number of migraine headaches per annum.

To investigate this matter further, in Chapter 8 a second cohort of subjects were tested and retinal structure was measured in addition to visual fields, since it had been suggested that some people with migraine have subtle visual field changes and this has been used in the past to argue that people with migraine may have a predisposition to open angle glaucoma. However, recent evidence (Tan 2005) suggests that the retinal nerve fibre layer structure is unaltered in migraine, implying that any visual field changes found in people with migraine arise from changes in the post photoreceptor visual pathway. In this new study with a fresh cohort, differences in a migraine and an age- and sex-matched control group using Optical Coherence Tomography (OCT), Humphrey VFA II Swedish Interactive Threshold Algorithm (SITA) visual fields, Humphrey Frequency

Doubling Technology (FDT) visual fields and non contact intra-ocular pressure measurements were studied. No significant differences were found between the groups (migraine and control) for any of the OCT, visual fields or intra-ocular pressure measurements. It was concluded that in the sample investigated, migraine is not associated with retinal changes or visual field changes using the methods assessed.

The visual field findings may have been obtained because in contrast to other work, (e.g. Yenice et al 2005; McKendrick AM, Badcock DR 2004b) a statistical approach was used that did not pool the data from each eye. Such data pooling may over-estimate the statistical significance of any difference in visual field parameters in people with migraine (Harle and Evans 2006b) and exaggerate the clinical significance of the findings. Recently, the data presented by Yenice et al have been re-analysed (Harle and Evans 2006b). This re-analysis argued that Yenice et al's data demonstrated the importance of not using SWAP to as a diagnostic tool for glaucoma in people with migraine and suggested that this may be because, in common with a number of other central neurological disorders (Shepherd 2005), the disorder itself may be associated with general central neurological visual changes demonstrable as dysfunction of the colour vision S–cone mechanism, because of lower levels of redundancy associated with this system.

An assessment of colour vision was included in Chapter 6, which concentrated on an investigation of the associations between interictal pattern glare, visual stress and visual triggers of migraine (Harle et al 2006). It was shown that, in concordance with the limited literature, patients who are prone to visually triggered migraines report more illusions on viewing striped patterns ('pattern glare') and coloured filters may be an effective intervention for these people. Headache symptoms and headache triggers were investigated in migraine and control groups in two separate experiments. In one experiment it was also determined, for each participant, the severity of pattern glare, whether coloured filters reduced it and, if so, what the optimum colour of filter was. It was found that people with migraine saw significantly more illusions on viewing each striped pattern and experienced greater pattern glare. They were also more likely to select a coloured filter to aid visual comfort, particularly colours in the blue to green sector of the spectrum. Colour vision was also assessed with the D15 test. Colour vision was impaired subtly, but significantly, for tritan (S-cone) colours in migraine. Principal component analyses grouped common headache triggers into five broadly equal components: food, visual triggers, alcohol, stress and tiredness, and the environment. In a second analysis, the overall number of illusions seen in striped patterns was associated with visual triggers whilst pattern glare, use of coloured filters and interictal light sensitivity together formed a sixth component interpreted as visual stress.

It was concluded that clinicians should ask migraine patients whether visual stimuli trigger their migraine, about interictal visual symptoms, and use the pattern glare test to ensure that those who may benefit from optometric interventions are appropriately managed.

These optometric correlates of migraine headache raise the possibility that optometric interventions may reduce visual triggers and ameliorate migraine frequency and, perhaps, severity. Although this thesis concentrates on identifying the optometric correlates of migraine and an investigation of interventions was not a primary goal of this work, a small intervention study in Chapter 9 was included. Chapter 9 describes how, using a single-subject double-masked randomised controlled double-cross over design, the effectiveness of optometric interventions on migraine frequency, duration, severity, aura and palliation in seven subjects was evaluated.

Refractive, orthoptic and precision tinted lens interventions were assessed in different individuals. In all cases the active intervention was preferred over the control intervention, and every subject asserted that the active intervention helped their migraine headaches more than the control intervention. Refractive or precision tint interventions did not have a significant effect on migraine factors compared to a control intervention, but prism spectacles were associated with significantly improved pain in one individual and reduced medication use in another. It was suggested that all optometric interventions may add benefit not associated with the measured migraine factors since the subjects preferred the intervention spectacles to the control in every case. One explanation for this may be that the spectacles improved the co-morbid optometric conditions leading to less visual symptoms even though the measured migraine variables were unchanged.

In summary, it has been established that some optometric variables, notably visual fields, that were thought from the previous literature to be associated with migraine are, from these data, not strong correlates. It has been demonstrated that, in accordance with the literature, pupil responses are different in people with migraine, both in increased anisocoria and in the inter eye latency to light response. The present data demonstrates that visual triggers are important in migraine, and adds to the considerable evidence that pattern glare responses to square wave gratings of 3cpd are increased in people with migraine. People with migraine who have pattern glare, are more likely to select coloured filters to relieve this pattern glare than people without migraine. The migraine sample had slightly but clinically significantly increased astigmatism, both corrected and uncorrected and it has been demonstrated that people with migraine have subtle changes to their binocular vision. In some individuals, correcting these binocular vision problems with prism spectacles does improve migraine variables. Nonetheless, the correlates

investigated in this study are not likely to be major causes of migraine. Further research may provide insights into how these correlates of migraine interact.

Section 6

Appendices, Supporting Published Work and References

Appendix 1 Recruitment Letters and Correspondence

Participation letter

Dear Migraine Patient,

As a known migraine sufferer of the Princess Margaret Migraine Clinic, we would like to invite you to take part in a new study into the causes and treatments of migraine. This is a non–drug trial and involves no invasive procedures at all.

We would ask you to complete a headache diary for six weeks, which will be issued to you. After this six-week period you will be invited to attend the Neville Chappell Research clinic where a number of tests will be performed.

Migraine Research
Neville Chappell Research Clinic
56-62 Newington Causeway
London
SE1 6DS

These tests are painless and the testing procedure should take no more than a couple of hours. It is hoped that you will also be able to bring a friend or colleague at this stage to act as a control (non-migraine sufferer). After the tests, treatments and / or recommendations will be given. Three months later another six-week headache diary will need to be completed.

I do hope that you will be able to give up just a little of your time to volunteer for this study. Please return the tear off slip below to the Neville Chappell Research Clinic (NOT Charing Cross Hospital).

Thank you so much.

General medical practitioner participation letter

Dear Dr xxx

Migraine research

The Institute of Optometry is based near the Elephant and Castle and, for over 75 years, we have provided optometric clinics, CPD courses for optometrists, and have carried out clinical vision research. We have recently been awarded funding for a research study to investigate the optometric correlates of migraine.

Migraine is a very common symptom for optometrists as well as GPs. The literature on migraine and vision is equivocal. Some authorities believe that visual factors can trigger migraine, whilst others argue that visual factors play no role in migraine. Our research will use a masked controlled design to determine what role, if any, visual problems play in migraine.

Some previous research in this field has suffered from a referral bias since subjects have been recruited through an eyecare clinic. We hope to avoid this by using subjects who are not attracted to the trial because of any suspected visual problems. To this end, we hope to collaborate with GPs who might be interested in referring subjects to our trial. The purpose of this letter is to ask whether you might be interested in collaborating in this way.

The attached sheet provides information about the research. If you would like more details about our study then we would be very pleased to meet with you and/or to send you the full protocol. The study has been approved by the Institute's Research and Ethical Committee.

Migraine research: information for GPs

We are seeking patients aged between 10 and 50 years old, with migraine attacks occurring at least once a month, and who are otherwise generally fit and well. If you see any such patients who might be interested in participating in our study then we would be very grateful if you could give them one of the enclosed sheets. If they contact us then we will give them more detailed information and will obtain informed consent before starting the research.

It is crucial that the study investigates migraineurs who have not been pre-selected as having visual problems. This is so that we can establish the true prevalence of visual problems in people suffering from migraine.

In practice, we hope that the following suggestions will help to avoid any referral bias:

Please could practitioners who are willing to participate give the attached leaflet to all patients they see with migraine aged 10-50 years

It is very important that patients whose vision is believed to be a factor in their migraines are not especially singled out for or barred from the research

If possible, please do not mention that the study is about vision

We will inform subjects of this, and all other details, before starting the research, but after we have obtained initial information from questionnaires

Thank you

Migraine research: preliminary information for patients

Thank you for showing an interest in this research study.

Migraine

The aim of the research is to investigate factors that may trigger migraine or migraine-like headaches. Factors that have been suggested as triggers for migraine include certain foodstuffs (e.g., red wine or chocolate), stress, lack of sleep, noise, lights, and general fatigue. Some people are not aware of anything that triggers their migraine.

Participants

We are interested in seeing people who suffer from migraine, whether or not they are aware of any factors triggering their migraine. People who participate in the research will need to:

be aged between 10 and 50
experience at least one migraine headache a month
complete an initial questionnaire about their headaches and health
complete a daily diary for six weeks before attending our clinic. This diary asks whether you have experienced any headaches and takes about one minute a day to complete

Depending on the information that we receive in the questionnaire and diaries, some participants will be invited to attend our clinic (near the Elephant and Castle) for an appointment. The testing at this appointment is designed to investigate factors that may trigger your migraine. This testing is painless and free of charge, and takes about two hours. So that we have someone to compare your results with, we ask participants who come for this testing to bring a friend or family member of similar age and of the same sex. There is, of course, no charge for this testing but we regret that we are unable to reimburse travel expenses.

We hope that, as a result of this research, we will discover more about any factors that might trigger migraine and we may be able to help you and others alleviate some of the symptoms of this unpleasant condition.

If you think that you might be interested in participating this research then please complete the form at the bottom of this letter and post it to:

Mr Deacon Harle BSc (Hons) MSc MCOptom
Migraine Research
Neville Chappell Research Clinic
56-62 Newington Causeway
London
SE1 6DS

Secretary's recruitment letter

Migraine Research Study

Date: .....

Dear .....

I would like to confirm the appointment that was arranged by telephone. Your appointment has been made for .....

You will find enclosed a map giving details as to how to find the Institute of Optometry.

I will give a detailed eye examination including some special tests of vision that may be related to migraine. None of these tests will be painful.

With this in mind, please bring a friend with you, someone who is prepared to undergo the same tests. The friend should be a person of a similar age to you (within ten years), of the same sex, and should be someone who does not have migraines and not have more than 12 headaches per year.

The testing will be very thorough and will take approximately 1½ to 2 hours per person. Tea or coffee will be provided.

In order for me not to know which of you (you or your friend) are the migraine sufferer (which is important for our study), I would be grateful if you can try and not me give me any indications until the end of the examination.

A six-week headache diary is enclosed. Please complete this before your appointment and bring it to the appointment.

Appendix 2 Headache Diary

Name .....

Week beginning Monday.....200x

Every day, please tick the box or boxes that apply and complete the Headache record sheets, if necessary.

Monday I did not have any symptoms I had a headache and I have completed a Headache record sheet
Tuesday I did not have any symptoms I had a headache and I have completed a Headache record sheet
Wednesday I did not have any symptoms I had a headache and I have completed a Headache record sheet
Thursday I did not have any symptoms I had a headache and I have completed a Headache record sheet
Friday I did not have any symptoms I had a headache and I have completed a Headache record sheet
Saturday I did not have any symptoms I had a headache and I have completed a Headache record sheet
Sunday I did not have any symptoms I had a headache and I have completed a Headache record sheet

Appendix 3 Headache Record Sheet

Full Name: _____

Date Headache Started:_____ Time Headache Started:_____

Hours of Sleep Last Night: _____Hrs

Quality of Sleep:
- ❒ Poor
- ❒ Fair
- ❒ Good
- ❒ Excellent

Medications Taken: Name: _____
Dose: _____mg

General Health Today:
- ❒ Poor
- ❒ Fair
- ❒ Good
- ❒ Excellent

Headache Rating:
- ❒ Mild
- ❒ Moderate
- ❒ Severe

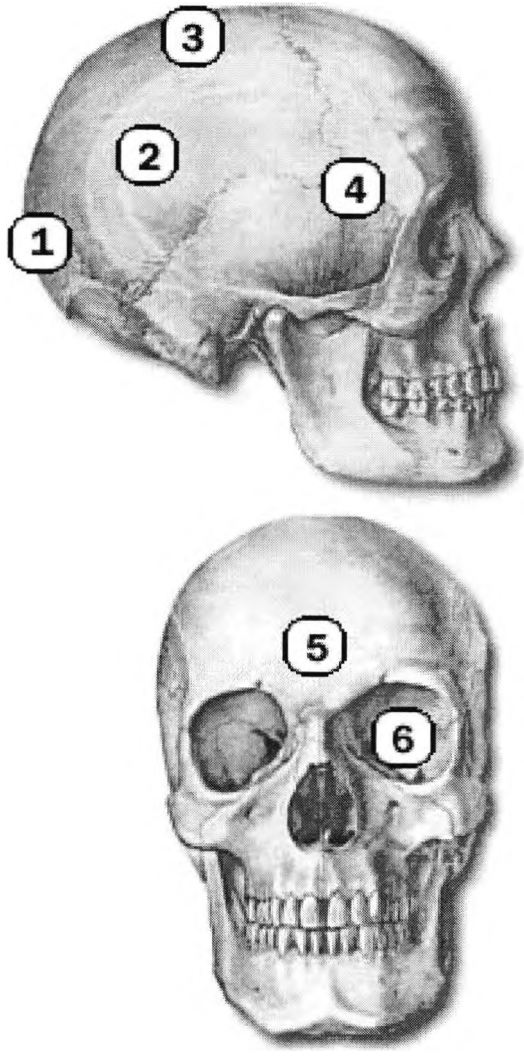
How Long Did Pain Last: _____Hrs

Description of Pain:
- ❒ Aching
- ❒ Throbbing / Pulsating
- ❒ Sharp / Lancing
- ❒ Pressure / Squeeze

Associated Symptoms:
- ❒ Sensitivity to Light
- ❒ Sensitivity to Noise
- ❒ Feeling Sick
- ❒ Vomiting
- ❒ Ringing in the Ears
- ❒ Decreased Hearing
- ❒ Speech Difficulties
- ❒ Stammering
- ❒ Dizziness
- ❒ Numbness
- ❒ Tingling
- ❒ Weakness
- ❒ Double Vision
- ❒ Difficulty with movement
- ❒ Decreased level of consciousness
- ❒ Blind patches or blindness in one eye lasting less than one hour

Location of Pain (Please see pictures below):

- ❒ 1: Occipital
- ❒ 2: Parietal
- ❒ 3: Vertex
- ❒ 4: Temple
- ❒ 5: Frontal
- ❒ 6: Orbital



Which side of the head was the pain mostly concentrated:

- ❒ Only Left
- ❒ Mainly Left
- ❒ Both Sides
- ❒ Mainly Right
- ❒ Only Right

Appendix 4 Patient Consent Forms

Information and consent form for the people with migraine

Patient Informed Consent Form

Migraine is a specific type of headache usually diagnosed by a neurologist or occasionally by your GP. It can have many factors associated with it and often certain activities can trigger it. A migraine headache is not the same as a really bad headache. Through trial and error some patients can work out for themselves what activities trigger their migraine and can then avoid them. For others no obvious triggers present themselves and the patient is left without any help.

Some practitioners believe that certain visual stimuli or problems can trigger migraine in much the same way that we know certain flashing lights can produce a fit in epileptics. This visual stimuli to trigger migraine is as yet unproven and this is what our study hopes to resolve.

To work out if vision is associated with migraine we will perform standard eye tests on two groups of people. One group will be migraine sufferers and one group will not be migraine sufferers. We can then compare the results of the two groups. By giving you questionnaires before and after your eye tests we will also be able to see if any of the treatments that are given after the eye test are helping your migraines.

First of all we will contact you to check that you are suitable for the research. You will then be sent a headache questionnaire to fill out for six weeks.

An appointment will then be made to come to the Institute of Optometry for your eye tests. It is hoped that you will be able to bring a friend or colleague of about your age who does not have migraine. They will also have their eyes tested. It is important that when you come for your eye test that you do not mention which of you has migraine until after all the tests have been performed.

Following your eye tests certain treatments may be advised. Commonly these treatments will be things like new spectacles or eye exercises. You will then be asked to fill out another headache questionnaire for another six weeks.

There are no known risks associated with any of the tests that you may receive. The tests will be very thorough and may last over an hour or two. It is anticipated that you may feel a little tired after your visit. You are of course free to withdraw from the trial at any time.

To be suitable for the research a strict criteria needs to be applied:

You must be:

Between ten and fifty years old

Have Migraine headaches at least once a month

Generally fit and well with no general health problems

Have no eye diseases (glasses are OK)

Not Pregnant

Not changing any migraine medication you may be taking

Not changing your spectacles

Consent Form

The purpose and conditions of the above study have been explained to me and I have read the information on this form. I agree to participate in this research.

Signed.....

Print Name .....

Date.....

Witness

Signature.....

Print Name.....

Date.....

Witness

Address.....

.....

Information and consent form for the people without migraine headache

Patient Informed Consent Form

Migraine is a specific type of headache usually diagnosed by a neurologist or occasionally by your GP. It can have many factors associated with it and often certain activities can trigger it. A migraine headache is not the same as a really bad headache.

Through trial and error some patients can work out for themselves what activities trigger their migraine and can then avoid them. For others no obvious triggers present themselves and the patient is left without any help.

Some practitioners believe that certain visual stimuli or problems can trigger migraine in much the same way that we know certain flashing lights can produce a fit in epileptics. This visual stimuli to trigger migraine is as yet unproven and this is what our study hopes to resolve.

To work out if vision is associated with migraine we will perform standard eye tests on two groups of people. One group will be migraine sufferers and one group will not be migraine sufferers. We can then compare the results of the two groups.

You have agreed to participate as part of the non-migraine group.

An appointment will then be made to come to the Institute of Optometry for your eye tests. You will attend as the friend or colleague of about your age who has migraine. They will also have their eyes tested. It is important that when you come for your eye test that you do not mention which of you has migraine until after all the tests have been performed.

There are no known risks associated with any of the tests that you may receive. The tests will be very thorough and may last over an hour or two. It is anticipated that you may feel a little tired after your visit. You are of course free to withdraw from the trial at any time

To be suitable for the research a strict criteria needs to be applied:

You must be:

Between ten and fifty years old

Attending with a friend or colleague who has migraines at least once a month

Generally fit and well with no general health problems

Have no eye diseases (glasses are OK)

Not Pregnant

Not changing your spectacles

Consent Form

The purpose and conditions of the above study have been explained to me and I have read the information on this form. I agree to participate in this research.

Signed.....

Print Name .....

Date.....

Witness

Signature.....

Print Name.....

Date.....

Witness

Address.....

.....

Appendix 5 Migraine Clinic Questionniare

Date: ___/___/___

Full Name: _____

Date of Birth: ___/___/___

Address: _____
_____

Sex: ***Male*** ♂ ***Female*** ♀

Please try to answer all the questions if possible.

History and Symptoms:

Occupation: .....

Do you work under fluorescent lighting? Yes ❒ No ❒

If yes, how much time do you typically spend under fluorescent lights?

- ❒ more than 4 hours a day
- ❒ 1 to 4 hours a day
- ❒ 1 to 7 hours a week
- ❒ less than a one hour a week

Do you use computer screens? Yes ❒ No ❒

If yes, how much time do you typically use a computer?

- ❒ many hours a day
- ❒ a few hours a day
- ❒ a few hours a week
- ❒ less than a few hours a week

Ophthalmic History

Date of last eye examination:.....

Were you given glasses Yes ❒ No ❒

If so, when are they worn? ❒Just Distance Vision

❒Just Near Vision

❒All the Time

Has anyone ever noticed your eye(s) turning inwards or outwards?

Yes ❒ No ❒

If yes, at what age, how often, and how long did it normally last?.....

.....

Have you ever had an eye operation?

Yes ❒ No ❒

Please give any details you can of what the operation was for and how you were at the time.....

Have you ever received eye exercises, or eye patching for a lazy eye?

Yes ❒ No ❒

Please give details of the type of treatment and how old you were at the time.....

.....

Have you ever had an injury to your eyes?

Yes ❒ No ❒

Please give details of the injury and how you were at the time.....

Developmental History

Please state whether your mother's pregnancy was full term, or how many months/weeks early or late you were born: .....

Please state whether the birth was normal, or give details of any complications (for example, was it a forceps delivery?): .....

.....

.....

Please list any severe illnesses / operations that you had in your first year, with approximate age at the time: .....

.....

.....

Visual Symptoms

When you look at writing in the distance (e.g. on a traffic sign), is it normally clear?
Yes ❒ No ❒

Do things in the distance ever go blurred?

Yes ❒ No ❒

When you are reading or writing in a book, is it normally clear?
Yes ❒ No ❒

Do words in a book ever:

go blurred? Yes ❒ No ❒
jump around? Yes ❒ No ❒
go smaller/ bigger? Yes ❒ No ❒
fade or disappear? Yes ❒ No ❒
get faint colours round them? Yes ❒ No ❒

other .....

Have you ever experienced double vision? Yes ❒ No ❒

Do you ever experience sore or tired eyes? Yes ❒ No ❒

Visual Behaviour

Have you or anyone else ever noted that you ;

	Yes	No	If so, please give details
Hold reading or materials unusually close or far away:	❒	❒	.....
Close or cover one eye:	❒	❒	.....
Rub your eyes frequently:	❒	❒	.....
Blink your eyes excessively:	❒	❒	.....
Tilt your head when reading or writing:	❒	❒	.....
Move your head when reading:	❒	❒	.....
Use your finger as a marker:	❒	❒	.....
Confuse letters or words:	❒	❒	.....
Reverse letters or words:	❒	❒	.....
Skip, re-read or omit words or lines:	❒	❒	.....
Read slowly:	❒	❒	.....
Tire easily:	❒	❒	.....
Have poor general coordination:	❒	❒	.....
Are light sensitive:	❒	❒	.....

General Health

Are you in good physical condition and healthy? Yes ❒ No ❒
If no, please give details:

Please list any pills or medicines that you are currently using excluding any for migraine or headaches, which are detailed below:

Have you ever received hospital treatment as an in-patient? Yes❒ No❒
If yes, please give brief details

Have you ever suffered from epilepsy, or any fits or convulsions? Yes❒ No❒
If yes, please give brief details, including age at time

Please give details of any allergies, including hay fever and asthma, that you have ever suffered from. Please say how old you were, how long the problem lasted and how severe it was:

Headaches

Have you ever been diagnosed as suffering with migraine headache?

Yes ❒ No ❒

If yes, was the diagnosis made by GP ❒ Neurologist ❒ Other ❒

Think of the worst headache you have had in the last 12 months. How bad was it?

- ❒ Mild
- ❒ Moderate
- ❒ Severe

How Long Did The Pain Last: _____Hrs

Description of Pain:

- ❒ Aching
- ❒ Throbbing / Pulsating
- ❒ Sharp / Lancing
- ❒ Pressure / Squeeze

Associated Symptoms:

- ❒ Sensitivity to Noise
- ❒ Feeling Sick
- ❒ Vomiting
- ❒ Ringing in the Ears
- ❒ Decreased Hearing
- ❒ Speech Difficulties
- ❒ Stammering
- ❒ Dizziness
- ❒ Numbness
- ❒ Tingling
- ❒ Weakness
- ❒ Double Vision
- ❒ Difficulty with movement
- ❒ Decreased level of consciousness
- ❒ Blind patches or blindness in one eye lasting less than one hour

Light Sensitivity:

When you have a headache, how much of a problem do you find pain or discomfort from lights to be in your every day life?

- ❒ None
- ❒ Slight Problem
- ❒ Moderate Problem
- ❒ Marked Problem
- ❒ Severe Problem

When you have a headache, do lights or light cause your eyes to water?

- ❒ Not at all
- ❒ Slightly
- ❒ Moderately
- ❒ Markedly
- ❒ A lot

When you **DO NOT** have a headache, how much of a problem do you find pain or discomfort from lights to be in your every day life?

- ❒ None
- ❒ Slight Problem
- ❒ Moderate Problem
- ❒ Marked Problem
- ❒ Severe Problem

When you **DO NOT** have a headache, do lights or light cause your eyes to water?

- ❒ Not at all
- ❒ Slightly
- ❒ Moderately
- ❒ Markedly
- ❒ A lot

Please think of the headaches you have had over the last month, and whether they have been getting more frequent or less frequent. Use this information to arrive at your best guess as to how many headaches you have had in the last **12 months**, and write the number here_____

Please name any medications that have been prescribed by your doctor for headaches

_____

Are your headaches aggravated by walking stairs or similar routine physical activity?

Yes ❒ No ❒

Did you have any medical problems or injuries at or about the time the headaches started?

Yes ❒ No ❒

If yes, please list;

_____

_____

Migraine Aura

Do you get changes before the headache starts (for example zig zag lines in your vision, speech difficulties, weakness or numbness)?

Yes ❒ No ❒

If yes, please answer the following ;

Do these changes go away when the headache stops?

Yes ❒ No ❒

Do these changes develop over more than four minutes?

Yes ❒ No ❒

Do these changes last more than 60 minutes?

Yes ❒ No ❒

Does the headache start within an hour of the changes starting?

Yes ❒ No ❒

Headache Triggers

Some people notice that certain activities can start their headache. For the following activities please could you note if the following commonly, occasionally or never cause headaches:

Hormonal factors (females) (time of the month)	❒Commonly Causes Headache ❒Occasionally Causes Headache ❒Never Causes Headache
Stress	❒Commonly Causes Headache ❒Occasionally Causes Headache ❒Never Causes Headache
Noise	❒Commonly Causes Headache ❒Occasionally Causes Headache ❒Never Causes Headache
Tiredness	❒Commonly Causes Headache ❒Occasionally Causes Headache ❒Never Causes Headache
Smells	❒Commonly Causes Headache ❒Occasionally Causes Headache ❒Never Causes Headache
Chocolate	❒Commonly Causes Headache ❒Occasionally Causes Headache ❒Never Causes Headache
Cheese	❒Commonly Causes Headache ❒Occasionally Causes Headache ❒Never Causes Headache
Other foodstuffs	❒Commonly Causes Headache ❒Occasionally Causes Headache ❒Never Causes Headache
Red Wine	❒Commonly Causes Headache ❒Occasionally Causes Headache ❒Never Causes Headache
Other Alcohol	❒Commonly Causes Headache ❒Occasionally Causes Headache ❒Never Causes Headache
Caffiene (Tea, Coffee etc)	❒Commonly Causes Headache ❒Occasionally Causes Headache ❒Never Causes Headache

Flickering Lights	❒Commonly Causes Headache ❒Occasionally Causes Headache ❒Never Causes Headache
Certain Patterns	❒Commonly Causes Headache ❒Occasionally Causes Headache ❒Never Causes Headache
Alternate Light and Shade	❒Commonly Causes Headache ❒Occasionally Causes Headache ❒Never Causes Headache
Other Visual Simuli	❒Commonly Causes Headache ❒Occasionally Causes Headache ❒Never Causes Headache

Please describe any of these "other" visual stimuli that may trigger headaches:

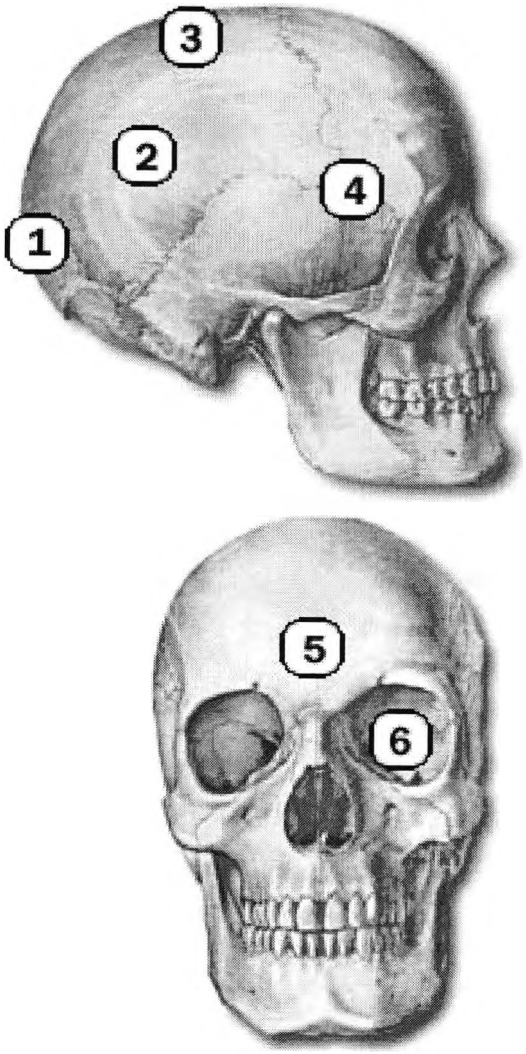
_____

_____

Location of Pain

When you gat a headache, please could you indicate the usual location of the pain.
(Please see pictures below):

- ❒ 1: Occipital
- ❒ 2: Parietal
- ❒ 3: Vertex
- ❒ 4: Temple
- ❒ 5: Frontal
- ❒ 6: Orbital



Which side of the head was the pain mostly concentrated:

- ❒ Only Left
- ❒ Mainly Left
- ❒ Both Sides
- ❒ Mainly Right
- ❒ Only Right

Family History

Did your parents or any of the other children in your family have reading problems?
Yes ❒ No ❒ If yes, state who (e.g. father) .....

Did your parents or any of the other children in your family ever have a turning eye, patching, or eye exercises? Yes ❒ No ❒ If yes, state who .....

Are your parents or any of the other children in your family colour-blind?
Yes ❒ No ❒ If yes, state who .....

Are there any other eye conditions that run in the family?
Yes ❒ No ❒ If yes, please list .....

Did any relatives ever have epilepsy? Yes ❒ No ❒ If yes, state who .....

Did your parents or any of the other children in your family ever have migraine headaches? Yes ❒ No ❒ If yes, state who .....

Are there any other general health problems that run in the family?
Yes ❒ No ❒ If yes, please list .....

Appendix 6 Telephone Survey

The Institute of Optometry Migraine Spectacle Trial

Telephone Questionnaire Date _____

Name _____

"Hello, My name is * and I am calling from the Institute of Optometry Migraine Trial. I was wondering if you would mind answering a few questions about the spectacles that you have been trialing. There is no pressure to answer one way or the other, we just would like to get a feel for the way you might be using the spectacles."**

Have you worn the spectacles today? | Yes | No |

How many days over the last week have you used the spectacles?

1	2	3	4	5	6	7

Please could you answer the following questions on a scale of zero to four, where four is all the time and zero is none of the time

When you have been driving in daylight hours, how much have you used the spectacles:

0	1	2	3	4

In daylight hours,generally outdoors, have you used the spectacles:

0	1	2	3	4

When you have been around the house, how much have you used the spectacles:

0	1	2	3	4

When you have been watching television, how much have you used the spectacles:

0	1	2	3	4

When you have been shopping, how much have you used the spectacles:

0	1	2	3	4

When you have been reading, how much have you used the spectacles:

0	1	2	3	4

When you have been writing, how much have you used the spectacles:

0	1	2	3	4

When you have been using a computer, how much have you used the spectacles:

0	1	2	3	4

When you have been at your place of work, how much have you used the spectacles:

0	1	2	3	4

When you shave or apply make-up, how much have you used the spectacles:

0	1	2	3	4

Thank you so much for your time. Please just carry on using the spectacles as you have been doing. There is no need to change the way you have been using the spectacles because of this short survey

Appendix 7 Final Questionnaire

The Institute of Optometry Migraine Spectacle Trial

End of second phase patient statement Date _____

Name _____

Address _____

_____

PLEASE COMPLETE SECTIONS A, B and C

Please Tick

A *Either:*

I wish to keep the spectacles I have presently ☐

Or:

I wish to keep the other pair of spectacles and am returning this pair ☐

Or:

I do not wish to keep either pair ☐

B *Either:*

I think this pair of spectacles is the best for helping my migraines ☐

Or:

I think the other pair of spectacles is the best for helping my migraines ☐

Or:

I do not think either pair help my migraines ☐

C Please read and answer all of the following questions

Example Question

Do you find party political broadcasts:

very boring

of average interest

very interesting

(in this example, the question was answered by drawing a horizontal line near the very boring end. This answer suggests that broadcasts are quite boring)

Please note that the horizontal mark can be placed anywhere on the vertical line
Please think about the spectacles that you have at the moment and have been wearing for the last 6 weeks

When you have been driving,in daylight hours, have you used the spectacles:

- all of the time
- some of the time
- none of the time

When you have been generally outdoors,in daylight hours, have you used the spectacles:

- all of the time
- some of the time
- none of the time

When you have been around the house, have you used the spectacles:

- all of the time
- some of the time
- none of the time

When you have been watching television, have you used the spectacles:

- all of the time
- some of the time
- none of the time

When you have been shopping, have you used the spectacles:

- all of the time
- some of the time
- none of the time

When you have been reading, have you used the spectacles:

- all of the time
- some of the time
- none of the time

When you have been writing, have you used the spectacles:

- all of the time
- some of the time
- none of the time

When you have been using a computer, have you used the spectacles:

- all of the time
- some of the time
- none of the time

When you have been at your place of work, have you used the spectacles:

- all of the time
- some of the time
- none of the time

When you shave or apply make-up, have you used the spectacles:

- all of the time
- some of the time
- none of the time

Please think about the other pair of spectacles that you had been using for the previous 6 weeks

When you have been driving, in daylight hours, have you used the spectacles:

- all of the time
- some of the time
- none of the time

When you have been generally outdoors, in daylight hours, have you used the spectacles:

- all of the time
- some of the time
- none of the time

When you have been around the house, have you used the spectacles:

- all of the time
- some of the time
- none of the time

When you have been watching television, have you used the spectacles:

- all of the time
- some of the time
- none of the time

When you have been shopping, have you used the spectacles:

- [ ] all of the time
- [ ] some of the time
- [ ] none of the time

When you have been reading, have you used the spectacles:

- [ ] all of the time
- [ ] some of the time
- [ ] none of the time

When you have been writing, have you used the spectacles:

- [ ] all of the time
- [ ] some of the time
- [ ] none of the time

When you have been using a computer, have you used the spectacles:

- [ ] all of the time
- [ ] some of the time
- [ ] none of the time

When you have been at your place of work, have you used the spectacles:

- [ ] all of the time
- [ ] some of the time
- [ ] none of the time

When you shave or apply make-up, have you used the spectacles:

- all of the time
- some of the time
- none of the time

Thank you very much for completing this questionnaire, please return it in the stamped addressed envelope provided

Supporting Published Work

Ophthal. Physiol. Opt. 2004 **24:** 369–383

Review Article

The optometric correlates of migraine

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Abstract

Migraine is a common, chronic, multi-factorial, neuro-vascular disorder typically characterised by recurrent attacks of unilateral, pulsating headache and autonomic nervous system dysfunction. Migraine may additionally be associated with aura; those focal neurological symptoms that may precede or sometimes accompany the headache. This review describes the optometric aspects of migraine headache. There have been claims of a relationship between migraine headaches and errors of refraction, binocular vision anomalies, pupil anomalies, visual field changes and pattern glare. The quality of the evidence for a relationship between errors of refraction and binocular vision and migraine is poor. The quality of the evidence to suggest a relationship between migraine headache and pupil anomalies, visual field defects and pattern glare is stronger. In particular the link between migraine headache and pattern glare is striking. The therapeutic use of precision-tinted spectacles to reduce pattern glare (visual stress) and to help some migraine sufferers is described.

Keywords: migraine, orthoptics, pattern glare, pupils, refraction, tinted lenses, visual fields

Brief historical overview of explanations of migraine

From 3000 BC, vision has been linked to migraine headache (Alvarez, 1945; Pearce, 1986). Hippocrates himself alluded to the visual prodrome of migraine (Allory, 1859). Migraine has been described in other ancient writings, too numerous to review here. Particularly relevant to the present review, Celsus (AD 30, cited by Thomas, 1887) listed sunlight among the triggers of migraine. The severity of migraine, and its association with photophobia, was highlighted by Araetaeus (AD 81, translated by Adams, 1856):

> For they flee the light; the darkness soothes the disease; nor can they bear readily to look upon or hear anything pleasant... The patients are weary of life and wish to die.

Gowers (1886) referred to the two main theories of migraine, vascular and neural; an observation which is equally valid today. The 1920s saw allergic theories come and go, as did the psychosomatic theories of the 1950s (Pearce, 1986). Nowadays migraine headache can be considered to be a reaction or biological adaption determined by a primary disorder of brain threshold in combination with a variety of external precipitating factors. Together, these lower this threshold to a point when a migraine attack will occur.

Pathophysiology of migraine

Goadsby *et al.* (2002) have reviewed migraine pathophysiology from a medical perspective, but in a broad sense, migraine can be thought of as a tendency to have headache that is characterised by certain associated symptoms. The basis of this predisposition has been attributed to a lack of stability in the control of pain, the control of sensory information coming from the pain producing intracranial structures and sensitivity to cyclic changes in the central nervous system (Lance and Goadsby, 1998).

The migraine brain has a reduced threshold to a variety of stimuli, and this has been described as cortical hyperexcitability. The factors that set this threshold are genetic (Ophoff *et al.*, 1996; Ducros *et al.*, 2001), and involve magnesium deficiency, excitory amino acids, sensitivity of the dopamine system and the hypothalamus, reduced habituation to visual and auditory stimuli, and vascular reactivity. Because of this reduced

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threshold, migraines can be initiated by 'triggers'. Such triggers can be divided into internal and external. One example of an internal trigger might be hormonal factors, whilst external triggers could be flickering lights, certain patterns or strong smells. External triggers have the potential to cause, and therefore to prevent, migraine and will be outlined in more detail later.

Once triggered, a migraine has two main consequences: spreading depression (which may or not be perceived as aura) and pain. Leão (1944) described 'spreading depression' as a progressive shutdown of cortical function and suggested that it may be related to the fortification spectra of migraine. Waves of cortical inhibition, sometimes preceded by transient excitation, move slowly over the cortex (2–3 mm min^{-1}), suppressing normal activity, and take 5–60 min before recovery takes place.

Spreading depression is associated with vascular changes (Lauritzen *et al.*, 1982; Piper *et al.*, 1991; Goadsby, 1992). One such vascular change that has been suggested in patients with migraine with aura is a 'spreading oligaemia' (Olesen *et al.*, 1981; Dreier *et al.*, 2001). Dreier *et al.* (2002) have suggested that the link between the vascular oligaemia and the neurological spreading depression may be that endothelial irritation triggers cortical spreading depression. Hadjikhani *et al.* (2001) showed vasoconstriction and then vasodilation followed the cortical spreading depression using an imaging study. The oligaemic waves of reduced blood flow progress over the cortex at the same rate of 2–3 mm min^{-1} as cortical spreading depression. They start in the visual cortex and advance forward without respecting arteriolar territories. These vascular changes can last several hours and are followed by delayed hyperaemia (Andersen *et al.*, 1988). As the spreading oligaemia reaches sensory motor areas of the brain, the patient experiences the focal neurological aura symptoms. The neurological changes during aura parallel what is seen if the brain is directly stimulated (Penfield and Perot, 1963; Brindley and Lewin, 1968) and are also remarkably similar to the changes that would be predicted if ocular dominance columns (Hubel and Weisel, 1968) in the cortex were serially activated.

Woods *et al.* (1994) demonstrated a spreading oligaemia directly with a positron emission tomography study. Interestingly, the patient in this study did not perceive aura in any traditional sense, suggesting that the oligaemia can traverse the whole cortex without the patient experiencing symptoms. Indeed, Lance and Anthony (1966) claimed that only 10% of migraine patients perceive the fortification spectra but 25% of patients perceive less specific symptoms of 'spots before the eyes' or 'shimmering vision' covering the entire visual field.

Other neuro-vascular interactions can occur with migraine. Kruit *et al.* (2004) found that some patients with migraine were at risk of subclinical lesions in certain brain areas and suggested that the cerebellar region of the posterior circulation territory was an area where migraine sufferers had a greater number of infarcts than controls. Lipton and Pan (2004) considered that this might be evidence that migraine is a progressive brain disease as this area had been previously implicated in persons with stroke and migraine (De Benedittis *et al.*, 1995; Hoekstra-van Dalen *et al.*, 1996).

There is some pathophysiological evidence linking the aura phase of migraine and the pain phase of migraine. Moskowitz (1984) considered that the spreading depression of the cortex might depolarise trigeminal nerve fibres and initiate pain. However, if this hypothesis were true then the headache would always develop on the side of the head responsible for the aura symptoms (e.g. a left sided headache would arise from a right field aura). Olesen *et al.* (1990) showed that in 38 patients with migraine with aura, three experienced headache on the 'wrong' side and Jensen *et al.* (1986) showed that aura symptoms were ipsilateral to the headache in 19 patients and contralateral in 18 patients. Thus, there must be some 'central link' which can trigger pain on either side of the head for one-sided aura symptoms. Bolay *et al.* (2002) have suggested that cortical spreading depression activates trigeminal vascular afferents to evoke meningeal and brainstem events that potentially lead to the development of headache.

An alternative explanation to the link between pain and aura was provided by May *et al.* (2001) who examined neural influences on the cranial circulation by studying healthy volunteers' responses to injection of the pain-producing compound 'capsaicin' using magnetic resonance angiographic techniques. They concluded that their data was consistent with the notion that pain drives changes in vessel calibre in migraine, not vice versa.

Migraine classification

Headache is an extremely common symptom presenting to primary health care professionals, and an accurate diagnosis is essential to ensure both the correct management of benign conditions and to ensure that when headache presents as a symptom of serious disease then it is dealt with appropriately. The International Headache Society (IHS) published the second edition of The International Classification of Headache Disorders recently (Headache Classification Sub-Committee of the International Headache Society, 2004). The IHS classification is lengthy and is briefly summarised in *Table 1*. The first edition has been summarised, from a clinical optometric viewpoint, by Patel *et al.* (2003).

Migraine is described in section 1 of the IHS classification. Section 11 of the classification describes

Table 1. A summary of the classification of migraine

Migraine without aura
Migraine with aura
Typical aura with migraine headache
Typical aura with non-migraine headache
Typical aura without headache
Family hemiplegic migraine
Sporadic hemiplegic migraine
Basilar-type migraine
Retinal migraine
Childhood periodic syndromes that are commonly precursors of migraine
Benign paroxysmal vertigo of childhood
Abdominal migraine
Cyclical vomiting
Complications of migraine
Chronic migraine
Status migrainosus
Persistent aura without infarction
Migrainous infarction
Migraine-triggered seizure
Probable migraine
Probable migraine without aura
Probable migraine with aura
Probable chronic migraine

headache or facial pain associated with disorders of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cranial structures. The 'eyes' section is further subdivided into acute glaucoma, refractive errors, heterophoria or heterotropia and ocular inflammatory disorder. Section 13 of the classification describes cranial neuralgias and central causes of facial pain: ophthalmoplegic migraine, optic neuritis and ocular diabetic neuropathy are included in this section. Since the present review is concerned only with migraine, these other types of eye headache will not be discussed. However, it should be noted that, to an optometrist, these sections of the IHS classification would appear weak.

Notwithstanding these comments, it must be recognised that the IHS classification is a useful framework for classifying headaches (Leone *et al.*, 1994). However, others have suggested that the classification is more useful for research than for clinical practice (Cady and Dodick, 2002).

The visual disturbances of migraine

Visual aura

The cornerstone to visual aura in migraine are fortification spectra or 'teichopsia', although this may present in only 10% of migraine patients (Lance and Anthony, 1966). Originally described by Airy (1870), the term 'teichopsia' was coined from the Greek terms 'teckhos' meaning fortification and 'opsis' meaning seeing, alluding to the zig-zag design of early Italian military fortifications with which Airy was familiar. The symptoms of scintillating scotoma and a marching fortification figure that gradually expands and then breaks up is characteristic of migraine with aura. Wilkinson (2004) has reviewed migraine visual aura in the context of other visual hallucinations and suggested how these might relate to the neural mechanism of aura.

Queiroz *et al.* (1997) showed that visual aura accompanied the patient's first headache in 39% of patients but only 19% had visual aura with every attack. The free period between visual aura and head pain was <30 min in 75% of cases. The symptoms were described as 'small bright dots' (42%), 'flashes of light' (39%), 'blind spots' (32%) and 'foggy vision' (27%). Fortification spectra were reported by only 20%.

Usually migraine aura are binocular but rarely migraine can affect the anterior visual pathway and produce monocular symptoms. These retinal migraines produce monocular scotomas, and are caused if any of the circulation of the anterior visual pathway becomes involved in the angio-spastic disturbances of migraine. Often the visual loss is described as a black-out or grey-out which can last from seconds to hours, the vast majority lasting <30 min (Hupp *et al.*, 1989).

Migraine aura can occur without headache. The Framingham Study (Wijman *et al.*, 1998) demonstrated that these migrainous visual accompaniments occur in just over 1% of the population aged between 30 and 62 years. This study showed that the mean age of onset of these symptoms was 56 years and in 58% of subjects no headache was reported. Indeed, 42% had no headache history at all.

A variety of ophthalmic conditions may produce visual-aura-like symptoms and need to be differentially diagnosed. *Table 2* contrasts the signs and symptoms of these conditions.

Photophobia and glare

Most migraine sufferers avoid bright light during headache (Selby and Lance, 1960) and many migraine sufferers feel the need to use sunglasses even in between attacks (Drummond, 1986). Wolff (1963) argued that true photophobia is pain induced and exacerbated by bright light, for example in corneal disease or anterior uveitis, and is derived from stimulation of the trigeminal nerve. He argued that glare or dazzle, on the other hand, is uncomfortable but not painful. Glare can be caused by stray light scattering into the eye from ocular structures (such as cataract) or environmental factors (such as a poorly placed lamp). Glare might also be caused by a general excitability of the senses in migraine sufferers, and they have been shown to be more susceptible to glare than controls (Drummond, 1986).

Table 2. A variety of ophthalmic conditions may produce visual-aura-like symptoms and need to be differentially diagnosed. The characteristic signs and symptoms of these conditions are shown

Diagnosis	Monocular or binocular disturbances	Onset of symptoms	Usual duration of symptoms	Scotoma	Photopsiae	Build up of scotoma	Migration of scotoma
Migraine with aura	Binocular	Gradual	15–30 min	Yes	Yes	Yes	Yes
Retinal migraine	Monocular	Gradual	15–30 min	Yes	No	No	No
Amaurosis fugax	Monocular	Sudden	Minutes	Yes	No	No	No
Occipital transient ischaemic attack	Binocular	Sudden	Minutes	Yes	Yes	No	No
Posterior vitreous detachment	Monocular	Sudden	1 month	No	Yes	No	No
Retinal break or detachment	Monocular	Sudden	1 month to continuous	Yes	Yes	Yes	No

Stimulation of the trigeminal nerve during a migraine attack probably accounts for photophobia. Drummond and Woodhouse (1993) stimulated the trigeminal nerve with ice on the forehead and measured discomfort thresholds for migraine sufferers and controls. They showed that trigeminal discharge contributes to photophobia in migraine sufferers and that this trigeminal discharge continued during headache-free periods. However, Drummond (1997) has shown that it is glare, rather than true photophobia, that probably accounts for the light sensitivity experienced by migraine sufferers between attacks. This heightened sensitivity to light is consistent with the heightened sensitivity found to other visual stimuli in migraine sufferers, such as pattern glare, which is discussed later.

Visual migraine triggers

Migraine triggers are the internal or external factors that excite the migraine brain above its genetically reduced threshold and in so doing, precipitate the chain of neurovascular events that produce a migraine headache. It has been suggested that common triggers include certain foods, stress, smells, hormonal changes, irregular meals, changes in sleep pattern and environmental factors such as excessive heat, light or noise (Peatfield and Olesen, 1993). It should be noted that some authors suggest that migraines occur spontaneously and that the triggers that patients associate with their migraine headache are actually due to the fact that in the 'prodrome' phase of a migraine attack some migraine sufferers have a craving for certain foods or drinks (Dowson and Cady, 2002). These then may be blamed for the attack when in fact they are a consequence. Nevertheless, it is generally considered that by making lifestyle changes, the frequency and severity of migraine headache can be reduced.

Migraine patients are sensitive to light during and between headaches (Drummond, 1986). It has also been stated that migraine, as compared with other headaches, is worse during midnight-sun summer than during the polar night (Salvesen and Bekkelund, 2000). These visual stimuli do not have to be strong. Jacome (1998) described a patient who, on multiple occasions, could trigger his typical headache within 30 min just by rubbing his eyes gently and inducing bilateral photopsias. Liveing (1873) described falling snow as a migraine trigger. Debney (1984) produced a thorough review of the literature relating to visual stimuli as migraine trigger factors. She showed that visual stimuli were quoted by at least 10 other authors and ranked visual triggers as similarly important to other more obvious triggers such as stress and hormonal factors.

Debney (1984) reviewed the medical notes of 344 migraine patients and showed that 62% had 'glare' as a precipitating factor, 53% had 'flicker' as a precipitating factor and 1% had 'colour' as a precipitating factor. Debney analysed these findings further and sought to correlate other precipitating factors to those patients who claimed their migraines were induced by visual stimuli. She found significance only with two factors: 1, 'other sensory and environmental factors'; 2, 'dietary factors'. Debney (1984) suggested:

> ...that it would be interesting if the aberrant biochemistry underlying dietary triggers of migraine also affected the sensitivity of the sufferer to visual triggers and to other sensory and environmental triggers.

Debney (1984) then analysed her data further and split them into two groups, one detailing visual tasks quoted to have induced migraine because of glare, and one detailing visual tasks quoted to have induced migraine because they involve flicker. In the glare group, she found that the following situations had all been implicated in precipitating migraine: sun reflections; rippling water or sea; at the beach; snow; paper; chrome trim on a car; microscopy; facing bright windows; fluorescent lighting. In the flicker group, she found that the following situations had all been implicated in precipitating migraine: television; cinema; faulty fluorescent lighting; lighting in vehicular tunnels;

flashlights; headlights; stroboscope; travelling past railings, telegraph poles and fences (by train).

Debney (1984) listed many visual stimuli reported to induce migraine. This list was lengthy but can be summarised by splitting visual triggers into four simple groups; glare, flicker, patterns and colours. Glare could be explained by the trigeminal nerve sensitivity demonstrated by migraine sufferers (Drummond, 1986) or, with flicker, patterns and colour, by cortical hypersensitivity theories (Wilkins, 1995). Both these aspects will be discussed later.

Traditional clinical advice is to avoid trigger factors. Interestingly however, Martin (2000) showed that in patients with visually triggered headaches, there is a desensitisation period such that the visual triggers become less likely to produce headache symptoms with continued exposure. This finding could conceivably alter the way headaches are managed, with exposure to triggers to produce desensitisation as a possible approach, rather than avoidance.

In conclusion, visual stimuli are common and potent migraine triggers. This is emphasised by the fact that some experimenters have used an alternating red and green checkerboard as a strong visual stimulus to cause migraine headache for experimental purposes (Cao *et al.*, 1999).

Refractive errors and migraine

In the early 1900s, uncontrolled studies by Gould (1904) and Snell (1904) argued that low refractive errors, particularly astigmatism, are associated with migraine.

Turville (1934) claimed that uncorrected errors of refraction were a major cause, or at least an important precipitating factor, in cases of migraine. He also claimed that the conventional methods of the time used to provide correction for refractive errors were inadequate. In his opinion, the investigation of refractive errors must include both manifest and latent errors. He defined a latent error not just as latent hyperopia but also as heterophorias, accommodative anomalies 'and in fact any departure from normal visual activity, physiologically, optically, functionally, mentally and psychologically.'

Turville stated that even an inequality of refractive error of 0.25 dioptres was important in many cases and noted that the difference was rarely more than 0.75 dioptres. Turville's study lacked a control group and lacked any form of statistical analysis. It is unclear whether it was the correction of refractive errors, the correction of any decompensated phorias, or placebo effects that were relieving symptoms.

Wilmut (1956), although mostly concerned with the effect of binocular vision on migraine (described below), considered the refractive errors of 116 cases of migraine and compared them to a non-migraine group. He found a similar prevalence of refractive errors in migraine and a non-migraine control group.

Several other authors have argued that headaches or migraine are associated with uncorrected refractive errors, but these studies will not be described in detail because there were no control groups or statistical analyses (Gordon, 1966; Lanche, 1966; Vaithilingham and Khare, 1967; Cameron, 1976; Hedges, 1979; Worthen, 1980).

Waters (1970) identified by a questionnaire, in a random sample of a general population, groups of individuals with; headache, unilateral headache, migraine, and a fourth group who had not had a headache for a year. A masked assessment of the visual acuity and ocular-motor balance was then performed on each group. Visual acuity was measured unaided and aided if spectacles were worn. Waters found that there was no significant difference between the unaided vision, or visual acuity with spectacles if normally used, of either men or women in the four groups. In addition, he found no significant difference between groups in the number of individuals wearing spectacles for either distance or near vision. He concluded by suggesting that these data showed that in the general population headaches are seldom caused by a visual defect. However, Waters did not assess refractive error at all and so doubt must be raised over his conclusions.

Vincent *et al.* (1989) determined the prevalence of visual symptoms and eyestrain factors in a group of chronic headache sufferers as compared with age- and sex-matched controls and found near visual tasks to be one of the many visual triggers to chronic headache. However, this questionnaire survey did not take account of whether the near visual tasks were carried out with corrected or uncorrected refractive errors. Nevertheless, it has been suggested (Gordon *et al.*, 2001) that Vincent's data could suggest a relationship between headache, refractive error, accommodation and convergence.

Gordon *et al.* (2001) reviewed the experimental and clinical evidence on possible links between refractive errors and headaches and listed several issues that were still to be resolved. This review did not relate specifically to migraine, so will not be described in detail. Evans *et al.* (2002), in a study described in the next section, found no significant difference between a group of migraine and a group of control patients in the subjective refractive error or in the proportion of participants who wore spectacles.

To conclude, the association between uncorrected refractive errors and migraine seems to be equivocal. Early studies reported much anecdotal evidence but the few modern studies, which included masked control groups and statistical analyses, have found little

evidence. Often researchers have failed to classify headaches correctly and so data relating specifically to migraine is rare. In addition, little or no evidence appears to relate to any possible pathogenic link between refractive errors and migraine.

Binocular vision (orthoptic anomalies) and migraine

Snell (1904) argued that heterophoria is a cause of headache, especially esophoria when found in conjunction with myopia. Turville (1934) suggested that low convergent and divergent fusional reserves are correlates of migraine and that base in prisms are an effective treatment for many cases of severe classical migraine. Turville describes his first successful case of relief of migraine with base in prisms and it is interesting to note that this patient was esophoric rather than exophoric as might have been expected. The prism power was determined in an unconventional way: as one-third of the recovery point from the measurement of the *divergent* fusional reserves. He described a migraine sample of 123 cases, but there was no control group or placebo treatment. As recently as 2000, the use of base in prism to relieve migraine headache was still advocated (Bush, 2000).

Wilmut (1956), using a polarised version of the Turville Infinity Balance, found that 91% of patients with migraine had 'excessive exophoria' and had previous argued that 56% of his cases were cured with base in prism (Wilmut, 1951). Wilmut's (1956) study was of a clinical sample and may have suffered from referral bias, and does not appear to have been a randomised control trial. However the results were compared with an unspecified control group in which exophoria occurred in only 25%.

Waters' (1970) questionnaire regarding headache and migraine sufferers, discussed in the previous section, not only looked at visual acuity but also ocular-motor balance. The ocular-motor balance was assessed by the cover test and a Maddox hand frame with habitual spectacle correction, if worn. Thus, the total dissociated strabismus or phoria was assessed. Waters stated that there was no evidence that the proportion of subjects with esophoria or exophoria for either distance or near vision differed in the four groups in either sex. Unfortunately, the data for esophoria and exophoria were combined and so data on this aspect are not meaningful. The only statistically significant finding Waters made was that the migraine group had a higher proportion of individuals who had hyperphoria at near. Waters stressed however that this result was only meaningful when the male and female groups were analysed together and over 20 chi-squared tests had been completed. He concluded by suggesting that these data showed that in the general population headaches are seldom caused by a visual defect. He also noted that the beneficial effect of any treatment, if applied in an uncontrolled manner, could not be considered as evidence relevant to the aetiology of headache.

Friedman (1977) claimed that 'fusional stress' could accompany 'dynamic binocular seeing' and that this could be a cause of migraine. He advocated a specific instrument for intensive visual training. Friedman presented no data to back up his claims, only case study reports.

Worthen (1980) studied the effects of stimulating extraocular muscles in patients on whom operations for strabismus were performed under local anaesthesia. The muscles were exposed under light anaesthesia and then stimulated in various ways. Pinching, pricking or cutting the recti muscles caused no sensations, but traction produced prompt exclamations of pain. The pain was always described as an aching sensation localised deep in the eye/orbit on the side of the stimulated muscle. Worthen went on to describe two case studies where the reproduction of extraocular muscle imbalances produced consistent results of headache and aesthenopic symptoms. Electromyographic recording of these patients suggested that the symptoms arose from increased tension in the muscles of the head and neck. Nevertheless, Worthen claimed that the headaches caused by muscle imbalance (heterophoria) could be eliminated by proper alignment of the visual axes and stated that prisms, orthoptic training, or even surgery may be necessary. He suggested that occlusion could be used to diagnose headaches associated with binocular anomalies. Although Worthen (1980) used an interesting approach, his small number of subjects limits the strength of his conclusions.

Sucher (1994) related the symptoms of headache to the 'monocular blur effect': a consistent blur of one eye when viewing the 6/18 letters on a letter chart during the Turville infinity balance test, whilst the patient raises and lowers their chin. Sucher found a statistical relationship between this monocular blur effect and patients who have three or more headaches a month. He also found that the monocular blur occurred on the same side as lateralized headaches in 94%, and then in 93%, of two cohorts of patients tested. Sucher speculated that the monocular blur effect could be corrected by prisms, and that this correction would then relieve tension on the ocular motor system and so remove a source of headache. However, Sucher's study did not look at the effect of treatment.

Evans *et al.* (2002) compared 21 migraine sufferers to 11 controls and found no difference between the groups in relation to strabismus or hyperphoria. The main purpose of this study was to investigate the effect of coloured filters (Wilkins *et al.*, 2002), so the migraine sufferers were selected as those who found a coloured

filter to be helpful. They therefore did not represent a 'normal' group of migraine sufferers. Evans *et al.* (2002) did find using one test method, that the migraine group tended to have a marginally decompensated exophoria at near; however, other test methods suggested that the migraine group were as able to compensate for their exophoria as the control group.

Decompensated heterophoria, the diagnosis of which is discussed by Evans (2002), has been linked to headaches by many authors (e.g. Jenkins *et al.*, 1989; Yekta *et al.*, 1989; Evans, 2002). However, these authors do not specifically discuss migraine.

The association between anomalies of binocular vision and migraine seems to be equivocal. Early studies have suggested anecdotal evidence but the few modern studies, which have been more statistically and methodologically robust, have either found little evidence, or have generally related to headache or aesthenopic symptoms, rather than specifically to migraine.

Visual fields and migraine

The visual system beyond the eye can be investigated in a number of ways. Psychophysical testing of visual processing can shed light on perceptual issues in migraine as discussed by Coleston *et al.* (1994), McKendrick *et al.* (1998) and others. These studies do not involve clinical optometric approaches and will not be discussed in detail here, but are reviewed by Chronicle and Mulleners (1996). Electrophysiology can directly measure cortical activation but is also not an optometric procedure and is extensively reviewed elsewhere (Aurora *et al.*, 1998; Afra *et al.*, 1998, 2000; Cao *et al.*, 1999).

Several studies have assessed visual fields in migraine. McKendrick *et al.* (1998) showed deficits to tasks involving 16 Hz flicker using a Medmont 6000 perimeter auto flicker paradigm in a single migraine sufferer. Later, McKendrick *et al.* (2000) performed similar temporally modulated perimetry in 16 migraine sufferers and 16 controls and suggested that migraine sufferers have selective visual dysfunction for temporally modulated targets of a temporal frequency > 9 Hz.

Other visual field anomalies have been found in migraine patients. McKendrick *et al.* (2002) performed short-wavelength automated perimetry (SWAP) and standard automated perimetry (SAP) using a Humphrey Visual Field Analyser. Although they did not find a significant difference in mean deviation and pattern standard deviation between migraine sufferers and controls using SAP, both these parameters were significantly worse in the migraine group using SWAP. The authors suggested that migraineurs should not be included in visual field normative databases.

Klein *et al.* (1993) reported results from the Beaver Dam Eye Study that showed no relationship between open-angle glaucoma and migraine headache. They used diagnostic criteria based on visual fields, intraocular pressure, cup/disc ratio and history. Usui *et al.* (1991) found no greater prevalence of migraine in a glaucoma population compared with a normal population and Pradalier *et al.* (1998) commented that migraine prevalence was not significantly different between normal and high tension glaucoma sufferers.

Alternatively, other authors have found that there is a relationship between normal tension glaucoma and migraine headache (Cursiefen *et al.*, 2000). In particular, migraine has been considered a risk factor for glaucomatous visual field progression (Drance *et al.*, 2001). Comoglu *et al.* (2003) found glaucomatous-like visual field defects in patients with migraine in the absence of raised intraocular pressures and suggested that there might be a relationship between the pathophysiology of normal tension glaucoma and migraine. McKendrick agreed with this viewpoint (McKendrick *et al.*, 2000, 2002) and concluded that the similarity of SWAP defects and temporally modulated perimetry defects in migraine sufferers and glaucoma sufferers might raise the possibility of a common pre-cortical vascular involvement in these two conditions.

We would suggest an alternative explanation that migraine headache might cause a magnocellular-specific dysfunction unrelated to glaucoma. Such an interpretation would account for the fact that some studies have suggested a link to normal tension glaucoma, as intraocular pressures would remain unaffected. We are currently comparing visual fields, ocular tensions, and optic nerve head analysis in migraine and control groups to investigate this hypothesis.

Interestingly, McKendrick and Badcock (2003) have shown that migraine sufferers with visual field loss to temporally modulated targets but not to SAP exhibit dysfunction of both the parvo-cellular and magnocellular pathways. How this might relate to the mechanism of visual field dysfunction in migraine is yet to be investigated. Coleston *et al.* (1994) also found evidence suggesting both magno- and parvo-cellular deficits in migraine. These authors suggested that the deficit was pre-cortical, and they noted that this could reflect either intrinsic abnormalities or a consequence of attacks. As considerably more nerve fibres run from the cortex back to the lateral geniculate nucleus than the ascending geniculostriate pathway, they hypothesised that recurrent migraine episodes might cause cortical damage which in turn causes pre-cortical deficits. Chronicle and Mulleners (1994) suggested that cerebral ischaemia occurs in migraine and that this results in long-term damage to GABA-ergic cells in the visual cortex, which are especially sensitive to hypoxia.

Pupil anomalies and migraine

Lance (1993) has suggested that migraine could be viewed as a derangement of autonomic monoaminergic function. If so, then pupil dysfunction should be a feature of the migraine headache. However, the issue is confused by Rubin *et al.* (1985) who found that any difference in pupil responses between migraine sufferers and controls can be attributed, at least in part, to differences in personality. They claim that the migraine personality is more neurotic and depressive, and so responds emotionally in a different way to non-migraine controls. This, they claim, can affect the pupil responses as emotional factors are related to the autonomic nervous system.

Whilst the pupil abnormalities associated with migraine headache are often subclinical, there is some good evidence that such pupil anomalies can be unmasked by experimental procedures. Often this has involved the use of pharmacological agents to elicit different responses in migraine and non-migraine sufferers and this research is reviewed below.

Sympathetic hypofunction

Fanciullacci *et al.* (1977) have shown greater pupil dilation from instillation of phenylephrine and a reduced pupil dilation from the instillation of fenfluramine in idiopathic headache, as compared with controls. They concluded that this showed a supersensitivity of iris adrenergic receptors in idiopathic headache. Herman (1983) has shown that anisocoria exists in both migraine and cluster headache sufferers but by only a mean of 0.8 mm. Gotoh *et al.* (1984) found sympathetic hypofunction in migraine sufferers during headache-free periods with a variety of neurological tests. Rubin *et al.* (1985) have shown that 70% of migraine sufferers in the inter-ictal phase have deficient sympathetic innervation of the dilator pupillae as compared with controls if challenged by a cold compress. Drummond (1987) compared the pupil diameter of the headache side and non-headache side in migraine sufferers, tension headache sufferers and non-headache controls. He showed that pupil diameter was smaller on the side of the headache both during headache and during headache-free periods in patients who habitually had headache on the same side of the head. Drummond (1990) has shown that facial temperature and pupil responses show a sympathetic deficit in migraine sufferers. The facial temperature was asymmetric and associated with the side of headache during a headache attack but not between attacks. In contrast, pupil diameter was smaller on the usual side of headache both during the headache and during the headache-free interval.

De Marinis (1994) stated that the evidence was so strong that pharmacological tests of the pupils could be used to differentially diagnose different forms of idiopathic headache. De Marinis *et al.* (1998) used pharmacological pupillary tests to investigate the oculosympathetic system in patients diagnosed as having migraine without aura. In contrast to the findings of Drummond (1987, 1990), De Marinis *et al.* claimed that the oculosympathetic hypofunction was not related to headache side and was temporally related to the migraine attack, being absent after 15 days. Battistella *et al.* (1989) showed that this sympathetic hypofunction existed in children with migraine but to a lesser extent which suggests a progression of the sympathetic hypofunction from childhood into adulthood.

Parasympathetic deficits

Purvin (1995) described a case of a 46-year-old woman who had suffered migraine headaches for the previous 20 years. Following one attack, she developed Adie's tonic pupil in one eye. He stated this could be caused by an unusually prolonged migrainous vasospasm leading to local ischaemia of the posterior lateral ciliary artery supplying the ciliary ganglion.

Overall considerations of the pupil and migraine

The evidence for a sympathetic hypofunction in migraine is strong although authors disagree on whether it persists in the headache-free period and if it is related to the side of the habitual headache.

The evidence of Adie's tonic pupil relates to one case study which although detailed is not good evidence and may represent a unique patient event rather than a general trend for all migraine sufferers.

Evans and Jacobson (2003) recently presented a case study of transient anisocoria in a migraineur and suggested that migraine headache can exaggerate physiological anisocoria and that in their case there were no sympathetic or parasympathetic deficits.

Pattern glare/visual stress and its relief with colour

Some people will report visual perceptual distortions (illusions), eyestrain, and headaches when viewing patterned stimuli. This has been termed 'patterned glare' (Wilkins and Nimmo-Smith, 1984) and more recently 'pattern glare' (Evans and Drasdo, 1991). *Table 3* summarises the feature of patterns that cause pattern glare. When the symptoms of pattern glare are present in everyday life then this is called visual discomfort or visual stress. The early literature included several references to the anomalous visual effects of such patterns (e.g. Purkinje, 1823; Brewster, 1832) and by

Table 3. A summary of the features which make geometric patterns most likely to produce an epileptic response

Feature	Reference
Contrast energy concentrated within one orientation	Wilkins *et al.* (1979)
The length of line is long	Wilkins *et al.* (1979)
High luminance, high contrast	Wilkins (1995, p. 17)
Square wave grating	Soso *et al.* (1980)
Increased size of pattern	Wilkins *et al.* (1979)
Spatial frequencies between two and four cycles per degree	Wilkins *et al.* (1979)
Pattern direction is reversed 10–20 times a second	Wilkins (1995, pp. 31–34)
Binocular rather than monocular viewing	Jeavons and Harding (1975), Wilkins *et al.* (1979, 1980).
Pattern presented in the visual hemi-field that corresponds to the side of the patients cortex that is most easily excited	Wilkins *et al.* (1980), Soso *et al.* (1980), Binnie *et al.* (1981)

the 1960s and 70s these effects were being used in the art world, in a movement called 'Op Art'.

Wade (1978) listed the visual phenomena exploited in op-art and included afterimages, Hermann grid effects, Gestalt grouping principles, blurring and movement due to astigmatic fluctuations in accommodation, scintillation and streaming (possibly due to eye movements) and visual persistence. Symptoms produced from such visual phenomena can range from 'unpleasantness' to producing epileptic fits in susceptible individuals.

Wilkins (1995) summarised the various effects that normal subjects perceive when viewing a striped pattern as follows: red, green, blue, yellow, blurring, bending of the lines, shadowy shapes amongst the lines, shimmering of the lines, flickering of the lines, nausea, dizziness and pain. Wilkins (1995) suggested that if a person suffered from two or more of these illusions when looking at a striped pattern then they were more sensitive than average, should avoid looking at such a pattern for a long time, and could be diagnosed with visual stress. Conlon *et al.* (2001) showed that her patients with visual stress reported most perceptual distortions with a grating of 4 cycles per degree but that patients with little or no visual stress still had perceptual distortion but at a much higher spatial frequency of 12 cycles per degree. A commercially available test is now available for pattern glare/visual stress, which takes advantage of this (IOO Sales Ltd, London, UK).

Mechanism of visual stress

Wade (1977) had earlier suggested three mechanisms that could explain some of these illusions: physiological fixation instability, accommodative changes and the chromatic aberrations of the eye. Zanker (2002) agreed from a computational viewpoint, and claimed that the illusions could have an almost trivial solution in terms of small involuntary eye movements leading to image shifts that are picked up by motion detectors in the early motion system. Wilkins (1995) suggested that these explanations were not adequate to explain the illusions and agreed with Georgeson (1976, 1980) that the illusions had a structure that could more readily be attributed to inhibitory connections in the visual cortex.

A detailed paper by Wilkins *et al.* (1984) was the seminal work in establishing a neurological basis for visual stress. These authors demonstrated in a number of experiments that the illusions were produced by pattern glare, showed that if the number of illusions was more than two then the patients was more likely to have visual stress, that the illusions produced were lateralized with other symptoms and that the same stimuli that produced pattern glare also produced epileptiform EEG activity in susceptible individuals. Unlike the epileptic response to patterns, the illusion response to patterns does not spread widely across a hemisphere probably because the processing is more focal. This focal (localised) response does not spread widely because the cortex is not sufficiently hyper-excitable (Wilkins, 1995).

It should be noted that this visual stress is conceptually different to the sensory visual deficits discussed earlier (e.g. Coleston *et al.*, 1994; McKendrick and Badcock, 2003). Visual stress seems to be a manifestation of cortical hyperexcitability resulting in a visual trigger for migraine (Wray *et al.*, 1995), eyestrain and visual perceptual distortions. It can be thought of as a visual component to the migraine brain's over-sensitivity to environmental triggers (Welch, 2003). In contrast, the sensory visual deficits seem more likely to be a consequence of neural damage caused by migraine over a number of years. In contrast with this view, Shepherd (2000) reported a correlation between pattern glare and contrast sensitivity and supra-threshold contrast scaling in migraine, but did not find any overall effects due to migraine duration or frequency of migraine attacks.

Pattern glare, visual stress and headache

Interestingly, this illusion response to patterns has a relationship to headache frequency. Wilkins *et al.* (1984) showed that there is a direct correlation between the number of headaches reported and the number of illusions seen whilst viewing a striped pattern of about 4 cycles per degree. Unfortunately, several of the experiments cited in this paper excluded migraine sufferers. However, experiment 7 in this paper did show that migraine sufferers perceive more illusions with a pattern glare stimulus than tension headache sufferers. The correlation between migraine headache and pattern glare only held when the pattern design was within the

epileptogenic range and did not hold when other symptoms such as back pain were discussed. For these reasons Wilkins and his team suggested that the finding could not be attributed to response bias.

People are more susceptible to illusions on days when they have headaches (Nulty *et al.*, 1987). In addition, people show more aversion to striped patterns if they are headache sufferers particularly if the headaches are migraines. Marcus and Soso (1989) showed that when viewing epileptogenic striped patterns, 82% of migraine suffers demonstrated aversion whist only 18% of a control group did so. There was no difference between migraine with and without aura. If the illusions appear more pronounced on one side of a pattern then that patient is more likely than others to experience head-pain that is consistently lateralized (Wilkins *et al.*, 1984).

Aurora *et al.* (1998, 1999) used transcranial magnetic stimulation to demonstrate that the visual cortex is indeed hyperexcitable in people who suffer from migraine. Huang *et al.* (2003) used functional MRI in patients who had migraine with aura to show that square-wave gratings that produced pattern glare did induce a hyperneuronal response in the visual cortex.

The relief of pattern glare and visual stress with colour

Colour preference can be related to psychology (red for danger and excitement or blue being a calming colour) or to ocular pathological conditions such as the brunescence of nuclear sclerotic cataract producing yellowing vision. Some individuals may wear tinted lenses due to neuroses (Howard and Valori, 1989). Other people with certain neurological disorders, such as dyslexia, migraine or epilepsy can be helped by using individually prescribed coloured filters (Lightstone, 2000), most likely through their effect on pattern glare/visual stress (Wilkins, 2003). Griffiths (2001) stated that measuring colour preference should be part of a routine optometric examination and produced a six-colour system to do this. However, the randomised controlled trials of Wilkins *et al.* (1994, 2002) and Robinson and Foreman (1999) suggest that a greater degree of precision is required and this is supported by recent data alluded to by Wilkins *et al.* (2004). The Intuitive Colorimeter (Wilkins and Sihra, 2000) is commonly used for this purpose in the UK.

The use of individually prescribed coloured filters for children with reading difficulties has been described as Meares-Irlen syndrome, which is likely to be a manifestation of visual stress. This subject has recently been reviewed by Evans (2001) and Wilkins (2003). The benefit from coloured filters is not solely attributable to placebo effects (Wilkins *et al.*, 1994; Robinson and Foreman, 1999); conventional optometric or orthoptic anomalies (Evans *et al.*, 1995, 1996b; Scott *et al.*, 2002); spatio-temporal contrast sensitivity functions (Simmers *et al.*, 2001); or a magnocellular deficit (Evans *et al.*, 1995, 1996a; Simmers *et al.*, 2001). Instead, the benefit from coloured filters is most likely attributable to pattern glare (Evans *et al.*, 1995, 1996a) which can be caused by lines of text (Wilkins and Nimmo-Smith, 1984). Deficits of visual attention in some people with reading difficulties might make them particularly sensitive to pattern glare (Evans, 2001). As people with migraine are particularly sensitive to pattern glare, it is not surprising that migraine-like headaches are prevalent in children with reading difficulties who benefit from precision-tinted lenses (Evans *et al.*, 1996b).

It is argued that coloured filters change the distribution of the firing pattern within the visual cortex and, since cortical hyperexcitability may vary locally within the visual cortex, individually prescribed coloured filters are an effective treatment (Wilkins, 1995; Wilkins *et al.*, 2004). This hypothesis has been supported by recent work showing that the representation of colour in the visual cortex follows topographic maps (Xiao *et al.*, 2003).

Chronicle and Wilkins (1991) have found that the visual stress of migraineurs is determined by the colour of the illuminating light, tending to avoid red illumination. In contrast, Good *et al.* (1991) showed that migraine frequency was reduced in children who wore rose tinted spectacles compared with a blue tint. If the tint is prescribed precisely and individually, then the reduction in symptoms with colour is not due to alterations in binocular function or refraction (Evans *et al.*, 1996a,b, 2002).

Wilkins *et al.* (2002), in a double-masked randomised controlled study, compared the effectiveness of precision-tinted ophthalmic lenses in the prevention of headache in migraine sufferers. They showed with headache diaries that headache frequency was significantly lower when a precise optimal tint was worn when compared with a suboptimal tint used as a control. The group was a selected group of migraine sufferers that found colour helpful and their optometric characteristics were described by Evans *et al.* (2002). Evans *et al.* (2002) showed that pattern glare symptoms of visual stress were reduced with a precisely selected colour of tinted spectacles. However, this reduction in visual stress was not significantly different from that produced by only a slightly different tint that was used as a control.

To conclude, certain visual stimuli produce visual stress. Migraine sufferers are particularly susceptible to visual stress and it can be reduced with precision-tinted spectacles. By reducing visual stress in migraine sufferers, migraine frequency can be reduced.

Table 4. Summary of visual correlates of migraine. The visual correlates have been divided into sensory and motor correlates. Levels of evidence based on the Centre for Evidence Based Medicine (Oxford, UK) (1999) recommendations have been assigned (where 1 is high evidence and 5 is low evidence) by the present authors

Factor	Assessment (clinical or research)	Evidence (levels 1–5)	Relevance (correlate, cause, treatable?)
Visual sensory factors			
Pupil (sympathetic hypofunction)	Research tests Routine clinical tests	Level 1b	Correlate
Pupil (parasympathetic hyperfunction)	Research tests	Level 4	Correlate
Flicker	Routine clinical tests	Level 2b	Correlate
Visual stress/pattern glare	Routine clinical tests	Level 1b	Correlate Cause? Treatable
Visual motor factors and refractive error			
Exophoria	Routine clinical tests	Level 4	Correlate Cause? Treatable
Hyperphoria	Routine clinical tests	Level 4	Correlate Cause? Treatable
Refractive error	Routine clinical tests	Level 4	Correlate Cause? Treatable

Summary

Headache is a common symptom reported by patients who consult optometrists (Barnard and Edgar, 1996). As migraine accounts for as many as 54% of all headaches (Leone *et al.*, 1994) this suggests that optometrists are likely to encounter patients with migraine very commonly.

Some authors have argued that optometric anomalies are a trigger for migraine (Snell, 1904; Turville, 1934; Wilmut, 1956; Waters, 1970; Griffin, 1996; McKendrick *et al.*, 1998). In contrast, the medical literature is sceptical about the role of visual factors in headaches and migraine (Lyle, 1968; Headache Classification Sub-Committee of the International Headache Society, 2004).

In the current climate of clinical governance, there is a need for evidence-based research to guide optometrists as to the role they can play, if any, in managing some cases of migraine. This review has critically examined the evidence that correlates migraine headache and optometric factors. Each optometric correlate of migraine can be segregated into either a visual sensory or visual motor factor, and *Table 4* summarises the evidence. With the exception of the sensory visual factor of visual stress/pattern glare, and sympathetic hypofunction, the evidence correlating optometric factors with migraine is generally poor.

Thus, it appears that there is acceptable evidence in the literature to suggest that both cortical hyperexcitability (as demonstrated by pattern glare) and peripheral neurological defects (as demonstrated by the sympathetic hypofunction with pupil responses in migraine sufferers) are associated with migraine headache. The cortical and peripheral theories are not incompatible. It could be suggested that cortical hyperexcitability is an interictal status that leads to pattern glare and that this sensory visual factor is a trigger for migraine. This is consistent with many other authors who have found that migraine can be triggered by certain visual stimuli. It seems that precision-tinted lenses might be one method of minimising the impact of visual triggers for migraine headache sufferers. Additionally, pre-cortical changes to the visual system (such as the pupil changes and some of the visual field anomalies found) may be a long-term consequence of the neuro-vascular interactions of migraine headache.

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Frequency Doubling Technology perimetry and standard automated perimetry in migraine

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Abstract

The literature suggests that visual field defects may be more common in people who experience migraine. The Humphrey frequency doubling (FDT) visual field instrument selectively examines the magnocellular visual pathway, but has not previously been used to investigate visual function in migraine. In a masked controlled study we compared Humphrey FDT and Humphrey Swedish Interactive Threshold Algorithm fields of 25 migraine sufferers with 25 age- and gender-matched controls. Although both mean deviation and pattern standard deviation were a little worse in the migraine group, these differences did not reach statistical significance. There were no inter-eye visual field differences in the migraine group compared with controls. Comparing the mean of all the contrast thresholds in each hemisphere, there were no more inter-hemifield visual field differences in the migraine group compared with controls. There was no significant difference between the migraine and control groups in intra-ocular pressures. The visual field parameters were not correlated with the interval since the last migraine headache, the severity of migraine headache, the duration of migraine headache or the number of migraine headaches per annum. In our data, there was no evidence of visual field deficits, a magnocellular deficit, or indications of glaucomatous pathology.

Keywords: glaucoma, migraine, vision, visual fields

Introduction

People who suffer from migraine headaches have been found to perform less well than non-headache controls when undergoing psychophysical tests that involve the magnocellular pathway. For example, it has been shown (Coleston *et al.*, 1994; Coleston and Kennard, 1995; McKendrick *et al.*, 1998, 2001) that migraine sufferers have a reduced ability to detect some temporal visual stimuli in the range of 10–20 Hz and that migraine sufferers also have impaired perception of spatial frequency stimuli around four to five cycles per degree (Coleston *et al.*, 1994).

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This magnocellular deficit in migraine sufferers has been revealed in perimetric studies. McKendrick *et al.* (1998) compared a single migraine sufferer to 15 control participants, measuring the visual fields within 24 h of a migraine event and then at regular intervals for the next 5 months. This revealed deficits to tasks of 16 Hz, which are believed to be responsible for localised magnocellular processing (McKendrick *et al.*, 1998). However, these results are of one migraine sufferer only and so need to be interpreted with caution. Similar temporally modulated perimetry has been used to investigate 16 migraine sufferers and 16 controls and showed that migraine sufferers have selective visual dysfunction for temporally modulated targets of a temporal frequency >9 Hz (McKendrick *et al.*, 2000). Other visual field anomalies have been found in migraine patients. Comparing short-wavelength automated perimetry (SWAP) and standard automated perimetry using a Humphrey Visual Field Analyser it has been found that, compared with a control group, about 50% of migraine sufferers (with or without aura) demonstrated a SWAP sensitivity deficit (McKendrick *et al.*, 2002). McKendrick and

Badcock (2004a) also found evidence of deficits in some cases of migraine using motion coherence perimetry but did not find defects with frequency doubling stimuli.

These visual field findings raise questions about whether migraine might be associated with glaucoma, although this is controversial. One explanation of the conflicting views regarding migraine and glaucoma is that migraine headache might be associated with visual field changes unrelated to glaucoma. This was recently discussed by Harle and Evans (2004). Such an interpretation would predict that intra-ocular pressures should remain unaffected, which would account for the fact that some studies have suggested a link with normal tension glaucoma. We sought to investigate visual fields in migraine using both frequency doubling technology (FDT) perimetry and Humphrey Swedish Interactive Threshold Algorithm (SITA) visual fields.

Method

Participants were recruited to the study as part of a collaboration with local general medical practitioners and with a London Hospital Neurology Unit specialising in migraine headache. All patients had a formal medical diagnosis of migraine and this was confirmed with a headache questionnaire, which ensured the migraine diagnosis met International Headache Society criteria (Headache Classification Sub-Committee of the International Headache Society, 2004). Participants for the migraine group were aged between 10 and 50 years with a frequency of migraine headaches of at least one per month. People with systemic health problems, pregnancy, or ocular disease were excluded from the study.

We were careful to avoid referral bias: at no time was the nature of the study, its association to vision, or words associated with vision, the eyes, or eye-care mentioned to participants during the initial stages of recruitment. The visual nature of the research was only revealed when participants arrived at the clinic, when full informed consent was obtained. The tenets of the Helsinki declaration were followed, specifically advising patients of their ability to abstain or withdraw at any time. No participants withdrew after they had arrived at the clinic. The Institute of Optometry and City University Research and Ethical committees approved the study.

Of the 250 names supplied by the hospital neurological unit, 54 replied to the initial contact. At this stage (before the first appointment) written correspondence was sent out to request that each participant attend together with a friend (non-migraineur) of appropriate age and gender as a control. This correspondence explained and stressed the importance of the masked controlled design. From this group 20 migraineurs eventually attended the research clinic. In addition to these 20, a further five migraine patients were recruited from local GPs, and these participants were similarly requested to attend with a friend as a control.

All but three of the 25 migraine participants brought with them a person of the same gender and of a similar age, but who did not experience migraine or frequent headaches or have any health problems as listed above. These people undertook the same battery of tests as the migraine sufferers and were used to constitute a control group and completed a consent form on attending the clinic. Three members of the staff of the Institute of Optometry were used to complete the control group and were paired with the three migraine sufferers who did not bring a friend.

Prior to attending the research clinic, participants in the migraine group were asked to complete a 6-week headache diary. This indicated the last migraine headache. On attending the clinic, all participants were asked to complete a short questionnaire detailing their symptoms and history, including questions relating to headaches (see Appendix). This ensured that the migraine group met all the IHS criteria for migraine headache (Headache Classification Sub-Committee of the International Headache Society, 2004) and ensured that the control group were truly migraine free. The responses to this questionnaire were not revealed to the research optometrist until the end of the tests of both the migraineur and the control participant. All participants were headache free at the time of testing (see *Table 3*).

Following completion of the questionnaire, the first examination procedure was an assessment of intra-ocular pressure using the average of three readings for each eye with an American Optical Non-Contact II Tonometer. Then N30 FDT Humphrey Visual Fields were performed with the patients' own habitual far refractive correction. The procedure was explained and demonstrated to the participant, and the right eye was assessed first, followed by the left eye. Then 30:2 SITA Humphrey Visual Fields were performed with the patients' own habitual near refractive correction. The procedure was explained and demonstrated to the participant, and the right eye was again assessed first, followed by the left eye. SITA 30:2 and FDT N30 perimetry both give an assessment of the central 30 degrees of visual field. Mean deviation (MD, an indication of any general depression across the visual field compared with the internal normative database of the perimeter) and pattern standard deviation (PSD, an indication of any local abnormalities in a individual's visual field relative to the remainder of their visual field) are calculated and reported by both instruments. Reliability indices are also reported so that any unreliable visual fields could be rejected. For

SITA, an unreliable field was classified as one that had >20% false positive errors or >20% false negative errors. For FDT fields, an unreliable field was classified as one that had >1/8 false positives or >1/5 false negatives.

Results

Sample size

The data described in the paper are part of a large study looking at several potential optometric correlates of migraine. The sample size was determined using sample size calculations based on two variables (heterophoria and pattern glare) for which we have data from previous studies on population difference and variance, and which will be reported in future publications. These calculations suggested 25 migraine sufferers and 25 non-migraine controls were required.

Age and gender

There was no significant difference ($p = 0.78$) between the mean ages of the migraine group (37.5 years) and the control group (36.8 years). The age ranges were 14–50 years for the migraine group and 25–49 years for the control group. Only two subjects (one in each group) were under the age of 25 years. Each group contained 21 females and four males.

Global indices

The reliability criteria for all field results were met and so none were rejected. The reliability indices for false positives and false negatives for each instrument were not significantly different in the two groups (Mann–Whitney *U*-test, $p \geq 0.30$).

Clinically, MD and PSD data are analysed by comparison with normative databases. However, migraine sufferers are included in the instruments' normative databases thus weakening the validity of comparing a migraine group with the instrument norms. Therefore, we compared the MD and PSD in the migraine group with equivalent variables in the control group. The statistical analysis of multi-eye data in ophthalmic research is discussed in the literature (Ray and O'Day, 1985; Murdoch *et al.*, 1998). The inclusion of data from each eye of each participant, especially where the data from each eye are highly correlated (e.g. McKendrick and Badcock, 2004b), is deprecated because it overestimates the statistical significance of the data. An acceptable solution is to average the data from right and left eyes for each participant, and this was the approach that we followed (Ray and O'Day, 1985; Murdoch *et al.*, 1998). *Figures 1–4* show the frequency

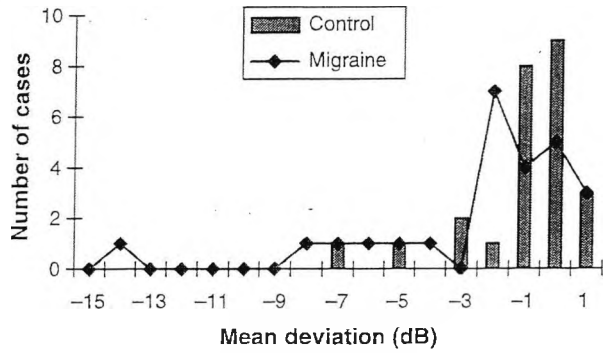

Figure 1. Histogram of the mean deviation for the Humphrey Swedish Interactive Threshold Algorithm visual field test.

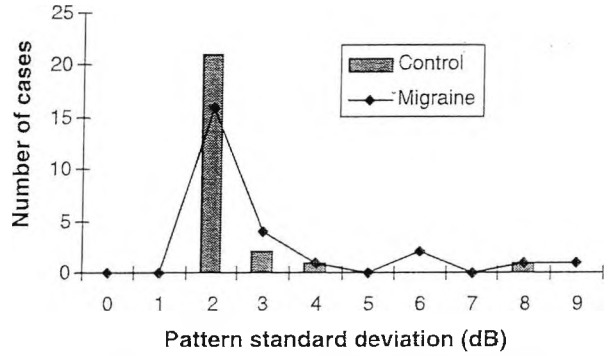

Figure 2. Histogram of the pattern standard deviation for the Humphrey Swedish Interactive Threshold Algorithm visual field test.

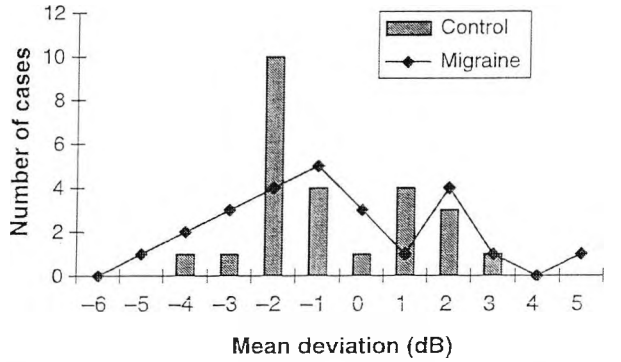

Figure 3. Histogram of the mean deviation for the Humphrey Frequency Doubling Technology visual field test.

distributions for the MD and PSD for the SITA and FDT results. The distributions of both SITA variables appeared skewed and a Kolmogorov–Smirnov test confirmed that these data were not normally distributed ($p < 0.05$), whereas the distributions of the FDT variables were normally distributed ($p > 0.10$). Therefore, non-parametric statistical tests were used for the SITA variables and parametric tests for the FDT variables. Appropriate descriptive statistics are given

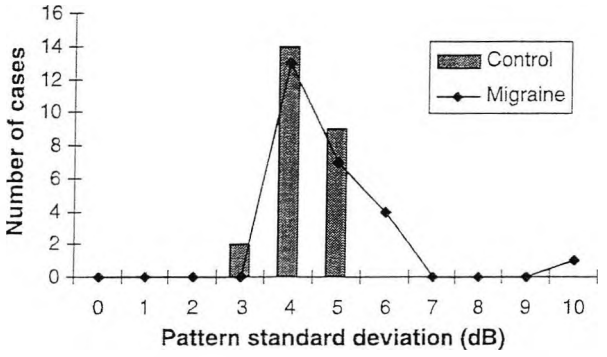

Figure 4. Histogram of the pattern standard deviation for the Humphrey Frequency Doubling Technology visual field test.

in *Tables 1* and *2* which, for completeness, also include the data for each eye individually. *Figures 1–4* are suggestive of a 'tail' of worse performance in the migraine group, but using the Mann–Whitney *U*-test this did not reach statistical significance with the SITA test for either the MD ($p = 0.20$) or PSD ($p = 0.71$) variables. Similarly, using an unpaired *t*-test the performance of the two groups at the FDT test did not differ significantly for either the MD ($p = 0.95$) or PSD ($p = 0.14$) variables.

To evaluate inter-ocular asymmetries, for each participant we calculated the absolute value of the difference between the right and left eye data. Inspection of the frequency distributions of this inter-ocular difference for the MD and PSD variables for each instrument showed that these data are not normally distributed, and this was confirmed by Kolmogorov–Smirnov tests ($p < 0.04$). These four variables did not differ significantly in the two groups (Mann–Whitney *U*-test, $p > 0.12$).

To evaluate inter-hemifield asymmetries, thresholds for each hemifield were averaged. The mean of the right hemifield and the mean of the left hemifield were calculated and then the difference between the right and left hemifield was obtained by finding the absolute difference between these two mean values. There were no significant differences in hemifield data in the migraine group when compared to the control group for both SITA visual fields (Mann–Whitney *U*-test, $p = 0.99$) and FDT visual fields (unpaired *t*-test, $p = 0.39$).

Table 2. Descriptive statistics for the mean deviation (MD) and pattern standard deviation (PSD) results for the Frequency Doubling Technology visual field test

Group	Mean RE	S.D. RE	Mean LE	S.D. LE	Mean (R + L)	S.D. (R + L)
MD						
Control	−1.14	1.90	−1.30	2.03	−1.22	1.91
Migraine	−1.13	2.37	−1.23	2.74	−1.18	2.33
PSD						
Control	3.84	0.63	3.82	0.82	3.83	0.61
Migraine	3.85	0.66	4.65	2.27	4.25	1.26

S.D., standard deviation; (R + L), mean of right and left eye data.

Correlation between results from the two field instruments

To ascertain whether the participants who performed poorly on the SITA task were the same as those who performed poorly on FDT, and to note if there was significant correlation between the global indices for SITA and FDT when compared for individual participants, a correlation analysis was performed. The Spearman correlation coefficients for the total study population of 50 participants were low for each eye MD ($r_s < 0.29$) and PSD ($r_s < 0.22$) and for the signed (right eye minus left eye) inter-ocular difference for MD ($r_s < 0.14$) and PSD ($r_s < 0.14$).

Intra-ocular pressure

The mean IOP for the migraine sufferers was 14 mmHg in each eye and the mean IOP for the control group was 15 mmHg in each eye. These values did not differ significantly in the two groups ($p \geq 0.14$), and neither did the difference between the eyes ($p = 0.14$).

The headache variables

Table 3 shows the descriptive data for the key headache variables: the number of headaches per year, the number of days since the last migraine, the duration of the worst headache, and the severity of the worst headache.

Table 1. Descriptive statistics for the mean deviation (MD) and pattern standard deviation (PSD) results for the Swedish Interactive Threshold Algorithm visual field test

Group	Median RE	IQR RE	Median LE	IQR LE	Median (R + L)	IQR (R + L)
MD						
Control	−1.32	−2.63 to −0.40	−0.98	−1.88 to −0.41	−1.39	−1.81 to −0.57
Migraine	−1.88	−3.79 to −0.47	−1.63	−3.36 to −0.74	−2.14	−2.98 to −0.66
PSD						
Control	1.48	1.34 to 2.02	1.60	1.28 to 1.99	1.62	1.35 to 1.91
Migraine	1.72	1.33 to 2.73	1.53	1.33 to 2.17	1.57	1.35 to 2.37

IQR, inter-quartile range; (R + L), mean of right and left eye data.

Table 3. The descriptive data for the headache parameters

	Number of migraine headaches per year	Duration of worst migraine headache (h)	Severity of worst migraine headache (1 = mild, 2 = mod, 3 = severe)	Time since last migraine headache (days)
Median	24	25	3	14
First quartile	20	7	3	11
Third quartile	43	53	3	20
Minimum	8	2	1	4
Maximum	200	120	3	45

Correlations between headache variables and visual field results

The Spearman correlation coefficients between visual field data (averaged right and left eye values) and headache variables were calculated. The correlations for both PSD and MD for SITA visual fields and the number of headaches per year, number of days since last migraine, and severity of worst headache were all low ($r_s < 0.37$) and non-significant ($p > 0.05$). There were significant correlations between the duration of worst headache and SITA MD ($r_s = -0.42$, $p = 0.04$) and PSD ($r_s = 0.45$, $p = 0.03$). The correlation coefficients between both PSD and MD for FDT visual fields and the number of migraine headaches per year, duration of worst headache, and severity of worst headache were all low ($r_s < 0.30$) and non-significant ($p > 0.05$). The correlation between the FDT MD and the number of days since last migraine approached significance ($r_s = -0.46$, $p = 0.05$), but the correlation between FDT PSD and number of days since last migraine was not significant ($r_s = 0.15$, $p = 0.56$).

Finally, we investigated whether the inter-ocular visual field differences were related to whether the headaches were typically unilateral. Migraine participants were divided into those whose headaches were usually unilateral ($n = 13$) and those whose headaches were not typically unilateral ($n = 12$). For each visual field parameter with each instrument, the absolute inter-ocular difference of the participants with unilateral headaches did not differ significantly from those with non-unilateral headaches (Mann–Whitney *U*-test, $p > 0.15$).

Discussion

Several authors have evaluated test–retest repeatability of perimetry, for both methods that we used (e.g. Artes *et al.*, 2002; Horani *et al.*, 2002) and concerns over repeatability have led many researchers to repeat visual field testing to confirm the presence of any defects. However, in migraine research it is possible that visual field defects might vary with the interval since the last headache (McKendrick and Badcock, 2004c) and this raises serious doubts over the usefulness of repeat testing in this population. In other words, the interval since the last headache may be a confounding variable influencing visual field reproducibility. We therefore chose to evaluate the validity of our data using the intra-test reliability data. The reliability indices were good and showed that the results were of similar reliability in each group. As the reliability indices of the visual fields were within acceptable limits, the fact that participants were not trained in perimetry would seem not to be an issue. The participants wore their habitual refractive correction, rather than their optimal refractive correction and all participants completed all the visual field tests. An advantage of using the habitual refractive correction is that our data were gathered under conditions reflecting participants' everyday visual status and we have no reason to believe that under-corrected refractive errors were any more or less prevalent in our migraine group than in our control group.

Our results suggest that migraine sufferers are no more likely to have abnormal visual fields than controls. We found no more inter-eye differences or inter-hemifield differences in migraine sufferers than in controls. As these non-significant results were found for both FDT and SITA, our data do not support a magnocellular specific dysfunction in migraine. This is in disagreement with some of the literature that suggests visual field defects in migraine (McKendrick and Badcock, 2004b,c; McKendrick *et al.*, 1998, 2001) and we doubt that this is an effect of statistical power as our subject numbers exceeded those in most of these studies (McKendrick and Badcock, 2004c; McKendrick *et al.*, 1998, 2001). McKendrick and Badcock (2004b) compared 24 controls with 28 migraine with aura and 25 migraine without aura participants. They found significantly lower general sensitivity across the visual field and a higher prevalence of localised defects in their migraine group. The discrepancy between their findings and ours might be explained by the fact that they used different flickering stimuli, although our FDT method did involve flickering stimuli. Another possible explanation is that McKendrick and Badcock (2004b) pooled the data from right and left eyes. This approach has been criticised, especially when the right and left eyes' data are strongly correlated as McKendrick and Badcock demonstrated, as being likely to 'give a greater measure of statistical significance than the data warrant' (Ray and O'Day, 1985).

McKendrick and Badcock (2004a) used a computer driven display with custom software to produce an FDT stimulus and compared these results to motion coherence thresholds. The object of this study was to evaluate

motion coherence and frequency doubling at the same points in the visual field and so MD and PSD findings were not reported. Nevertheless these authors did not find differences in their migraine participants compared with controls with their custom software FDT method and our study agrees with these findings.

As noted in the introduction, any link between glaucoma and migraine needs to be carefully considered. The literature suggests that people with glaucoma are not especially likely to have had a migraine (Usui *et al.*, 1991) and migraine prevalence is not significantly different between normal and high-tension glaucoma sufferers (Pradalier *et al.*, 1998). The Beaver Dam Eye Study also showed no relationship between open-angle glaucoma and migraine headache (Klein *et al.*, 1993), using diagnostic criteria based on visual fields, intra-ocular eye pressure, cup/disc ratio and history. Other authors have found that there is a relationship between normal tension glaucoma and migraine headache (Cursiefen *et al.*, 2000). In particular, migraine has been considered a risk factor for glaucomatous visual field progression (Drance *et al.*, 2001). Recently, glaucomatous-like visual field defects have been found in patients with migraine in the absence of raised intra-ocular pressures and this has led to the suggestion that there might be a relationship between the pathophysiology of normal tension glaucoma and migraine (Comoglu *et al.*, 2003). This relationship was also the conclusion of the perimetric studies that suggested a possibility of a common pre-cortical vascular involvement in these two conditions (McKendrick *et al.*, 2000, 2002). In our study we found no significant differences between the migraine and control group in visual fields or intra-ocular pressure. This suggests that in our young (up to age 50 years) sample of participants, migraine sufferers do not have changes associated with glaucoma. However, it would be interesting to investigate whether the subgroup of individuals with migraine that some studies suggest might show periodic visual field deficits when they are younger, are more likely to be diagnosed with glaucoma when they are older.

All our migraine sufferers were headache-free at the time of testing and nearly all had been headache free for a week. The relationship between severity of visual field defect and duration of worst migraine could be explained if the visual field loss results from neural damage occurring during prolonged migraine attacks. There is some support in the literature for a hypothesized chronic damage to the visual system from migraine (Chronicle and Mulleners, 1994). Our results were however equivocal on this issue as the relationship was found only by SITA field analysis and not by FDT field analysis. Nevertheless a relationship between both length of migraine history and frequency of migraine occurrence and lower general sensitivity to flickering visual field stimuli have been recently reported to add weight to this argument (McKendrick and Badcock, 2004c).

To conclude, our data do not support the argument for a magnocellular specific deficit in migraine and do not reveal visual field abnormalities or other signs of glaucoma in migraine headache sufferers. We would conclude that any visual field deficits in migraine are likely to be subtle and not clinically significant.

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Appendix: Some of the sections of the questionnaire relating to headache

- Have you ever been diagnosed as suffering with migraine headache?

  Yes ❒ No ❒

- Think of the worst headache you have had in the last 12 months. How bad was it?

  ❒ Mild

  ❒ Moderate

  ❒ Severe

- How Long Did The Pain Last: _____Hrs

- Please think of the headaches you have had over the last month, and whether they have been getting more frequent or less frequent. Use this information to arrive at your best guess as to how many headaches you have had in the last **12 months**, and write the number here_____

- When you get a headache, which side of the head is the pain mostly concentrated:

  ❒Only Left

  ❒Mainly Left

  ❒Both Sides

  ❒Mainly Right

  ❒Only Right

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The pupillary light reflex in migraine

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Abstract

The literature suggests that there may be pupil size and response abnormalities in migraine headache sufferers. We used an infra-red pupillometer to measure dynamic pupil responses to light in 20 migraine sufferers (during non-headache periods) and 16 non-migraine age and gender matched controls. There was a significant increase in the absolute inter-ocular difference of the latency of the pupil light response in the migraine group compared with the controls (0.062 s vs 0.025 s, $p = 0.014$). There was also a significant correlation between anisocoria and lateralisation of headache such that migraine sufferers with a habitual head pain side have more anisocoria ($r = 0.59$, $p < 0.01$), but this was not related to headache laterality. The pupil changes were not correlated with the interval since the last migraine headache, the severity of migraine headache or the number of migraine headaches per annum. We conclude that subtle sympathetic and parasympathetic pupil abnormalities persist in the inter-ictal phase of migraine.

Keywords: anisocoria, migraine, pupil size, pupillary light response

Introduction

Lance (1993) suggested that migraine could be viewed as a derangement of autonomic monoaminergic function, but controversy still exists as to whether migraine is a chronic sympathetic nervous system disorder (Peroutka, 2004a,b) or whether there are possible parasympathetic contributions (Yarnitsky *et al.*, 2003; Yarnitsky and Burstein, 2004). If migraine is either a sympathetic or parasympathetic disorder, it would be expected that pupil dysfunction should be a feature of the migraine headache. Some clinically significant pupil abnormalities have been reported in migraine sufferers (Woods *et al.*, 1984; Miller *et al.*, 1986; Purvin, 1995; Evans and Jacobson, 2003; Hodge and Friedrich, 2004), but generally the pupil abnormalities associated with migraine headache can be considered to be sub-clinical.

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There is, however, some evidence that these subtle pupil anomalies can be unmasked by experimental procedures such as those using pharmacological agents (see review by Harle and Evans, 2004). Fanciullacci *et al.* (1977) compared patients suffering from idiopathic headache with controls and found that the headache sufferers demonstrated greater pupil dilation from instillation of phenylephrine and reduced pupil dilation from the instillation of fenfluramine. The authors concluded that this showed a super-sensitivity of the iris adrenergic receptors in idiopathic headache. Herman (1983) demonstrated that anisocoria exists in both migraine and cluster headache sufferers, but by only a mean of 0.34 mm. However, this anisocoria increased to 0.8 mm with the instillation of cocaine eye drops suggesting a sympathetic deficiency. Gotoh *et al.* (1984) also found sympathetic hypofunction in migraine sufferers during headache free periods with a variety of neurological tests. Rubin *et al.* (1985) have shown that 70% of migraine sufferers in the inter-ictal phase (between headaches) have deficient sympathetic innervation of the dilator pupillae as compared with controls if challenged by a cold compress. Drummond (1987) compared the pupil diameter of the headache side and non-headache side in migraine sufferers, tension

headache sufferers and non-headache controls. He showed that pupil diameter was smaller on the side of the headache, both during headache and during headache-free periods in patients who habitually had headache on the same side of the head. Drummond (1990) found that facial temperature and pupil responses show a sympathetic deficit in migraine sufferers. The facial temperature was asymmetric and associated with the side of headache during a headache attack, but not between attacks. In contrast, pupil diameter was smaller on the usual side of headaches, both during the headache and during the headache-free interval.

De Marinis (1994) stated that the evidence was so strong that pharmacological tests of the pupils could be used to differentially diagnose different forms of idiopathic headache. De Marinis *et al.* (1998) used pharmacological pupillary tests to investigate the oculosympathetic system in patients diagnosed as having migraine without aura. In contrast to the findings of Drummond (Drummond, 1987, 1990), De Marinis *et al.* suggested that the oculosympathetic hypofunction was not related to headache side and was temporally related to the migraine attack, being absent after 15 days. Battistella *et al.* (1989) showed that this sympathetic hypofunction existed in children with migraine, but to a lesser extent, which may suggest a progression of the sympathetic hypofunction from childhood into adulthood.

The aim of our masked study was to compare the magnitude and latency of the pupil light response in migraine sufferers with age and gender matched controls to establish if pupil changes persisted in the inter-ictal phase of migraine sufferers. If pupil changes occur in this non-headache phase then this would support theories of sustained autonomic imbalance in migraine sufferers.

Method

This study is part of a large case–control study looking at the optometric correlates of migraine, using a battery of optometric tests. The recruitment of the migraine sufferers and age and gender matched controls has been described elsewhere (Harle and Evans, 2005). Participants for the migraine group were aged between 10 and 50 years with a frequency of migraine headaches of at least, on average, one per month. Individuals with systemic health problems, pregnancy, or ocular disease were excluded from the trial. The tenets of the Helsinki declaration were followed: full informed consent was obtained and participants were able to abstain or withdraw from the research at any time without having to give a reason. No participants withdrew after they had arrived at the clinic. The study was approved by the Institute of Optometry and City University Research & Ethics Committees.

Prior to attending the research clinic, participants in the migraine group were asked to complete a 6-week headache diary. This indicated the last migraine headache. On attending the research clinic, all participants were asked to complete a questionnaire detailing their symptoms and history, including questions relating to headaches. The design of the questionnaire allowed for confirmation that the migraine group met the International Headache Society criteria for migraine headache (International Headache Society Headache Classification Sub-committee, 2004) and that the control group were truly migraine free. Participants attended in pairs, one from the migraine group and one from the control group. To ensure that the researcher was masked (Harle and Evans, 2005) as to the identity of the participant: they were seen in random order, were asked not to reveal their identity, and the contents of the questionnaire were not revealed to the research optometrist until the end of the tests of both the migraine sufferer and the control participant. All participants were headache free at the time of testing. The results of the battery of optometric tests conducted have been (Harle and Evans, 2005) or will be reported elsewhere.

The pupil recording apparatus was constructed specifically for this experiment but was conceptually similar to that described in a previous technical note (Wolffsohn *et al.*, 2004). The patient viewed a fixation spot at 20 cm from a 15″ cathode ray tube monitor on which was mounted an infra-red sensitive camera surrounded by six infra-red light emitting diodes (area covered 20 cm^2). The camera was linked to a National Instruments PCI-1407 image acquisition card in a Pentium III 700 MHz PC via the BNC connector. Thresholding image analysis using a purpose-written program in LabView and Vision software (National Instruments, Austin, TX, USA) allowed the pupil size to be detected in real-time at up to 60 Hz. Although the National Television Systems Committee signal is completely refreshed at a frequency of 30 Hz, by analysing the non-interlaced signal a frequency of 60 Hz can be achieved on a half-height image. Conventional image analysis for edge detection is limited to a resolution of 1 pixel for a given intensity threshold criterion. However in a real image, an 'edge' is contained within a pixel 'staircase' of changing intensity. By fitting the 'staircase' with a quadratic profile, a given intensity threshold criterion (to detect the edge of the pupil) was extrapolated to determine the horizontal pupil diameter at an accuracy of 1/1000th of a pixel, allowing a system resolution of < 0.01 mm. The intensity of the monitor surrounding the camera was increased (from 2.6 to 128 cd m^{-2} for a duration of 0.25 s) to produce a screen 'flash' four times at random intervals (to avoid adaptive or prediction effects) to stimulate a time-synchronised

change in pupil size. Each screen flash was not repeated until baseline pupil diameter had been re-established. Testing was carried out under room illumination of approximately 100 cd m^{-2}. Results were obtained for 20 of the migraine group and 16 of the control group.

The data were saved into a Microsoft Excel spreadsheet for each subject and graphed. The mean of the horizontal pupil size for 0.5 s before each flash of light was taken as the baseline pupil size. Blinks or eye movement artefacts (defined as any value outside ± 3 S.D. of the mean) were excluded. The time taken for the horizontal pupil to reach maximum constriction from the flash presentation and the minimum pupil size at this point was recorded (see *Figure 1*). This was averaged over the four repeated measures for each eye individually.

Distributions were tested for normality by inspecting frequency distributions and carrying out the Kolmogorov–Smirnov and Shapiro–Wilk tests of normality. Parametric and non-parametric statistical tests were used as appropriate and when group means are quoted the 95% confidence limits are given in parentheses. The statistical analysis of multi-eye data in ophthalmic research is discussed in the literature (Ray and O'Day, 1985; Murdoch *et al.*, 1998). The inclusion of data from each eye of each participant, especially where the data from each eye are highly correlated (as in the present data), is deprecated because it overestimates the statistical significance of the data. An acceptable solution is to average the data from right and left eyes for each participant, and this was the approach that we followed (Ray and O'Day, 1985; Murdoch *et al.*, 1998).

Results

Age and gender

There was no significant difference (*t*-test, $p = 0.79$) between the mean age of the migraine group (37.3 years, 32.2–42.4) and the control group (36.4 years, 31.7–41.0). Only two subjects (one in each group) were under the age of 25 years. The migraine group contained three males and 17 females and the control group contained two males and 14 females.

Pre-stimulus pupil size

There was no significant difference (*t*-test, $p = 0.74$) between the mean pre-stimulus pupil size of the migraine group (3.062 mm, 2.803–3.322) and the control group (3.003 mm, 2.735–3.271). Nor was there a significant difference (*t*-test, $p = 0.26$) between the pre-stimulus anisocoria between the migraine group (mean, 0.197 mm, 0.110–0.284) and the control group (mean, 0.264 mm, 0.179–0.349).

Amplitude of pupillary light response

The amplitude of the pupillary light response was calculated as the change in pupil size of each eye following the light stimulus. The amplitude of pupillary light response did not differ significantly in the migraine group and the control group for either eye (Mann–Whitney test, $p > 0.36$). Nor was there a significant difference between the absolute inter-eye difference in pupillary light response between the

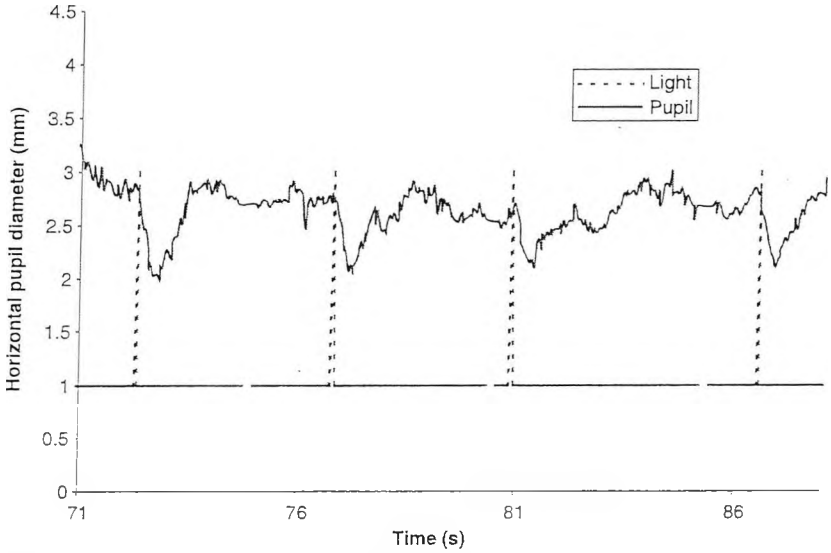

Figure 1. A pupil light response trace was produced for each eye. The latency was taken as the time from stimulus to minimum pupil size. The base line pupil diameter was taken as the mean diameter 0.5 s before the stimulus. A blink artefact is shown at 62 s.

migraine group and the control group (Mann–Whitney test, $p = 0.52$).

Latency to the maximum pupillary light response

The latency to the pupil light response was that time recorded from the light flash until maximum constriction. There was no significant difference (t-test, $p = 0.78$) between the latency of the mean (right and left) pupil light response of the migraine group (mean, 0.638 s, 0.605–0.671) and the control group (mean, 0.631 s, 0.591–0.671). There was however a significant difference (t-test, $p = 0.014$) in the mean absolute inter-eye difference in latency between the migraine group (0.062 s, 0.037–0.088) and the control group (0.025 s, 0.014–0.035). This is shown in *Figure 2*. This inter-eye difference in latency was not strongly related to anisocoria ($r < 0.30$) for either signed or absolute data.

Correlation between migraine characteristics and pupil responses to light

Table 1 shows the measure of central tendency as the median, spread as the inter-quartile ranges and minimum and maximum for the number of days since the last migraine headache, the severity of the worst headache, the duration of the worst headache and the number of headaches per year. Using the Spearman non-parametric correlation, there were no significant correlations ($r_s < 0.43$, $p > 0.08$) between these variables and baseline anisocoria, and the two amplitude and two latency pupillary variables described above.

There was however a significant correlation between anisocoria at baseline and lateralisation of headache ($r_s = 0.59$, $p = 0.006$). Interestingly, when the signed difference between the pupil sizes at baseline was compared with lateralisation of the headache, the correlation lost significance ($r_z = -0.42$, $p = 0.066$). To investigate this further, the migraine group was split into those who had a habitual head pain side ($n = 10$) and those who did not have a habitual head pain side ($n = 10$). The mean anisocoria of the group with a habitual head pain side was 0.281 mm (0.138–0.424) and the mean anisocoria of the group without a habitual head pain side was 0.113 mm (0.018–0.208). This difference was statistically significant (t-test, $p = 0.015$). Of those with a habitual head pain side, there were those with habitual left-sided head pain ($n = 4$) and those with habitual right-sided head pain ($n = 6$). The mean pupil size on the affected side was 2.881 mm (2.51–3.24) and 3.012 mm (2.70–3.32) on the un-affected side and these results were not statistically different (t-test, $p > 0.38$). The mean anisocoria of the group with left-sided habitual head pain was 0.109 mm (−0.107 to 0.326) and the mean anisocoria of the group with right-sided habitual head pain was 0.396 mm (0.242–0.549). This difference was statistically significant (t-test, $p = 0.0075$).

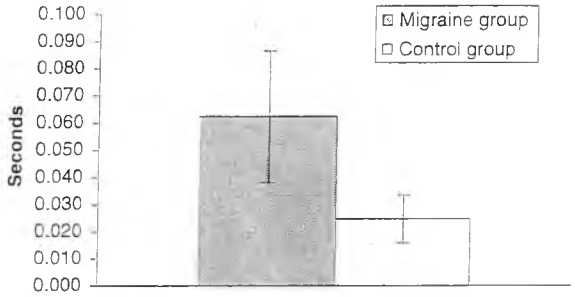

Figure 2. The absolute inter-eye difference in latency of the pupil light response is greater in migraine sufferers compared with controls. Error bars show 95% confidence limits.

Table 1. The descriptive data for the headache parameters of the migraine group

	Number of migraine headaches per year	Duration of worst migraine headache (h)	Severity of worst migraine headache (1 = mild, 2 = mod, 3 = severe)	Time since last migraine headache (days)
Median	24	25	3	14
First quartile	20	7	3	11
Third quartile	43	53	3	20
Minimum	8	2	1	4
Maximum	200	120	3	45

Discussion

Barbur (2004) has recently discussed the pupil response to a variety of stimuli and reached tentative conclusions regarding components of the sympathetic pupil pathway. The evidence presented in that work suggests a pathway involving inhibitory projections from the visual cortex to the Edinger–Wesphal nucleus and both a sustained and a transient projection from the retina to the olivary pretectal nucleus. This differs from previous suggestions that the pupil light response is a single subcortical neural pathway (Snell and Lemp, 1989). If it is true that migrainous cortical hyperexcitability (Wilkins *et al.*, 1984; Wilkins, 1995; Welch, 2003) is linked to a failure of cortical inhibition (Palmer *et al.*, 2000) then a possible hypothesis could be that migraine sufferers may have reduced inhibition of the cortical projections to the Edinger–Westphal nucleus that contributes to the pupil responses seen in migraine sufferers and may be the link between these two well-known correlates of migraine (Chronicle and Mulleners, 1996).

Our data suggest that between headache events, migraine sufferers do not differ significantly from controls in their pupil diameters or degree of anisocoria under room illumination, nor in the latency of the pupillary light reaction. For the two of these three variables that were normally distributed, we calculated the effect size that our study would have been able to detect, given our sample size, a p-value of 0.05, and power of 80% (Jones *et al.*, 2003). We would have been able to detect a difference between the mean pupil size of the two groups of 0.509 mm and a difference in mean latency of 0.071 s.

Migraine sufferers who have a habitual head pain side demonstrated significantly more anisocoria than migraine sufferers who do not have a habitual head pain side. However, overall there is no significant relationship between the pupil size or laterality of the anisocoric pupil and the side of the habitual head pain. This can be explained because for our data it was the migraine sufferers with right-sided habitual head pain that had more anisocoria that those with left-sided head pain. Therefore migraine sufferers with a typical head pain side have more inter-ictal anisocoria, but not necessarily on the side of the head pain. This might suggest that the sympathetic hypofunction found in previous studies during or shortly after migraine events may persist into the non-headache phase for those migraine sufferers who have a habitual head pain side, but does not persist for those migraine sufferers who do not have a habitual head pain side. It may also add further weight to experimental evidence of autonomic asymmetry in unilateral migraine sufferers (Avnon *et al.*, 2004). Alternatively, perhaps those migraine sufferers who do not have a habitual head pain side have more symmetrical sympathetic hypofunction in the non-headache phase than migraine sufferers who do have a habitual head pain side.

Although the latency to the maximum pupil light response was not significantly different between migraine sufferers and controls, the absolute inter-eye difference in this latency was significantly different between the two groups. This suggests that migraine sufferers do, on average, have one eye whose pupillary light response is slower relative to the other. This could be considered to be some evidence of a mild parasympathetic dysfunction (Micieli *et al.*, 1995). Previous studies in this area have also found parasympathetic dysfunction, but only within a few days of a migraine attack (Mylius *et al.*, 2003). Our data suggest that subtle inter-eye differences in pupil light response latency occur in migraine sufferers, and are not correlated to the number of days since the last migraine headache.

Our findings lend weight to the argument that migraine sufferers do indeed have subtle autonomic disturbances in the inter-ictal phase and that both sympathetic and parasympathetic deficits can be demonstrated. Although too small to be considered clinically important, the subtle abnormalities of pupillary light responses do demonstrate that migraine sufferers have a different autonomic nervous system response and that in migraine sufferers with a habitual head pain side, this different response may be asymmetrical.

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ORIGINAL ARTICLE

The Correlation Between Migraine Headache and Refractive Errors

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ABSTRACT

Purpose. A literature review reveals historical references to an association between migraine headache and refractive errors, but a lack of scientific evidence relating to these claims.

Methods. In a masked case–controlled study, we investigated the four aspects of refractive errors that have been implicated in the literature as correlated with migraine: spherical refractive error, astigmatic refractive error, anisometropia, and uncorrected ametropia. We also compared the calculated scalar value of refractive error, aided and unaided visual acuity, and spectacle use in migraine and control groups. We then investigated the relationship between refractive components and key migraine headache variables.

Results. Compared with the control group, the migraine group had higher degrees of astigmatic components of refractive error assessed both objectively (C, $p = 0.01$; C_{0}, $p = 0.01$; C_{45}, $p = 0.05$) and subjectively (C, $p = 0.03$; C_{0}, $p = 0.03$; C_{45}, $p = 0.05$), uncorrected astigmatic components of refractive error (C_{0}, $p = 0.02$; C_{45}, $p = 0.04$), and anisometropia ($p = 0.06$).

Conclusions. Perhaps the historical literature is indeed correct that low degrees of astigmatism and anisometropia are relevant in migraine. Our most significant finding was of higher degrees of astigmatism in the migraine group. This study does indicate that people who experience migraine headaches should attend their optometrist regularly to ensure that their refractive errors are appropriately corrected.

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Key Words: refractive error, migraine, spectacles, astigmatism, anisometropia

A recent review of the association between refractive errors and migraine shows the literature to be equivocal.[1] Early studies provide anecdotal evidence, but the few modern studies, which included control groups and masked experimenters, have found little evidence of an association. The early uncontrolled studies argued that migraine is associated with low refractive errors, notably astigmatism,[2,3] or latent errors, particularly low anisometropia.[4] A slightly later study found little difference in refractive error in people with migraine and control subjects.[5] Subsequent studies are difficult to interpret because of a lack of a control group or statistical analysis[6–11] or because they did not relate to migraine specifically but rather to headache generally.[12–14]

Chronicle and Mulleners[15] suggested that there was a lack of conclusive evidence concerning the involvement of refractive error in the etiology of migraine. In a more recent study,[16] no significant difference between a group of migraine and a group of control patients was found in the subjective refractive error or the proportion of participants who wore spectacles. Yet there is evidence that the public remains convinced that there is an association between their eyesight and headaches[17] with 21% of people with headache having consulted an eye care practitioner for advice, second only to a visit to a general medical practitioner (28%) and far more commonly than a visit to a pharmacist (8%).

The present article describes a masked case–controlled study of the optometric correlates of migraine, some of the results of which have been published elsewhere.[18,19] The migraine and control groups were compared with respect to the four aspects of refractive error historically suggested to be linked to migraine: spherical refractive error, astigmatic refractive error, anisometropia (the intereye difference in the spherical equivalent), and uncorrected ametropia (the difference in the mean spherical equivalent between the spectacle refractive correction and the final subjective refractive error found). Scalar calculations were performed to compare total refractive error and intereye difference in total refractive error together with the recorded aided and unaided visual acuity and habitual spectacle use. The correlations between the key migraine headache variables and the key refractive variables were then investigated.

METHOD

This study is part of a case–controlled study looking at the optometric correlates of migraine using a large battery of optometric tests. The recruitment of the people with migraine and age- and gender-matched control subjects has been described elsewhere.[18] Participants were recruited to the study as part of collaboration with local general medical practitioners (who referred consecutive patients with migraine) and with a London Hospital Neurology Unit specializing in Migraine Headache (who selected patients with migraine from a database). All patients had a formal medical diagnosis of migraine and this was confirmed with a headache questionnaire, which ensured the diagnosis of migraine met International Headache Society (IHS) criteria.[20] Participants for the migraine group were aged between 10 years and 50 years with a frequency of migraine headaches of at least one per month. Individuals with systemic health problems, pregnancy, or ocular disease were excluded from the study. The tenets of the Helsinki declaration were followed: full informed consent was obtained and participants were able to abstain or withdraw from the research at any time without having to give a reason. No participants withdrew after they had arrived at the clinic. The research and ethics committees of the Institute of Optometry (London) and City University (London) approved the study.

Before attending the research clinic, participants in the migraine group were asked to complete a 6-week headache diary, including data on the last migraine headache. On attending the research clinic, all participants were asked to complete a questionnaire[20] detailing their symptoms and history, including questions relating to headaches. The design of the questionnaire allowed for confirmation that the migraine group met the IHS criteria for migraine headache[21] and that the control group were truly migraine-free. Participants attended in pairs, one from the migraine group and one from the control group. We took several measures to ensure that the researcher was masked[18] as to the identity of the participant: the members of each pair were seen in random order, participants were asked not to reveal their identity, and the contents of the questionnaire were not revealed to the research optometrist until the end of the tests of both the migraine sufferer and the control participant. The masked nature of the study was successfully maintained for all migraine participants and all but three of the control participants. All participants were headache-free at the time of testing.

Participants own spectacles were analyzed using a Shin-Nippon -15C lensometer (focimeter) to establish their own habitual spectacle refractive error. Aided and unaided visual acuities were taken monocularly using a National Vision Research Institute of Australia Bailey–Lovie Chart[22] and were rated using the VAR score and counting per letter correctly identified.[23] To ensure full optical correction of all the participants, the subjects then underwent objective refractive assessment using a Keeler spot retinoscope with 6-m fixation[24] followed by subjective refractive assessment using standard optometric procedures that included assessment of spherical error,[24] crossed cylinder evaluation of astigmatism corrected with negative cylindrical lenses,[24] and a binocular balancing technique.[24]

Refractive errors were analyzed using both the raw data and the components of astigmatic decompensation calculations.[25] Humphrey's principle of astigmatic decompensation represents the cylindrical power C as a combination of two obliquely crossed cylinders, C_0 at axis 0° and C_{45} at axis 45°, and has been suggested as a good method to statistically analyze ophthalmic prescriptions,[26] because all cylinders are put on a common basis.

A given prescription of sphere S, cylinder C, and axis θ can be used to calculate:

$$C_0 = C\cos 2\theta$$

$$C_{45} = C\sin 2\theta$$

and it follows that

$$C = \sqrt{C_0^2 + C_{45}^2}$$

The spherical equivalent power m is the algebraic mean of the two principle powers S and (S + C) such that

$$M = S + (C/2)$$

As such, for any given prescription, the total spherocylindrical power can be represented by a single scalar quantity[26,27] as:

$$u = \sqrt{C_0^2 + C_{45}^2 + M^2}$$

where u is given the same sign as M.

Distributions were tested for normality by inspecting frequency distributions and carrying out the Kolmogorov–Smirnov test of normality. It is well known that refractive error is not, strictly speaking, normally distributed with the distribution of spherical refractive error showing leptokurtosis.[28,29] However, refractive errors seem reasonably well-described by parametric descriptive statistics and, as is usual practice,[28–32] we described our variables in this way. When carrying out comparative statistics, we took a conservative approach and used the nonparametric Mann–Whitney U test. When group means are quoted, the 95% confidence limits are given in parentheses. Spearman correlations were carried out to compare spherical refractive error, astigmatic refractive error, anisometropia, and uncorrected errors with migraine variables of severity of worst headache, duration of worst headache, the number of headaches in the last 12 months, and the number of days since the last migraine headache.

The statistical analysis of multieye data in ophthalmic research is discussed in the literature.[33,34] The inclusion of data from each eye of each participant, especially when the data from each eye are highly correlated (like in the present data), is deprecated because it overestimates the statistical significance of the data. An acceptable solution is to average the data from right and left eyes for each participant,[33,34] and this was the approach that was followed here with the obvious exception of the data for anisometropia.

The key variables found to be statistically different in the migraine group were reanalyzed with outliers (values >3 interquartile ranges [IQRs]) from the upper or lower interquartile range) removed to determine the contribution of these few subjects compared with the entire sample.

RESULTS

Age, Gender, and Spectacle Use

There were 25 participants in each group. The mean age of the migraine group was 37.5 years (33.2–41.8 years), which did not differ significantly (t test, $p = 0.77$) from the mean age of the control group of 36.8 years (33.3–40.2 years). Each group had 21 female and four male participants. Similar numbers wore specta-

cles in each group (χ^2 test, $p = 0.77$). In the migraine group, 14 used spectacles and in the control group, 12 wore spectacles.

Visual Acuity

The mean VAR score for unaided visual acuity was 82.6 (73.1–92.0) for the migraine group and 79.8 (68.8–90.9) for the control group. The groups were not significantly different (Mann-Whitney U test, $p = 0.96$). The LogMAR (and Snellen) equivalents for the mean unaided visual acuities are 0.35 ($20/40^{-2}$) for the migraine group and 0.4 (20/50) for the control group. The mean VAR score for aided visual acuity was 101.3 (99.4–103.3) for the migraine group and 101.1 (99.5–102.7) for the control group. The two groups did not differ significantly. The LogMAR (and Snellen) equivalents for the mean aided visual acuities are −0.02 ($20/20^{+1}$) for the migraine group and −0.02 ($20/20^{+1}$) for the control group.

Total and Spherical Refractive Error

The mean of the spherical refractive error S, from the right and left eyes, were calculated and then compared in the two groups. The true (signed) rather than absolute values were taken so that bias toward myopia or hyperopia could be distinguished. This mean subjective spherical refractive error S_v was −0.540 DS (−1.581–0.501) for the migraine group and −1.080 DS (−1.926–0.234) for the control group and the groups were not significantly different (Mann-Whitney U test, $p = 0.10$).

The mean scalar value u_v of the absolute value of u from the right and left eyes of the subjective refraction (a representation of the total spectacle prescription found) was 2.037 (1.143–2.931) for the migraine group and 1.482 (0.660–2.304) for the control group and the groups were not significantly different (Mann-Whitney U test, $p = 0.11$).

Astigmatic Refractive Error

The average of the absolute astigmatic refractive error C from the right and left eyes was calculated and then compared in the two groups. The mean objective (retinoscopy) astigmatic refractive error C_{obj} was also calculated in the same way to ascertain if these results held for both objective and subjective data. To establish if these astigmatic results were influenced by axis, the C_0 and the C_{45} components of the Humphrey decompensation were analyzed for both objective and subjective data. The average of the absolute value for C_0 and C_{45} from the right and left eyes were calculated and then analyzed between the groups. The astigmatic data are shown in Figures 1, 2, and 3. To compare the data, Mann-Whitney U tests were performed. Outliers (those data points further than 3 IQRs) were removed and the Mann-Whitney U tests reperformed on the amended dataset to establish the influence of the outliers on the group as a whole. These results are in Table 1.

Anisometropia

Anisometropia was considered as a continuous variable and was calculated as the absolute interocular difference in M, the spherical equivalent of each eye. The mean degree of anisometropia was

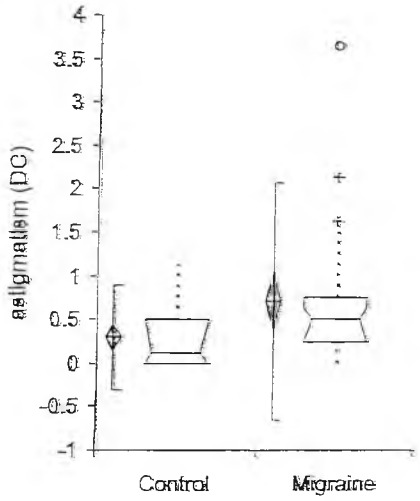

FIGURE 1.
A box plot showing the distribution of mean subjective astigmatic power C (y axis) for people with migraine and control subjects (x axis). The diamond and line shows parametric statistics. The center of the diamond shows the mean and the height of the diamond shows the 95% confidence interval. The notched box and whiskers show nonparametric statistics. The center line of the box is the median, the notch is the confidence interval of the median, whereas the overall size of the box is the interquartile range (IQR). The dotted line connects the nearest observations within 1.5 IQRs of the lower and upper quartiles. "+" markers indicate near outliers between 1.5 and 3.0 IQRs away, whereas "o" markers indicate outliers over 3.0 IQR away.

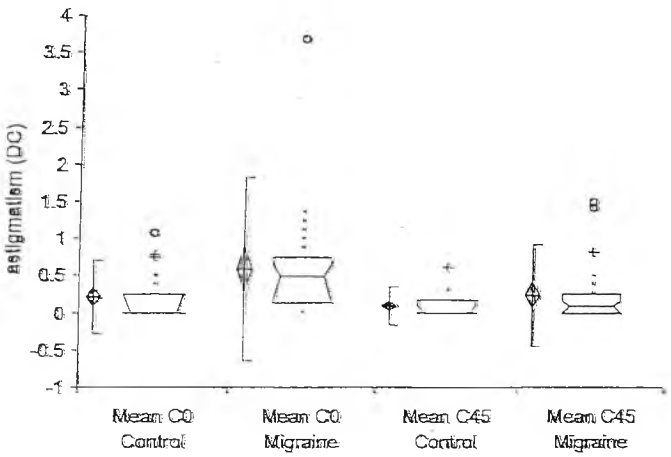

FIGURE 2.
A box plot showing the distribution of mean objective astigmatic power by its C_0 and C_{45} components (y axis) for people with migraine and controls (x axis). For figure description, see Figure 1.

0.515 DS (0.297–0.733) for the migraine group and 0.295 DS (0.145–0.445 DS) for the control group. This difference approached significance (Mann-Whitney U test, $p = 0.06$). The intereye difference in u (a representation of total anisometropia) was 0.623 (0.356–0.890) in the migraine group and 0.332 (0.182–0.482) and this difference was not significant (Mann-Whitney U test, $p = 0.09$).

Uncorrected Ametropia

The spherical equivalents of the lensometry results of the participants' own spectacles M_s were calculated and then averaged for

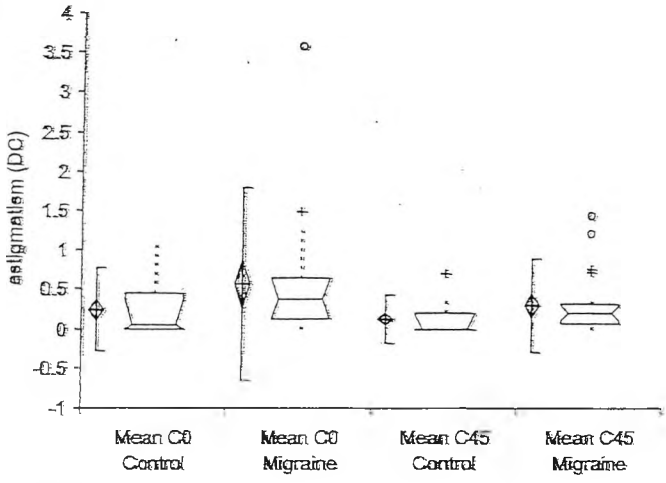

FIGURE 3.

A box plot showing the distribution of mean subjective astigmatic power by its C_0 and C_{45} components (y axis) for people with migraine and control subjects (x axis). For figure description, see Figure 1.

the lenses of the two eyes. The absolute difference between this mean spectacle spherical equivalent M_s and the mean subjective refraction spherical equivalent M_r was calculated to give a value of uncorrected ametropia. The mean uncorrected ametropia in the migraine group was 0.339 D (0.214–0.463 D) and was 0.221 D (0.118–0.325 D) in the control group, and these results were not significantly different (Mann-Whitney U test, $p = 0.13$).

The u value lensometry results of the participants' own spectacles u_s was calculated and then averaged for the lenses of the two eyes. The difference between this mean u_s and the mean subjective refraction spherical equivalent u_r was calculated to give a value of uncorrected scalar u. The mean uncorrected u in the migraine group was 0.715 (0.123–1.306) and was 0.558 (−0.073–1.190) in the control group, and the difference between the two groups was not significant (Mann-Whitney U test, $p = 0.09$). To assess whether these results were influenced by the astigmatic component, we assessed the uncorrected decompensated astigmatic component, i.e., the absolute difference between the mean C_{0s}, C_{45s} of the participant's own spectacles and the C_{0r}, C_{45r} of the participants' subjective refraction was calculated. The mean uncorrected C_0 in the migraine group was 0.279 DC (0.144–0.413 DC) and was 0.126 DC (0.044–0.209 DC) in the control group. The difference between the two groups was statistically significant (Mann-Whitney U test, $p = 0.02$). The mean uncorrected C_{45} in the migraine group was 0.116 DC (0.068–0.165 DC) and was 0.075 DC (0.025–0.125 DC) in the control group. The difference between the two groups was statistically significant (Mann-Whitney U test, $p = 0.04$).

Correlations

The Spearman correlations between severity of worst headache ($r_s < 0.33$, $p > 0.11$), duration of worst headache ($r_s < 0.17$, $p > 0.42$) and the days since the last migraine headache ($r_s < 0.32$, $p > 0.18$) and each of the refractive variables of mean sphere, mean astigmatic power, anisometropia, and uncorrected error were all low and not significant. The number of headaches in the last 12 months did show a statistically significant correlation with anisometropia such that the fewer the headaches, the more the anisometropia ($r_s = -0.42$, $p = 0.04$). The number of headaches in the last 12 months was not significantly correlated with each refractive variable ($r_s < 0.27$, $p > 0.21$).

DISCUSSION

It is not uncommon for optometrists to encounter patients who believe that migraine has a visual trigger or that the headache might be ameliorated by an optometric intervention. However, the lack of evidence-based research led Gordon et al.[14] to conclude that the whole issue of headache and refractive error has been dominated "by clinical anecdote throughout the 20th century." They asked that future research in this area addressed (1) the scale of the problem; (2) whether people with migraine are optometrically unusual; (3) if they are optometrically unusual, what is the mechanism generating the headache; and (4) whether correction ameliorates the headache. Because the level of evidence in the literature for any association between migraine and refractive error is, by modern standards, weak, it is not surprising that the IHS classification system[21] classifies headache attributed to refractive errors quite separately from those of migraine.

Although only large epidemiologic studies can hope to address the scale of the problem, it is known that migraine is a very common condition with more than 2.5 million persons in North America having at least one day of migraine per week.[35] Our sample of people with migraine had a higher mean level of astigmatism than our control group. If only a small number of these people need refractive corrections then, in view of the prevalence of migraine, the number of these people who might benefit from optometric intervention is substantial.

The range of low degrees of refractive errors in both our groups was fairly typical of the age group in a U.K. population.[24] Our masked case–controlled study provides some evidence that astigmatic refractive error and possibly anisometropia are greater in people with migraine than control subjects, as suggested in the historical texts. For astigmatism, the difference was driven in part by a few people with migraine who were particularly optometrically unusual but still held for the group as a whole (when the outliers were removed) for C and C_0 components. Objective, subjective, and uncorrected astigmatic refractive components were all significant findings.

The differences between the two groups were not large and, as a result of the large number of statistical comparisons made, it is possible that some of the statistically significant findings resulted by chance. In any event, it seems unlikely that the degree of uncorrected astigmatism that we found is a direct cause of migraine, but a subtler path may exist. One hypothesis might be that astigmatic errors of refraction cause changes to visual perception that alter the hyperexcitability in the visual cortex of the brain of some migraine sufferers[36–38] perhaps because astigmatic blur may exacerbate the perception of striped patterns thought to be important in the visual triggers of migraine.[36,37] An alternative hypothesis could be that neurotic personality traits that are associated with migraine[39–41] result in a greater likelihood of people with migraine demanding small cylindrical corrections during a subjective refraction, particularly because more of the control subjects than the migraineurs had zero astigmatism. However, greater astigmatic

TABLE 1.
The astigmatic refractive components of total mean astigmatism (C) and the decompensated astigmatic components (C_0, C_{45}) for the migraine and the control group were compared for both subjective and objective refractive data[a]

	Subjective Refractive Results (DC)			Objective Refractive Results (DC)		
	Migraine	Control	p Value	Migraine	Control	p Value
C	0.705 (0.363–1.047)	0.295 (0.143–0.447)	0.03 [0.04]	0.710 (0.359–1.061)	0.245 (0.106–0.384)	0.01 [0.01]
C_0	0.565 (0.257–0.874)	0.247 (0.115–0.380)	0.03 [0.05]	0.588 (0.279–0.898)	0.205 (0.082–0.329)	0.01 [0.01]
C_{45}	0.295 (0.145–0.445)	0.131 (0.055–0.208)	0.05 [0.11]	0.235 (0.065–0.404)	0.088 (0.023–0.153)	0.05 [0.12]

[a]The mean results are shown with the 95% confidence limits in parentheses. Mann-Whitney U tests were performed to compare these results and the statistical significance of the differences found between the groups is shown as the p value in the table. Finally, outliers were removed from the data and the Mann-Whitney U tests comparisons repeated; these are shown in small font and in square brackets in the p value column.

power was found in the migraine group for both objective (retinoscopy) and subjective testing and so this would seem unlikely.

The higher levels of astigmatism in the migraine group reached statistical significance and an inspection of Figure 1 indicates that there were more cases in the migraine group than the control group in which the degree of astigmatism was of a level that would be considered by many practitioners to be clinically significant.[42] Uncorrected astigmatic refractive errors were significantly greater in people with migraine than control subjects. A theoretical causative effect is weakened by a lack of significant correlations between the headache characteristics and refractive error, although it is possible that refractive error could have an association with migraine headaches while having no impact on the severity or frequency of headaches. Whether correcting refractive errors does, or does not, have an impact on migraine severity or frequency is a matter for future research, but this study does suggest that people with migraine headaches should attend their optometrist regularly to ensure that their refractive errors are appropriately corrected.

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Subtle binocular vision anomalies in migraine

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Abstract

A literature review reveals old references to an association between migraine headache and binocular vision anomalies, but a lack of scientific evidence evaluating these claims. In a masked case control study, we investigated binocular vision using standard clinical tests in people with migraine and in controls. Some test results suggest that heterophoria and fixation disparity are more common in the migraine group. The migraine group also had slightly reduced stereopsis. We found significant correlations between some migraine variables and some binocular vision variables (e.g., duration of worst headache and impaired stereopsis) but our analyses do not suggest that a causal relationship is likely. In conclusion, people with migraine have on average a slightly higher prevalence of heterophoria and aligning prism, and reduced stereopsis compared with controls. However, the differences are subtle and our data do not support the use of binocular vision interventions prescribed solely on the basis of the presence of migraine.

Keywords: binocular vision anomalies, migraine, orthoptics

Introduction

A recent literature review (Harle and Evans, 2004) reveals historical papers suggesting that binocular vision anomalies are correlates or causes of headache or migraine (Snell, 1904; Turville, 1934). It has been suggested that exophoria (Wilmut, 1956) and its correction with base-in prisms (Turville, 1934; Wilmut, 1951) or vision therapy (Friedman, 1977) is associated with migraine, but the evidence comes from poorly-controlled trials. A study (Waters, 1970) which suggested that migraine is not correlated with horizontal heterophoria but may be correlated with hyperphoria, was also poorly executed in that the study failed to differentiate between esophoria and exophoria.

Electromyographic case studies have demonstrated that migraine-type pain can be reproduced by stimulating the extra-ocular muscles directly (Worthen, 1980). These findings led to claims that the headaches caused by muscle imbalance (heterophoria) could be eliminated by proper alignment of the visual axes and that prisms, orthoptic training, or even surgery may be necessary, diagnosis being made with a trial period of monocular occlusion (Worthen, 1980).

Several authors have linked decompensated heterophoria or convergence insufficiency with headache (Jenkins *et al.*, 1989; Yekta *et al.*, 1989; Rouse *et al.*, 2004; Karania and Evans, 2006) or as part of general asthenopia (Sheedy *et al.*, 2003). However, these authors do not specifically discuss migraine. In the only modern controlled trial that we have been able to find that did specifically address migraine, Evans *et al.* (2002) compared 21 migraine sufferers with 11 controls and found no difference between the groups in relation to strabismus or hyperphoria. The main purpose of this study was to investigate the effect of coloured filters (Wilkins *et al.*, 2002), so the migraine sufferers were selected as those who found a coloured filter to be helpful. They therefore did not represent a 'normal' group of migraine sufferers. Evans *et al.* (2002) did find that the migraine group tended to have a marginally decompensated exophoria at near, but this result was equivocal depending on the diagnostic criteria for decompensated heterophoria.

Ocular motor paresis (Daroff, 2000, 2001; Carlow, 2002; Lee, 2003; Levin and Ward, 2004; Weiss and

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Phillips, 2004; Celebisoy *et al.*, 2005; De Silva and Siow, 2005) and eye movement disorders associated with vertigo (Dieterich and Brandt, 1999; Harno *et al.*, 2003; Liao and Young, 2004; von Brevern *et al.*, 2005; Marano *et al.*, 2005) and their link to migraine are well documented, but the literature on the association between the more subtle anomalies of binocular vision and migraine seems to be equivocal. To investigate this, we compared migraine and control groups with respect to clinical optometric measures of binocular vision. The correlations between the key migraine headache variables and the key binocular vision variables were then investigated.

Method

Participants

The data reported here are part of a large case control study investigating the optometric correlates of migraine, using an extensive battery of optometric tests. The recruitment of the people with migraine and age and sex matched controls has been described elsewhere (Harle and Evans, 2006; Harle *et al.*, 2005). Participants were recruited to the study as a part of collaboration with local general medical practitioners and with a London hospital neurology unit specialising in migraine headache. All patients had a formal medical diagnosis of migraine and this was confirmed with a headache questionnaire, which ensured that the migraine diagnoses met International Headache Society (IHS) criteria (IHS, 2004). Participants for the migraine group were aged between 10 and 50 years with a frequency of migraine headaches of at least one per month. Individuals with systemic health problems, pregnancy, or any ocular pathology (no people were excluded for this reason) were excluded from the study. The tenets of the Helsinki declaration were followed: full informed consent was obtained and participants were able to abstain or withdraw from the research at any time without having to give a reason. No participants withdrew after they had arrived at the clinic. The research and ethics committees of The Institute of Optometry, London and City University, London approved the study.

Sample size calculation

Several authors, reviewed by Harle and Evans (2004), have argued that an exophoria is a common feature in migraine. Most of these authors have used the Turville infinity balance, which is no longer in widespread clinical use. Evans *et al.* (2002) found a migraine group to be more exophoric than a control group by 1^{Δ} (mean 3.5^{Δ} exophoria in migraineurs, 2.5^{Δ} exophoria in controls), but 1^{Δ} would not be considered to be clinically significant. Goss (1995) cited norms for near exophoria as 3^{Δ} exophoria with a S.D. of 5^{Δ}. Therefore, we assumed that a difference between our migraine and control groups of more than 3^{Δ} would likely be clinically significant. From the data of Evans *et al.* (2002), the S.D. of near dissociated heterophoria in their control group was 3.04, and in the migraine group 5.15. The S.D. of the two populations were different, so the square root of the mean of the variances was taken as the estimate of S.D.; this was 4.2 ($=\sigma$).

To obtain the sample size required, these figures were used in the formula given by Armitage and Berry (1987). This gave a required sample size of 19 participants in each group. To be conservative, we continued the study until 25 participants had been recruited into each group.

Procedure

Prior to attending the research clinic, participants in the migraine group were asked to complete a 6-week headache diary. This included an indication of the last migraine headache. On attending the research clinic, all participants were asked to complete a questionnaire detailing their symptoms and history, including questions relating to headaches. The design of the questionnaire allowed for confirmation that the migraine group met the IHS criteria for migraine headache (IHS, 2004) and that the control group were truly migraine free. Participants attended in pairs, one from the migraine group and one from the control group. To ensure that the researcher was masked as to the identity of the participant: participants were seen in random order, were asked not to reveal their identity, and the contents of the questionnaire were not revealed to the research optometrist until the end of the tests of both the migraine sufferer and the control participant. The masked nature of the study was successfully maintained for all migraine participants and all but three of the control participants and all participants were headache free at the time of testing. Clinical tests were then undertaken in the following order: cover–uncover test, alternate cover test, aligning prism, and foveal suppression on the Mallett Unit, Randot stereopsis, Maddox Rod, Maddox Wing, convergence tests, fusional reserves, and finally ocular motility. The test methods are detailed below and are described in more detail in Evans (2002, 2005).

Clinical tests

For all binocular vision tests except ocular motility, the patient wore a refractive correction if it was habitually worn for more than 50% of the time at the appropriate test distance. Ocular motility was assessed by observing the eye movements whilst the patient fixated a point

light source at a distance of 50 cm which was moved into the cardinal positions of gaze. The corneal reflections of the light source were observed and if either eye lost fixation then the incomitant deviation was investigated with cover testing in peripheral gaze.

Ocular alignment was assessed at distance (6 m) and then near (40 cm) by the cover–uncover test with an opaque occluder, followed by an alternate cover test. A clinically experienced optometrist estimated the magnitude of deviation (in prism diopters, Δ) for both distance and near, in the horizontal and vertical planes. The type (heterophoria or heterotropia) and direction of movement was recorded. Esophoria and right hyperphoria were recorded as positive values and exophoria and left hyperphoria were recorded as negative values. Separate data were obtained for both the cover–uncover test and the alternate cover test, which is associated with greater dissociation and is therefore likely to reveal a larger deviation.

If heterophoria was detected on cover testing, then the quality of the recovery was subjectively graded by the optometrist on a scale of 1–5, 1 being an excellent recovery and 5 being a very poor recovery breaking down to strabismus.

The Maddox Rod test was used to measure horizontal and vertical dissociated deviations at distance. A red Maddox Rod was placed before the right eye and the patient was instructed to view a bright spot light kept at a 6 m distance. Trial lens prisms were used to align the Maddox streak with the spot light first in the horizontal and then in the vertical plane. As for the cover test results, eso-deviations and right hyper-deviations were recorded as positive values.

The Maddox Wing test was used to measure horizontal and vertical dissociated deviations at near. The horizontal and vertical values were recorded as the number read from the scale by the patient. The variability in the horizontal reading was recorded as a measure of vergence instability by asking the patient to report the range of numbers over which the reading varied.

The presence of fixation disparity and degree of aligning prism found by the distance Mallett Unit at 6 m and the near Mallett Unit at 40 cm were recorded. Polarised visors were placed in front of the refractive correction and any aligning prism (the minimum amount of prism required to cause alignment) was recorded with the base direction (In or Out/Up or Down), and the eye to which the prism needed to be applied. As for the other measurements of eye alignment, eso-deviations and right hyper-deviations were recorded as positive values. The precise test instructions with the Mallett Fixation Disparity test are important (Karania and Evans, 2006) and we used the instructions recommended by Evans (2002); Figure 4.4) which have been shown to be best at predicting symptoms (Karania and Evans, 2006). Using the near Mallett Unit, foveal suppression was recorded as the difference between the monocular and binocular acuity (in minutes of arc) with the polarised visor always in place (Evans, 2002).

The Randot shapes and circles tests (Stereo Optical Company Inc., 1988) were used to assess random dot stereopsis and contoured stereopsis. Each test was terminated when one error was made and stereoacuity was recorded as the stereodisparity of the last target correctly identified.

Near point of convergence measured by the RAF rule was recorded as the nearest distance to which the patient could converge without experiencing subjective diplopia of the line target. Eye movements were observed and the objective break point was recorded if there was no subjective break point. Vergence facility was measured by the number of cycles of convergence and divergence that the patient could perform whilst viewing a near N5 print target through prism 'flippers' that alternated the vergence stimulus between 1.5Δ base-in each eye (3Δ total) and 6Δ base-out each eye (12Δ total). The prisms were 'flipped' when the subject reported verbally that no blur or diplopia was present.

Fusional reserves were measured with a Variable Prism Stereoscope which uses linked rotary prisms in front of each eye with an accommodative target. Distance divergent (base-in) followed by (see Discussion) convergent (base-out) reserves were recorded as three values, the blur point, the break point, and the recovery point with a prism rate change of ~1Δ/s. Near base-in and base-out fusional reserves were recorded in the same way. At both distance and near, the fusional amplitudes were calculated as the differences between the convergent and divergent blur points, or if there was no blur point, then break point.

Sheard's criterion assesses whether the fusional reserve that opposes the heterophoria is adequate to overcome the heterophoria, stating that the fusional reserve (blur point, or if no blur point then break point) that opposes the heterophoria should be at least twice the heterophoria (Sheard, 1931). Percival's criterion states that the working fixation point should lie in the middle third of the total fusional amplitude; that is to say, the complementary fusional reserves should be balanced within the limits that one should not be less than half the other (Percival, 1928). We calculated, for both distance and near vision, the proportion of participants passing Sheard's criterion and the proportion passing Percival's criterion. We also calculated variables, which we called Sheard's value and Percival's value, which graded on a continuous scale the degree to which each participant passed or failed Sheard's and Percival's criteria at each distance.

Clinically, the diagnosis of decompensated heterophoria is usually based on a combination of several test results. This led Evans (2002) to develop an algorithm that combines relevant test results to give a score indicating the likelihood of decompensated heterophoria. The algorithm was amended (Appendix) and the results were calculated separately for horizontal heterophoria at distance and near. A score was produced for compensation and a pass/fail criterion, which was then compared between the groups.

Results

Distributions for each measurement were tested for normality by inspecting frequency distributions and carrying out the Kolmogorov–Smirnov test of normality. Statistical calculations were performed using v1.71 Analyse-it for Excel, based on two-tailed tests. Parametric and non-parametric statistical tests were used as appropriate and when group means or medians are quoted, the 95% confidence limits are given in parentheses. When comparing proportions, the chi-square test was used, unless the number in any cell was less than 5, in which case the Fisher exact test was used. Where the same hypothesis was tested with more than statistical test then Bonferroni corrections were made.

Age and gender

There were 25 subjects in each group. The mean age of the migraine group was 37.5 years (33.2–41.8), which did not differ significantly (t-test; $p = 0.78$) from the mean age of the control group of 36.8 years (33.3–40.2). Each group had 21 female and 4 male participants.

Ocular motility and cover testing

No cases of incomitancy were apparent on motility testing. The cover–uncover test revealed no cases of strabismus in either group. Seven of the 25 people with migraine demonstrated a heterophoria at 6 m by cover–uncover testing but only 3 of the control group did so. This increased to 11 of the migraine group and 5 of the control group on alternate cover testing. At near, 10 of the migraine group and 9 of the control group demonstrated a heterophoria by cover–uncover testing. This increased to 16 of the migraine group and 11 of the control group on near alternate cover testing. These differences between the two groups were not statistically significant (χ^2-test; $p > 0.13$). The magnitude of horizontal heterophoria by both methods of cover testing in the two groups are shown in *Figure 1a,b*. The results were not significantly different between the groups (Mann–Whitney U-test; $p > 0.25$). It is clear from *Figure 1* that hardly any subjects had a vertical heterophoria and the two groups were similar in this respect.

Maddox Rod and Maddox Wing

One person with migraine could not be tested with the Maddox Rod test as the streak produced by the Maddox Rod was not perceived. A total of 19 out of 24 people with migraine demonstrated a heterophoria at 6 m by Maddox Rod but only 8 of the 25 in the control group did so. This difference was statistically significant (χ^2-test; $p = 0.0024$). Nineteen out of 25 people with migraine demonstrated a heterophoria at near by Maddox Wing but only 12 of the 25 in the control group did so. This difference was not statistically significant (χ^2-test; $p = 0.080$).

The magnitude of dissociated heterophoria determined by the Maddox Rod and Wing tests are shown in *Figure 2a,b*. These results were not significantly different between the groups, and nor was the difference in the variability of the Maddox Wing result (Mann–Whitney U-test; $p > 0.080$). *Figure 2a* indicates a greater spread of results for the horizontal distance heterophoria in the migraine group than in the control group. We therefore repeated the Mann–Whitney U-test but using unsigned horizontal heterophoria to investigate whether the two groups differed in terms of the unsigned magnitude of horizontal heterophoria regardless of whether esophoria or exophoria. This revealed a significantly greater horizontal distance heterophoria in the migraine group than in the control group (unsigned data, Mann–Whitney U-test; $p = 0.001$). No such effect was apparent at near (Maddox Wing test, unsigned data, Mann–Whitney U-test; $p = 0.22$).

Fixation disparity, aligning prism, and foveal suppression

Seven of the 25 people with migraine demonstrated some degree of fixation disparity (at either distance) but only 1 of the 25 controls did so. This difference was statistically significant (Fisher exact test; $p = 0.049$). At distance (6 m), 3 of the 25 people with migraine had horizontal fixation disparity and 1 had vertical fixation disparity but no control did so (Fisher exact test; $p = 0.11$). At near, 3 of the 25 people with migraine had horizontal fixation disparity and 1 had vertical fixation disparity and 1 control had horizontal fixation disparity (Fisher exact test; $p = 0.35$). This one control subject also demonstrated 3 s of foveal suppression in the eye that required an aligning prism. No other subjects demonstrated any foveal suppression. The magnitude of aligning prism in the two groups is compared in *Figure 3a,b*. The results were not significantly different between the groups for signed and unsigned data (Mann–Whitney U-test; $p > 0.077$).

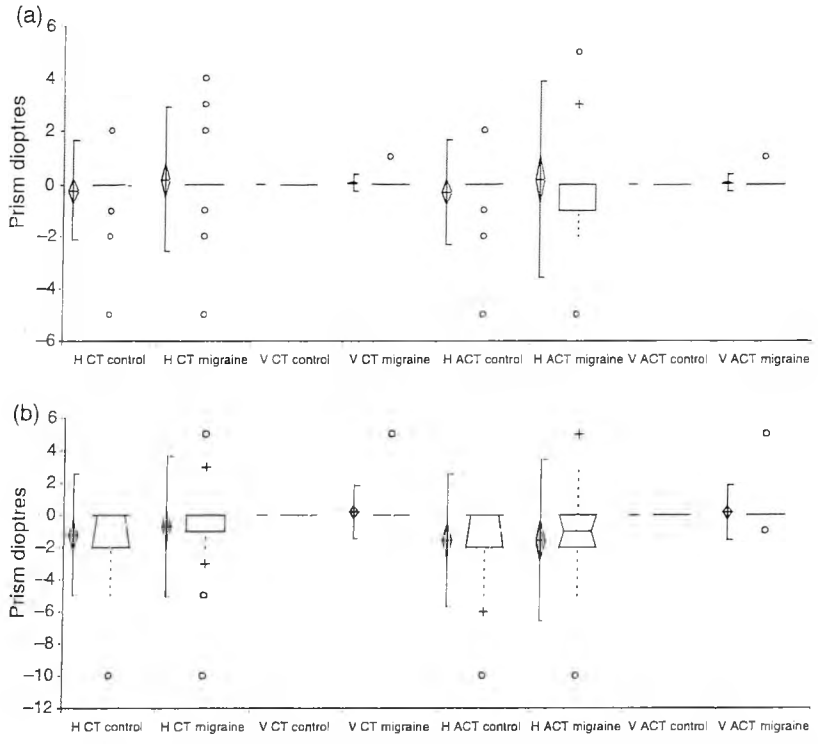

Figure 1. (a) Distance cover test (CT) and alternate cover test (ACT) results for both horizontal (H) and vertical (V) readings in migraine and control groups. The *y*-axis shows heterophoria in prism diopters. The diamond and line shows parametric statistics. The centre of the diamond shows the mean and the height of the diamond shows the 95% confidence interval. The notched box and whiskers show non-parametric statistics. The centre line of the box is the median, a notch is the confidence interval of the median, while the overall size of the box is the inter-quartile range (IQR). In some cases, the inter-quartile values are 0, so there is just a line and no box. The dotted line connects the nearest observations within 1.5 IQRs of the lower and upper quartiles. '+' markers indicate near outliers between 1.5 and 3.0 IQRs away, while 'o' markers indicate far outliers over 3.0 IQR away. (b) Near cover test (CT) and alternate cover test (ACT) results for both horizontal (H) and vertical (V) in migraine and control groups. The *y*-axis shows heterophoria in prism diopters [for figure description see (a)].

Stereopsis

On the Randot shapes test, three people with migraine had stereopsis less than 500 s and one had stereopsis of 500 s. The remaining 21 people with migraine and all 25 controls had at least 250 s of stereopsis by Randot shape testing (Fisher exact test; $p = 0.11$). On the Randot circles test, the median stereopsis was 50.0 s (50.0–70.0) in the migraine group and 40.0 s (40.0–50.0) in the control group. These results were significantly different (Mann–Whitney *U*-test; $p = 0.0045$) (*Figure 4*).

Near point of convergence and convergence facility

The mean near point of convergence in the migraine group was 5.12 cm (3.89–6.35) and was 4.88 cm (3.88–5.88) in the control group. Convergence facility was 11.5 cycles per min (9.7–13.3) in the migraine group and 13.0 cycles per min (11.6–14.4) in the control group. These results were not significantly different between the groups (Mann–Whitney *U*-test; $p > 0.15$).

Fusional reserves, Sheard's and Percival's criteria

The fusional amplitudes were calculated as a measure of total fusion in reserve. At distance, the mean fusion amplitude was 30.4^{Δ} (26.4–43.4) in the migraine group and 31.5^{Δ} (25.9–37.1) in the control group. At near, the mean fusion amplitude was 24.7^{Δ} (19.9–29.5) in the migraine group and 23.6^{Δ} (19.0–28.3) in the control group. The fusional amplitudes of the two groups did not differ significantly at distance (*t*-test; $p = 0.74$) or at near (*t*-test; $p = 0.74$).

Sheard's criterion was passed by 24 of the control group and 22 of the migraine group at distance (Fisher exact test; $p = 0.61$), and 21 of the control group and 23 of the migraine group at near (Fisher exact test; $p = 0.67$). Sheard's value indicated reduced ability to overcome Sheard's criterion in the migraine group compared with the control group at distance (Mann–Whitney *U*-test; $p = 0.038$). However, since the null hypothesis for this variable, that Sheard's criterion was not significantly different in the migraine and control groups, was essentially tested in two ways

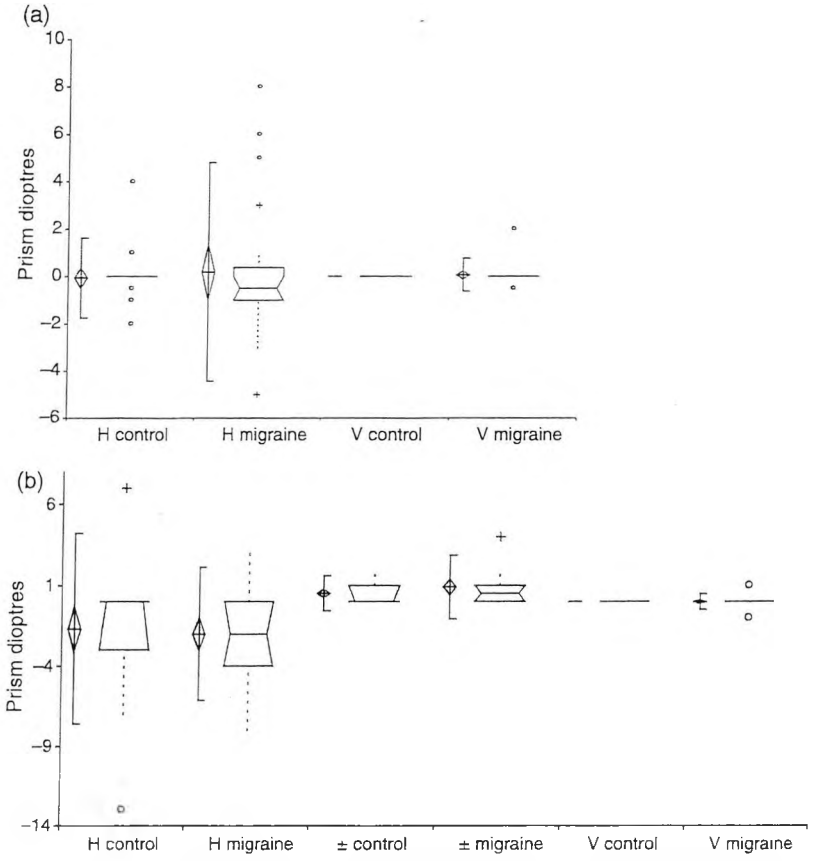

Figure 2. (a) Maddox rod at 6 m results for both horizontal (H) and vertical (V) in migraine and control groups. The *y*-axis shows heterophoria in prism diopters (for figure description see Figure 1a). (b) Maddox Wing results for horizontal (H); horizontal variability (+/−); and Maddox Wing results for vertical (V) in migraine and control groups. The *y*-axis shows heterophoria in prism diopters (for figure description see Figure 1a).

then a Bonferroni correction is required. This lowers the p-value for statistical significance to $p = 0.025$, suggesting that the two groups were not significantly different. There was no significant difference between the groups in Sheard's value at near (Mann–Whitney U-test; $p = 0.34$).

Percival's criterion was passed by 17 of the control group and 19 of the migraine group at distance (χ^2-test; $p = 0.75$), and 20 in both groups at near. Percival's value indicated a similar ability to overcome Percival's criterion in the migraine group compared with the control group at distance and near (Mann–Whitney U-test; $p > 0.08$).

Algorithm for diagnosing decompensated heterophoria

The decompensation algorithm was passed by 21 of the migraine group and 24 of the control group at distance (Fisher exact test; $p = 0.35$) and 24 in both groups at near. The mean algorithm score at distance was 1.9 (1.1–2.8) in the migraine group and 1.4 (0.9–1.9) in the control group and these results were not significantly different (t-test; $p = 0.28$). The mean algorithm score at near was 1.6 (1.1–2.1) in the migraine group and 1.5 (0.8–2.1) in the control group and these results were not significantly different (t-test; $p = 0.77$).

Correlations

Because fixation disparity, dissociated heterophoria at distance (Maddox Rod), fusional amplitude measures, and stereopsis were found to be different in the migraine group, Spearman correlations were calculated for the migraine group between these variables and the headache variables of lateralisation of headache, severity of worst headache, duration of worst headache, the number of headaches in the last 12 months, and the number of days since the last migraine headache.

Lateralisation of headache was correlated with near horizontal fixation disparity ($r_s = -0.43$, $p = 0.031$). The signing of these variables meant that right-sided headaches are more likely to be associated with exophoria. Lateralisation of headache was not correlated to any other of the binocular vision variables that

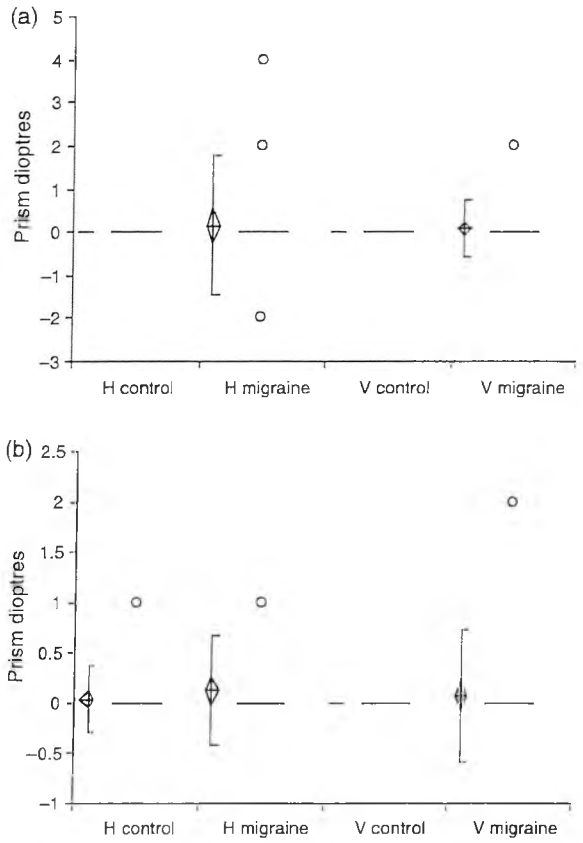

Figure 3. (a) Distance aligning prism results for both horizontal (H) and vertical (V) in migraine and control groups. The *y*-axis shows aligning prism in prism diopters (for figure description see Figure 1a). (b) Near aligning prism results for both horizontal (H) and vertical (V) in migraine and control groups. The *y*-axis shows aligning prism in prism diopters (for figure description see Figure 1a).

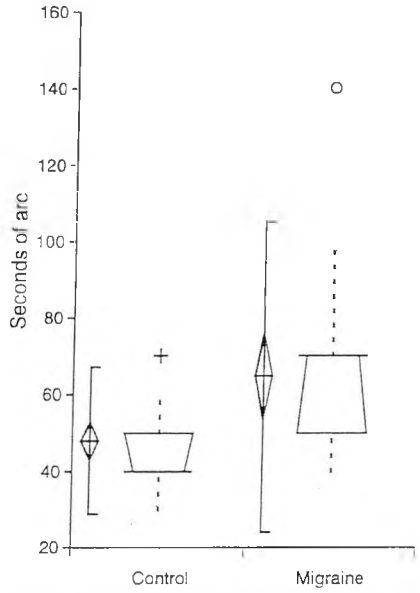

Figure 4. Randot stereopsis results for migraine and control groups (for figure description see Figure 1a).

were found to be different in the migraine group ($r_s \leq 0.35$, $p \geq 0.086$), and this result seems most likely to represent a chance finding.

The severity of worst headache was not significantly correlated to any binocular vision variable ($r_s \leq 0.38$, $p \geq 0.060$) but the duration of worst headache was quite strongly correlated with Randot circle stereopsis ($r_s = 0.59$, $n = 21$, $p = 0.0053$), such that the longer the worst headache, the poorer the stereopsis. To evaluate the clinical significance of this correlation we chose a duration of worst headache of 12 h as significant, and a stereopsis less than or equal to 50 s as normal, which led to a calculation of the odds ratio of 33.2 (0.2–105.7). The duration of worst headache was not correlated to any other binocular vision variable ($r_s \leq 0.36$, $p \geq 0.096$).

The number of headaches in the last 12 months was not correlated with any of the binocular vision variables that were found to be different in the migraine group ($r_s \leq 0.39$, $p \geq 0.069$).

The number of days since the last migraine headache was correlated with near fusional amplitude ($r_s = 0.56$, $n = 18$, $p = 0.017$). To investigate the clinical significance of this, we took a period of 7 days since the last headache as significant, and calculated the odds ratio for the presence of a near fusional amplitude greater than 20 prism diopters as 3.9 (0.1–24.3). The days since last migraine headache was not correlated with any other binocular vision variable ($r_s \leq 0.37$, $p \geq 0.15$).

Discussion

The evidence in the literature for any association between migraine and the more subtle binocular vision anomalies is weak, yet it is not uncommon for optometrists to encounter patients who believe that migraine might be ameliorated by an optometric or orthoptic intervention. Incomitant deviations and strabismus, although part of the migraine spectrum, can be serious signs of underlying neurological disease, and it is reassuring that these conditions were not present in any of our migraine (or control) participants using our test methods. Objective recording of eye movements was not undertaken and so subtle alterations in eye movements might not have been detected.

By both methods of simple cover testing, people in our migraine group were not more likely to have a heterophoria than controls and have, on average, a size of heterophoria within normal limits. An advantage of the cover–uncover test is that it provides an insight into the immediate effect of covering before the eyes are dissociated for prolonged periods. The disadvantage is that the precision of an estimated cover test reading might not be as great as that obtained with a

dissociation test (e.g., Maddox Rod or Maddox Wing test). This is why we used both approaches.

When distance heterophoria was assessed under completely dissociated conditions using the Maddox Rod, people with migraine were statistically significantly more likely to demonstrate a heterophoria than controls, but did not have a statistically different amount of heterophoria than the control group. There was no correlation between the heterophoria measured by Maddox Rod and any of the headache variables.

The presence and degree of heterophoria are poor predictors of symptoms: the key question is whether the person can compensate for their heterophoria. Two key methods of assessing this are to determine whether the person has a fixation disparity/aligning prism under natural and fused viewing conditions and to assess the adequacy of their fusional reserves to overcome the heterophoria (Evans, 2002). The test order can influence the test results in patients with a history of unstable binocular vision (Brautaset and Jennings, 1999) and so aligning prism measurements on the Mallett Unit were undertaken before the dissociating measures of Maddox Rod, Wing, and fusional reserves. People with migraine are slightly more likely to have a fixation disparity on the Mallett Unit, but overall the degree of aligning prism was not significantly different in the two groups. The near aligning prism was correlated to lateralisation of headache such that left-sided headaches are associated with base-in aligning prisms and right-sided headaches associated with base-out aligning prisms. This correlation only just reached statistical significance and would seem difficult to explain from current knowledge. We wonder if this is a chance finding, especially since several correlations were tested.

The near point of convergence was no different in the two groups and within normal limits (Hayes *et al.*, 1998) for both people with migraine and the controls. When testing fusional reserves, we always measured the divergent reserve before the convergent reserve. This conflicts with the recommendation of Rosenfield *et al.* (1995) and our results could therefore be confounded by prism adaptation effects. However, we think that this is unlikely to have influenced our conclusions concerning differences between the migraine and control groups because the type of heterophoria did not differ significantly in the two groups.

Percival's value was not different between the groups, and the migraine group only showed a slightly reduced ability to overcome Sheard's criterion at distance. However, this was only apparent for one method of analysing the results and lost significance when a Bonferroni correction was applied. Interestingly, Evans *et al.* (2002) found an increased tendency for people with migraine to fail Sheard's criterion at near, but as noted above, the migraine group in this study were selected as reporting a benefit from coloured filters so do not represent a normal cross-section of migraine sufferers.

Near fusional reserves were correlated to the number of days since the last migraine headache and this is some temporal evidence for causation (since the more days since a migraine attack, the bigger the near fusional reserves) with an odds ratio that suggests more than a three times relative risk (although with broad confidence intervals).

Stereoacuity was reduced in the migraine group but within normal limits in the control group. Stereoacuity was correlated to the duration of worst headache such that the longer the worst migraine headache, the lower the stereopsis. The odds ratio indicated a 33 times increase in risk but the lower confidence limit of this odds ratio was less than 1, reducing the confidence we can have that this correlation is causal. Again, we highlight the fact that several correlations were investigated so that chance findings of statistical significance are possible.

Our data suggest that people with migraine are predisposed to have subtle deficits in their binocular co-ordination that slightly increase the risk of decompensated heterophoria and reduce stereopsis. Although more of our sample of people with migraine met usual clinical criteria for decompensated heterophoria at distance, this did not reach statistical significance, and was not the case at near. Therefore, we think it unlikely that binocular vision anomalies were causally related to the headaches in the majority of cases. However, headache is a recognised symptom of decompensated heterophoria (IHS, 2004) and in view of our findings we suggest that patients with migraine or suspected migraine ought to have an eye examination in case visual problems are a contributory factor.

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Appendix: Algorithm for diagnosing decompensated heterophoria

An algorithm (Evans, 2002) for indicating whether a patient has a decompensated binocular vision anomaly was adapted. The standard algorithm uses a score of +3 for the presence or absence of headache. As this would bias towards our migraine group, this question was removed. The distance algorithm also removed questions (5 and 8) that related to near vision results. The pass criterion of the standard algorithm was a score of 5/16. As the maximum score for our adapted algorithm was 10 for distance and 13 for near, we used a pass criterion of [(5/16) × 10] for distance and [(5/16) × 13] for near.

	Score
1. Is the patient orthophoric on cover testing?	
Yes ☐ or No ☐	*If no, score +1*
2. Is the cover test recovery rapid and smooth?	
Yes ☐ or No ☐	*If no, score +2 (+1 if borderline)*
3. Is the Mallett Hz aligning prism: <1Δ for patients under 40, or <2Δ for pxs over 40?	
Yes ☐ or No ☐	*If no, score +2*
ALL THE FOLLOWING QUESTIONS APPLY TO HORIZONTAL RESULTS	
4. Is the Mallett aligning prism stable (Nonius strips stationary with any required prism)?	
Yes ☐ or No ☐	*If no, score +1*
5. Using the polarised letters binocular status test, is any foveal suppression <4°?	
Yes ☐ or No ☐	*If no, score +2*
6. Sheard's criterion:	
(a) measure the dissociated phoria (e.g., Maddox Wing, prism cover test); record size & stability	
(b) measure the fusional reserve opposing the heterophoria (i.e., convergent, or base-out, in exophoria). Record as blur/break/recovery in Δ.	
Is the blur point, or if no blur point the break point, [in (b)] at least twice the phoria [in (a)]?	
Yes ☐ or No ☐	*If no, score +2*
7. Percival's criterion: measure the other fusional reserve and compare the two break points.	
Is the larger break point less than twice the smaller break point?	*If no, score +1*
Yes ☐ or No ☐	
8. When you measured the dissociated heterophoria, was the result stable, or unstable (varying over a range of ±2Δ or more). (e.g., during Maddox Wing test, if the Hz phoria was 4Δ XOP and the arrow was moving from 2 to 6, then result unstable)	*If unstable, score +1*
Stable ☐ or Unstable ☐	
9. Using the fusional reserve measurements, add the divergent break point to the convergent break point. Is the total (=fusional amplitude) at least 20Δ?	
Yes ☐ or No ☐	*If no, score +1*

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Research Submission

Visual Stimuli Are Common Triggers of Migraine and Are Associated With Pattern Glare

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Objective.—To investigate the associations between interictal pattern glare, visual stress, and visual triggers of migraine.

Background.—There has been relatively little research on the visual stimuli that can trigger migraine episodes. This is surprising, since if practitioners can obviate such triggers, then some attacks may be prevented. The existing literature suggests that patients who are prone to visually triggered migraines report more illusions on viewing striped patterns ("pattern glare") and that colored filters may be an effective intervention for these people.

Methods.—Headache symptoms and headache triggers were investigated in migraine and control groups in 2 separate experiments. In one experiment, we also determined, for each participant, pattern glare, whether it was reduced by colored filters and, if so, what the optimum color of filter was. Color vision was also assessed with the D15 test.

Results.—People with migraine saw significantly more illusions on viewing each striped pattern and experienced greater pattern glare. They were also more likely to select a colored filter to aid visual comfort, particularly colors in the blue-to-green sector of the spectrum. Color vision was impaired subtly but significantly in migraine. Principal component analyses grouped common headache triggers into 5 broadly equal components: food, visual triggers, alcohol, stress and tiredness, and the environment. In a second analysis, the overall number of illusions seen in striped patterns was associated with visual triggers while pattern glare, use of colored filters, and interictal light sensitivity together formed a sixth component interpreted as visual stress.

Conclusions.—It is suggested that clinicians should ask migraine patients whether visual stimuli trigger their migraine, about interictal visual symptoms, and use the pattern glare test to ensure that those who may benefit from optometric interventions are appropriately managed.

Key words: migraine, vision, triggers, pattern glare, color

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Visual triggers of migraine are common[1] and include visual environmental stimuli[2,3] and self-induced photopsiae (the perception of flashes of light in one's vision).[4] People with migraine, both during and between headaches,[5-7] are particularly prone to glare[1] and to after-images following light exposure.[8] A review of the literature relating to visual stimuli as migraine trigger factors suggested that visual stimuli are of similar importance to other nonvisual triggers such as stress and hormonal factors.[9] In that review, it was

noted that in a sample of 344 migraine patients, 62% had "glare" as a precipitating factor, 53% had "flicker" as a precipitating factor, and 1% had "color" as a precipitating factor.[9] Simple striped patterns have also been implicated as stimuli that can trigger migraine.[10] Migraineurs find striped patterns of 2 to 4 cycles per degree (cpd) particularly aversive[10,11] and this had led to the development of a clinical test, the "pattern glare test," to investigate visual stress responses.[12,13] Mulleners et al[14] found that interictal photophobia was more common in migraine groups than control groups in both a North American and a European cohort, and that people with migraine had lower thresholds for visual stress. However, Mulleners et al did not link their data to the visual triggers of migraine.

In this study, we investigated the links between interictal pattern glare, visual stress, and visual triggers of migraine, in between migraine episodes, using questionnaire data collected prior to participation in 2 separate experiments. The experimental data from a battery of optometric tests have already been reported.[15-19] Here, we report on the association between the questionnaire data and the optometric variables of pattern glare, use of colored filters, and color vision. Pattern glare was assessed by means of the pattern glare test,[12] which gives a score for the number of visual illusions reported on viewing square-wave gratings of spatial frequencies 0.5 cpd, 3 cpd, and 12 cpd. Since there is some evidence that colored filters or filters are an effective intervention for people who are prone to pattern glare[20,21] or visually precipitated migraine,[22] the participants' color vision, preferences for colored filters,[23] and the effects of these colored filters on visual performance, using the Wilkins Rate of Reading Test,[24] were also investigated.

To explore the relationships between headache triggers, a principal component analysis was performed to determine general clusterings between the variables. A further analysis was then conducted to determine how the choice of colored filter, or the illusions seen in striped patterns in the pattern glare test, related to these triggers.

METHODS

Participants.—*Experiment 1.*—The recruitment of the people with migraine and age- and gender-matched controls has been described elsewhere,[15-18] and is summarized briefly below. Our recruitment literature and procedures ensured no referral bias by omitting any mention of vision or optometry. The sample size (25) was calculated[25] using the means and standard deviations of pattern glare scores in migraine and control groups obtained by Evans et al.[22] Systemic health problems, pregnancy, or ocular disease were part of the exclusion criteria. All migraine participants had a formal medical diagnosis of migraine following IHS criteria.[26] There were 25 participants in the migraine group, mean age 37.5 years (95% CI; 33.2 to 41.8) and 25 in the control group, mean age 36.8 years (95% CI; 33.3 to 40.2). Each group contained 21 females and 4 males.

Participants attended in pairs, one from the migraine group and one from the control group. To ensure that the researcher was unaware of the identity of the participants, each of the pair was seen in random order, was asked not to reveal their identity, and the contents of the symptoms and triggers questionnaire were not revealed to the researcher until all tests on both members of the pair had been completed.

Experiment 2.—Participants were recruited from the Psychology Department volunteer database at Birkbeck College, University of London. All migraine participants had a formal medical diagnosis of migraine following IHS criteria[26] and met similar exclusion criteria as Experiment 1. Two migraine groups (with aura and without) were each approximately age- and gender-matched to a control group. The grouping was masked until after the results were analyzed. There were 19 participants in the migraine group (8 with aura and 11 without), mean age 39.2 years (95% CI; 33.1 to 45.3) and 16 participants in the control group, mean age 40.2 years (95% CI; 33.5 to 46.8). The migraine groups contained 12 females and 7 males, while the control group contained 10 females and 6 males.

Materials and Procedures.—In each experiment, participants were asked to complete a questionnaire,[27] which confirmed that those in the migraine group had a migraine diagnosis that conformed to IHS criteria,[26] or confirmed that those in the control group did not experience migraine. The questionnaire detailed the subjects' symptoms and history, including questions

relating to headache severity, frequency, and duration. Part of the questionnaire listed potential triggers and participants were asked to record if that trigger commonly, occasionally, or never triggered a headache. Potential triggers were given a score of 2 if the factor precipitated headaches "commonly," 1 for "occasionally," and 0 for "never."

Experiment 1.—The first study was a case-control study looking at the optometric correlates of migraine, using a battery of clinical tests. The pattern glare test was administered binocularly as described in the test instructions:[12] printed square wave gratings were presented together with a list of visual perceptual distortions (illusions) that may be perceived while viewing the grating (Fig. 1). Three square wave gratings were used with spatial frequencies of 0.5 cpd, 3 cpd, and 12 cpd. To increase sensitivity, we asked participants to grade each visual perceptual distortion as not present, mild, or severe; scored as 0, 1, or 2, respectively. The total score for each grating was then summed for each participant, as previous research has shown that the sum is a good measure of pattern glare.[13] We also investigated an alternative scoring method in the test instructions:[12,13] the difference between the illusion score for the 3 cpd and the 12 cpd.

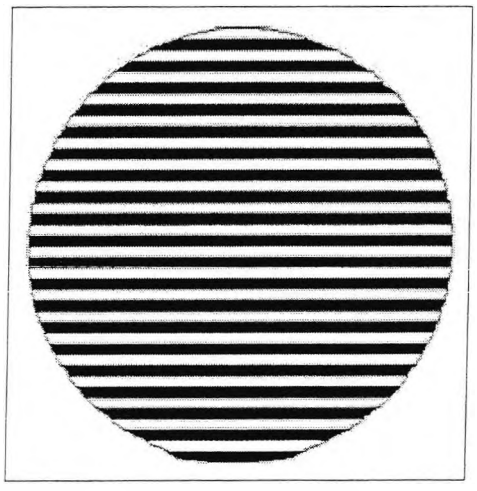

Fig 1.—Participants of Study 1 viewed each of the 3 test patterns (0.5 cpd; 3 cpd; 12 cpd) of the pattern glare test and were asked to report if they noticed any of the following illusions: colors, bending of lines, blurring of lines, shimmer/flicker, fading, and shadowy shapes. If an illusion was reported, then its severity was graded subjectively by the participant as not present, mildly present, or severely present. An example of the test pattern is shown.

The Intuitive Overlay Test uses a range of transparent plastic filters that are of colors designed to systematically sample color space.[23] Participants viewed (binocularly) the standard test pattern of text, which is designed so that the pattern that the lines of text form can trigger pattern glare. Any visual perceptual distortions that were perceived were reported and recorded. Participants then viewed the text through the colored filters, presented in the same standard way, to determine the colored filter (or combination), if any, which most improved their perception of the text. The Wilkins Rate of Reading Test[24] is a simple test that is used to quantify the benefit from colored filters and has been used in a variety of studies.[28] After selecting an individual's optimum filter, the rate of reading test was then completed (binocularly) to compare the rate of reading with and without that filter.

Color vision was assessed binocularly using the Farnsworth saturated D15 test under a MacBeth solsource desk lamp. Scores were analyzed using the Optical Diagnostics Color Vision Recorder computer programme (version 2.3) which generates a Color Confusion Index (CCI) for each participant. The color vision test comprises 15 colored Munsell papers set in black caps. The participants were asked to place the 15 colored caps in to form a smooth color sequence from a single fixed reference cap. There was no time constraint.

Experiment 2.—The second study also assessed performance on a series of optometric tests, although pattern glare and the use of colored filters were not included. The experimental data will be reported elsewhere. Here, the questionnaire data were combined with those from the first study to increase the number of respondents.

RESULTS

Data were tested for normality by inspecting frequency distributions and carrying out Kolmogorov-Smirnov tests. Parametric and nonparametric statistical tests were used as appropriate. When group means are quoted, the 95% confidence limits are given in parentheses.

Color Vision Data.—No subject had a clinically demonstrable diagnosis of a color vision defect on the Farnsworth D15 test. However, the mean CCI was significantly higher in the migraine group at 1.0696

(1.0251 to 1.1142) as compared to 1.0301 (0.9972 to 1.0630) in the control group (Mann-Whitney U-test, one-tailed $P = .034$). This is consistent with previous work.[29]

Pattern Glare Data.—The Pattern Glare Test can be quantified in 2 ways: as the number of illusions with the 3 cpd grating and as the difference between the number of illusions on viewing the 3 cpd grating and the 12 cpd grating.[12,13] Specifically, patients with pattern glare or visual stress should report more visual perceptual distortions on viewing the 3 cpd pattern than the 12 cpd pattern, whereas control participants should exhibit the opposite tendency. Figure 2 shows that the migraine group saw significantly more illusions than the control group on viewing the 3 cpd grating (Mann-Whitney U-test, $P < .0001$), and the difference between the number of illusions with the 3 and 12 cpd gratings was significantly greater in the migraine group than the control group (t-test, $P = .0036$). These findings were still significant when a Bonferroni correction was applied. There was a significant positive correlation between the 2 scoring methods (Spearman $r_s = 0.53$, $P < .01$).

Pattern glare can be diagnosed by a score on the 3 cpd grating of at least 1.0 greater than the score on the 12 cpd pattern.[12] Using this criterion, it can be seen in Figure 3 that of the 25 participants in the migraine group, 16 had pattern glare while only 6 of the 25 controls had pattern glare. Using these findings in a 2 × 2 contingency table, the performance of the pattern

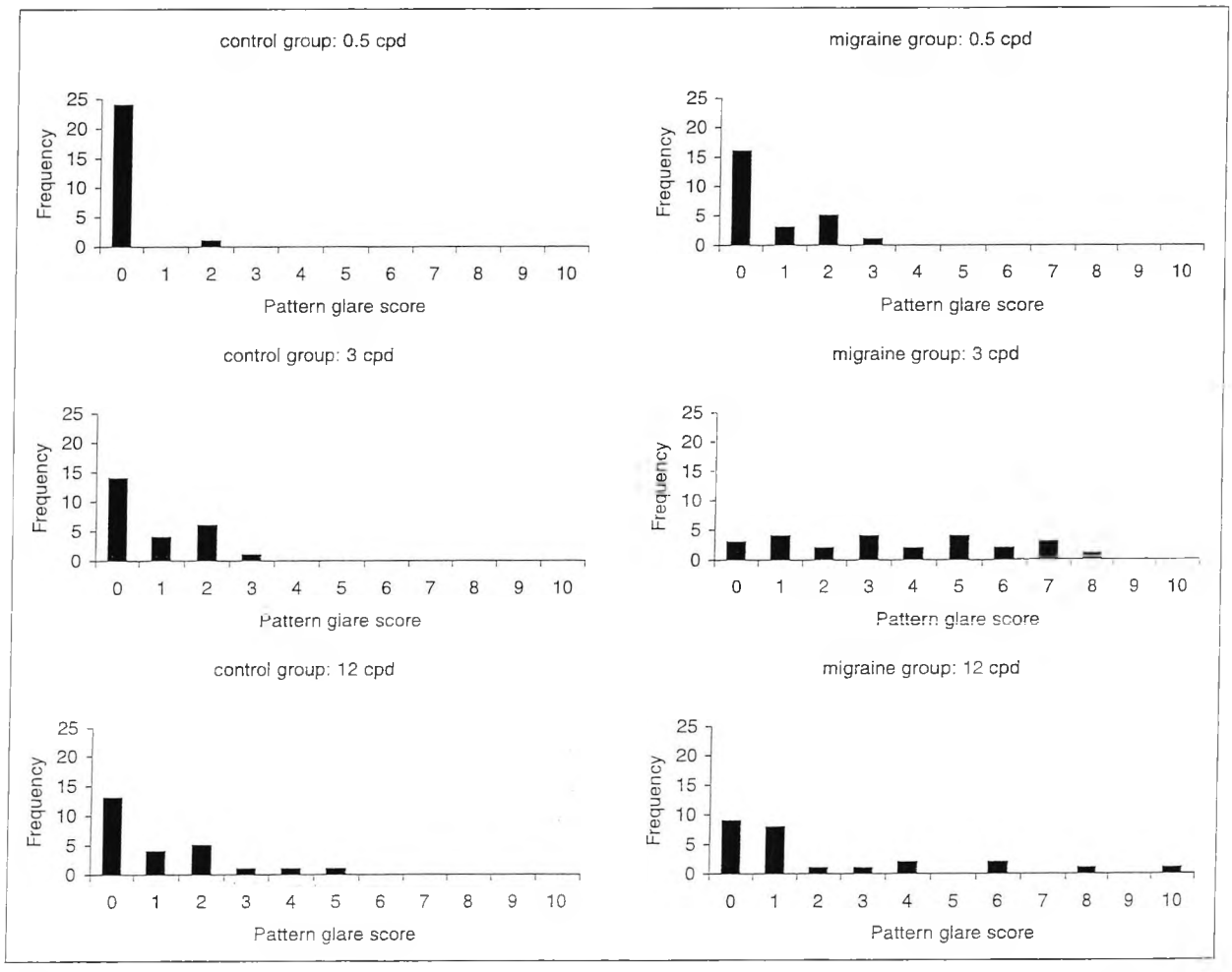

Fig 2.—Frequency distributions of pattern glare test results in the control and migraine groups. People with migraine tend to have a higher score to all test patterns as compared to a control group, and especially so to the 3 cpd test pattern.

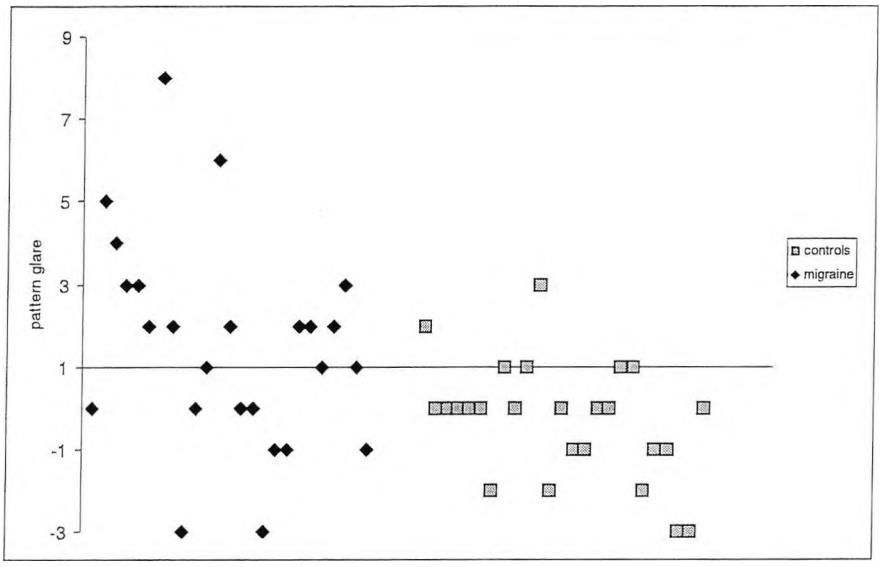

Fig 3.—For each subject (x axis), the difference between the number of illusions seen in the 3 cpd and 12 cpd patterns was calculated (y axis). A value of 1 or greater can be considered to be indicative of pattern glare. Migraine subjects are recorded as black diamonds and control subjects as light gray squares. As can be seen, the control data tend to lie below 1, whereas the migraine data tend to lie on or above 1.

glare test as a diagnostic test for migraine can be illustrated in terms of the number of non-migraine and migraine cases correctly identified by pattern glare. In our subjects, the pattern glare test had a sensitivity of 64% and a specificity of 76% for diagnosing migraine (positive predictor value 73%, negative predictor value 68%).

Colored Filters and Rate of Reading Data.—In the migraine group, 8 subjects did not find any filter-reduced pattern glare, 13 selected a colored filter, and 4 selected a gray filter. In the control group, 19 subjects did not select a filter, 5 selected a colored filter, and 1 selected a gray filter (Fig. 4). There was a significant association between group (migraine or control) and the likelihood of subjects selecting a filter to reduce pattern glare or increase the comfort of the text (χ^2, $P = .0073$).

Rate of reading was recorded for those participants who selected a colored filter. Clinically, a rate of reading increase of 5% is considered significant.[30] The mean rate of reading in words per minute with the filter (control group: 130.2 [101.1 to 159.3], migraine group: 156.7 [144.7 to 168.7]) and without it (control group: 134.0 [113.7 to 154.3], migraine group: 157.5 [142.4 to 172.6]) was similar and there was no association between group (migraine or control) and the number in each group who manifested at least a 5% increase in reading rate (χ^2, $P = .557$).

Symptom Data.—The symptom data in Study 1 reveal the characteristic features of migraine. For example, a high proportion of the migraine groups reported nausea with headache (88%), pulsating quality (72%),

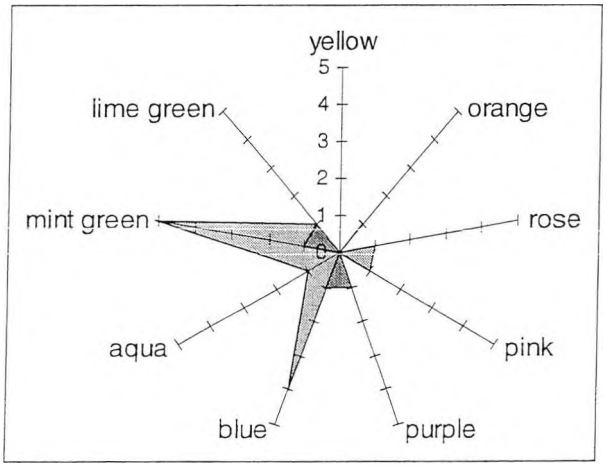

Fig 4.—For those participants who selected a colored filter, the color was recorded. Each spoke represents a color of filter (those who chose a noncolored [gray] filter are not shown). People with migraine (recorded in light gray) as compared to people in the control group (recorded in darker gray) were more likely to select a colored filter, and the colors tended to be green to blue.

phonophobia (68%), photophobia (68%), unilaterality of headache (56%), and aggravation by routine physical activity (48%).

Not surprisingly, people with migraine in Study 1 had significantly more headaches (t-test, $P = .0019$) in the last 12 months (mean 56.2 days/year) as compared to controls (mean 3.8 days/year), and these headaches lasted longer (t-test, $P < .0001$) in people with migraine (mean 37.0 hours) as compared to controls (3.6 hours).

Principal Components Analyses: Migraine Triggers.—Participants in both studies were asked about triggers for their migraines (Table 1). To explore the relationships between the headache trigger data, an exploratory principal components analysis was conducted. Although the trigger data were coded with limited scales, principal components or factor analyses can be performed to determine general clusterings between variables.[31,32] Tests of multicollinearity, sampling adequacy (Kaiser-Meyer-Olkin measure), and the strength of relationships between the variables (Bartlett's test) indicated that the data were suitable for the analyses.

The data from both studies were combined and 5 components were extracted with eigenvalues greater than 1, which accounted for 70% of the variance in the original variables. The rotated solution (varimax rotation) lead to an interpretation of these components as (1) general food, (2) visual triggers, (3) alcohol, (4) stress and tiredness, and (5) the environment (Table 1). Although listed in order, the amount of variance that was explained by each component was broadly similar. These components accounted for 18%, 14%, 13%, 13%, and 12% of the variance, respectively. A cut-off correlation was selected (0.5) that resulted in all but 2 variables (flicker and noise) loading on only one component (allowing an oblique rotation did not alter this pattern). The correlations between each variable and the component to which it contributes are shown in Table 1. Flicker correlated moderately with both the visual trigger and the environment components.

Table 1.—Subjects Were Presented With a List of Possible Headache Triggers and Were Asked to Record Whether Each of These Triggered Their Headaches Either "Commonly" (Scored as 2), "Occasionally" (Scored as 1), or "Never" (Scored as 0). The Correlations Between Each Variable and the Component to Which It Contributes Are Shown From the Rotated Principal Component Analysis

Triggers	General Food	Visual Triggers	Alcohol	Stress and Tiredness	The Environment
Chocolate	0.79				
Cheese	0.71				
Other food	0.81				
Caffeine	0.59				
Flickering lights		0.56			0.60
Certain patterns		0.78			
Other visual stimuli		0.81			
Red wine			0.74		
Other alcohol			0.92		
Stress				0.82	
Tiredness				0.86	
Noise				0.43	0.41
Smells					0.73
Light sensitivity					0.57

The first study included data on the illusions seen in striped patterns, and the number of people who found colored filters beneficial when reading. A second analysis on the data from just Experiment 1, which also included the pattern glare and filter data, was conducted to determine how the choice of colored filter, or the illusions seen in striped patterns related to the clusters of visual triggers. The second analysis produced 6 components with eigenvalues greater than 1, and these accounted for 72% of the variance in the original variables. The rotated solution (varimax rotation) lead to similar interpretations for 4 components: (1) general food, (2) visual triggers, (3) stress/tiredness, and (4) alcohol. The scope of the environment component was reduced (smells and flicker) and an extra component emerged as a visual stress component. These 6 components accounted for 17%, 13%, 12%, 10%, 10%, and 11% of the variance in the variables, respectively. Each variable correlated strongly with only one component. The correlations between each variable and the component to which it contributes are shown in Table 2. Flicker again correlated moderately with both the visual trigger (0.37) and the environment components (0.59), but reached the cut-off correlation only for the environment.

COMMENTS

Three measures, color vision, pattern glare, and the selection of colored filters to reduce pattern glare, each differed between the migraine and control

Table 2.—A Second Analysis Was Conducted to Determine How the Choice of Colored Filter, and the Illusions Seen in Striped Patterns, Related to the Clustering of the Triggers. The Pattern Glare Test Was Scored Using Both Methods: Pattern Glare Score 1 (as the Total Illusion Score for the 3 cpd Pattern) and Pattern Glare Score 2 (as the Difference in the Illusions Score Between the 3 cpd and 12 cpd Square Wave Grating)

Triggers	General Food	Visual Triggers	Stress and Tiredness	Visual Stress	Alcohol	The Environment
Chocolate	0.76					
Cheese	0.68					
Other food	0.90					
Caffeine	0.85					
Certain patterns		0.79				
Other visual stimuli		0.80				
Pattern glare score 1		0.63				
Stress			0.83			
Tiredness			0.71			
Noise			0.57			
Light sensitivity				0.60		
Pattern glare score 2				0.79		
Colored filter chosen				0.73		
Red wine					0.73	
Other alcohol					0.91	
Smells						0.86
Flickering lights						0.59

groups. The questionnaire data revealed visual stimuli to be relevant as triggers for migraine, whereas in the principal components analysis, a measure of visual stress emerged as a separate component that was not strongly associated with visual triggers. The significance of these results, and the interactions between them, will now be discussed in more detail.

Color vision scored as the CCI on standard D15 testing was subtly, but significantly, different between the groups. Other recent work[29] has suggested subtle alterations in color perception in people with migraine, using both psychophysical tests and the Farnsworth-Munsell 100-hue test. In that study, Farnsworth-Munsell partial error scores along the blue-yellow axis were found to be elevated in migraine. While type 3 (blue-yellow) defects are reminiscent of congenital tritan anomalies, it is the chromatic mechanism rather than the blue cones that appear dysfunctional in migraine[33] as is typical in acquired color defects with preserved acuity. Further evidence of normal overall retinal function in migraine[19,34] supports this view. Subtle color perception dysfunction has also been used as an argument to explain blue-on-yellow visual field changes in people with migraine.[35,36]

As described in the introduction, some people report headaches during or after viewing patterned stimuli.[11] This is a component of "patterned glare"[37] or more commonly "pattern glare."[38] A correlation between the number of headaches reported and the illusions seen while viewing a striped pattern has been reported previously,[11] and many more people with migraine report aversion to these patterns as compared to people without migraine.[39] In our study, the pattern of 3 cpd had a markedly increased likelihood of producing visual perceptual distortions in people with migraine as compared to the control group.

The questionnaire data revealed that our migraine groups, not surprisingly, had the characteristic features of migraine.[26] Visual stimuli that trigger migraine headache are commonly reported,[1-4] and here, in the main analysis, general visual stimuli and certain patterns formed a cluster of triggers with flickering lights. Flicker also correlated with other environmental triggers (noise, smells, and sensitivity to bright lights). Flicker has been implicated in the past as a significant migraine trigger,[9] with some authors reporting a direct relationship to flicker frequency[40] and others noting abnormal flicker thresholds in

people with migraine, with a variety of experimental procedures.[41-45]

In the second analysis on the data from Experiment 1 only, the overall number of illusions for the 3 cpd grating clustered with the visual triggers, suggesting that this grating is a potent visual trigger to migraine. Pattern glare (calculated as the difference between the number of illusions seen in the 3 cpd grating and the number of illusions seen in the 12 cpd grating) clustered separately with light sensitivity and with whether a colored filter was chosen. These data might suggest that visual triggers and visual stress are separable, though this requires replication before further conclusions can be drawn.

It has been suggested that in migraine, hyperexcitability of the visual cortex may manifest as pattern glare.[46] Furthermore, this hyperexcitability has been proposed to explain increased pattern glare in 3 conditions:[46] specific learning difficulties,[47] migraine,[48] and epilepsy.[49] The Rate of Reading Test is commonly used to evaluate the effect of colored filters on pattern glare in people with specific learning difficulties,[28] but it does not appear to be similarly useful in migraine. The present data showed that there was not a significant association between the diagnosis of migraine and reaching the test criterion of at least a 5% increase in reading speed with that filter.

Nonetheless, there was a preponderance of people with migraine who selected a color to improve text clarity and there was a relationship between the pattern glare score and the selection of color. The distribution of the color selection was not random and was dissimilar to that found in studies which have looked at the color selection to benefit reading.[50] One hypothesis is that the number of symptomatic neurological conditions, including migraine, that are associated with visual stress, may relate to one another on a continuum of cortical hyperexcitability, possibly affecting different areas or extent within the visual cortex. The precision of color choice for any alleviating filter may reduce as the extent of the area of cortical hyperexcitability increases. An alternative hypothesis would be that the blue-green preference in our study supports the previously discussed color vision studies[29] showing S-cone deficits in migraine.

In migraine, visual triggers are important because they are relatively easy to alleviate. We suggest that the investigation, by healthcare professionals, of people with migraine should include questions about visual triggers and visual stress. The pattern glare or pattern glare difference score, rather than the rate of reading test, might be useful as a screening tool for this purpose. Those who report visual triggers such as flicker or patterns, or those who give a positive response to the pattern glare test, may benefit from consulting eye-care practitioners to investigate the potential for optometric intervention.[17,18,51]

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