<u>Visual Discomfort and Visual Function: Colour and Contrast</u>

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A thesis submitted for the degree of PhD

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March 2019

Dedication

For my grandfather, Derek, my mum, Anna, and my aunt, Ruth.

Abstract

In six studies, vision and visual discomfort were investigated in individuals who experienced migraine or reading difficulty. Contrast discrimination thresholds were measured at two pedestal contrasts (10% and 50%) in volunteers with migraine with aura (MA), without aura (MO) and controls (C). There was no significant difference in thresholds between groups, although participants with unilateral aura had superior discrimination thresholds in the visual field affected by the aura. Similar groups of volunteers viewed gratings illuminated by light of a colour previously selected as "comfortable" or "uncomfortable" for viewing text. They viewed gratings of increasing contrast until discomfort occurred. The thresholds were lower in MA and MO groups and the "comfortable" colour of lighting raised the contrast at which discomfort was reported. In a further group of volunteers the "comfortable" colour raised the contrast discrimination thresholds. The visual evoked potential and haemodynamic response to gratings with low, mid and high contrast was measured in MA and C groups. There were no differences between groups, although the amplitude of the N2 component increased with contrast. Schoolchildren who habitually used a coloured overlay to read selected a colour of light comfortable for viewing text. Reading speed was no greater with lenses that matched the chosen colour. The study was repeated with patients attending Anglia Ruskin Visual Stress Clinic and patients read more quickly with the appropriate tint under double-masked conditions. The above findings are interpreted in terms of cortical hyperexcitability.

Table of Contents

Table of Tables

Table of Figures

Chapter 1 Introduction

1.1   Overview

The thesis presented here forms a report of the effects of migraine on sensitivity to discomfort from striped patterns, contrast discrimination performance and the physiological response to uncomfortable patterns of stripes. Discomfort and reading speed were investigated in individuals who regularly used a coloured filter when reading. The possible therapeutic effects of colour in reducing discomfort were also examined in those who experience migraine. The effects of colour were investigated in these two groups because individuals with migraine are known to be particularly susceptible to visual discomfort from strong patterns (Marcus & Soso, 1989; Wilkins et al., 1984). The research findings will show that contrast discrimination is superior for individuals who experience migraine and that a colour of light chosen individually as comfortable for viewing text can raise the threshold for discrimination of contrast. Individuals with migraine were also found to be particularly susceptible to discomfort from patterns of striped lines, but discomfort was lessened when the patterns were illuminated by a colour chosen individually as comfortable. The physiological effects of patterns of striped lines were also measured. Double-masked trials of the effects of coloured filters on reading speed were undertaken in two settings: a school and an optometric practice. The research conducted as part of this thesis will now be briefly outlined in the context of the background literature.

Contrast Discrimination

Individuals with migraine, particularly migraine with visual aura, demonstrate impairment when completing a variety of visual and psychophysical tasks. There is now much evidence to suggest that migraine is associated with a hyperexcitability of the visual cortex that would explain the anomalous visual illusions caused by strong stimuli (see Welch, D'andrea, Tepley, Barkley, & Ramadan, 1990, for review). The visual processing differences observed in migraine may be the result of a greater response to visual stimuli or an increase in the background neuronal activity or random variation in the response, which will be discussed in detail in section 1.3.1 (O'Hare & Hibbard, 2016). Whilst the majority of research in this area demonstrates impaired performance of individuals with migraine, there is also a small body of research that demonstrates superior performance when completing visual tasks such as flicker detection and metacontrast masking (Karanovic, Thabet, Wilson, & Wilkinson, 2011; Palmer, Chronicle, Rolan, & Mulleners, 2000; Shepherd, Wyatt, & Tibber, 2011). Superior performance may be attributed to the hyperexcitability of the cortex and a consequent greater sensitivity to certain visual stimuli. It is therefore important to investigate the possible effects of hyperexcitability on the ability of individuals with migraine to complete a visual discrimination task. We have measured contrast discrimination thresholds in individuals with migraine and controls at two pedestal contrasts. The effect of a unilateral visual migraine aura on contrast discrimination has also been measured. The results of this experiment are reported in Chapter 2. The effect of a unilateral migraine aura on contrast discrimination was further investigated in chapter 4 in which individuals completed the same task as that described in Chapter 2 whilst wearing coloured lenses and control grey lenses.

Contrast Threshold for Discomfort

A colour to aid reading comfort is commonly presented in the form of lenses or a coloured sheet of plastic placed upon a page, called an overlay (Wilkins, Lewis, Smith, Rowland, & Tweedie, 2001). An individually selected colour has been shown to improve comfort and reduce the number of headaches in individuals with migraine (Wilkins, Patel, Adjamian, & Evans, 2002). Few investigations have examined the effects of coloured filters on visual tasks that do not involve reading (Chronicle, Wilkins, & Coleston, 1995). The effects of coloured filters on psychophysical tasks may help reveal the mechanism for the reported beneficial perceptual effects of colour. It was therefore important to test the possible benefits of coloured filters for individuals with migraine completing pattern-related visual tasks designed to be uncomfortable. We presented grating patterns of increasing contrast, illuminated by two colours of light: a colour identified as comfortable and a second uncomfortable colour. Participants viewed the grating patterns until discomfort is experienced. The results of this experiment are reported in Chapter 3.

Physiological correlates of Visual Discomfort

Some uncomfortable images have been associated with a greater metabolic demand by the brain, which can be observed as an increase in the oxygenated component of haemoglobin (Haigh, Barningham, et al., 2013; Le et al., 2017). A difference in the shape of the haemodynamic response has been demonstrated when individuals with migraine view uncomfortable patterns (Coutts, Cooper, Elwell, & Wilkins, 2012). The haemodynamic response, therefore, appears to be a useful biological marker for the heightened cortical response observed in individuals with migraine. It is not yet clear whether the shape of the

haemodynamic response will vary with pattern contrast. We have measured the shape of the haemodynamic response, using near infrared spectroscopy (NIRS), in participants with migraine and controls in response to achromatic grating patterns of low mid and high contrast.

Simultaneously, the electrical activity of the brain will be measured in the form of visual evoked potentials (VEP's), which are the time-locked synchronous discharge of appropriately oriented cortical neurones in response to a stimulus measured at the scalp. VEP's of abnormally high amplitude have been demonstrated in individuals with migraine (Schoenen, Wang, Albert, & Delwaide, 1995). Typically, after an initial increase of neuronal activity, the discharge of activity becomes stable as the individual habituates to the stimuli. Habituation to a repetitive stimulus has been shown to be impaired in individuals with migraine (Afra, Cecchini, De Pasqua, Albert, & Schoenen, 1998). The amplitude of the VEP would be expected to increase with contrast, reflecting hyperexcitability of the cortex in response to uncomfortable grating patterns. We have examined the amplitude of the VEP response to three grating patterns of low, mid and high contrast. The results of this experiment are reported in Chapter 5.

Double-masked Trials of Coloured Filters

The efficacy of coloured filters as an intervention to improve reading speed and comprehension of text remains unclear due partly to the various experimental methods that have been used to investigate their effects (Wilkins, 2002b). Coloured filters, in the form of precision tinted lenses and overlays, are now prescribed in optometric practice and

used in schools. Two double-masked trials of precision spectral filters were undertaken: the first study investigated reading speed in children who used overlays to read; the second study was conducted in an optometry clinic for individuals who experience visual discomfort. The influence on reading speed of a comfortable 'active' set of lenses and lenses of similar colour 'placebo' was examined. One of the prerequisites of any assessment of the possible benefits of colour is that the assessment should be repeatable. This thesis will show that individuals who experience a therapeutic benefit from the use of colour will reliably select the chosen colour on two separate conditions under double-masked conditions. The results of these experiments are reported in Chapters 6 and 7.

The work of this thesis has examined the effects of migraine on visual processing using psychophysical and physiological techniques. The role of visual discomfort in migraine was also examined and the use of coloured filters was investigated as a non-invasive intervention for migraine and reading difficulty.

1.2   Visual Discomfort

Many people experience the symptoms of visual discomfort on a daily basis or when undertaking visual tasks. The symptoms may include: eyestrain, fatigue, sore eyes and headache (Sheedy, Hayes, & Engle, 2003). Underlying optical problems can contribute to the experience of visual discomfort; such as an abnormal accommodative response, convergence insufficiency or uncorrected refractive error (Adler, 2002; Chase, Tosha, Borsting, & Ridder, 2009; Gordon, Chronicle, & Rolan, 2001; Tosha, Borsting, Ridder, & Chase, 2009). It is not clear how these optical abnormalities contribute to visual discomfort, but it is likely that they create an impoverished image on the retina. Most physical optical abnormalities can be corrected to some extent, thereby reducing visual discomfort. Some individuals nevertheless experience pain and anomalous visual illusions in the absence of any observable ocular abnormality (Evans, 2005). When individuals susceptible to visual discomfort observe a high contrast pattern of striped lines, for example, illusions of colour, shape and movement are often reported (Wilkins 1995). Monger, Shah, Wilkins, and Allen (2016) varied the viewing distance of striped patterns without changing their spatial frequency, but the experience of anomalous visual illusions did not change, as might have been expected had the illusions been the result of anomalies of accommodation or vergence. The patterns of stripes that can evoke visual discomfort and anomalous visual illusions possess particular spatial characteristics (Wilkins, Nimmo-Smith, Tait, McManus, Della Salla, Tilley, Arnold, Barrie & Scott, 1984). Striped patterns of high contrast with a spatial frequency between 0.5 and 12 cycles deg^{-1} are usually uncomfortable to view for those who habitually experience visual discomfort.

The quantitative measurement of visual discomfort presents difficulty because the associated anomalous visual illusions and pain are subjective. Various methods have been used to assess the effects of visual discomfort including questionnaires and psychophysical methods. Questionnaires usually assess common symptoms of visual stress such as eye-pain from striped-patterns, visual difficulty when reading and discomfort from bright or fluorescent lighting. Conlon, Lovegrove, Chekaluk, and Pattison (1999) validated a questionnaire assessing visual discomfort by subsequently presenting square-wave patterns of varying spatial frequency. They found high scores on the visual discomfort questionnaire related to an increased number of unpleasant visual symptoms when viewing the patterns. The questionnaire developed by Conlon et al. (1999) creates a profile of visual discomfort for an individual based on responses to all items in the questionnaire. Due to the ordered response pattern of the questionnaire, the authors conclude that visual discomfort can be measured on a single dimension. Borsting, Chase, and Ridder (2007) used the visual discomfort questionnaire of Conlon et al. (1999) to investigate whether there is a single dimension to visual discomfort or whether there are various sub-types. The authors replicated the results of Conlon et al. (1999) and found that the single symptom severity dimension accounted for 73.5% of the variance. For individuals who experienced moderate to high levels of visual discomfort, symptoms sharing the same characteristics were grouped into clusters and the number of individuals who experienced a particular group of symptoms was calculated. The symptoms reported by 40% of the individuals with high levels of discomfort did not fit the mixed symptom profile that accounted for the majority of the variance. These individuals reported specific types of symptoms. The authors suggest there exist various causes of visual discomfort. Sheedy et al. (2003) report two groups of symptoms relating to eyestrain, which predicted the cause of eyestrain, e.g. viewing distance and flickering stimuli. The authors suggest the two

groups of symptoms and their causes represent two separate pathways for the symptoms of eyestrain.

The effects of visual discomfort on objective psychophysical tasks have also been measured. Conlon, Sanders, and Wright (2009) assessed global motion processing and visual processing speed in individuals with visual discomfort and those who experience dyslexia. Participants with visual discomfort showed reduced sensitivity upon the first completion of a global motion task, and reduced visual processing speed. The effects of visual discomfort can therefore be investigated using various methods, including objective assessments of visual processing.

The level of discomfort experienced varies widely in the general population, but individuals with certain neurological conditions such as migraine or photosensitive epilepsy are particularly susceptible (Debney, 1984; Radhakrishnan et al., 2005). When patients with photosensitive epilepsy view certain patterns of stripes, epileptiform EEG activity is evoked, which is indicative of a seizure susceptibility (Wilkins et al, 1984).

In a computational model of the visual cortex, uncomfortable images that can trigger migraine attacks or epileptic seizures have been shown to produce a larger and less sparse neuronal response (Hibbard & O'Hare, 2015). Images of filtered random noise were judged to be more comfortable to look at when they possessed a Fourier amplitude spectrum of $1/f$ (Fernandez & Wilkins, 2008; O'Hare & Hibbard, 2011). A Fourier amplitude spectrum of $1/f$ is characteristic of natural images as these images show the greatest amplitude at low spatial frequencies and the amplitude falls away quickly as spatial frequency increases.

Following adaptation to natural images, selective changes in contrast sensitivity in the low spatial frequency range, suggest an adaptation bias that favours low rather than mid-high spatial frequency information (Webster & Miyahara, 1997). Images with an excess of energy at mid-range spatial frequencies are judged to be uncomfortable to look at and have a Fourier amplitude that departs from 1/f (Fernandez & Wilkins, 2008).

The neurological cause of visual discomfort is not clear, although the stimuli that evoke visual illusions are almost the same as those that trigger a pattern of EEG activity in patients with epilepsy, that includes spikes and is known as *epileptiform* because of its association with epilepsy (Wilkins, 1995). A failure of cortical inhibitory processes has been suggested as the shared neural mechanism that underlies both anomalous visual illusions and the characteristic EEG discharge observed in individuals with epilepsy (Wilkins et al, 1984). One explanation that has been put forward is that for individuals who are particularly susceptible to visual discomfort, the pain may act as a homeostatic protective mechanism, reducing excessive brain metabolism much as does a reflex withdrawal of a limb from a painful stimulus (Haigh, Barningham, Bernsten, Coutts, Hobbs, Irabor, Lever, Tang, & Wilkins, 2013).

Coloured filters in the form of lenses or plastic overlays, placed upon the page, have been used to help alleviate some of the anomalous perceptual distortions and pain associated with visual discomfort. Helen Irlen (1990) first developed a system of coloured lenses to reduce the symptoms of visual discomfort when reading. Participants who regularly wore lenses tinted with the Irlen system showed improvement in the symptoms of visual

discomfort and small improvements on a visual search task when wearing the lenses (Wilkins & Neary, 1991). The experience of anomalous visual illusions is subjective and it is therefore difficult to measure the possible benefit of coloured glasses on visual discomfort.

The terms 'visual discomfort' and 'visual stress' are used synonymously throughout this thesis. The majority of the work described in the experimental chapters focuses on visual function and visual discomfort from grating patterns in individuals with migraine. The term 'visual stress' has also been associated with visual distortions when reading, which is the subject of Chapters 6 and 7. 'Visual discomfort' was therefore thought to be an appropriate description of the adverse visual symptoms associated with strong patterns in individuals with migraine and a generic term for distortions of text when reading.

Comment

In summary, visual discomfort is a term that encompasses a variety of perceptual distortions together with eye-pain. The experience of visual discomfort varies widely and some clinical groups of individuals are more susceptible than others, particularly those with migraine or photosensitive epilepsy. Strong patterns of stripes are common triggers of discomfort and visual distortions, which can occur in individuals without obvious ocular abnormalities. There have been claims that the unpleasant symptoms of visual discomfort can be reduced with lenses with a colour individually selected as comfortable.

1.2.1   Photosensitivity and Pattern-glare

Glare is usually understood to be a dazzling effect caused by a bright source of light and is typically categorized as disability glare (due to a reduction of contrast by scattered light) and discomfort glare (of largely unknown origin) (Luckiesh & Holladay, 1925). Discomfort glare is, however, often also experienced not only from a source of light but also when viewing patterns of high contrast. The Pattern Glare test (i.O.O Sales Ltd, London, England) comprises high contrast patterns of low, mid- and high spatial frequency and is used in the assessment of visual discomfort (Wilkins & Evans 2001). Patients report the number of anomalous visual illusions experienced whilst observing each pattern in turn. Patients often report illusions of colour, shape and motion when completing the Pattern Glare test. One explanation for discomfort glare is that the adverse symptoms may result from a hyperexcitablilty of visual neurons (Bargary, Furlan, Raynham, Barbur, & Smith, 2015). In the absence of migraine or another headache disorder, an individual may still experience discomfort glare and anomalous visual illusions when completing the Pattern Glare test.

The pain of migraine is worsened by exposure to ambient lighting when compared to pain level in darkness (Kasteleijn-Nolst et al., 2010). During an attack of chronic migraine 83% of hospital patients reported being photophobic (Beckmann, Seçil, Kendir, & Başoĝlu, 2009). The links between migraine and photosensitivity are discussed below in section 1.3.

1.3   Migraine

Approximately 11% of the population experience a severe form of headache known as migraine (Lipton et al., 2007). The International Headache Society ICHD III diagnostic criteria specify the symptoms of the two forms of migraine (IHS, 2013). Diagnostic criteria for migraine without aura are detailed in Table 1:1.

Table 1:1: ICHD III diagnostic criteria for migraine without aura (MO).

Diagnostic criteria for Migraine without aura

At least 5 attacks fulfilling these criteria:
Headache lasting 4 to 72 hours (untreated or unsuccessfully treated)
Headache has at least 2 of the following characteristics:
   1. Unilateral location
   2. Pulsating quality
   3. Moderate or severe intensity
   4. Aggravated by physical activity
 	
During the headache at least 1 of the following:
 	
   1. Nausea and/or vomiting
   2. Photophobia and phonophobia
 	
No evidence of organic disease

In some patients an attack of migraine is preceded by a set of sensory disturbances known as the aura, which is commonly experienced as positive visual illusions and an area of impaired vision called the scotoma. These symptoms are in addition to the diagnostic criteria detailed in Table 1:1 (see Table 1:2). Sir Hubert Airy described several of his own experiences of migraine aura, most notably the geometric pattern as 'like the drawing of a fortification' (Airy, 1870). Common forms of migraine aura include small flashes of light

and simple geometric patterns. The simple structure of the visual aura of migraine differs from the hallucinations of other neurological conditions in that there are no reports of hallucinations of complex objects or scenes (Wilkinson, 2004). Visual aura is the most common form (Rasmussen & Olesen, 1992) and visual disturbances, other than blurring, were found to occur in 41% of 448 individuals with migraine (Selby & Lance, 1960). Blurring of vision was excluded as the main visual phenomenon by the authors of this study because they state that this symptom is almost universal. There is a strong visual component to migraine both in the form the aura takes and the visual stimuli that trigger headaches, and these vary widely between individuals. Many sufferers report visual triggers such as strong patterns, colours and flickering or fluorescent lights (Debney, 1984). One of the diagnostic criteria for migraine is the aversion to light (photophobia) and sound (phonophobia); see Table 1:1, which suggests that discomfort from strong sensory input is a feature of the disorder. Some individuals experience a non-visual aura, which can take the form of numbness (Peatfield, Gawel, & Rose, 1981), typically beginning in the hand and moving up the arm. Perceptual distortions during the aura phase present difficulty in measurement, as all illusions are subjective experiences. Patients are often asked to draw the visual illusions seen during migraine aura to aid with diagnosis. See Figure 2:1 in Chapter 2 for an illustration of a 'typical' migraine aura.

Table 1:2: ICHD III diagnostic criteria for migraine with aura (MA).

Diagnostic criteria for Migraine with aura

    A. At least 2 attacks fulfilling criteria B and C.
    B. One or more of the following fully reversible aura symptoms:
        1. Visual
        2. Sensory
        3. Speech and/or language
        4. Motor
        5. Brainstem
        6. Retinal
    C. At least two of the following four characteristics:
        1. At least one aura symptom spreads gradually over ≥5 minutes, and/or two or more symptoms occur in succession
        2. Each individual aura symptom lasts 5-60 minutes
        3. At least one aura symptom is unilateral
        4. The aura is accompanied, or followed within 60 minutes, by headache

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Diagnostic tests and history exclude a secondary cause

Contrast threshold for visual discomfort and responses to questions concerning diagnosis and photophobic symptoms, appear to be correlated and predict diagnostic category accurately (e.g. Control, MA, MO) (Mulleners, Aurora, et al., 2001). This finding suggests the assessment of symptoms of photophobia may be a useful diagnostic tool.

The triggers for an attack of migraine or a seizure induced by visual stimulation (photosensitive epilepsy) are very similar in nature (Kasteleijn-Nolst et al., 2010). Individuals who experience photosensitive epilepsy may have seizures induced by visual stimuli such as flashing lights and strong patterns (Wilkins et al., 2005). Alternating red and blue flicker that occurs in some television programmes is particularly likely to induce a seizure (Zifkin & Inoue, 2004). There are similarities in the triggers of migraine and photosensitive epilepsy and comorbidity between the two disorders. Patients with epilepsy

are 2.4 times as likely to also suffer with migraine when compared to relatives without epilepsy (Haut, Markowitz, & Lipton, 2011). It may be the case that there is a shared neural mechanism for the two conditions.

Migraine headache is exacerbated by light in a majority of patients including individuals who are blind but whose visual system remains intact (Noseda, Kainz, Jakubowski, Gooley,Saper, Digre, & Burstein, 2010). There were various causes of blindness for the individuals who participated in the study conducted by Noseda et al. (2010), which included; inherited retinal degeneration, retinal detachment and glaucoma. The level of anisocoria (unequal size of the pupils) in migraineurs during the inter-ictal period has been found to be greater in those with a habitual side of head pain but the increased dilation is not necessarily on the same side as the pain (Harle, Wolffsohn, & Evans, 2005). Individuals who experience unilateral migraine pain on the left side of the head appear to have a different parasympathetic nervous system response to painful stimulation of the eyes (Avnon, Nitzan, Sprecher, Rogowski, & Yarnitsky, 2004). Avnon et al. (2004) placed a diluted soap solution in each eye and measured vasodilation of the skin on the forehead, vasoconstriction of the index finger and heart rate. Participants with unilateral migraine pain on the left of the head showed more vasodilation and bradycardia, which may influence cerebral vasodilation during a migraine attack. Parasympathetic nervous system function is predominantly controlled in the left hemisphere of the brain and activation influences vasodilation. This link may be an inherent part of the pathophysiology for those who experience unilateral migraine pain on the left side of the head.

The underlying cause of migraine is not yet known, however there is much experimental evidence for hyperexcitability of the neurones in the visual cortex that is discussed in detail in section 1.3.1 (Welch et al., 1990). A wave of depressed neuronal activity known as cortical spreading depression has been observed when an area of the brain is stimulated with an electric current (Leão, 1944). Cortical spreading depression has been linked to visual migraine aura because the wave of depressed neuronal activity appears to advance at the same rate as the visual aura (Leao & Morison, 1945; Milner, 1958). Hyperexcitability and cortical spreading depression may be linked, as hyperexcitability of the visual cortex could predispose an individual with migraine to cortical spreading depression (Welch & Ramadan, 1995).

Haigh, Karanovic, Wilkinson, and Wilkins (2012) presented both individuals with migraine and migraine-free controls with grating patterns that were drifting, vibrating or static. The contrast of the grating patterns was increased until the participant experienced discomfort in order to obtain an aversion threshold. Individuals in the migraine group set lower aversion thresholds than controls, which is indicative of a greater level of visual discomfort. Achromatic grating patterns are known to cause discomfort and visual illusions but coloured gratings (on cardinal axes - red/green, blue/yellow) are less uncomfortable for individuals with migraine (Shepherd, Hine, & Beaumont, 2013a). The authors presented achromatic and coloured (purple, yellow, red and green) square-wave grating patterns of varying spatial frequency to individuals with migraine and controls. Participants were asked about the number of illusions that were experienced from viewing each pattern. Participants in the migraine group experienced a greater number of illusions but these were reduced when the coloured gratings were viewed. Coloured grating patterns may

reduce the excessive neuronal activity that is thought to result from viewing an achromatic grating pattern.

Coloured filters have been used as a prophylactic treatment for migraine to help reduce visual discomfort and pattern glare (Evans, Patel, & Wilkins, 2002). The development of a colorizer (Intuitive Colorimeter) enabled patients to easily vary the colour and saturation of light, at constant luminance, to help identify a colour that was comfortable for viewing text (Wilkins & Sihra, 1993). The colour of light identified by the individual could then be reproduced as lenses. The mechanism of coloured filters in reducing the visual discomfort associated with migraine is not yet clear, but studies using electrophysiological techniques have begun to explore the effects. In children with migraine and those with visual stress, it is possible to test objectively the perceptual benefits of tinted lenses by observing their effect on the visual evoked potential (VEP) (Riddell, Wilkins, & Hainline, 2006). Riddell et al. (2006), presented checked patterns of low contrast to children who wore Intuitive Colorimeter lenses. Participants viewed the checked patterns whilst wearing the following lenses in turn: no lens, Colorimeter lens, lens of complimentary colour and spectrally neutral lens of similar transmission. The authors found the largest VEP amplitude response in the no lens condition for children with visual stress, whereas children with a history of migraine showed the largest response when wearing precision tinted lenses. Participants with migraine were possibly gaining a perceptual advantage from the precision tinted lenses, possibly in the form of increased signal to noise. Huang, Zong, Wilkins, Jenkins, Bozoki, and Cao (2011) conducted an fMRI study to investigate the effects of precision spectral filters on cortical activation and visual discomfort. Low mid and high spatial frequency pattern gratings were presented to participants whilst they wore three sets of

lenses in turn: precision tinted lenses, control-coloured lenses and grey lenses. They found precision spectral filters, and not control-coloured or grey lenses, suppressed cortical activation in V2 and other posterior areas in individuals with migraine but not controls. The abnormal neuronal activity observed in the participants with migraine is consistent with insufficient inhibition of the output from area V1. If precision spectral filters can suppress cortical activation, they may be useful as a non-invasive treatment to reduce the frequency of attacks of migraine.

Behavioural and psychophysical studies have also demonstrated the sensitivity of individuals with migraine to strong patterns and the possible ameliorating effects of coloured filters. Patients with visually-triggered migraine demonstrate a marginal reduction of headache incidence with the use of precision tinted lenses, which may redistribute areas of cortical excitation caused by uncomfortable visual stimuli (Wilkins et al., 2002). Chronicle and Wilkins (1991), asked participants with migraine, and those without, to identify a colour of light that was (a) comfortable and (b) uncomfortable for viewing text inside the Intuitive Colorimeter. Individuals in the migraine group were more likely than controls to identify a red hue as uncomfortable, which suggests that the level of visual discomfort may be dependent on the colour of light used to illuminate stimuli.

Double-masked trials indicate that aversive visual symptoms and headache are reduced when lenses selected by the participant are worn, rather than placebo lenses that are similar in colour (Wilkins et al., 1994). Due to the effects of colour adaptation, and the elapsed time between identification of the lenses and testing, it may be the case that the

participant has difficulty identifying which of the lenses are 'active'. If participants do recognise the colour of the beneficial 'active' lenses then this may produce a change in motivation of the participant. Individuals for whom colour is of benefit may recognise the colour identified as comfortable because any anomalous visual illusions or discomfort may have been reduced. It would therefore be difficult to design an experiment to mask a participant who experiences a reduction of symptoms with the use of colour. D'Ath, Thomson, and Wilkins (2007) showed the ability of participants to immediately reproduce a colour, presented on a screen, was poor even when they had been given instructions to remember the hue. The underlying mechanism of precision tinted lenses is not yet known, but it is unlikely that the observed effects are wholly the result of individuals recognising the 'beneficial colour'. The results of this study suggest that for those participants who do not experience a benefit from the use of colour (i.e. controls) the ability to remember a particular hue is poor.

1.3.1   Hyperexcitability and hyper-responsiveness

Several independent lines of evidence have arisen to suggest that hyperexcitablilty of the visual cortex is evident in migraine. Individuals with migraine are known to be susceptible to visual discomfort from strong patterns and bright, usually fluorescent, lighting (Hay, Mortimer, Barker, Debney, & Good, 1994). It has been proposed that the visual cortex is hyperexcitable (Welch et al., 1990) or hyper-responsive (Coppola, Pierelli, & Schoenen, 2007) in migraine. If a strict definition were applied, the cortex would be hyperexcitable if it produces a neuronal response of increased amplitude or is sensitive to stimuli that would normally be sub-threshold. Coppola et al. (2007) define 'hyper-responsive' as an excessive

reaction to repetitive, but not single stimuli. The author's challenge the term 'hyperexcitability' because the amplitude of the visual evoked potential (VEP) is decreased in individuals with migraine for low numbers of stimuli followed by a deficit of habituation (section 1.4.1). The author's propose that in migraine the cortex is under-responsive to single stimuli. When large numbers of stimuli are presented an over-response (potentiation) is observed and the metabolic demand cannot be maintained, which leads to hyperexcitability. There is also evidence of impaired intra-cortical inhibition in migraine, which would result in the inappropriate firing of neurones (Palmer et al., 2000). Individuals with migraine have demonstrated impairment on a range of psychophysical tasks (see section 1.7). It has been argued that reduced neural responsiveness is consistent with hyperexcitability. Hyperexcitability might be expected to create more neural noise. An increased level of noise would impair detection and discrimination near threshold.

There are various models to explain the differences in visual processing observed in migraine. O'Hare & Hibbard (2016) propose a model to explain hyperexcitability and hyperesponsiveness in migraine. The strength of the response of the visual system or gain, is dependent on the signal to noise ratio. If the ratio is low then greater gain will be required to maintain the signal. Multiplicative noise must also be considered and is the random variation of the neuronal activity in response to a stimulus, which does not provide any information about the nature of the stimulus. The authors describe two ways in which the increase in neuronal activity in migraine could arise. Firstly, if the brain responds more strongly in migraine (hyper-responsiveness) a larger response for a given input would be expected. Hyperexcitability would also cause an increase in neuronal activity, which may result from an increase in the background level of noise or stimulus-induced noise. The

model described here therefore suggests that increased neuronal activity in individuals with migraine could be the result of an increase in the gain function resulting from a greater level of background noise or stimulus-induced noise.

An increase in gain would place a greater metabolic demand on the brain, which cannot be maintained for long periods of time. This would explain the illusions and discomfort experienced by individuals with migraine when viewing strong patterns but would also explain the impaired performance of these individuals when completing psychophysical tasks.

Antiepileptic drugs (AED's) have been found to be of benefit for both individuals who experience migraine and those who experience epilepsy, which is consistent with a shared brain state of excitability (Welch, 2005). Commonly prescribed antiepileptic drugs include lamotrigine and sodium valproate, which block sodium-dependent action potentials to increase stability of the membrane. In a study examining the effects of Lamotrigine, Lampl, Katsarava, Diener, and Limmroth (2005) showed that over a period of 3 years, patients who experienced MA saw a marked reduction in aura symptoms and attacks of migraine with use of the drug. The reduction of migraine headaches in this study provides evidence of a link between cortical spreading depression and migraine headache. Cortical spreading depression will be discussed later but there is strong evidence that a spreading depression of neuronal activity triggers the migraine aura. If the frequency of aura and migrainous pain is reduced with the use of Lamotrigine then the aura may activate the trigeminal vascular system, which causes the pain. Individuals with MA also respond well to treatment

with sodium valproate on a range of headache indices including the threshold for eliciting phosphenes from transcranial magnetic stimulation, or TMS (Mulleners, Chronicle, Vredeveld, & Koehler, 2002).

TMS has been employed to investigate the threshold for eliciting phosphenes, commonly brief white flashes, in individuals with migraine. Individuals who experience migraine with aura have lower thresholds for eliciting phosphenes than those without aura or controls (Aurora, Ahmed, Welch, Bhardhwaj, & Ramadan, 1998; Aurora, Welch, & Al-Sayed, 2003; Young et al., 2004). Lower thresholds in individuals with migraine have been used as evidence for cortical hyperexcitability between migraine attacks, as the visual neurones may be less able to withstand disruption of electrical stability by an external magnetic source (Gerwig, Niehaus, Kastrup, Stude, & Diener, 2005; Khedr, Ahmed, & Mohamed, 2006; Mulleners, Chronicle, Palmer, Koehler, & Vredeveld, 2001). In contrast, increased thresholds for eliciting phosphenes have been found in individuals with migraine, which may suggest the visual cortex is hypoexcitable between attacks of migraine (Bohotin et al., 2002; Bohotin, Fumal, Vandenheede, Bohotin, & Schoenen, 2003). Technical differences such as the coil shape and size may help partly explain the discrepancy of results. If the visual cortex is hyperexcitable in the interictal period, the anomalous visual illusions and discomfort experienced from strong patterns may be the result of an excessive neuronal response.

Comment

In conclusion, migraine is a common neurological disorder with a strong visual component. The underlying pathophysiology of migraine is not yet clear, but there is growing evidence for a state of general neuronal hyperexcitability. Coloured filters have been used to reduce visual discomfort and attack frequency in migraine. Coloured filters may suppress excessive cortical activation and thereby reduce the number of visually triggered migraine attacks.

1.3.2   Cortical Spreading Depression

There is growing neuroanatomical evidence to explain the underlying mechanisms of migraine and it has been suggested that cortical spreading depression (CSD) may be linked to the propagation of visual aura. Leão (1944) administered electrical stimulation to the cerebral cortex of rabbits and described a spread of depression of spontaneous neural activity in all directions from the stimulated region at a rate of ~3mm/minute. Recovery of the initial level of spontaneous neuronal activity requires 5-10 minutes at each brain region. The visual aura of migraine also moves across the visual field at a rate of ~3mm/minute and is followed by a longer period of inhibition (Lashley, 1941). A slow-voltage variation has been shown to accompany CSD, which is of the same nature as that elicited from an interruption to the circulation of the cortex (Leão, 1947). van Harreveld (1946) observed the same voltage variation in the spinal cord during asphyxiation. The author describes the voltage change as being the result of the depolarisation of nerve cells and nerve fibres in the spinal cord. The negative voltage can be reversed with a normal supply of oxygen. Cortical spreading depression and an interruption of circulation both

produce a negative voltage change, which may suggest a change of oxygenation during CSD. Brain regions vary in their susceptibility to CSD, the visual cortex being highly sensitive. GABA-ergic cells in the visual cortex are particularly susceptible to changes in regional cerebral blood flow and oxygenation, which makes these cells sensitive to damage during cortical spreading depression (Chronicle & Mulleners, 1994). Patients who report many illusions have headaches more frequently suggesting a relationship between headaches and cortical inhibitory failure (Wilkins et al., 1984). The authors suggest the breakdown of inhibitory mechanisms may remain localised in the visual cortex so as to produce anomalous visual illusions.

Leão (1944) was the first to describe the spread of depressed neuronal activity but Milner (1958) linked spreading depression to the visual aura of migraine due to the similarities of propagation. van Harreveld & Stamm (1955) administered the proconvulsant Metrazol to rabbits and presented single and repeated (8-10/second) flashes of light. Cortical spreading depression was elicited by the flashes of light, which indicates that with heightened neuronal sensitivity, visual stimuli can trigger spreading depression of activity. Grafstein (1956) described a period of intense neuronal activity at the advancing margin of CSD, which, if disrupted by electrical stimulation, resulted in the arrest of the spread of depression. The period of excitation could therefore be an intrinsic part of the propagation of CSD that is responsible for the subsequent depressed activity. Cortical excitability and CSD may be linked in such a way that existing excitability may make an individual susceptible to CSD (Welch et al., 1990).

It has been proposed that CSD protects the brain against subsequent ischemia (Matsushima, Schmidt-Kastner, Hogan, & Hakim, 1998; Taga, Patel, Drummond, Cole, & Kelly, 1997). In animal models Taga et al. (1997) induced CSD in one hemisphere of the forebrain of rats with the application of potassium chloride. Neuronal injury was measured in the striatum, hippocampus and the cortex. After forebrain ischemia, neuronal injury was significantly less in the hemisphere previously subjected to CSD. The protective effects of CSD were only observed in the cortex and lasted up to 7 days after the episode of CSD. Matsushima et al. (1998) also induced CSD in rats with the application of potassium chloride. The authors investigated the levels of neurotrophic factors in the brain, which support the growth and survival of neurons. The authors report that the neurotrophic factors investigated are an integral part of the neuroprotective effects of CSD. Olesen, Larsen, and Lauritzen (1981) investigated regional cerebral blood-flow (rCBF) during attacks of migraine. During an attack of migraine, rCBF levels became critically low in one participant. If regional levels of blood-flow can be affected by migraine in such an extreme manner, then a protective mechanism such as CSD may help prevent repeated neuronal injury.

1.4   The mechanisms associated with abnormal EEG in migraine

Grating patterns that induce epileptiform activity in individuals with photosensitive epilepsy can also cause an abnormal VEP in individuals with migraine that can be observed on an electroencephalogram (EEG) recording (Wilkins, 1995). Pattern reversal visual evoked potentials (PVEP's) are commonly recorded to investigate physiological changes both during and after an attack of migraine. Stimuli for this procedure include

checkerboard patterns that reverse at regular time intervals. The neuronal activity of the brain in response to the checkerboard stimuli is recorded using EEG. PVEP's of abnormally high amplitude have been demonstrated in individuals with MA when compared to controls; MO and control groups did not differ (Shibata, Osawa, & Iwata, 1997a). Uncomfortable, high spatial frequency checkerboard patterns have been shown to produce a prolonged N2 component in participants who experience migraine with aura, which may reflect dysfunction of the magnocellular pathway (Oelkers et al., 1999).

1.4.1   Hypoexcitability

Differences in the amplitude of VEP's in migraine may be due to a lack of habituation rather than inherent hyperexcitability of the visual cortex (Schoenen et al., 1995). The visual system continually adapts to the environment and adjusts the neuronal response accordingly. When a visual stimulus is repetitively presented, a reduction in the neuronal response can be observed. Defective habituation (lack of VEP amplitude reduction) to a repetitive stimulus has been demonstrated for individuals with MA and those with MO (Schoenen et al., 1995). The underlying cause of impaired habituation is not yet clear, however several mechanisms have been suggested: hyperexcitability, defective cortical inhibitory processes and low preactivation (Coppola et al., 2007). A low pre-activation level means there is a greater range of excitability in individuals with migraine before a ceiling of maximal cortical activation is reached (Bohotin et al., 2002; Coppola et al., 2005; Knott & Irwin, 1973). Low-amplitude responses during early blocks of trials have typically been found in individuals with migraine, followed by a lack of habituation in later blocks of trials.

This may reflect the greater range of activation necessary for individuals with migraine to reach the ceiling where habituation begins (Schoenen, 1996). In this model, habituation to repetitive stimuli is a protective mechanism that occurs when excitability of the cortex reaches a ceiling (Bohotin et al., 2002). Afra, Proietti Cecchini, Sándor, and Schoenen (2000) found low amplitude VEP responses in individuals with MA and MO for the first block of stimulus presentation. There was habituation of the VEP in healthy controls in the fifth block of trials but potentiation in the migraine groups.

Coppola et al. (2007) explain that the disparate support for hyper and hypo-excitability in the literature may be the result of a 'semantic misunderstanding'. As discussed in section 1.3.1, 'hyperexcitability' would suggest a general over-response to stimuli but this is not the case during initial blocks of trials during VEP recording. Later blocks of trials show potentiation of the VEP, which would support the theory of hyperexcitability. The authors suggest that individuals with migraine are sensitive to repeated but not single stimuli and that a more appropriate description of these effects is 'hyper-responsive'.

Comment

The effects of migraine on visual processing can be measured using various psychophysical and physiological techniques. Patterns that are aversive for individuals who experience visual discomfort share common spatial characteristics. In section 1.5 it will be shown that the spatial structure of uncomfortable patterns departs from that observed in natural images.

1.5   Natural Images

Natural images possess consistent statistical properties despite apparent complexity and variation of shadow, colour and orientation of contours. The Fourier amplitude spectra of natural images fall by a factor of 1/f, with the greatest amplitude at low spatial frequencies (Burton & Moorhead, 1987; Field, 1987, 1994; Mezrich, Carlson, & Cohen, 1977; Tolhurst, Tadmor, & Chao, 1992). A slope of -1 on log-log coordinates would be expected for images that are scale invariant, and retain the same complexity, irrespective of viewing distance. Natural scenes have been found to exhibit a limited range of chromatic distributions, which constrain the range of adaptation states for the visual system (Webster & Mollon, 1997).

The human visual system responds to natural visual stimuli in a metabolically efficient way (Barlow, 1961). The neuronal coding of visual information places a high metabolic load on the visual cortex. For this reason, only a small percentage of cortical neurones can be active at any one time. The visual system has developed an energy efficient neuronal firing rate, with an optimal firing frequency between 6 and 43Hz over a 25ms period (Levy & Baxter, 1996). Energy-efficiency is judged against the metabolic cost of the action potential. The idea of an energy-efficient neuronal firing rate is linked to 'sparse coding', which is discussed below and relates to the proportion of cells that are active at any one time. Levy and Baxter (1996) support the hypothesis of an energy-efficient neuronal firing rate and that neurons firing above or below this rate are less efficient. Lennie (2003) calculated that, in the visual cortex, the 'active' neurones account for less than 2% of the total. 'Sparse coding' has been proposed as an efficient model for the processing of visual information from natural scenes (Barlow, 1972; Field, 1987, 1989). Barlow and Földiák (1989) describe

a model where the responses of neurons are correlated to begin with, that is, there is overlap of the sensitivities of the units. After training of these units, the outputs of the network become decorrelated. For elements with a limited dynamic range, it would be optimal for two neurons to develop mutual inhibition so that excitation of one will inhibit the other. The authors explain that the strength of mutual-inhibition should be variable depending on the correlation of activities between neurons. The goal of sparse coding is to create a code where only a small proportion of cells respond to an input, whilst the majority remain inactive. Hibbard and O'Hare (2015) produced a model of the visual cortex and presented natural images, sine gratings and filtered noise stimuli. The model response distributions were similar for all stimuli with a peak at 0, which indicates that the activity of most units was low. Kurtosis of the response peak and greater amplitude was found for the sine gratings and filtered noise stimuli. The kurtosis of the increased amplitude responses reflects a neuronal response that is less sparse in a distribution with a single peak. The kurtosis of the response was least sparse for sine gratings of 3 cycles per degree, which have been shown previously to cause visual discomfort for those who are susceptible. Barlow (1961) suggests the aim of visual processing is to represent the natural world with minimal neural redundancy. Field (1987) partially supports the hypothesis of minimal neural redundancy, however the author makes the distinction that cortical cells transform information so that later stages of the visual system are less redundant.

Comment

The visual system has evolved to process natural images in an energy-efficient manner. In section 1.2 it was shown that images with spatial characteristics that depart from those of natural images are judged to be uncomfortable to view. In section 1.6 it will be shown that printed text possesses spatial characteristics that are unnatural and can induce visual discomfort.

1.6   Reading

An early detailed investigation of the visual component of disordered reading in children, of average intelligence, was conducted by a school teacher, Olive Meares, (1980). Meares (1980) reported that some children pay particular attention to the white page when reading and can be 'dazzled' or notice rivers of white flowing through the text. The anomalous visual effects experienced by some children have a negative effect on reading ability and comprehension of the text. The size and spacing of letters in children's books may have a significant impact on reading ability. Vertical lines in a paragraph of text, as from the vertical strokes of letters, approximate a striped pattern, particularly when the neighbouring letter strokes have scored highly on a measure of repetitive stripes (horizontal autocorrelation) (Wilkins et al., 2007). Patterns of striped lines are known to be uncomfortable for individuals susceptible to visual discomfort. Illusions of colour, shape, and motion may be seen during reading by an individual who experiences visual discomfort (Wilkins 1995). The appearance of text can affect the ability of children learning to read unfamiliar words who appear to benefit from large, widely spaced text (Hughes &

Wilkins, 2000). Hughes & Wilkins (2002) suggest that text with crowded spacing has a negative effect on clarity and can contribute to visual stress.

Developmental dyslexia and visual discomfort when reading are often confused because of the impact of the two conditions on reading ability. Developmental dyslexia is a reading impairment that is unrelated to the individual's general intelligence and is unexpected based on the level of reading instruction. Dyslexia has been attributed to a phonological deficit (Snowling, 1981) but sensory deficits may also be a contributing factor (Stein & Walsh, 1997). Dysfunction of the magnocellular pathway has been proposed as a cause of the visual impairments observed in developmental dyslexia. Reading requires fast processing of transient stimuli for which the magnocellular system is specialised (Breitmeyer, 1989). The neurones of the magnocellular system are also specialised to process stimuli of low contrast. When reading, the eyes fixate for short periods of time and make saccades between words (Rayner, 1978). Saccades may activate the magnocellular system and inhibit the parvocellular system (Breitmeyer, 1989). Inhibition may help prevent the visual information obtained from each saccade from being confused or merged. Skottun and Parke (1999) reviewed six studies that provide evidence against Breitmeyer's (1989) theory, instead the authors propose that the magnocellular rather than the parvocellular system is suppressed during saccades. Reading requires visual and phonological information to be processed efficiently and a deficit of one or both of these systems could result in reading impairment. Much scepticism surrounds the idea of a magnocellular deficit in dyslexia and some studies using psychophysical and physiological techniques have failed to find a difference between individuals with developmental dyslexia and controls, which is discussed in detail below.

The visual evoked potential to checkerboard stimuli in individuals with developmental dyslexia and controls revealed no difference between the two groups (Johannes, Kussmaul, Münte, & Mangun, 1996; Victor, Conte, Burton, & Nass, 1993). The pattern stimuli reversed at differing rates in order to replicate the transient nature of reading. Gross-Glenn et al. (1995) measured the contrast sensitivity of individuals with dyslexia, and controls, by presenting sine-gratings with a gradual temporal onset and offset. The dyslexic group showed deficits of contrast sensitivity for high spatial frequency gratings but not for gratings of low spatial frequency. If an impairment of the magnocellular system was responsible for the visual differences observed in dyslexia then a sensitivity deficit for gratings of low spatial frequency and flickering or transient stimuli would be expected. The ability to detect a transient stimulus was also found to be unimpaired in the dyslexic group. These results do not indicate a deficit of transient processing in dyslexia.

In contrast, Lovegrove et al. (1982) measured the contrast sensitivity function of participants with specific reading disability and controls. Stimuli were sine-wave gratings of 2, 4, 8 and 12cpd and were presented at nine stimulus durations between 40-1000msec. Control participants demonstrated a monotonic decrease in sensitivity as spatial frequency increased. The contrast sensitivity function peaked at 4cpd. Participants with specific reading disability did not show a clear sensitivity peak at 4cpd, but were significantly more sensitive to the gratings with a spatial frequency of 2cpd. In the second part of their study Lovegrove et al. (1982) found that the reading disabled group was more sensitive to gratings of 8cpd and 12cpd. The authors suggest that the discrepancy of the results may be due to an increase in the luminance of the stimuli in the second experiment.

The discrepancy of the results in the above studies may be due to differences in participant groups and the psychophysical methods used. Goodbourn et al. (2012) assessed the correlation between four measures of magnocellular function, which were as follows: a frequency-doubled grating task (detection of grating patterns reversing in contrast), a steady-pedestal grating task (detection of pulsed grating patterns with a steady luminance pedestal), an auditory temporal order task and a coherent motion task. The authors report that performance on different magnocellular tasks is attributable to different sources of variance, which would help explain the contradictory results of reports of magnocellular function. Lovegrove, Garzia, and Nicholson (1990) conclude that 75% of severely dyslexic children demonstrate a magnocellular system deficit, however Walther-Müller (1995) found only 12% of their severely dyslexic sample showed an impairment. Walther-Müller (1995) measured contrast sensitivity, excitatory and inhibitory mechanisms (measured using the line-spread function), visible persistence and motion perception. All 4 tasks were designed to assess a magnocellular deficit in dyslexia but only two participants demonstrated a magnocellular deficit in three of the tasks. The reliability of different psychophysical tasks in detecting a magnocellular deficit has been compared in participants with dyslexia. Demb, Boynton, Best, & Heeger (1998) compared motion and contrast detection thresholds in individuals with dyslexia and controls. Dyslexic participants thresholds were higher for both tasks but only significant for the motion detection, which indicates that motion tasks may be more reliable correlates of dyslexia. Evans, Drasdo, and Richards, (1994) presented individuals with dyslexia and controls with a test of contrast sensitivity and a simulated-reading visual search task designed to assess magnocellular function. The two tests of magnocellular function were only weakly correlated, which indicates that the two tests do not measure the same function. The impairments associated with dyslexia vary between individuals and there may be more

than one factor that contributes to disordered reading. The link between dyslexia and a deficit of the magnocellular system is complex and at present unclear.

A quantitative measure of children's reading was required to objectively test any differences after an intervention be it refractive or in the form of precision spectral filters (Wilkins, Jeanes, Pumfrey, & Laskier, 1996). The Wilkins Rate of Reading Test (WRRT) (i.O.O. Sales Limited, London, England) was developed to maximise visual stress when reading by presenting small, closely spaced, random words, thus minimizing semantic and linguistic aspects or cues. The Wilkins rate of reading test has been used to investigate the possible benefits of coloured filters for those who experience discomfort when reading because the test does not include semantic cues and is uncomfortable to view. Because of the random order of common words, patients do not notice the omission of words or lines of text when taking the test.

Discomfort caused by the vertical stokes of letters, and other patterns, may be reduced by coloured sheets of plastic called overlays, which are placed upon a page of text. Seven differently coloured overlays were first developed by Helen Irlen, but they did not systematically sample colour space, omitting purple (Wilkins, 1993). The Intuitive Overlays were then developed by Wilkins (1993) that sample the CIE 1976 UCS diagram systematically and can be combined in an intuitive manner to facilitate the selection of a chromaticity suitable for the patient (Wilkins, 1993). The Intuitive overlays may benefit around 5% of the school population, improving reading speed substantially (Wilkins, 2002). The Wilkins Rate of Reading Test has been used to estimate the prevalence of visual

discomfort in individuals with dyslexia and controls (Kriss & Evans, 2005). A >10% increase in reading speed with the use of coloured overlays was used as the criterion for a beneficial effect of colour. According to this criterion 12.5% of the control group and 31% of the dyslexic group experienced visual discomfort. Kriss & Evans (2005) were critical of the use of a 5% increase in reading speed to assess whether colour would be of benefit and thus recommended the more stringent criterion of a 10% increase in reading speed. A ≥15% increase in reading speed is now used to assess the beneficial effects of colour (Evans, Allen, & Wilkins, 2017; Wilkins, Allen, Monger, & Gilchrist, 2016). As discussed above, individuals with dyslexia have been shown to be sensitive to pattern gratings of high spatial frequency. During an assessment for a diagnosis of dyslexia, it may be necessary to conduct an in-depth optometric examination to exclude a primary optometric cause. It is difficult to know whether dyslexic participants in the studies reviewed in this section experienced visual discomfort from text. Reading may be a particularly difficult task for individuals who experience a combination of visual discomfort and dyslexia. Coloured overlays may help reduce visual discomfort and remove the perceptual distortions that further impede reading for these individuals.

Comment

Disordered reading can be observed in children of average intelligence and social background. Coloured sheets of plastic called overlays, placed upon the page, can improve reading speed in those individuals who experience visual discomfort when reading.

1.6.1   Accommodation

When viewing a fixed stimulus, such as a page of text, the accommodative system of pre-presbyopes continually adjusts the refractive power of the eye to produce a clear image on the retina. Individuals with high levels of visual discomfort have been shown to experience higher levels of accommodative lag, that is a larger difference between the accommodative demand and response, compared to a low visual discomfort group (Tosha et al., 2009). The authors suggest that the accommodative lag observed in the high discomfort group may indicate a fatigue effect from prolonged viewing of targets at near distance. The accommodative response requires a certain level of high spatial frequency information and because of this, it has been hypothesised that blurred images are judged to be uncomfortable to look at due to impoverished feedback (O'Hare & Hibbard, 2013). Accommodative lag has been reduced by the use of a coloured screen background in individuals with pattern-related visual discomfort but the lag increased with the coloured background in the control group (Allen, Hussain, Usherwood, & Wilkins, 2010). Participants viewed a grey field with a central fixation cross, a grating pattern and a passage of text consisting of randomly ordered common words. The background colour was matched to that of a colour identified by the participant as improving clarity when reading. The reduction of lag may help to explain why colour is of benefit for some individuals when reading. A comfortable colour may aid accommodation when reading for those who experience visual discomfort. Accommodative fatigue may be one of the causes of visual discomfort in individuals susceptible to pattern glare and headache, however Haigh, Jaschinski, Allen, and Wilkins (2013) showed no effect of uncomfortable patterns on accommodative lag or microfluctuations. Evans and Allen (2016) suggest that under-

accommodation in visual stress may be an effect of visual stress itself rather than a cause. Under-accommodation can sometimes be reduced with the use of coloured filters.

1.7   Contrast Adaptation and Contrast Gain Control

After prolonged viewing of a high contrast sine wave grating, the contrast at which gratings with similar characteristics are detected is raised due to adaptation (Blakemore & Campbell, 1969). It has been suggested that the role of contrast adaptation is to adjust the response ranges of cortical cells around the mean contrast levels in the environment (Ohzawa, Sclar, & Freeman, 1985). As described in sections 1.4.1 and 1.5, visual information is encoded in a metabolically efficient manner and part of this is habituation to stimuli that are no longer novel. Both fast and slow adaptation has been observed in bipolar, amacrine and ganglion cells that respond to changes in contrast (Baccus & Meister, 2002). Contrast gain control appears to be abnormal in patients with photosensitive epilepsy when observing patterns with low temporal frequency and high luminance contrast (Porciatti, Bonanni, Fiorentini, & Guerrini, 2000).

Some patients who experience migraine demonstrate impairment in contrast sensitivity between attacks. Contrast sensitivity has been assessed using standard grating patterns, (Benedek, Tajti, Janaky, Vecsei, & Benedek, 2002; McColl & Wilkinson, 2000; Yenice et al., 2007) and perimetry to investigate sensitivity across the visual field (Lewis, Vijayan, Watson, Keltner, & Johnson, 1989; McKendrick & Badcock, 2003, 2004). Reduced sensitivity of the low spatial frequency sensitive channels of the magnocellular and

parvocellular pathways has been demonstrated using a pulsed-pedestal contrast sensitivity task (McKendrick & Sampson, 2009). Contrast discrimination deficits have been found in the mid-peripheral visual field, suggesting abnormal adaptation that is not pathway specific in patients with migraine (McKendrick & Badcock, 2003). Spatial contrast sensitivity in migraineurs without aura appears to be lateralised with large lateral asymmetries being found at low spatial frequencies (Benedek et al., 2002). Patients with migraine appear to have altered visual field and contrast sensitivity at all spatial frequencies and may share some features with early stage glaucoma suggesting a common vascular impairment (Yenice et al., 2007). Individuals with migraine have been shown to be particularly sensitive to suprathreshold flicker of high contrast, which is known to cause visual discomfort (Karanovic et al., 2011).

Comment

For individuals with migraine, a contrast sensitivity deficit may not be specific to the magnocellular or parvocellular visual pathways. Instead the abnormality may be dependent on location in the visual field. This may be one explanation for discrepancies in the literature concerning spatial frequency sensitive channels.

1.8   Introduction to experiments

The aim of this thesis was to investigate visual function and visual discomfort in individuals with migraine and controls. The use of coloured filters as a non-invasive intervention for reading difficulty and visual discomfort was also explored. Of particular interest was the effect of a unilateral visual migraine aura on visual function. The experiments presented in this thesis are outlined below.

Contrast discrimination threshold was investigated at two pedestal contrasts in three participant groups: Control, migraine without aura (MO) and migraine with aura (MA). All participants completed a detailed questionnaire regarding their experience of migraine and those found to experience migraine with unilateral visual aura were asked to draw the aura in order to ascertain the position in the visual field. Contrast discrimination threshold was higher for all 3 groups at 50% pedestal contrast. Overall, there was no difference between the individuals with migraine and those without. When individuals who experienced a consistently unilateral visual aura were considered, however, they demonstrated significantly lower thresholds in the visual field affected by the aura. Participants in this study, unlike those in previous studies, were not tertiary referrals from specialist neurology clinics and their attacks were presumably less frequent and severe. It is therefore less likely that the visual system was damaged. All threshold measurements were conducted in the inter-ictal period for the migraine groups and the minimum time since the previous attack of migraine was 2 days. The average number of days since the last attack was 54.5 for the MO group, 17.6 for those in the MA group who experienced bilateral visual

aura and 161 for those in the MA group who experienced a unilateral visual aura (Chapter 2).

Contrast threshold for discomfort was determined by the presentation of six patterns that increased in contrast until the participant experienced discomfort. Participants who experienced MA, MO and controls viewed the patterns illuminated by a colour that was comfortable and a second colour that was uncomfortable. Contrast threshold for discomfort was lower in both migraine groups, particularly when the grating patterns were illuminated by the uncomfortable colour of light. The comfortable colour raised the threshold significantly. Participants with MA had the lowest contrast thresholds for discomfort and chose as comfortable, colours of higher saturation. A comfortable colour of light can relieve discomfort and perceptual distortion for individuals with migraine. Individuals in the migraine groups were tested in the inter-ictal period and the minimum time since the previous attack of migraine was 3.5 days. The average number of weeks since the last attack was 2.5 for the MO group and 2.5 for the MA group (Chapter 3).

In order to examine the effect of colour on contrast discrimination threshold, participants who experienced migraine with unilateral visual aura and controls completed the task wearing two pairs of coloured lenses. The lenses were a colour that was comfortable for viewing high contrast text and control grey lenses matched for transmission. Individuals completed two blocks of trials wearing one set of lenses for each. Contrast discrimination threshold was raised in both visual fields when precision spectral filters were worn by the MA group but were not raised in the control group. Lenses of comfortable colour, may act

to reduce hyperexcitability of the visual cortex. Individuals in the migraine group were tested in the inter-ictal period and the minimum time since the previous attack of migraine was 2 days. The average number of days since the previous attack was 9.3 for those in the MA group who experienced visual aura in the left visual field and 43.8 for those who experienced aura in the right field (Chapter 4).

The EEG and NIRS response to three grating patterns of increasing contrast was measured in participants who experienced migraine with aura and controls. EEG and NIRS were recorded simultaneously and participants completed tests of visual discomfort and pattern-glare. No significant differences were found between level of contrast and NIRS amplitude or offset of the response. No group differences were found for EEG but there was a significant effect of contrast and hemisphere for the N2 component. Participants who experienced unilateral migraine pain had reduced N2 amplitude and latency in the hemisphere affected by pain. Individuals in the migraine group were tested in the inter-ictal period and the minimum time since the previous attack of migraine was 7 days. The average number of days since the previous attack was 32.1 for those individuals in the MA group whose data was included in the NIRS section and 30.5 for those whose data was included in the EEG section (Chapter 5).

In order to examine the effect of lenses of comfortable colour on reading speed, children were tested who habitually used coloured overlays to read. Participants read the Wilkins rate of reading test wearing the comfortable 'active' lenses and lenses of similar colour 'placebo'. Reading speed was not significantly faster with the 'active' lenses but the

improved reading speed observed in some participants occurred when the 'active' lenses were worn. Participants in this study were given an overlay to use by their school. It is therefore difficult to ascertain whether these individuals were experiencing a benefit from the use of an overlay. The over-use of coloured overlays in schools by children to whom they would be of little benefit, may explain the null result (Chapter 6).

The use of coloured lenses in a clinical setting was investigated in participants who experienced visual stress. Participants read the Wilkins rate of reading test whilst wearing lenses of comfortable colour ('active') and lenses of similar colour ('placebo'). Participants read more quickly when the 'active' set of lenses was worn. Individuals reliably identified the same colour of illumination during two separate examinations. Colour specificity appears to be necessary for individuals to experience a perceptual benefit from the use of colour. Careful screening of participants appears to be necessary to identify those for whom precision spectral filters would be of benefit (Chapter 7).

The work presented here has examined visual function and visual discomfort in individuals with migraine and those who experience discomfort when reading. The effects of colour have been examined throughout in both an experimental and in a clinical setting.

Chapter 2 Contrast Discrimination in Migraine

Abstract

Individuals with migraine may have a cortical hyperexcitability and are unusually susceptible to perceptual distortions in patterns of striped lines (Wilkins et al., 1984). They are sometimes impaired at perceiving the relative contrast of gratings, when the reference patterns are of high contrast (Shepherd, 2000), possibly as a result of brain damage from repeated attacks (Chronicle & Mulleners, 1994). We assessed suprathreshold contrast discrimination for low (10%) and high contrast (50%) sine wave gratings. Participants with migraine, 24 with aura (MA) and 15 without (MO), and 23 headache-free controls were recruited from staff and students at the University of Essex. Each participant viewed 4 grating patterns, one in each quadrant, presented simultaneously for 142ms. Three of the patterns had the same contrast, and the contrast was higher for the fourth. The participants were required to detect the location of the pattern with the highest contrast. Contrast discrimination thresholds were higher at 50% contrast, and did not differ overall between the three groups. For the MA and MO groups, the length of time since the most recent migraine attack was not related to discrimination threshold. All eight participants in the MA group who experienced consistently lateralised visual aura had lower discrimination thresholds (superior performance) in the affected field. Individuals with migraine may be abnormally sensitive to contrast because of a cortical hyperexcitability, perhaps until sensitivity is diminished as a result of repeated migraine attacks (Chronicle & Mulleners, 1994).

2.1   Introduction

As we saw in Chapter 1 migraine is a common neurological disorder, affecting 17% of women and 6% of men (Lipton et al., 2007). Of these individuals, approximately 6% experience visual warning symptoms known as the visual aura (Steiner et al., 2003). These individuals often report colours, flickering or zig-zag lines, most commonly before the onset of headache (Russell & Olesen, 1996). Cortical spreading depression occurs when the spontaneous neuronal activity decreases, either spontaneously or after electrical stimulation, with the depressed activity slowly spreading to adjacent areas of the brain (Leão, 1944). There is growing electrophysiological evidence to suggest that cortical spreading depression is the underlying cause of migraine aura (Bowyer, Aurora, Moran, Tepley, & Welch, 2001; Cao, Welch, Aurora, & Vikingstad, 1999; Hadjikhani et al., 2001; James, Smith, Boniface, Huang, & Leslie, 2001; Lauritzen, 1994). Individuals with migraine are also highly sensitive to visual discomfort from grating patterns with certain spatial characteristics. These patterns can induce illusions of colour, shape and motion to which individuals with migraine are particularly susceptible (Wilkins et al., 1984). There exists a strong visual component in migraine consisting of four strands: Firstly, sensitivity to light is an intrinsic part of a diagnosis of migraine; secondly, positive visual hallucinations are seen during migraine aura; thirdly, attacks of migraine are often visually triggered; finally, strong patterns can induce illusions of colour, shape and motion.

A state of cortical hyperexcitability may be characteristic of migraine and predispose the individual to cortical spreading depression (Welch et al., 1990). van Harreveld & Stamm (1955) found depression of neuronal activity in rabbits could be elicited with single flashes of light after the administration of a central nervous system pro-convulsant (Metrazol). The proconvulsant effects of Metrazol on the brain may mimic the hyperexcitability of cortical neurons observed in individuals with migraine. This may provide a link between visual stimulation when the neurones of the brain are in a hyperexcitable state and the induction of cortical spreading depression. Cortical hyperexcitability may be non-uniform in migraine as is the case in individuals who experience photosensitive epilepsy (Binnie, Wilkins, & De Korte, 1981). Small regions of hyperexcitability in the cortex may be responsible for migraine aura that is confined to one visual field. Visual migraine aura can appear in many forms including coloured flashes of light and organised patterns of lines. The links between cortical spreading depression and the propagation of visual migraine aura are discussed below.

 The characteristics of the migrainous visual aura are often consistent for the individual but differ from one individual to another. The distinct lines of the fortification spectra, drawn by Hubert Airy (1870), are commonly experienced by individuals with migraine (see Figure 2:1). The appearance of aura as short lines of varying orientation, suggests the involvement of orientation-tuned cells (Hubel & Wiesel, 1968). Richards (1971) suggested the lines of the fortification spectra were caused by depression of activity that enhanced the neuronal activity in adjacent brain regions. The onset of aura, repeatedly at specific sites within the visual field, would indicate that distinct regions of the occipital cortex are more likely to initiate aura than others (Hansen, Baca, VanValkenburgh, & Charles, 2013). Visual field

defects have been correlated with occipital lesions to create a retinotopic map of the visual fields in the cortex (Holmes & Lister, 1916). A visual aura typically begins near the fovea in one hemifield and moves outwards towards the periphery at a constant rate of ~3mm/minute (Lashley, 1941). The movement of aura would suggest a spreading pattern of excitation in a retinotopically organized region of the brain (Lashley, 1941). The characteristics of visual migraine aura vary widely between individuals and would suggest various brain regions as the site of the initiation of aura. For instance, the focus of an aura consisting of coloured phosphenes may be area V8, which is colour-selective (Hadjikhani, Liu, Dale, Cavanagh, & Tootell, 1998). There are many cortical areas, other than V1, that are retinotopic and from which the visual aura could arise; V2, V3/VP, V3A, V4v (Hadjikhani et al., 2001). fMRI techniques have been used to demonstrate that, at least in one individual, the BOLD response amplitude increased, beginning in area V3A, which follows the progression of the visual aura across the retinotopically organized occipital cortex (Hadjikhani et al., 2001). The increase of BOLD amplitude is followed by a decrease that follows the same progression. The wave of reduced amplitude may suggest that cortical spreading depression is responsible for generating the visual aura of migraine.

Figure 2:1: Fortification spectra drawn by Hubert Airy (1870).

The effects of migraine on the visual system are both long and short-term. Seven days after a migraine episode, losses of sensitivity in orientation discrimination and global dot motion tasks have been observed in individuals experiencing migraine with aura (Mckendrick, Vingrys, Badcock, & Heywood, 2001). Contrast sensitivity deficits are related to duration of disease in patients experiencing migraine for more than 30 years (Khalil, 1991). In some studies, contrast sensitivity has been shown to be reduced across all spatial frequencies in individuals with a disease duration of 30 years or less (Yenice et al., 2007) suggesting that a deficit can be observed earlier than the timescale reported by Khalil (1991). A decrease in the general sensitivity of migraine participants during flicker perimetry is also strongly correlated with length of migraine history and migraine incidence over the previous 12 months (McKendrick & Badcock, 2004). The prolonged experience of migraine may therefore reduce visual sensitivity.

Visual deficits, across a range of tasks, have been demonstrated in migraine. Individuals who experience MO appear to have reduced contrast sensitivity in the low spatial frequency range (Benedek et al., 2002). When compared to a control group, participants with MA and those with MO, demonstrate reduced sensitivity to 4cpd grating patterns of low contrast (Cambridge Low Contrast Gratings, Clement Clarke, Harlow) (Shepherd, 2000; Shepherd, Hine, & Beaumont, 2013b). In contrast, Palmer, Chronicle, Rolan, and Mulleners (2000) showed that individuals who experienced MA were more sensitive in a metacontrast masking task in which participants had to identify whether the target was a complete circle or a circle with an arc missing. In their study a baseline condition in which no mask was presented was not included. The authors suggest these results could be due to a reduction of cortical inhibitory mechanisms in individuals who experience migraine with aura. Accuracy increased with the frequency of migraine attacks. Using a similar task, Shepherd, Wyatt, and Tibber (2011) included baseline trials in which only the target was presented. Forward, backward and combined forward and backward masking was measured in individuals with migraine and controls. For the three forms of masking the individuals with migraine (MA and MO) were more sensitive, but when the baseline no-mask condition was taken into account the group differences were not significant. Participants in the MA and MO groups were more sensitive to the baseline condition than controls, which support the theory of cortical hyperexcitability in migraine. There were no group differences in the masking effect, which suggests that the processes involved in masking are unimpaired in migraine. When the forward and backward masking trials were combined, there was a positive correlation with frequency of migraine attacks. This effect indicates that individuals who experienced frequent attacks of migraine were more sensitive to the task. Time since last attack was negatively correlated with performance, which suggests the more recent an attack of migraine the better the performance.

Shepherd (2007) reviewed three models of hyperexcitability in migraine. The model that best fits the metacontrast data described above predicts a greater response of individuals with migraine without an increase in the background neuronal noise. A greater neuronal response to stimuli in individuals with migraine would predict better detection thresholds. Individuals who experience migraine would therefore be able to detect a less salient pattern than an individual without migraine. Shepherd (2006b) proposed a model with a short-lived effect, which would predict better detection thresholds in individuals with migraine for short stimulus presentation times because the response cannot be maintained. The model described above may also lead to impaired discrimination thresholds if the tuning curves of cortical neurones are broadened (Tibber, Guedes, & Shepherd, 2006).

Subtle visual field deficits have been demonstrated in 42% of individuals with migraine and no relationship has been found between the defect and migraine type (De Natale, Polimeni, Narbone, Scullica, & Pelicano, 1993). McKendrick & Badcock, (2003) assessed magnocellular and parvocellular function separately, utilising a steady-pedestal contrast discrimination task that allowed adaptation to the pedestal luminance and a pulsed-pedestal task in which the participant adapts to the background. In studies of contrast discrimination such as these, a stimulus that has a fixed pedestal contrast is presented with a second stimulus that is the fixed pedestal contrast plus an increment. Typically in pulsed-pedestal tasks, the stimulus of pedestal contrast and the pedestal plus increment are presented at the same time. In contrast, during steady-pedestal tasks both stimuli are initially of pedestal contrast and after a short delay the increment is added to one of the stimuli. McKendrick and Badcock (2003) found that when the steady and pulsed-pedestal

tasks were presented in the peripheral visual field, contrast discrimination thresholds were elevated in the migraine group but not in the control group, which suggests a non-selective impairment of adaptation in individuals with migraine.

 The presence of an additional stimulus has been shown to interfere with the detection of a target (visual masking) in individuals with migraine. McColl & Wilkinson (2000) attribute the greater masking effect observed at high contrasts in migraine to cortical hyperexcitablilty. In individuals who have migraine with aura (MA) the threshold contrast for detection of a probe letter target on a background grating is significantly elevated, which is consistent with an abnormal inhibition in the primary visual cortex (Chronicle, Wilkins, & Coleston, 1995).

Hyperexcitability of neurones in the occipital cortex has been proposed as the underlying mechanism that predisposes individuals with MA to attacks of aura, both spontaneous and induced (Welch et al., 1990). Welch et al. (1990) describe a state of neuronal hyperexcitability that triggers depolarisation and a spreading depression of spontaneous neuronal activity. Using the two-interval forced choice method of presentation, Karanovic *et al* (2011) demonstrated significantly *lower* discrimination thresholds for migraineurs viewing high contrast flicker after adaptation, but only a weak trend for the control group. Participants with migraine process low-level discrimination tasks more rapidly than a control group, but the advantage is lost for higher level tasks such as picture-naming (Wray, Mijovic-Prelec, & Kosslyn, 1995).

Loss of sensitivity is not necessarily uniform across the visual field, as has been shown by McKendrick & Badcock (2004). These authors also describe the negative effect of migraine history on generalised sensitivity across the visual field, but no relationship between migraine history and the experience of unilateral and mid-peripheral aura (scotoma).

Impaired visual performance of individuals with migraine is related to duration of disease and incidence of attacks (Khalil, 1991; McKendrick & Badcock, 2004; Yenice et al., 2007). One explanation for the loss of sensitivity is proposed by Chronicle & Mulleners (1994). The authors suggest that repeated reduction of the blood supply to cerebral tissue (ischemia) during attacks may be responsible for abnormal visual function in individuals with MA. Olesen et al., 1993, demonstrated that primary cerebral ischemia triggers a migraine with aura attack in some patients. Chronicle & Mulleners' (1994) hypothesis would suggest the visual performance of patients who experience frequent migraine attacks, and have experienced the disease for many years, may be impaired by repeated ischemia of the brain. This may be particularly apparent in the majority of participants in research investigating the visual effects of migraine, who have been referred to neurology clinics with relatively severe disease.

The participants who formed the migraine groups of the current study were sampled from the general population and therefore included less severe and non-clinical cases. We measured suprathreshold contrast discrimination in three participant groups; migraine with aura (MA), migraine without aura (MO) and a control group with no history of migraine. Individuals with migraine are known to be particularly sensitive to discomfort

from stripes but have shown impairment on tasks assessing contrast sensitivity. This study utilised a four-alternative forced choice (4AFC) task in which participants were required to discriminate the relative contrast of four gratings and select the grating with the highest contrast. The remaining three gratings had a pedestal contrast of either 10% or 50%. The effect of a unilateral visual migraine aura on contrast discrimination was also examined to investigate whether selective areas of hyperexcitability may affect visual performance.

2.2   Method

Participants

Sixty-two individuals were recruited from students and staff at the University of Essex; 23 headache-free controls, 15 MO and 24 MA (see Table 2:1). Participants with migraine fulfilled the International Headache Society's ICHD III criteria (IHS, 2013) for migraine with or without aura and provided data on time since last migraine attack and duration of disease (see Appendix A for the migraine questionnaire). Participants in the MA group were asked to draw their migraine aura. From these drawings, individuals whose aura was confined to one visual field were identified. Headache-free control participants had never experienced a migraine. 52 participants were paid for their time and 10 were given course-credit. All methods were approved by the University of Essex ethics committee.

Table 2:1: Participant information.

	C	MO	MA	
N	23	15	24	
Age Mean (SD)	22.4 (4.7)	22.4 (3.1)	27.3 (11.8)	
Age range	19-38	18-28	18-58	
Using refractive correction	11	10	12	
			Bilateral aura	**Unilateral aura** (N = 8)
Mean days since last attack (SD)	N/A	54.5 (100)	17.6 (31)	161 (258)
Mean (SD) duration of disease (years)	N/A	5.2 (2.9)	6.06 (3.7)	17.1 (17.6)

Apparatus

Stimuli were presented on a Sony Multiscan 500 Trinitron CRT monitor using a Windows PC. The screen had a resolution of 1280 x 1024 pixels and a refresh rate of 120Hz running custom Matlab (Mathworks R_2014b) software using the Psychophysics Toolbox extensions (Brainard, 1997; Kleiner, Brainard, & Pelli, 2007; Pelli, 1997). The luminance resolution of the screen was controlled by a 14-bit Datapixx system (VPixx Technologies, Quebec, Canada). A ResponsePixx (VPixx Technologies, Quebec, Canada) button box was used for participant responses.

Stimuli

The mean luminance was $27.5cd/m^2$, and the screen was calibrated using a spectroradiometer (Minolta, Tokyo, Japan). Stimuli were vertical Gabors with a spatial frequency of 2.6 cpd and a standard deviation of 59 min.arc and were presented for 142 ms (17 refresh cycles).

A four-alternative forced choice (4AFC) paradigm was utilised with three separate, interleaved staircase procedures (three-up, one-down; one-up, one-down; one-up, three-down), each consisting of 40 trials. There were separate staircases for each 'target' location, which were presented in a randomly intermixed fashion. For each staircase, the contrast of the 'target' pattern was incremented and decremented in steps of 0.05 Michelson contrast for the first 20 trials, and in steps of 0.025 for the remaining 20 trials.

Procedure

Individuals were seated 0.6m from the screen in a dark room. Participants completed 8 blocks of trials in total, which were split into 2 blocks of 4. Four blocks of trials had a pedestal contrast of 10% and the remaining 4 blocks trials had a pedestal contrast of 50%. Individuals were instructed to view a central fixation cross, which appeared on the screen for 100ms during each trial and subtended 30arc min.

A Gabor was presented in each quadrant of the screen, with its centre at a distance of 10 degrees from a fixation point at the centre of the screen, symmetrically in each quadrant as shown in Figure 2:2. The grating pattern in 3 quadrants of the screen was of the same pedestal contrast, but the remaining pattern was of higher contrast (target). Participants were instructed to identify the pattern of higher contrast using the corresponding button on the ResponsePixx button-box.
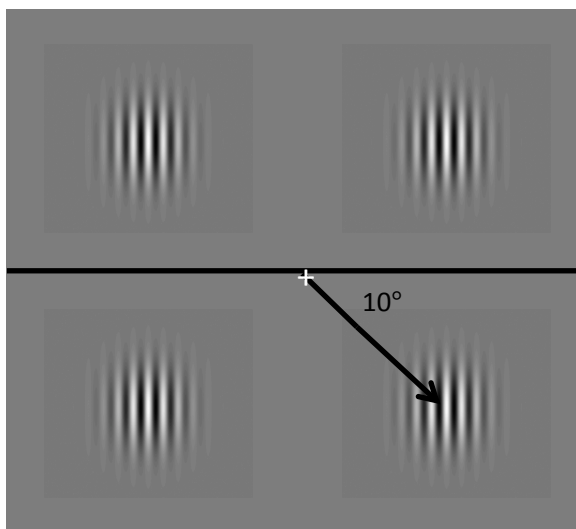
Figure 2:2: Schematic diagram of the four gratings with centres 10 degrees from fixation.

The blocks of trials with a pedestal contrast of 10% and 50% were counterbalanced between participants to minimise any practice effects. Upon finishing the first block of trials, participants completed a questionnaire regarding their experience of migraine.

2.3   Results

A cumulative Gaussian curve was fitted to the data using Matlab and the Palamedes toolbox (Prins, & Kingdom, 2009), with alpha (contrast threshold) and beta (slope) as free parameters, using a maximum likelihood fit. This was used to calculate the 62.5% contrast discrimination threshold for each observer, for the 10% and 50% contrast conditions (Figure 2:3). As this was a 4AFC task, a 75% correct threshold was too stringent, because chance level was only 25%. Table 2:2 shows the Mean (SD) contrast thresholds at 10% and 50% for the 3 groups.

Contrast Discrimination Threshold
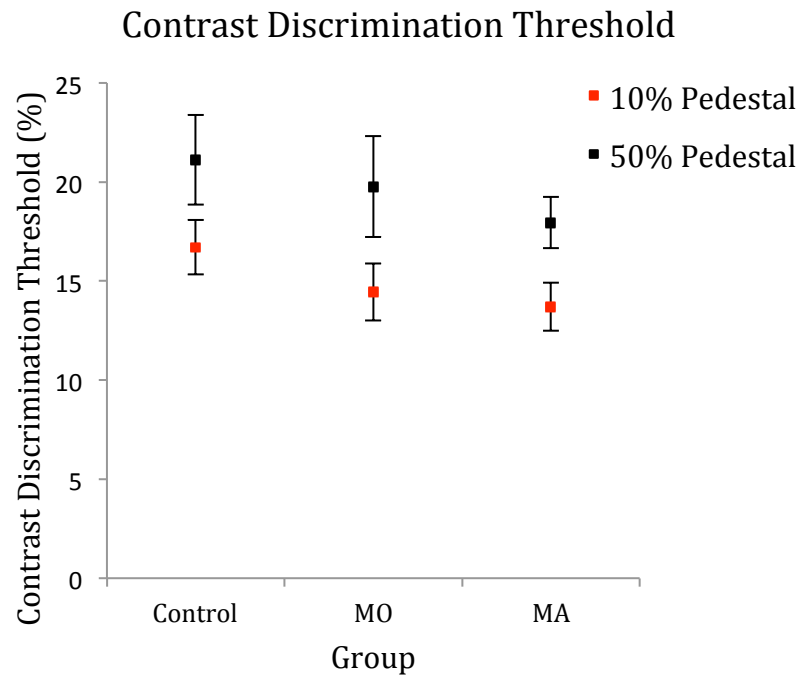
Figure 2:3: Contrast discrimination threshold for each group and pedestal contrast. Error bars denote the standard error of the mean.

Table 2:2: Mean (SD) contrast discrimination threshold at pedestal contrast of 10% and 50%.

Group	10%	50%
Control	16.9 (6.70)	21.9 (13.19)
MO	14.8 (5.95)	19.9 (9.86)
MA	13.9 (5.93)	18.5 (6.62)

The contrast discrimination thresholds for all observers for 10% and 50% contrast were subjected to a 3 (group) x 2 (contrast level) analysis of variance. Group was the between-subjects factor and contrast threshold for the low and high pedestal conditions, the within-subjects factor. Contrast discrimination threshold was significantly higher in the 50%

condition, $F(1, 59) = 36.91$, $p < 0.001$, $\eta^2 = 0.38$. There was no main effect of group $F(2, 59)$ = 0.94, $p = 0.395$, $\eta_p^2 = 0.031$ and no significant interaction between contrast and group, $F(2, 59) = 0.07$, $p = 0.936$, $\eta^2 = 0.0014$.

Alpha (contrast threshold) and beta (slope) parameters were calculated in order to assess differences in threshold and slope. A 3x2 mixed analysis of variance was conducted separately for the alpha and beta parameters. Analysis of the alpha parameter revealed a significant main effect of contrast, $F(1, 59) = 3152.119$, $p < 0.001$, $\eta^2 = 0.981$, but no significant interaction between the two contrast parameters and group, $F(2, 59) = 0.66$, $p = 0.937$, $\eta^2 = 0.00004$. There was no significant main effect of group $F(2, 59) = 0.943$, $p = 0.395$, $\eta^2 = 0.031$. Analysis of the beta parameter revealed a non-significant main effect of contrast, $F(1, 59) = 0.485$, $p = 0.489$, $\eta^2 = 0.011$ and a non-significant interaction between the two contrasts and group $F(2, 59) = 0.815$, $p = 0.448$, $\eta^2 = 0.022$. There was no significant main effect of group $F(2, 59) = 1.798$, $p = 0.175$, $\eta^2 = 0.06$.

Eight of the 24 participants in the MA group experienced a consistently unilateral visual aura. See Table 2:3 for the mean contrast discrimination threshold for the MA group, split by those who experienced bilateral aura and those who experienced unilateral visual aura. Contrast threshold was calculated separately for each quadrant of the screen. A psychometric curve was fitted to all of the data from the left, and from the right hemifields separately. Pedestal contrast was subtracted from the threshold in order to obtain the increment necessary for an individual to detect the target. The increment was generally smaller in the affected field for both the 10% and 50% pedestal conditions (Figure 2:4). For

all 8 participants with unilateral aura, contrast threshold was lower in the field affected by

aura when averaged across conditions. Paired-samples t-tests revealed significantly lower

thresholds in the affected field for the 10% and 50% conditions respectively, $t(7)= 2.94$, $p =$

0.022, $t(7) = 3.91$, $p = 0.006$.

Table 2:3: Mean (SD) contrast discrimination threshold for participants with bilateral and those with unilateral visual aura.

Group	10%	50%
MA Bilateral	14.84 (6.19)	19.12 (6.84)
MA Unilateral	11.39 (4.85)	15.60 (4.76)
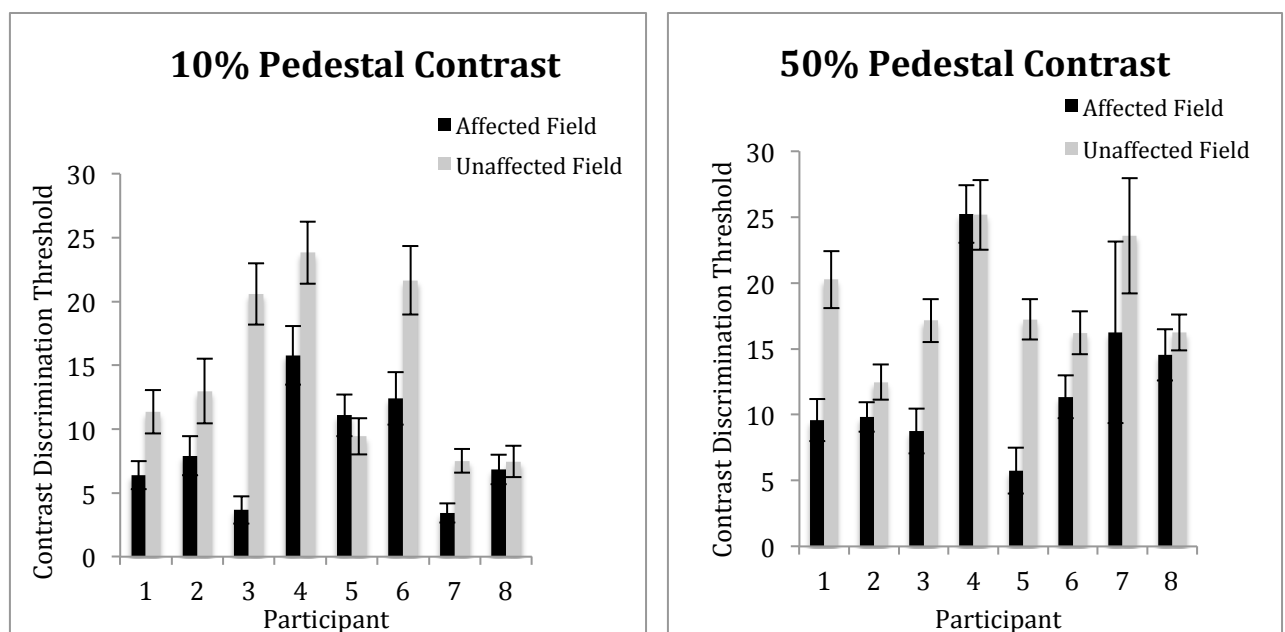
Figure 2:4: Contrast discrimination threshold for individuals who experience a consistently lateralised visual aura. Error bars denote the SD.

The average discrimination threshold across the 10% and 50% contrast conditions was calculated in order to examine whether performance was supranormal in the unilateral aura group, compared to controls. For the first analysis, a conservative one, the lowest contrast threshold in the control group (either from the left or right visual field) was selected and compared with the affected field of the unilateral aura group using an independent samples t-test, $t(29) = 1.901$, $p = 0.067$. A less conservative approach was to compare the affected field of the unilateral aura group with the thresholds for the right visual field of the controls which were significantly lower (more sensitive) than the left, $t(22) = 4.303$, $p < 0.001$. The contrast discrimination thresholds in the affected field of the unilateral aura group were significantly lower than those of the control group in the right visual field, $t(29) = 2.127$, $p = 0.042$. This second, less conservative, analysis thus indicates that performance may be supranormal in the unilateral aura group, compared to controls, but the sample size is small and this complex effect will require further examination.

The relationship between contrast threshold and time since last migraine attack (days) was examined using Spearman's rank correlation coefficient because of the range of values obtained. There was no relationship between time since last attack and contrast threshold for the 10% and 50% conditions in the MA group, $r_s = -0.072$, $N = 24$, $p = 0.738$, $r_s = -0.285$, $N = 24$, $p = 0.177$ respectively. Equally, there was no relationship for the MO group in the 10% and 50% conditions, $r_s = -0.038$, $N = 15$, $p = 0.894$, $r_s = 0.041$, $N = 15$, $p = 0.884$ respectively.

The relationship between contrast discrimination threshold and duration of disease was also examined using Spearman's rank correlation coefficient because of the distribution of results (Figure 2:5). As discussed in the introduction, there is evidence to suggest repeated attacks of migraine can affect sensitivity when completing visual tasks. For this reason, the MA group was split according to whether the aura was unilateral or bilateral because individuals with unilateral aura were found to be more sensitive in the affected field. There were no significant correlations for the MO group in the 10% (r_s = 0.100, N = 15, p = 0.722) and 50% (r_s = -0.011, N = 15, p = 0.969) contrast conditions. Again, there were no significant correlations for the MA bilateral aura group, 10% (r_s = -0.068, N = 16, p = 0.801) or 50% (r_s = -0.199, N = 16, p = 0.459). No significant correlations were found for MA with unilateral aura group, 10% (r_s = 0.333, N = 8, p = 0.420) or 50% (r_s = 0.262, N = 8, p = 0.531).
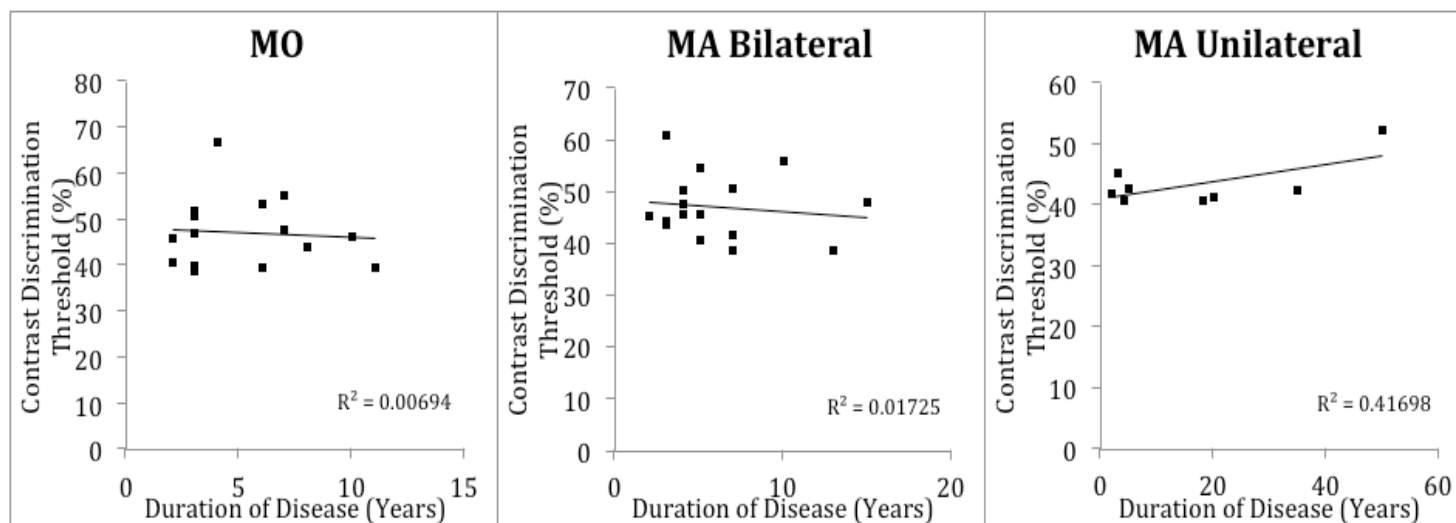
Figure 2:5: Average contrast discrimination threshold for the three migraine groups as a function of duration of disease.

2.4   Discussion

The results of the current study are evidence for superior visual function in the visual field affected by migraine aura. It is possible that contrast discrimination is supranormal but further work will be necessary to establish this. Contrast discrimination thresholds were significantly higher for the 50% contrast condition, which would be expected from Weber's Law. Thresholds did not differ significantly between groups. Thresholds were not associated with the time since last migraine attack, which is consistent with previous literature investigating contrast scaling (Shepherd, 2000).

Individuals with migraine are particularly averse to patterns of mid-range spatial frequency (Marcus & Soso, 1989). These patterns elicit anomalous visual symptoms (Harle, Shepherd, & Evans, 2006). In individuals with MA a susceptibility to illusions may be caused by a heightened sensitivity to visual stimuli, which could aid performance in the short-term. This may affect the performance of individuals with MA on low-level visual tasks that are processed mainly by early visual areas (Wray et al., 1995). Increased sensitivity in the visual field affected by migraine aura is consistent with the hypothesis that in migraine there exists a hyperexcitability of the visual cortex (Aurora & Wilkinson, 2007). It is possible that neuronal hyperexcitability selectively improved performance in the field affected by a lateralised visual migraine aura.

Chronicle and Mulleners (1994) hypothesized that ischemia damaged GABA-ergic neurones during the aura phase. Individuals who experience MA but have a relatively short migraine history may not yet show impairment on psychophysical tasks. The current study does not contradict the hypothesis of Chronicle and Mulleners (1994), because participants in the MA group had an average age of 27.2 years, and this may not have been sufficient to demonstrate the damaging effects of intermittent ischemia. Bridge et al. (2015) showed reduced GABA levels in individuals who experience migraine with visual aura. This is consistent with a reduction of local inhibition in migraine, which links to the theory of a hyperexcitability of the visual cortex.

Khalil (1991), reports impairment of contrast discrimination on the side of a lateralised visual aura. Hemi-field contrast discrimination deficits can be explained by a reduction of contrast sensitivity in individuals who have experienced MA over a long period of time (Khalil, 1991). Khalil's (1991) patients were recruited from neurology outpatient's clinics, whereas a university population was sampled in the current study. The sample used in the current study was probably not as clinically severe in terms of attack frequency and duration of disease, and did not demonstrate contrast discrimination deficits for this reason.

The findings of the current study are inconsistent with much of the previous literature, which suggests contrast processing is worse rather than better in participants with migraine (McKendrick & Badcock, 2003; Shepherd, 2000). Abnormalities of regional cerebral blood flow during a migraine attack may cause permanent deficits, which could

account for abnormalities of visual processing (Olesen et al., 1993). Reduced grey-matter density of the frontal and parietal lobes and reduced white-matter density of the frontal lobes has been demonstrated in patients with long-term migraine who also experience high attack frequency (Schmitz et al., 2008). Individuals who have experienced MA over many years demonstrate poor foveal performance when completing an orientation discrimination task compared to those with a shorter migraine history (Wilkinson & Crotogino, 2000).

There have also been reports of better performance in individuals with migraine when completing metacontrast masking tasks (Palmer et al., 2000; Shepherd et al., 2011). As discussed previously, Shepherd et al. (2011) demonstrated better performance of individuals with migraine on baseline measures of metacontrast masking and in the three masking conditions. The authors suggest that the superior performance of individuals with migraine may reflect an increased neuronal response to briefly presented stimuli, which cannot be maintained. Antal et al. (2005) report better performance of individuals with migraine (MA and MO) when discriminating the motion of coherently moving dots. This finding is also consistent with increased neuronal excitability in migraine.

The results of this study are consistent with reports that visual performance in migraine patients does not differ from controls. Wagner, Manahilov, Loffler, Gordon, and Dutton (2010) used a 2AFC design to measure the effect of added noise on contrast threshold in participants with MA, those with MO, and controls. There were no significant threshold differences between groups in the no-noise condition, which involved detecting a grey disc

at near-threshold levels. Webster, Dickinson, Battista, McKendrick, and Badcock (2012) utilised the same task with MA and control participants and found no differences between groups for the no-noise and low-noise conditions. These results do not indicate an impairment of contrast processing in migraine. McColl and Wilkinson (2000) presented participants who experienced MA or MO and controls with a briefly presented target superimposed on a 3cpd grating pattern. They found no evidence of reduced inhibitory feedback in participants with MA or MO, but this may be due to the age of participants in the migraine groups, 30.7 and 29.0 years respectively. Although the onset of migraine can occur at any time throughout the life span, it is likely that participant groups with a higher mean age have experienced more attacks of migraine. McColl & Wilkinson (2000) conducted correlations to examine the relationship between cortical inhibition and the estimated total number of aura episodes in the MA group. No significant relationships were found. It may be the case that participants groups with an early onset of the disease and a higher mean age would be more likely to demonstrate any dysfunction of the visual system as a result of migraine.

The range of tasks used to investigate visual function in migraine makes comparison of the results difficult. The small proportion of the literature reported in this chapter is summarised in Table 2:4 and Table 2:5. The literature has been divided into those reports that found better performance in individuals with migraine and those that found worse performance. There may be a relationship between duration of disease and impairment of visual function in migraine. Repeated attacks of migraine with aura may reduce the sensitivity of cortical cells, which would result in reduced sensitivity to visual tasks. A systematic long-term investigation into the effects of aura would be necessary in order to ascertain whether migraine with aura is a benign condition or whether the aura has damaging effects over time.

Table 2:4: Summary of the literature that demonstrates better performance in migraine.

Article	Task	Participants	Diagnosis	Mean age of Participants (years)	Mean duration of illness (years)	Results in relation to hyperexcitability
Palmer *et al*. (2005)	Metacontrast Masking	12 MA 12 MO 12 Control	Grouped according to IHS criteria	35.6 MA 36.3 MO 35.6 C	15.8 MA 20.0 MO	The masking effect was reduced in the MA group, which may indicate a reduction of inhibitory function in area V1.
Antal *et al*. (2005)	Motion-perception	11 MA 9 MO 20 Control	Grouped by a Neurologist according to IHS criteria	Combined MA and MO groups: 27.5 Control: 28.2	Not reported	MA and MO groups were more sensitive to coherently moving dots. Consistent with a hyperexcitability of the cortex.
Shepherd *et al*. (2011)	Metacontrast Masking	15 MA 15 MO 15 Control	Grouped according to IHS criteria	30.1 MA 31.2 MO 30.5 C	13.1 MA 15.1 MO	Both migraine groups were more sensitive in the baseline no-mask condition. This may reflect a heightened response to briefly presented stimuli. Individuals with migraine are more sensitive to flicker.
Karanovic *et al*. (2011)	Detection of flicker Discrimination of suprathreshold flicker	5 MA 9 MO 14 Control	Grouped according to IHS criteria	24.2 MA 23.8 MO 28.7 C	12.2 MA 9.89 MO	Adaptation to high contrast flicker significantly lowered discrimination thresholds at high contrast in the combined migraine group.
Wray *et al*. (1995)	*Low Level* Orientation detection Temporal order judgement *High Level* Picture-naming Word-priming	15 MA 15 Control	Grouped according to IHS criteria	47.3 MA 47.9 C	18.7 MA	MA group demonstrated greater sensitivity to the *low-level* tasks, which suggests a greater sensitivity that is possibly confined to area V1.

Table 2:5: Summary of the literature that demonstrates worse performance in migraine.

Article	Task	Participants	Diagnosis	Mean age of Participants (years)	Mean duration of illness (years)	Results in relation to hyperexcitability
Khalil (1991)	Hemi-field contrast discrimination	23 MA	Recruited from a neurology outpatient clinic. All participants fulfilled IHS criteria	Mean across 92 participants data reported in the thesis: 40.0	Mean across 92 participants data reported in the thesis: 18.5	Hemi-field contrast discrimination was normal in individuals with a short disease duration but impaired in individuals with a long disease duration in the affected field of those with a unilateral visual aura.
Shepherd (2000)	Contrast threshold (Cambridge low contrast gratings)	12 MA 12 non-visual aura 11 MO 35 Control	Grouped according to IHS criteria	40 (averaged across groups)	21 (averaged across groups)	Individuals in the combined migraine group were poorer at detecting a pattern grating and this effect was related to the number of illusions reported from a striped pattern. This result may be expected if there is increased noise in the visual system in migraine, which would impair the detection of gratings near threshold.
McKendrick & Badcock (2003)	Both flicker and standard perimetry Steady-pedestal and pulsed-pedestal contrast discrimination	10 Migraine 15 control	Grouped according to IHS criteria	27 Migraine 25 C	Not reported	Contrast discrimination was impaired in individuals with migraine in the mid-peripheral visual field.
Wilkinson & Crotogino (2000)	Orientation discrimination	20 MA 20 MO 20 Control	Grouped according to IHS criteria	31.1 MA 31.1 MO 27.9 C	11.4 MA 13.6 MO	The MA group was sub-divided into those individuals with a high incidence of attacks of MA and those with a low incidence. The trend towards worse foveal performance in the MA group was caused by individuals with a high lifetime incidence of MA. This finding may lend support to the hypothesis of Chronicle and Mulleners (1994), which suggests that repeated attacks of migraine may damage inhibitory cortical neurones.

The present results indicate superior inter-ictal performance in the affected field compared to the unaffected field of individuals who experience unilateral migraine aura. Participants in the migraine groups were recruited from the general population and the results are consistent with a cortical hyperexcitability. It is possible that a long history of migraine accompanied by a high incidence of visual aura is responsible for the poor visual performance previously reported, and would be consistent with the damage of GABA-ergic cells in V1, proposed by Chronicle & Mulleners, (1994).

Chapter 3 Colours for Comfort in Migraine

Abstract

Individuals who experience migraine with aura have been shown to be particularly sensitive when discriminating contrast. These individuals are also known to be sensitive to strong patterns and experience anomalous visual symptoms and visual discomfort.

Coloured filters in the form of lenses have been used to help alleviate discomfort from strong patterns. The colour chosen as comfortable is individual and there is wide variability in the colours chosen. Some colours, such as red hues, have been found to be more uncomfortable for individuals with migraine (Chronicle & Wilkins, 1991).

For the current study, Participants who experienced migraine, and controls, viewed 6 grating patterns of increasing contrast until visual discomfort was experienced. The effect of two colours of illumination on contrast threshold for discomfort was measured. The first colour of illumination was selected as comfortable for viewing high contrast text. The second colour was identified as being uncomfortable. A comfortable colour of illumination significantly raised the contrast threshold for discomfort in all 3 participant groups. Individuals in the MA group had the lowest thresholds when the gratings were illuminated by the uncomfortable colour. The MA group chose as comfortable, colours of significantly greater saturation. A comfortable colour of light appears to reduce perceptual distortion and improve comfort.

3.1   Introduction

As we saw in Chapter 1, patterns of stripes with a spatial frequency of 3 cycles/degree are known to cause discomfort and perceptual distortion, to which individuals with migraine are particularly susceptible (Wilkins et al., 1984). In migraine with aura (MA) the patterns evoke an abnormally large fMRI BOLD response (Huang et al., 2011), consistent with other evidence of a cortical hyperexcitability (Aurora & Wilkinson, 2007) . These patterns also evoke seizures in individuals with photosensitive epilepsy (Wilkins, Emmett, et al., 2005).

The threshold contrast at which discomfort occurs in response to a pattern of stripes is significantly lower for individuals with migraine compared to controls, and is a reliable predictor of diagnostic group (migraine or control) (Haigh et al., 2012; Mulleners, Aurora, et al., 2001).

In normal observers the threshold contrast at which discomfort occurs is higher (i.e. there is less discomfort) when the grating has an appropriate colour (Monger, Wilkins, & Allen, 2015). In participants with migraine, tinted lenses have been shown to reduce the BOLD response to patterns, provided their colour was chosen individually to reduce discomfort, but not otherwise (Huang et al., 2011). Shepherd, Hine, & Beaumont (2013) found that for individuals with visually triggered migraine, discomfort was generally greater from achromatic gratings than from coloured gratings. They used a limited range of colours that differed with respect to the energy captured by the three classes of cones, and found no differences in discomfort between the colours. Nevertheless it remains possible that a

larger gamut of colours is required to reveal any specificities in individual colour preference (Wilkins et al., 1992). Noseda et al. (2016) recorded electroretinography (ERG) and VEP's to measure the function of the retina and brain activation during exposure to light of various colours during an attack of migraine. They found green light exacerbates the pain of migraine less than white, blue, amber and red light. Green light was found to activate cone-driven pathways to a lesser extent than the other colours and there was less cortical activation. The authors suggest that the photophobia associated with migraine may originate in cone-driven retinal pathways.

When the hues chosen as comfortable by participants with migraine were compared with those chosen by headache-free controls, migraineurs generally reported red colours as least comfortable (Chronicle & Wilkins, 1991). In the present study individuals with migraine and those without chose a colour of lighting that was comfortable for viewing text and a second colour that was uncomfortable. The threshold grating contrast at which discomfort occurred was compared under light of the two colours. MA and MO groups were compared because they may represent two distinct clinical groups as regards symptoms and treatment (Manzoni & Torelli, 2008; Russell, Rasmussen, Fenger, & Olesen, 1996; Russell, Ulrich, Gervil, & Olesen, 2002).

3.2   Method

Participants

Participants were students and staff from the University of Essex. 134 students completed a computer-based questionnaire, which was based on the International Headache Society's criteria for migraine, both with and without aura. The first 15 individuals who fulfilled criteria were selected for the MA, MO and headache-free groups. The remaining 5 individuals in each group were recruited via an internal distribution list and completed the questionnaire on the day of testing. "Headache-free" individuals reported they had not experienced a headache attack lasting between 4 and 72 hours. Participants with migraine were also required to have a diagnosis by a medical professional. Participants gave written informed consent after a full explanation of the methods and were instructed to inform the researchers should any discomfort be experienced. All procedures were approved by the University of Essex ethics committee. The participant's details are given in Table 3:1.

Table 3:1: Participant information.

	Control	**MO**	**MA**
M/F	7 M 13 F	1 M 19 F	3 M 17 F
Age range	18-21	18-24	18-55
Mean age (SD)	19.7 (0.9)	20.7 (2.0)	23.2 (9.5)
Using refractive Correction	7	6	8
Mean (SD) duration of disease (years)	N/A	3.4 (2.0)	6.6 (7.2)
Mean weeks since last attack (SD)	N/A	3.1 (2.5)	2.5 (2.4)
Prophylactic medication	N/A	1	3

Materials

Gratings with square-wave luminance profile having a spatial frequency of 3 cycles/degree were printed on paper and calibrated using a spectroradiometer (Monolight, Model 6000, Optical Spectrum Analyser) and associated equipment for measuring reflectance, including a halon reflectance standard. All patterns had a diameter of 90mm and increased in Michelson contrast as follows: 14%, 23%, 35%, 46%, 68% and 75%. All patterns had a grey surround with a reflectance of 53%, the same space-averaged reflectance as that of the patterns.

Procedure

The 60 participants were individually tested. Individuals completed a questionnaire regarding their experience of severe headaches and use of glasses or contact lenses. None reported colour vision deficits. A refractive correction was used by 21 participants and was worn during testing. Participants underwent a colorimetry examination to identify a comfortable colour of illumination using a Colorimeter Mk.II (Cerium Visual Technologies, Tenterden, Kent). The procedure for colorimetry is described below.

3.2.1   Procedure for Colorimetry

A test plate consisting of randomly ordered lower case letters (3mm high), spaced as words in a paragraph, square in outline (210mm) and flanked by capital letters 5mm high in the periphery was illuminated by white light (chromaticity u'= 0.226 v'= 0.526) in the Intuitive Colorimeter Mark II. Figure 3:1 illustrates the gamut of colours sampled in the Intuitive Colorimeter. The outer ring shows the loci of chromaticities sampled at a saturation of "50" and the inner ring (dotted line) a saturation of "30" on the Colorimeter. The lines radiating from the centre show the loci of chromaticities at each of 12 hues separated by 30 degrees on the Colorimeter. The colour names are for guidance only. The first hue to be presented in the Colorimeter is red, which is followed by hues of orange, yellow, green, blue and purple.

Individuals were asked a series of questions regarding any perceptual distortions they experienced when viewing text. The questions were:

1. Are the letters clear or are they blurred (fuzzy)?

2. Are the letters too close together or far enough apart?

3. Is the page too bright, not bright enough or just about right?

4. Does it hurt your eyes to look at the print or is it OK?

Participants then viewed the test plate as the experimenter changed the Colorimeter hue sequentially from 0°(reddish) to 330° in 30° intervals (corresponding to about 30 degree increments of CIE h_{uv}). At each hue the saturation was increased to "30" and then decreased to "0", thereby enabling a large gamut of colours to be presented efficiently with luminance constrained within the range 11-17 cd.m^{-2}. At a saturation of 30 (see Figure 3:1), participants were asked 'Is the colour now more comfortable or less comfortable than the white light you have just seen, or is it about the same?' If the colour was reported to be more comfortable, participants were encouraged to vary the saturation (maximum Colorimeter setting 50), increasing it or decreasing it for themselves to find the optimal setting at that hue (see Figure 3:1). When all 12 hues had been presented, the participant was shown any optimal settings for comfortable colours in turn, and asked to compare them with the white (0 saturation) setting in order to check that the settings were still comfortable. If more than one comfortable colour was selected, the most comfortable was selected by a process of pair-wise successive comparison. For the selected comfortable

colours, the experimenter kept the saturation at the optimal setting and asked the

participant to close their eyes for a moment while the hue was increased by 15 degrees.

The participant was then asked to open their eyes and judge whether the new colour was

more comfortable or less comfortable than the one before. If the new hue was more

comfortable, this hue was chosen as the most comfortable. If not, the hue was decreased by

15 degrees from its original setting and they were asked whether this new colour was more

comfortable than the original. Again, the participant closed their eyes during the change in

hue. In each case participants were free to request a second presentation of each colour

before making their decision.
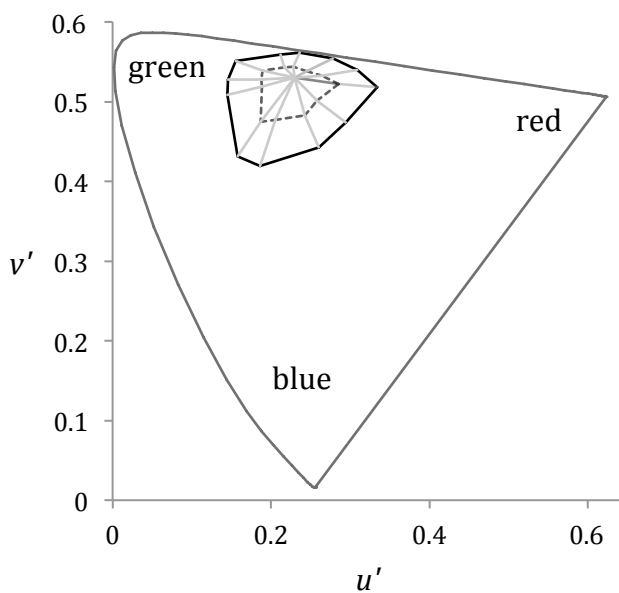
Figure 3:1: CIE 1976 UCS diagram showing the chromaticity coordinates sampled with the Intuitive Colorimeter. The colour names are for guidance only. The concentric curves show the saturation of "30" (inner) and "50" (outer).

Participants were also asked to choose the most uncomfortable colour of those seen. To minimise any discomfort, the method of identifying an uncomfortable colour differed in that no adjustment occurred – the settings were based simply on the reports of discomfort during the initial presentation of 12 moderately saturated colours.

Pattern gratings were then presented with the comfortable colour of lighting. The patterns appeared in order of increasing contrast until discomfort was experienced. When viewing each grating participants were asked 'Is it OK or does it hurt your eyes?' Three series of gratings were presented. The procedure was then repeated for the uncomfortable colour of lighting.

Because the patterns were presented in ascending contrast, an individual with a high threshold viewed more patterns. The influence of colour on threshold was assessed using analysis of variance and planned comparisons. All t-tests were two-tailed with the cut-off for significance set at p = 0.05. Mann-Whitney U-tests were undertaken when the data were not normally distributed.

3.3   Results

All participants identified both a comfortable and an uncomfortable colour of light during testing (see Figure 3:2).
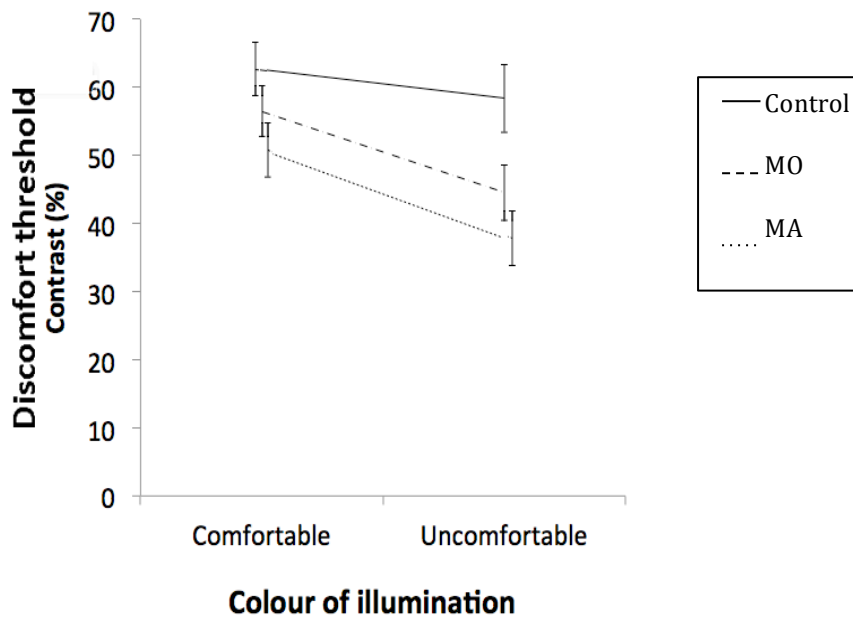
Figure 3:2: Mean thresholds for the comfortable and uncomfortable colours. Error bars denote the standard error of the mean.

Two repeated measures ANOVA were conducted separately for comfortable and uncomfortable colours of light. There was no effect of order of presentation (across the three repetitions) for the comfortable colour, $F(2, 114) = 0.333$, $p = 0.717$, $\eta^2 = 0.006$, no main effect of group, $F(2, 57) = 2.875$, $p = 0.065$, $\eta^2 = 0.101$ and no interaction with group, $F(4, 114) = 0.619$, $p = 0.650$, $\eta^2 = 0.021$. Similarly, there was no effect of order of presentation for the uncomfortable colour, $F(2, 114)= 0.505$, $p = 0.605$ $\eta^2 = 0.009$, there was a significant main effect of group, $F(2, 57) = 4.886$, $p = 0.011$, $\eta^2 = 0.146$, but no

interaction with group, $F(4, 114) = 0.403$, $p = 0.806$, $\eta^2 = 0.014$. The contrast threshold for discomfort did not differ significantly across the three series of gratings with comfortable and uncomfortable illumination, and there were no differences with respect to standard deviation, so further analyses were conducted on the average of the three contrast thresholds for each participant.

A 3x2 analysis of variance was conducted with group as the independent variable and *discomfort threshold* (the grating contrast at which discomfort was first reported) as the dependent variable (see Figure 3:2). A highly significant effect of colour (comfortable or uncomfortable) was obtained, $F(1, 57) = 37.35$, $p = < 0.001$, $\eta^2 = 0.373$. There was a main effect of group, $F(2, 57) = 4.415$, $p = 0.016$, $\eta^2 = 0.134$, but the interaction between threshold and group was not significant, $F(2, 57) = 2.96$, $p = 0.060$, $\eta^2 = 0.059$. A comfortable colour of illumination resulted in a higher contrast threshold for discomfort than the uncomfortable colour for the control, MO and MA groups respectively, $t(19) = 2.26$, $p = 0.036$, $t(19) = 3.80$, $p = 0.001$, $t(19) = 4.24$, $p < 0.001$. Planned comparisons revealed participants in the control group had significantly higher thresholds, when viewing patterns illuminated by the comfortable colour of light, than those in the MA group, $p = 0.034$, but the control and MO groups did not differ significantly, $p = 0.261$. A significant difference was not obtained between the MA and MO groups, $p = 0.303$.

The saturation of comfortable and uncomfortable colours was calculated for the three groups in terms of the Pythagorean distance from the white of the colorimeter, chromaticity $u' = 0.226$ $v' = 0.526$, see Table 3:2. A 3x2 repeated measures analysis of variance was conducted in order to assess group differences in the saturation of the chosen colours. There was a significant main effect of the comfortable and uncomfortable colours, $F(1, 57) = 5.943$, $p = 0.018$, $\eta^2 = 0.063$, but the main effect of group was not significant, $F(2,57) = 0.786$, $p = 0.406$, $\eta^2 = 0.030$. There was a significant interaction between comfort and group, $F(2, 57) = 3.940$, $p = 0.025$, $\eta^2 = 0.111$. Planned comparisons revealed the saturation of comfortable colours was greater for the MA group when compared with headache-free controls, $p = 0.043$, and with the MO group, $p = 0.023$. Individuals in the MA group chose as comfortable colours of significantly greater saturation than participants in the MO or control groups.

Table 3:2: Mean (standard deviation) saturation (CIE UCS s_{uv}) for comfortable and uncomfortable colours.

Group	Comfortable	Uncomfortable
Control	0.065 (0.043)	0.062 (0.026)
MO	0.062 (0.028)	0.061 (0.031)
MA	0.088 (0.031)	0.053 (0.028)

The shortest distance between each participant's comfortable colour and the locus of the Planckian radiator was also calculated (see Figure 3:3 and Table 3:3). The Planckian locus is the locus of a black body that will change in spectral irradiance (and therefore colour) as temperature increases from 1000K to 5000K. The colour will change from red initially to orange, yellow, white and finally to blue. The chromaticities of domestic lighting are close to the Planckian locus (and expressed in terms of correlated colour temperature). The chromaticities of colours that lie along the Planckian locus in CIE 1976 UCS colour space are of low saturation. Individuals for whom colour is of no benefit may simply select a colour that is familiar and of low saturation. The Pythagorean distance between each participant's comfortable colour of light and the Planckian locus was calculated (see Appendix B for the equation). Kim, Cho, Kang, & Hong (2006) used a cubic spline function to approximate the Planckian locus and the same method was used for the current study with points every 200K. The closest point on the Planckian locus to each participant's comfortable colour was calculated (see Figure 3:4). A one-way between-subjects ANOVA was conducted to examine the effect of participant group on the distance from comfortable colours to the Planckian locus. This revealed a significant effect of group, $F(2, 57) = 4.259$, $p = 0.019$. Planned comparisons with a Bonferroni correction revealed a significant difference between the control and MA group $p = 0.028$, no significant difference was found between the Control and MO group $p = 1.000$ or the MA and MO group $p = 0.071$.
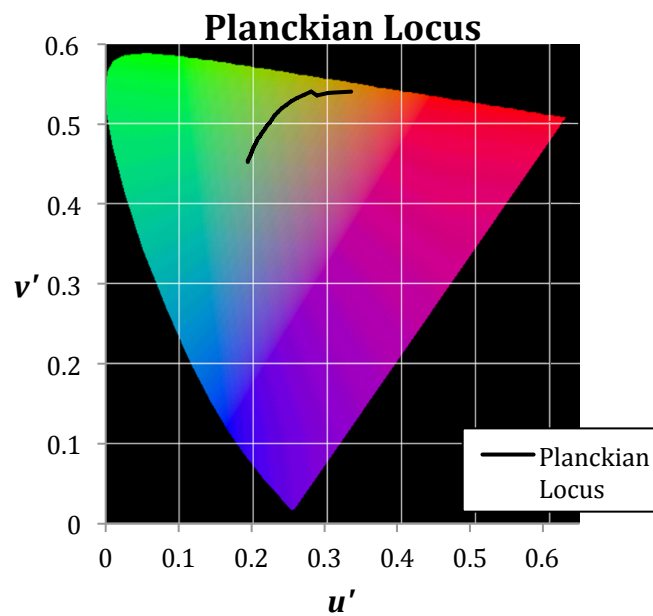
Figure 3:3: The Planckian radiator locus plotted in CIE 1976 UCS colour space.

Table 3:3: Mean (SD) distance from the Planckian locus for each group.

Group	Mean
Control	0.00107 (0.00158)
MO	0.00129 (0.00114)
MA	0.00265 (0.00256)

The chromaticities of the comfortable colours of light were plotted on a CIE 1976 UCS diagram separately for the migraine and control groups (Figure 3:4). Comfortable light for the control group is clustered around white on the CIE 1976 UCS diagram indicating a low saturation was preferred. In contrast, comfortable colours for the MA group are more widely distributed and of higher saturation. The Pythagorean distance between each participant's most and least preferred colour was calculated for all groups. The mean (and SD) distance between comfortable and uncomfortable colours was: control group 0.076 (0.028); MO group 0.068 (0.028); MA group 0.103 (0.033). The distance was greater for the MA group than for both the headache-free controls, $t(19) = 2.41$, $p = 0.026$ and the MO group $t(19) = 3.59$, $p = 0.002$. The distance between most and least preferred colour for the MO group was not significantly different from controls.
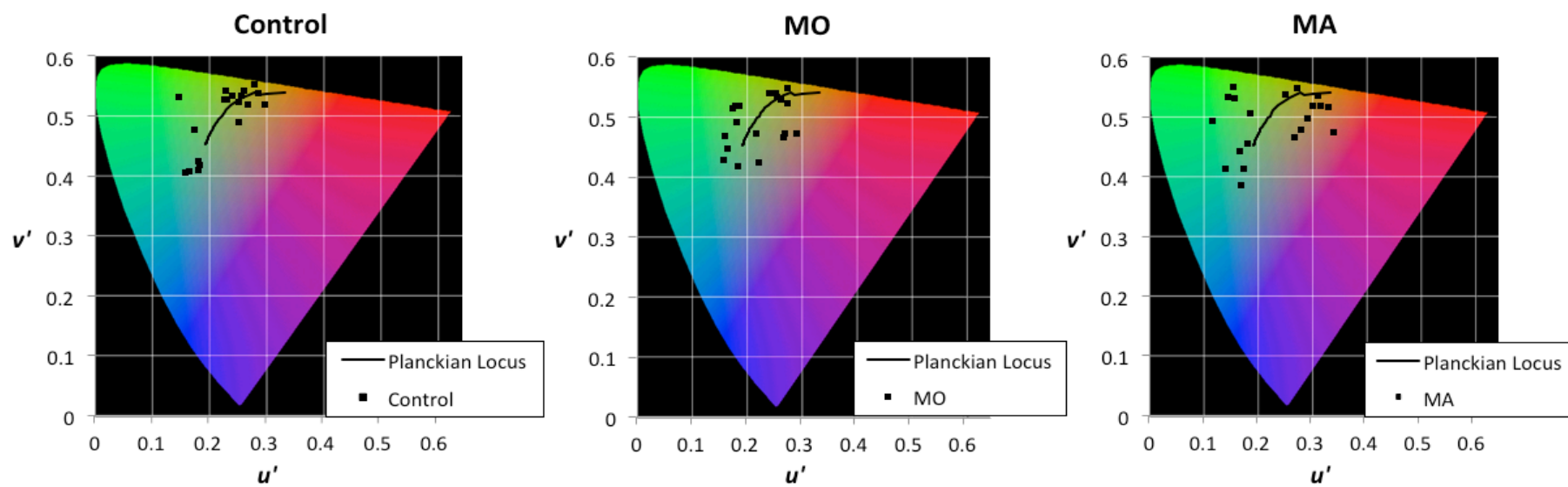
Figure 3:4: CIE 1976 UCS diagrams showing the comfortable colours selected by each group (black points) with the Planckian radiator superimposed.

The mean (and standard deviation) of the number of perceptual distortions reported in response to the first three Colorimeter questions was 0.25 (0.44) for the controls, 0.30 (0.47) for the MO group and 1.15 (0.75) for the MA group. Individuals in the MA group experienced significantly more illusions than those in the MO group, Mann-Whitney U = 75.0, N_1 = 20, N_2 = 20, p < 0.001 and the controls, Mann-Whitney U = 67.5, N_1 = 20, N_2 = 20, p < 0.001. Ten participants (6MA, 3MO and 1 Control) experienced pain from text, all of whom experienced perceptual distortions.

The relationship between duration of illness (years) and contrast threshold for discomfort for the comfortable and uncomfortable colours was examined using Spearman's correlations. No significant correlations were found for the MA group for the comfortable and uncomfortable colours respectively: r_s = 0.099, N = 20, p = 0.678 and r_s = 0.317, N = 20, p = 0.173. No significant correlations were found for the MO group for the comfortable and uncomfortable colours respectively: r_s = -0.172, N = 20, p = 0.469 and r_s = -0.022, N = 20, p = 0.928.

Time since last attack (weeks) and contrast threshold for discomfort was also examined using Spearman's correlations. No significant correlations were found for the MA group for the comfortable and uncomfortable colours respectively: r_s = 0.166, N = 20, p = 0.485 and r_s = 0.157, N = 20, p = 0.508. No significant correlations were found for the MO group for the comfortable and uncomfortable colours respectively: r_s = -0.278, N = 20, p = 0.236 and r_s = -0.016, N = 20, p = 0.948.

3.4   Discussion

The MA group reported more illusions and discomfort when looking at text. Individuals who report illusions from text often find a colour that reduces the distortions and increases comfort (Monger et al., 2015). A comfortable colour of illumination significantly increased the contrast threshold for discomfort in all participant groups. Individuals in the MA group showed a greater reduction in discomfort with a coloured light than did the other groups, ratified by the threshold contrast at which discomfort was first reported. In general, the choice of coloured light as comfortable was confirmed by the greater grating contrast tolerated. The MA group chose a more saturated colour of light as comfortable than did the other groups, which did not differ in this respect. The difference in colour between the light chosen as comfortable and that chosen as uncomfortable was greater for the MA group. These findings are consistent with those of Shepherd et al (2013) in showing that coloured gratings can be less aversive than achromatic gratings. Participants for whom colour was of no benefit may have chosen familiar colours of lighting. The colour temperatures of domestic lighting are near the Planckian locus and are familiar to participants. The wide range of colours of light chosen as comfortable by our participants suggests that a large gamut of colours is necessary to reveal the group differences in saturation.

The findings are consistent with earlier literature (Mulleners, Aurora, et al., 2001) in demonstrating that the grating contrast at which discomfort occurs is lower in patients with migraine. They are also consistent with literature suggesting that this threshold identifies individuals who find coloured filters useful (Monger et al., 2015).

None of the patients in our study reported colour vision deficits, although patients with migraine sometimes have subtle colour vision anomalies. Shepherd (2006) identified mild deficits in S-cone mechanisms, but in patients with photophobia the perception of surface red colours may be impaired (De Marinis, Rinalduzzi, & Accornero, 2007). Using a previous version of the Intuitive Colorimeter, Chronicle and Wilkins, (1991) suggested migraineurs identified orange/red hues as uncomfortable. This result has been replicated by Noseda et al. (2016) who showed that amber and red light exacerbate the pain of migraine more than green light. The hues identified as uncomfortable in our study varied widely; this may be due to the systematic presentation of colours in a progression around the hue circle, with red being the first colour to be viewed after white. Alternatively, the greater variability may have reflected the greater choice of colour.

An increase in reading speed has been demonstrated for individuals with visual discomfort, but only when a colour of light identified as beneficial is used to illuminate the text (Wilkins, Sihra, & Myers, 2005). Participants in the MA group chose as comfortable coloured light of greater saturation than participants in the other groups, which suggests this may be the sub-group for whom tinted lenses may be of benefit in prophylaxis. Patients with migraine sometimes show a reduction in the symptoms of pattern glare when wearing precision tinted lenses (Evans et al., 2002).

Participants in the MA group experienced significantly more illusions than the MO and control groups when viewing text. Individuals in the MA group may be more susceptible to discomfort and an increased number of perceptual distortions, possibly, as a result of the

cortical hyperexcitability evident in MA (Haigh et al., 2012). The difference between MA and MO with respect to the number of illusions experienced and the saturation of coloured light chosen as comfortable indicate important differences between the two classifications of migraine.

Chapter 4 Contrast Discrimination and the effects of Colour

Abstract

Participants with unilateral migraine aura and controls completed the contrast discrimination task of Chapter 2 wearing two pairs of coloured lenses in turn, one pair grey and the other coloured. The coloured pair was selected using the Intuitive Colorimeter: a 'comfortable' colour of illumination was identified by each participant and was matched with precision tinted lenses. The grey lenses had similar photopic transmission. Individuals in the MA group generally had lower contrast discrimination thresholds, as previously. For the MA group the lenses that provided a 'comfortable' colour of illumination raised the contrast discrimination threshold relative to that obtained with the grey lenses. There was no such difference for controls. Lenses of 'comfortable' colour may redistribute the activity of hyperexcitable regions of the brain in individuals with MA.

4.1   Introduction

In Chapter 2 individuals with a unilateral visual migraine aura were shown to have superior contrast discrimination in the field affected by the aura. Individuals with migraine were more susceptible to discomfort from patterns of striped lines in the study conducted in Chapter 3, but these effects were lessened when the patterns were viewed under light of a colour individually chosen to be comfortable for viewing text.

The underlying neural mechanisms responsible for the clinical effects of coloured filters are still debated, but it is possible that the use of filters affects in some way the neuronal hypersensitivity evident in individuals who experience visual discomfort and migraine (Huang et al., 2011). In the study by Huang et al. (2011) coloured filters, identified as comfortable by the participant, reduced excessive neuronal activation measured using fMRI BOLD. Excessive neuronal activation may be responsible for the superior performance in the affected field when compared to the unaffected field of those participants who experienced unilateral visual aura. Coloured filters would therefore be expected to reduce the excessive neuronal response and 'worsen' the contrast discrimination performance of this group of participants. We therefore investigated the effect of filters on the superior performance of individuals with unilateral migraine aura discovered in Chapter 2.

In the current study, individuals who experienced a unilateral visual migraine aura, and controls, completed the contrast discrimination task of Chapter 2, wearing two different sets of coloured lenses: 'active' and 'placebo'. A comfortable colour of illumination was

identified by the participant, and the 'active' lenses provided that same colour under CIE Type F3 lighting. Grey 'control' lenses were matched for transmission. Participants were unaware of the proposed effects of the coloured lenses.

The relationship between hyperexcitability, cortical spreading depression and visual migraine aura was discussed in Chapter 2. The effects of precision tinted lenses on the possible hyperexcitability of migraine are discussed below.

It has been hypothesized that cortical hyperexcitability is non-uniform in migraine, as is the case in individuals with epilepsy (Wilkins, 1995). Precision spectral filters may redistribute the excitation of neurons from hyperexcitable regions to other visual areas of the brain and reduce the likelihood of cortical spreading depression (Wilkins, Huang, & Cao, 2007). Coloured lenses would be expected to alter the activation of cones in the retina and thus the pattern of neuronal excitation in the brain, which may help reduce the symptoms of visual discomfort. If these beneficial effects were purely the result of a reduction in luminance then a single colour would be expected to reduce discomfort in all individuals (and to a similar extent as an equivalent grey filter). Coloured lenses are specific and individually chosen and the reasons for this are not yet understood. A consistently unilateral migraine aura may represent a lateralised area of hyperexcitability in the cortex. The hyperexcitable region may cause a heightened sensitivity to visual stimulation in the affected field.

Precision spectral filters have been shown to improve clarity and comfort when reading and reduce cortical hyperactivation measured using fMRI BOLD (Huang et al., 2011; Wilkins et al., 1994). Double-masked trials of precision spectral filters have employed 'control' tints, in a variety of forms, which are designed to provide no perceptual benefit. Coloured filters, which differ in chromaticity from the 'active' lenses, typically by 6 JND's, have most commonly been used as placebo, but neutral density filters have also been used. Participants in the following study were unaware of the proposed effects of precision spectral filters or that the 'active' lenses may have an effect on performance. The study was not designed as a double-masked trial of precision spectral filters, but to investigate the effects of colour on contrast discrimination performance. For these reasons, grey lenses of matched transmission were provided as the control. One might speculate that participants would assume the coloured filters were 'better' than the grey filters and would improve performance. If the coloured filters had an effect on concentration or motivation then this may lead to better performance with the active lenses across both visual fields and groups. This is contrary to the hypothesis that coloured filters will increase the contrast discrimination threshold. For these reasons, it is unlikely that performance will be affected by any changes in concentration or motivation of the participants when wearing the coloured lenses.

Individuals who experienced a unilateral visual migraine aura were found to be superior at discriminating contrast in the field affected by aura in Chapter 2. In Chapter 3, a comfortable colour of illumination was shown to increase the contrast at which a grating becomes uncomfortable to view by individuals who experience migraine with aura. It may be the case that filters that provide a colour previously selected as comfortable normalize

contrast discrimination threshold in the affected field in individuals with unilateral visual migraine aura. The transmission of the control grey lenses will be closely matched to that of the 'active' lenses, so the effects of colour on the task can be observed. The lenses will not significantly alter the contrast discrimination threshold due to the high luminance levels of the stimuli used in this experiment (De Valois, Morgan, & Snodderly, 1974). If the superior performance of individuals with MA in Chapter 2 is indicative of a cortical hyperexcitability, MA participants in the current study should again demonstrate superior performance in the field affected by visual aura when the control grey lenses are worn.

4.2   Method

<u>Participants</u>

Participants were recruited from students and staff of the University of Essex. Individuals in the migraine with aura (MA) group experienced a consistently unilateral visual aura. 19 participants were recruited for this study: 9 MA (4 who experienced aura in the left visual field and 5 who experienced aura in the right) and 10 migraine-free control participants (see Table 4:1). Individuals in the migraine group fulfilled the International Headache Society's ICHD III criteria for migraine with aura. Participants in the control group had never experienced a migraine. One of the MA participants had earlier participated in the study described in Chapter 2.

Table 4:1: Participant information.

	C	MA **Aura Left Field**	MA **Aura Right Field**
N	10	4	5
Mean age (SD)	19.7 (1.70)	21.5 (5.07)	34.2 (9.81)
Age Range	18-23	18-29	22-48
Using refractive correction	5	3	4
Mean days since last attack (SD)	N/A	9.3 (8.2)	43.8 (42.7)
Mean (SD) duration of disease (years)	N/A	8.5 (6.9)	22.0 (7.6)

Apparatus

The apparatus used for this experiment was the same as that used in Chapter 2.

Stimuli

The contrast discrimination stimuli used in Chapter 2 were also used in the current experiment. Only the stimuli with a 50% pedestal contrast were presented in this experiment, as contrast discrimination differences with respect to pedestal contrast were no longer being measured.

Procedure

An Intuitive Colorimeter Mk.2 (Cerium Visual Technologies, Tenterden, Kent) was used to identify a colour of illumination that was comfortable for viewing text. The procedure detailed in Chapter 3 was used to identify a comfortable colour of illumination. Colours of light presented within the Intuitive Colorimeter had a luminance constrained to be in the range 11-17 cd.m^{-2}. Each participant completed the contrast discrimination task wearing two sets of coloured lenses in counterbalanced order. One set of lenses matched the colour chosen as comfortable in the Intuitive Colorimeter, and the second set were grey lenses of closely matched transmission. The lenses were placed in a holder and secured with elastic around the participant's head. The lenses used in this experiment were the precision spectral filters, which accompany the Intuitive Colorimeter (Cerium Visual Technologies, Tenterden, Kent) and have spectral transmissions given by Wilkins et al. (1992).

Trial blocks were presented in groups of four with pedestal contrast of 50%. Individuals wore the first set of lenses to complete the first four blocks of trials of the contrast discrimination task.

Upon completing the first block of four trials, participants underwent the following visual tests: Cambridge Low Contrast Gratings (Clement Clarke International Ltd., Harlow, Essex), Ishihara tests of colour vision (Kanehara Shuppan Co., Ltd., Tokyo, Japan), City University Colour Vision Test 3rd Edition (Keeler, Windsor, England) and the Pattern Glare Test (i.O.O Sales Limited, London, England). Contrast threshold for discomfort was also tested using the procedure described in Chapter 3.

Participants then completed the last four trials of the contrast discrimination task wearing the second set of lenses.

4.3   Results

MA group results were organized according to the field affected by visual migraine aura and the field that was unaffected by aura (see Figure 4:1). It would be anticipated that the control grey lenses would have little or no effect on contrast discrimination threshold and that the threshold would be lower in the field affected by aura. Coloured lenses would be expected to raise the contrast discrimination threshold. Individuals in the MA group would therefore be expected to have a lower contrast discrimination threshold in the field affected by the aura when wearing the grey lenses (see Table 4:2 and Table 4:3). A 2 x 2 within-subjects ANOVA was conducted for the MA group with visual field (affected and unaffected by aura) and colour of the lenses as main effects, which revealed a significant effect of colour. There was no effect of visual field, $F(1, 8) = 1.737$, $p = 0.224$, $\eta^2 = 0.178$, but there was a significant effect of colour $F(1, 8) = 142.846$, $p<0.001$, $\eta^2 = 0.94$. The interaction between colour and field was not significant, $F(1, 8) = 0.198$, $p = 0.668$, $\eta^2 = 0.02$. Contrast discrimination threshold was not significantly lower for the MA group in the affected field compared to the unaffected field when wearing the grey lenses, $t(8) = 1.19$, $p = 0.267$. This result is in contrast to that observed in Chapter 2 in which the contrast discrimination threshold was significantly lower in the affected field. However, there is a trend towards greater sensitivity in the affected field in the current experiment. When the difference between the coloured and grey lenses was examined in the affected field, coloured lenses

increased the contrast discrimination threshold $t(8) = 5.71$, $p<0.001$. The coloured lenses also significantly raised the contrast discrimination threshold in the unaffected field $t(8) = 4.819$, $p<0.001$ (see Figure 4:1).
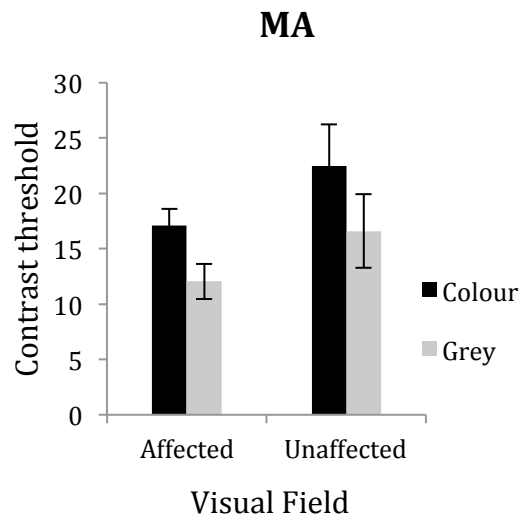
Figure 4:1: Average contrast discrimination threshold for both the visual field that was affected by aura and the field that was unaffected. Error bars denote 1 standard error of the mean.

Table 4:2: Contrast discrimination threshold (%) for the MA group.

Affected Field	Affected Field Coloured Lens	Affected Field Grey Lens	Unaffected Field Coloured Lens	Unaffected Field Grey Lens
Left	14.4	8.2	15.3	11.3
Left	13.6	6.2	12.3	7.8
Left	20.9	19.3	33.9	19.8
Left	25.8	20.2	6.7	5.9
Right	21.0	11.2	38.8	35.6
Right	11.5	10.2	21.0	14.7
Right	14.5	9.4	34.8	28.9
Right	16.5	12.5	23.3	15.9
Right	15.7	11.3	16.4	9.4
Mean (SD)	17.09 (4.5)	12.0 (4.7)	22.5 (11.1)	16.6 (9.9)

Table 4:3: The results of paired-samples t-tests for the MA group based on the visual field affected by aura and the colour of the lenses.

	Affected Field Coloured Lens	Unaffected Field Grey Lens
Unaffected Field Coloured Lens	$p = 0.212$	$p = 0.001$
Affected Field Grey Lens	$p < 0.001$	$p = 0.267$

A 2 x 2 within-subjects ANOVA was conducted for the control group with visual field and colour of the lenses as main effects (see Table 4:4 and Figure 4:2). There was no significant effect of visual field on contrast discrimination threshold in the left and right visual fields, $F(1,9) = 1.664$, $p = 0.229$, $\eta^2 = 0.156$. There was no effect of colour of the lenses, $F(1,9) = 4.839$, $p = 0.055$, $\eta^2 = 0.349$ and no interaction, $F(1,9) = 0.850$, $p = 0.381$, $\eta^2 = 0.086$. Contrast threshold when wearing the 'active' and the grey lenses was compared for the left visual field $t(9) = 2.26$, $p = 0.50$ and for the right, $t(9) = 1.40$, $p = 0.196$. The contrast discrimination threshold obtained in the left and right visual fields was therefore averaged for post hoc comparisons between controls and the MA group.

Table 4:4: Contrast discrimination threshold (%) for the control group.

Left Field Coloured Lens	Left Field Grey Lens	Right Field Coloured Lens	Right Field Grey Lens
16.2	10.1	14.3	12.2
24.7	22.1	23.2	19.9
27.4	22.0	20.1	22.4
28.9	25.6	12.7	10.9
11.9	8.5	16.1	11.6
13.7	15.8	16.7	16.0
13.6	11.6	14.9	18.5
11.5	11.5	13.8	9.63
22.6	14.6	15.6	9.39
25.9	29.3	19.4	21.7
19.6 (6.91)	**17.1 (7.18)**	**16.7 (3.26)**	**15.2 (5.08)**
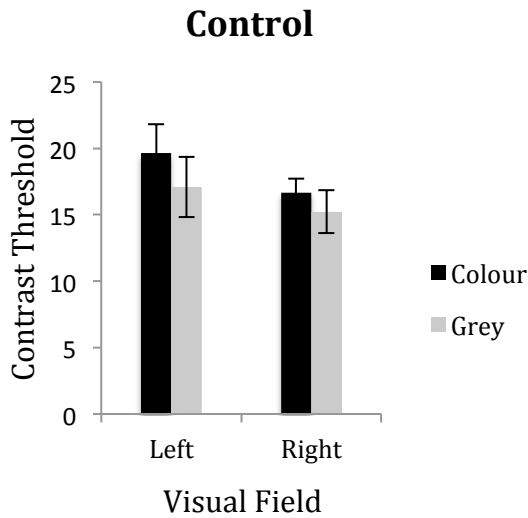
Figure 4:2: Mean contrast discrimination threshold for both the left and right visual fields. Error bars denote 1 standard error of the mean.

In order to examine whether performance in the affected field of the MA group was supranormal (i.e. compared to the average performance of controls) four independent–samples t-tests were conducted. The average threshold for controls when wearing the 'active' and 'placebo' lenses was compared with the threshold for the MA group in the affected and unaffected visual field. Because of the number of comparisons a Bonferroni corrected alpha level of 0.01 was used as the cut-off for significance. None of the comparisons reached significance. The average threshold for controls when wearing the coloured lenses did not differ from the threshold in the affected field of the MA group when wearing the coloured lenses, $t(17)= 0.52$, $p = 0.153$. The average threshold of the control group when wearing the coloured lenses did not differ from the threshold in the unaffected field of the MA group when wearing the coloured lenses, $t(10.2) = 1.10$, $p = 0.075$. A corrected value is reported because the data violate the assumption of homogeneity of variance. The average threshold of the control participants when wearing the grey lenses did not differ, with the Bonferroni correction, from the affected field of the MA group when

wearing the grey lenses, $t(17) = 1.76$, $p = 0.024$. The average threshold of the control group when wearing the grey lenses did not differ from the unaffected field of the MA group when wearing the grey lenses, $t(17) = 0.12$, $p = 0.227$. The between-group comparisons indicate that the contrast discrimination threshold for the MA group was not significantly lower than controls therefore the MA group did not demonstrate better performance.

An independent samples t-test was conducted to establish if the transmission of the 'active' coloured lenses, and that of the grey, differed between groups. The transmission of the grey lenses was significantly greater in the control group (i.e. the lenses were less saturated) $t(17) = 2.97$, $p = 0.009$. The transmission of the coloured lenses was also significantly greater for the control group, $t(17) = 2.91$, $p = 0.010$. Participants in the MA group chose 'active' lenses of greater saturation (see Figure 4:3).
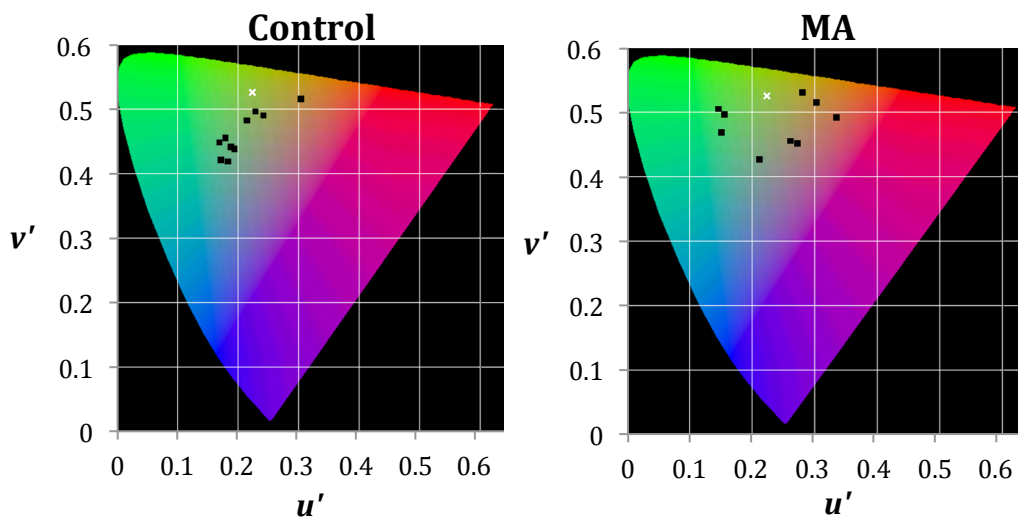
Figure 4:3: Chromaticity of the 'active' lenses plotted in CIE 1976 UCS colour space.

For the control group, the colours chosen as comfortable 'active' lenses lie close to the Planckian locus (see Figure 4:4). The values of the Planckian locus in CIE 1976 UCS colour space were calculated in increments of 200K (see Appendix B for the equation). The Pythagorean distance could therefore be calculated between the chromaticity of participants 'active' lenses and the values of the Planckian locus. The closest data point to the Planckian locus was taken as the distance. An independent samples t-test revealed that the colours of the 'active' lenses selected by controls, were significantly closer to the Planckian locus, $t(9.09) = 3.28$, $p = 0.009$. The t-value reported here does not assume equality of variance, as Levene's statistic was not significant for this test.
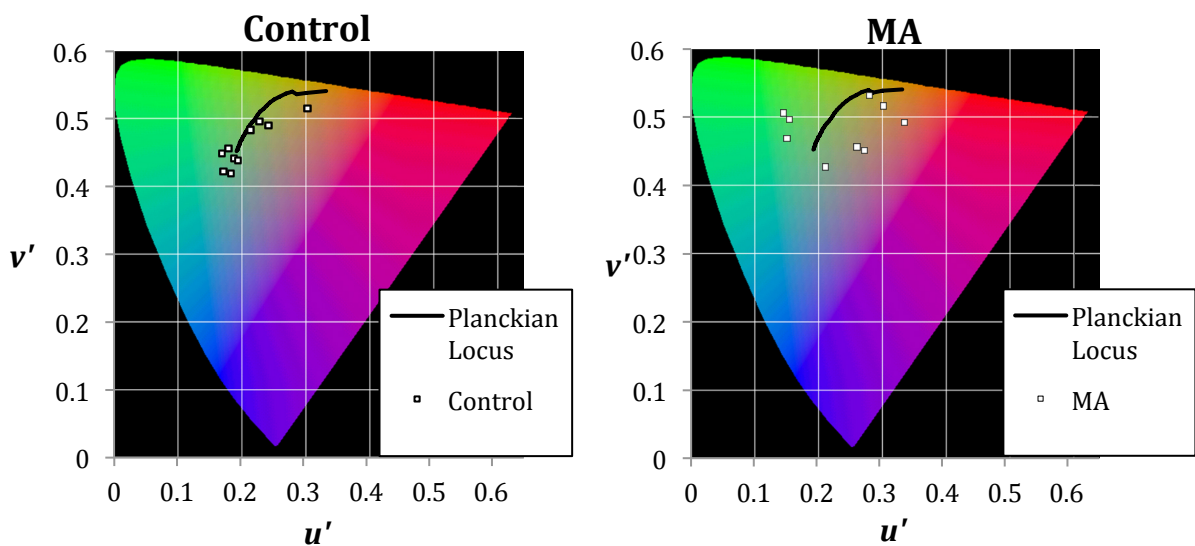
Figure 4:4: Chromaticity of the 'active' lenses for the MA and control groups with the Planckian locus superimposed.

The chromaticities of colours chosen as 'comfortable' during Experiment 2 (Chapter 3) were added to the current results to further examine this difference. Again the colours chosen by the control group were significantly closer to the Planckian locus $t(31.59) = 2.35$, $p = 0.025$ (see Figure 4:5). Again, the t-value reported here does not assume equality of variance.
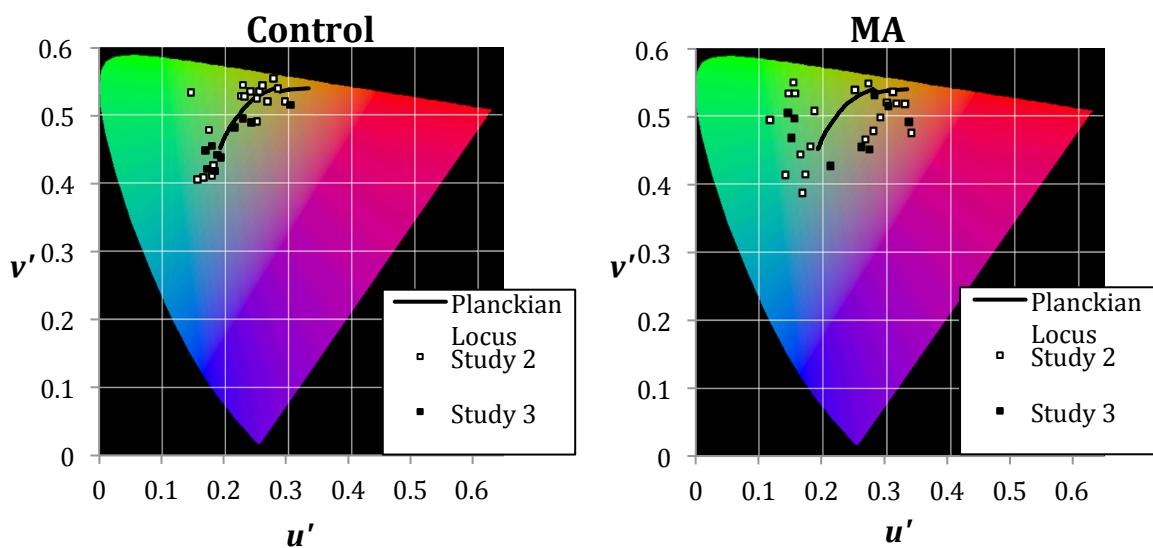
Figure 4:5: CIE 1976 UCS diagrams showing the chromaticities of the colours chosen as 'comfortable' for Study 2 and the 'active' lenses of Study 3 with the Planckian locus superimposed.

The chromaticities of the various forms of indoor lighting lie close to the Planckian locus. It can be hypothesized that individuals in the control group chose 'active' lenses of colour similar to the lighting they experience every day.

The effect of duration of illness (years) on contrast threshold was examined using Spearman's correlations. No significant correlations were found in the field affected by aura for the 'active' and grey lenses respectively: r_s = -0.234, N = 9, p = 0.544 and: r_s = -0.184, N = 9, p = 0.635. No significant correlations were found in the unaffected field for the 'active' and grey lenses: r_s = 0.494, N = 9, p = 0.177 and: r_s = 0.477, N = 9, p = 0.194. Time since last attack (days) was examined in the same manner and no significant correlations were found in the affected field: r_s = -0.565, N = 9, p = 0.113 and: r_s = 0.236, N = 9, p = 0.540 or the unaffected field: r_s = -0.152, N = 9, p = 0.696 and: r_s = -0.211, N = 9, p = 0.586.

The number of illusions that participants experienced whilst viewing pattern 2 (mid-range spatial frequency) of the Pattern Glare Test (i.O.O Sales Limited, London, England) was analysed. Participants in the MA group experienced an average of 4.4 visual illusions whilst viewing pattern 2, whereas control participants experienced an average of 2 illusions. An independent samples t-test revealed a significant difference in the number of illusions experienced by each group, $t(17)$ = 3.46, p = 0.003. Participants in the MA group viewed fewer patterns during the contrast threshold for discomfort assessment. The average contrast threshold for discomfort for the MA group was 63.6 and 68.9 for the control group.

The relationship between contrast discrimination threshold and threshold for discomfort was examined using Pearson's correlation. No significant correlations were found for the MA group in the field affected by aura for the coloured lens, r = -0.406, N = 9, p = 0.278 or the grey lens conditions, r = -0.425, N = 9, p = 0.254. Similarly, no significant correlations

were found in the field unaffected by aura for the coloured lens, r = -0.597, N = 9, p = 0.089, or grey lens conditions, r = -0.432, N = 9, p = 0.245.

All participants had contrast sensitivity scores within one standard deviation of the age-related norms of the Cambridge Low Contrast Gratings. The remaining participants had normal contrast sensitivity scores based on the normative values.

4.4   Discussion

Coloured filters raised the contrast discrimination threshold for individuals in the migraine group but not controls. In Chapter 2, individuals who experienced a consistently unilateral visual migraine aura were shown to have better contrast discrimination in the field affected by aura. There was a trend of lower contrast discrimination thresholds in the field affected by aura but this was not significant. Coloured 'active' lenses significantly raised the contrast threshold in the affected and unaffected field of individuals in the MA group. Concerning the mechanism of coloured filters, it seems plausible that the neural activity is redistributed so as to avoid hyperexcitable regions (Wilkins, Huang, et al., 2007). This hypothesis may explain why coloured filters selectively raised discrimination threshold for those in the migraine group. Participants in the control group chose as comfortable, colours of low saturation close to the Planckian locus. As the Planckian locus provides the basis for the colour temperature of various forms of indoor lighting, it is likely that controls selected a familiar colour.

Individuals who experience migraine demonstrate impairment of contrast sensitivity (Shepherd, 2000), and detection of low contrast letter targets (Chronicle et al., 1995), but are sensitive to flicker at high contrast (Karanovic et al., 2011). A reduction of contrast discrimination threshold in the field affected by visual aura may reflect heightened sensitivity caused by hyperexcitability of cortical neurons.

Reggia & Montgomery (1996) used a computational model of cortical spreading depression to show that during a wave of biochemical changes, the neuronal activity broke up into

small patches of excitatory activity on the leading edge of the spreading depression. When the patterns of excitation were mapped onto the visual fields, the model showed that the patterns resembled those of migraine aura. In this experiment, cortical spreading depression was reliably induced by elevated levels of extracellular potassium. Grafstein (1956) administered potassium chloride to the isolated cortex of cats and found that the neuronal excitation that precedes cortical spreading depression resulted in a discharge of potassium ions. A consistently unilateral migraine aura would indicate a specific region of the cortex that repeatedly initiates the aura. One might speculate that this region may represent an area of hyperexcitability that is susceptible to cortical spreading depression triggered by noxious stimuli. An already raised level of extracellular potassium in a hyperexcitable region would raise the probability of initiating cortical spreading depression. Unilateral visual aura is likely to originate in a brain region with a retinotopic representation that is continuous across the horizontal midline. This is the case in areas V1 (Holmes & Lister, 1916) and V3A (Tootell et al., 1997). The cut-off of a unilateral aura at the vertical meridian indicates a post-chiasmal origin (Wilkinson, 2004).

The hypothesis of Wilkins et al. (2007) would suggest coloured filters act selectively on areas of neural excitation and redistribute the activity to more stable cortical regions. It is not yet clear why altering the pattern of neuronal excitation with a specific colour has the effect of reducing the discomfort associated with migraine. Coloured filters may help normalise hyperexcitability of the visual cortex, thus reducing discomfort and hypersensitivity to visual stimuli. This may help explain why coloured lenses made performance worse in the current study.

Chapter 5 Physiological correlates of Visual Discomfort

Abstract

The visual evoked potential and haemodynamic response were measured in two groups of participants, MA and controls, while they viewed uncomfortable grating patterns. The amplitude of the VEP increased with contrast but there were no between-group differences. Three individuals in the MA group experienced unilateral migraine pain and the amplitude and latency of the N2 component of the VEP was smaller in the hemisphere affected by pain. No significant group or contrast differences were found for the amplitude or offset of the NIRS response. This study was exploratory and a larger sample size will be necessary to further investigate the effects of lateralised migraine pain on cortical activation.

5.1   Introduction

As discussed in Chapter 1, individuals with migraine are unusually sensitive to light and to grating patterns, which can cause discomfort (Wilkins et al., 1984). Due to differences in the nature of symptoms, attack triggers and genetic components, it has been suggested that migraine with (MA) and migraine without aura (MO) are distinct clinical disorders (Russell et al., 1996, 2002). Individuals who experience MA report more illusions and discomfort, than those with MO or a control group, when observing a grating pattern (Khalil, 1991). Individuals who experience MA are particularly likely to demonstrate an abnormal neuronal and metabolic response to uncomfortable grating patterns.

The haemodynamic response, measured by NIRS, reflects the change in blood flow in response to a stimulus. An increase in the level of oxygen to the brain is necessary to meet the metabolic demand of a neuronal response. The relationship between neuronal excitation and the haemodynamic response (measured using fMRI BOLD) has been investigated and is thought to be related to local field potentials (Logothetis, Pauis, Augath, Trinath, & Oeltermann, 2001). Local field potentials are characterised by stimulus-induced and stimulus-locked fast oscillations in the brain. The haemodynamic response can therefore be used as a correlate of neuronal activation and can be measured using NIRS. The NIRS response is measured using infrared light in the range 700-900nm, which can pass through the tissue of the scalp and the skull to the cortex of the brain. The light that is reflected is indicative of the colour of the cortex. Oxygenated and deoxygenated blood are of slightly different spectral reflectance and have different absorbencies of the infrared

light. It is therefore possible to measure the relative proportions of both oxygenated and deoxygenated haemoglobin using NIRS.

 The oxygenated component of the haemodynamic response has been shown to be of increased amplitude when uncomfortable grating patterns are viewed, which reflects a heightened neuronal response (Haigh, Cooper, & Wilkins, 2015). The haemodynamic response has been investigated previously in individuals with migraine. Coutts, Cooper, Elwell, and Wilkins (2012) measured the latency and amplitude of the haemodynamic response in individuals with migraine and controls. They showed that the peak of the haemodynamic response to uncomfortable checkerboard patterns occurred on average 3s earlier in individuals with migraine. The latency of the response is affected by the time it takes to rise and to fall and the results of this study indicate the response lasted a shorter time and began to decrease earlier in the migraine group. Haigh, Barningham, et al. (2013) presented coloured grating patterns that had bars of two alternating colours. The haemodynamic response increased as the colour difference between the bars was increased. Ratings of discomfort also increased with chromaticity separation. The authors hypothesise that visual discomfort is a protective mechanism to reduce a sustained metabolic response in the visual cortex (Haigh, Barningham, et al., 2013).

Pattern reversal visual evoked potentials (PVEP's) of abnormally high amplitude have been demonstrated in individuals with MA; when compared to controls, MO and control groups did not differ (Shibata et al., 1997a). Within 10 days of a migraine attack, PVEP's are increased significantly in individuals with MA and those with migraine aura without

headache but the amplitude decreases over time (Shibata, Osawa, & Iwata, 1998). The authors also found low amplitude PVEP's 21-30 days after an attack, which are likely to precede an oncoming attack, lending support to the cortical spreading depression theory of Leão, (1944). Differences in the VEP amplitude of participants with MA are dependent on the spatial frequency and size of a checkerboard pattern (Oelkers et al., 1999). Oelkers et al. (1999) describe a prolonged or delayed N2 component for the migraine groups at high spatial frequencies. The N2 component of the pattern-reversal VEP has largely been attributed to the magnocellular system (Kubová, Kuba, Spekreijse, & Blakemore, 1995) and should therefore be stimulated by large patterns of low spatial frequency. Oelkers et al. (1999) suggest that the prolonged N2 component observed in migraineurs may be due to an imbalance of the magnocellular and parvocellular pathways in the interictal period. If luminance processing is abnormal in migraine this may lead to greater sensitivity to visual stimuli in the migraine-free period.

In the current study participants with MA and controls viewed patterns of low, mid and high contrast while the haemodynamic response (NIRS) and VEPs were recorded. The amplitude of the haemodynamic response was measured as well as the slope of the onset and offset of the response. The VEP components that were investigated were P1, N2 and the P1N2 peak-peak amplitude. The P1 amplitude would be expected to be greater at high contrasts in the migraine group when compared to controls. If there is indeed an imbalance of magnocellular and parvocellular processing in migraine then a prolonged N2 latency would be expected in the MA group (Oelkers et al., 1999). P1N2 peak-peak amplitude would be expected to increase with contrast in both groups but a larger increase would be expected in the MA group.

5.2   Method

<u>Participants</u>

Participants were 16 controls (7 male, 9 female) and 11 MA (3 male, 8 female) recruited from the student and staff population of the University of Essex. Participants with migraine fulfilled the International Headache Society's ICHD III criteria for migraine with aura. Control participants had never experienced a migraine. The University of Essex ethics committee approved all methods. Participants gave written informed consent.

<u>Stimuli</u>

Stimuli were presented on a LCD Dell monitor (320mm high x 500mm wide) with a resolution of 1050 x 1680pixels and a refresh rate of 60Hz. Achromatic square-wave gratings with a spatial frequency of 3.5cpd, with a Michelson contrast of 5%, 20% or 80%, were presented using ePrime II software; all gratings had a square-wave luminance profile and subtended 14.3° of visual angle. Gratings were presented for 1s in blocks of 8. There was an interval of 1s between gratings and a random interval of 40-50s between blocks during which a grey screen of similar mean luminance of $48cd.m^{-2}$ was presented. Each contrast block of 8 presentations was repeated 6 times. A central fixation-cross appeared 1s before stimulus onset. The stimuli in each block had the same contrast but the presentation of the three contrasts was randomised and distributed evenly throughout the experiment.

Apparatus

The haemodynamic response was measured using an 8-channel NIRS system (Oxymon Mk II Artinis Medical Systems, BV Zetten, Netherlands). A photodiode against the screen was used as a trigger system for NIRS. Two frontal channels were recorded, covering F1 and F2 of the 10-20 system of electrode placement to check the responses to stimuli were purely visual. The signal from these channels was generally very low. Two transmitters were positioned 30mm behind the frontal receivers. Six posterior channels were recorded. Two receivers were placed 20mm above the inion, 30mm either side of the midline. One transmitter was placed vertically 30mm above each receiver. Two more transmitters were placed laterally around each receiver at 40° intervals with a radius of 30mm. The three posterior transmitters surrounded O1 and O2 on the 10/20 system of electrode placements (see Figure 5:1).
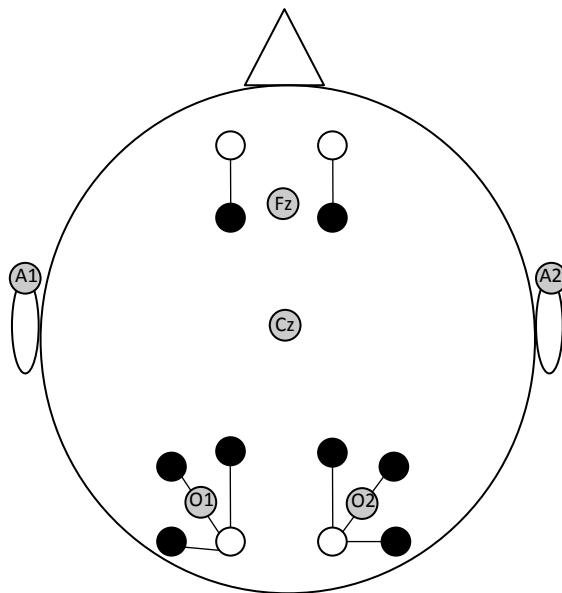
Figure 5:1: The montage for NIRS optode position. The black circles represent the transmitters and the white circles the receivers. Grey circles represent EEG electrodes according to the 10/20 system of electrode placement.

A Neuroscan SynAmps system (Compumedics USA Inc., Charlotte NC, USA) running Scan 4.5 software (Compumedics, Melbourne, Australia) was used to record VEP's. Electrodes were applied to the cap in the following 10/20 system positions: Fz, Cz, O1, O2, A1 and A2. Electrodes were grounded at Fz. Impedances were lowered to below 10kΩ before data acquisition. All data were continuously sampled at 1000Hz with a bandpass filter of 0.1-200Hz.

Procedure

Participants completed a questionnaire regarding their experience of headache and the following tests: Ishihara Tests For Colour-Blindness 38 plates edition (Kanehara Shuppan Co., Ltd, Tokyo, Japan), Pattern Glare Test (i.O.O Sales, London, England) and contrast threshold for discomfort (described in Chapter 3).

Participants viewed the presentation screen binocularly in a dark room, at a distance of 0.8m. Individuals were asked to inform the researcher should any discomfort be experienced. Electrodes were then applied to the cap already holding the NIRS optodes.

Data analysis-NIRS

A differential path length factor of 6.26 was assumed for the calculation of changes in oxygenated and deoxygenated haemoglobin concentration in μmolar units (Duncan et al., 1996). The differential path length factor relates the separation between the source of light and the detector (transmitter and receiver) to the average path length that light travels between the transmitter and receiver after it has passed through the soft tissue and the scull. Deoxygenated haemoglobin (Hhb) responses were smaller than the oxygenated haemoglobin (HbO_2) and were not analysed (Haigh, Barningham, et al., 2013). The detrend function in MATLAB was applied to the data. The raw signal was filtered with a running median over 6s from the time of stimulus onset.

The haemodynamic response amplitude was measured as the difference between the average of the signal over the 10s up to stimulus onset (baseline) and the average during the last 10s of stimulus presentation. Some optode channels were excluded because of a poor signal, often caused by hair obscuring the infrared light. Channels were accepted for analysis if the average HbO_2 amplitude during stimulus presentation was greater than 1 SD of the signal over the baseline 10s prior to stimulus presentation. The shape of the haemodynamic response was measured using the rise of the response at stimulus onset and the fall of the response at stimulus offset. The method for calculating the amplitude, 'ascent' and 'descent' of the haemodynamic response was the same as that described by (Haigh et al., 2015).

The slope of the 'ascent' and the slope of the 'descent' of the haemodynamic response were calculated by taking the smoothed response and subtracting the running average signal over 6s from the running average signal for the preceding 6s. The maximum difference during stimulus onset was used as the measure of the ascent of the response and the minimum difference after stimulus offset was used as the measure of the descent of the response.

5.3   Results

Ten participants in the control group had at least 1 NIRS channel that met the criterion and the average number of acceptable channels for this group was 3.8. Ten participants in the MA group had at least 1 channel that met the criterion and the average number of acceptable channels for this group was 4.9 (see Table 5:1 for participant details). The signal was stronger in posterior than frontal channels, and the effects of visual stimuli were analysed only for the posterior channels (Haigh, Barningham, et al., 2013; Le et al., 2017). The HbO$_2$ amplitude was obtained for each acceptable channel and was separate for each contrast condition (see Table 5:2 and Table 5:3).

Table 5:1: Participant information.

	Control	**MA**
N	10 (3 male, 7 female)	10 (3 male, 7 female)
Mean age (years)	20.7	34
Age Range	18-28	20-56
Using refractive correction	5	5
Mean days since last attack (SD)	N/A	32.1 (32.0)
Mean (SD) duration of disease (years)	N/A	17.5 (10.6)
Lateralised migraine pain (hemisphere)	N/A	2 Left, 1 Right
Lateralised migraine aura (field)	N/A	1 Left, 3 Right

Table 5:2: Average HbO$_2$ amplitude for each level of contrast.

Group	HbO$_2$ amplitude for each level of contrast (μmolar)		
	5%	20%	80%
C	1.06	0.10	0.94
C	-0.01	0.21	0.29
C	0.40	0.58	0.28
C	0.66	0.12	0.06
C	1.73	0.41	-0.25
C	0.82	0.49	0.52
C	0.16	0.69	0.55
C	0.35	0.37	0.26
C	0.36	0.78	0.59
C	0.09	0.56	0.41
MA	0.74	0.69	0.79
MA	0.45	0.11	0.66
MA	-0.004	0.99	0.49
MA	0.91	0.54	-0.54
MA	0.39	1.01	-0.06
MA	0.40	0.02	0.18
MA	-0.05	0.63	0.22
MA	0.55	0.73	0.84
MA	0.21	0.13	0.19
MA	0.37	0.37	0.48

Table 5:3: Mean (SD) HbO$_2$ amplitude (μmolar) for both participant groups at each level of contrast.

	Contrast		
Group	**5%**	**20%**	**80%**
Control	0.56 (0.53)	0.43 (0.23)	0.37 (0.32)
MA	0.40 (0.30)	0.52 (0.36)	0.33 (0.42)

A 3x2 mixed ANOVA with contrast as the within-subjects factor (see Table 5:2 and Table

5:3) revealed that grating patterns of high contrast did not evoke a significantly larger

haemodynamic response $F(2,36) = 0.751$, $p = 0.479$, $\eta^2 = 0.039$ (see Figure 5:2). The interaction between contrast and group was not significant $F(2,36) = 0.524$, $p = 0.597$, $\eta^2 = 0.027$ and neither was the main effect of group $F(1,18) = 0.217$, $p = 0.647$, $\eta^2 = 0.012$.
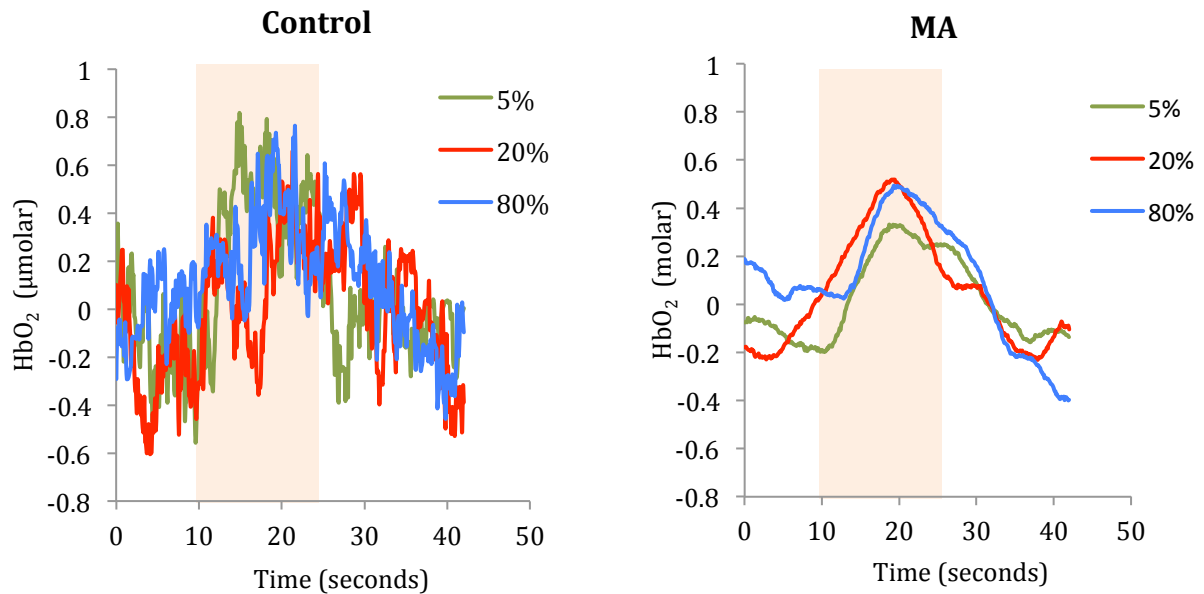
Figure 5:2: The oxyhaemodynamic response to the grating patterns. The shaded area represents presentation of the stimulus.

Upon inspection of the control group data, the noise on the signal was related to changes in the experimenter's use of the NIRS equipment. Eight participants in the control group were tested before testing began for the migraine group. After the initial 8 control participants were tested, the NIRS cap was made more tightly fitting using bandages, which is reflected in the lower noise level on the migraine group signal. The responses for the 8 control participants tested before the technical change, and the two participants after, are plotted in Figure 5:3. Because of the technical change, the control participants data were excluded and a second repeated measures ANOVA with contrast as the within-subjects factor was conducted with the MA group data, $F(2,18) = 0.704$, $p = 0.508$. The main effect of contrast was not significant in the ANOVA conducted above, which indicates that even in the

migraine group, after the technical change, the amplitude of the response did not significantly increase with contrast. For this reason no further control data was collected.
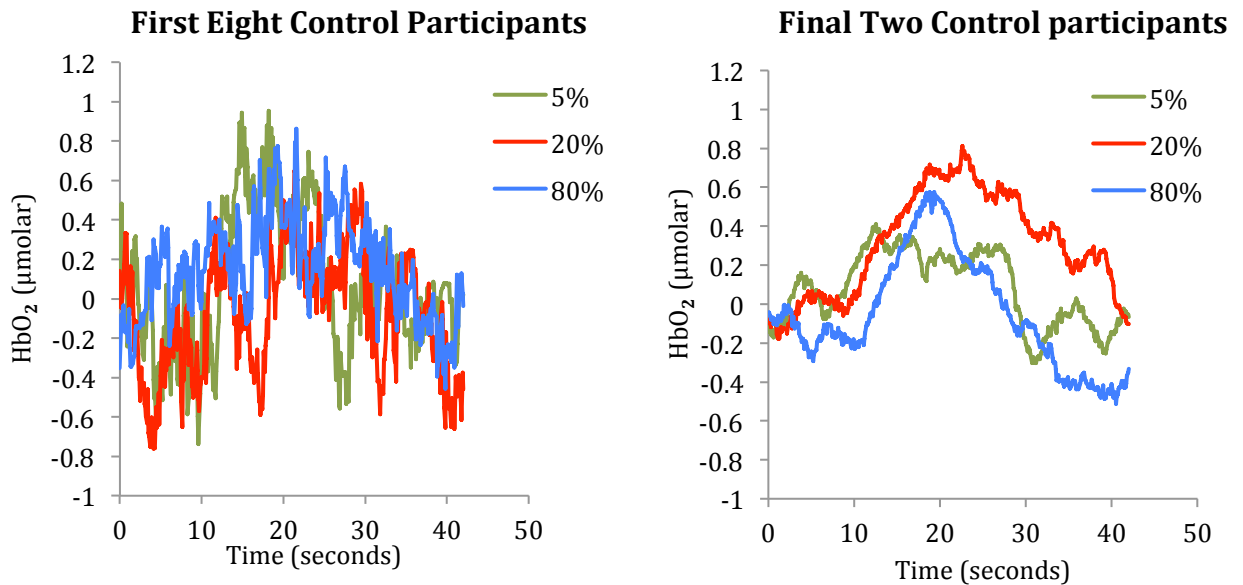
Figure 5:3: The control group split according to when the technical change occurred.

The 'ascent' of the haemodynamic response after stimulus onset was also examined using repeated measures ANOVA for the MA group only. The main effect of contrast level was not significant, $F(2,18) = 0.485$, $p = 0.623$, which indicates that the ascent of the haemodynamic response did not vary in shape with contrast for the MA group.

A second repeated measures ANOVA was conducted for the MA group with the 'descent' of the haemodynamic response as a main effect. The slope of the fall in HbO_2 did not differ significantly with contrast level $F(2,18) = 0.189$, $p = 0.829$. The 'descent' of the haemodynamic response did not vary in shape with contrast for the MA group.

The peak to trough amplitude of the NIRS response was analysed for the migraine group. The post stimulus undershoot was calculated as the period 25s after stimulus onset for a period of 10s. The peak to trough amplitude was then calculated by subtracting the post stimulus undershoot from the amplitude of the NIRS response (6s after stimulus onset for a period of 10s). A repeated measures ANOVA revealed no significant effect of contrast on the peak to trough amplitude, $F(2,18) = 0.590$, $p = 0.565$.

Data analysis-EEG

EEG was recorded from two electrodes: O1 and O2, referenced to Cz. During data analysis, electrodes were re-referenced to the average of A1 and A2. Automated artefact rejection was applied with exclusion parameters set at ±75mV. The average responses for each contrast condition were visually inspected for peak latencies to ensure that N2 and P1 had been identified. A P1 component was identified as having a latency between 140-240ms and an N2 component was identified as between 180-280ms.

Results

Fourteen participants in the control group provided data for analysis. Two participants were excluded because of a poor quality EEG recording. Eleven participants in the MA group provided data for analysis (see Table 5:4).

Table 5:4: Participant information.

	Control	MA
N	14 (5 male, 9 female)	11 (3 male, 8 female)
Mean age (years)	20.8	33.6
Age Range	18-28	20-56
Using refractive correction	7	5
Days since last attack (SD)	N/A	30.5 (30.8)
Mean (SD) duration of disease (years)	N/A	18.2 (10.3)
Lateralised migraine pain (hemisphere)	N/A	2 Left, 1 Right
Lateralised migraine aura (visual field)	N/A	1 Left, 4 Right

The P1N2 peak-peak amplitude difference was calculated as the amplitude of N2-P1 for each hemisphere and contrast condition (see Table 5:5). The average amplitude was then calculated for each level of contrast. These data were analysed using a mixed effects model, with peak-peak amplitude as a fixed covariate, contrast and group as fixed factors, and random intercepts and random slopes over participant for amplitude. Peak-peak amplitude increased with contrast, $t(1, 56.1) = 4.05$, $p<0.001$. There was no significant effect of group, $t(1, 48) = 1.39$, $p = 0.170$ and no interaction between contrast and group, $t(1, 56.1) = 0.95$, $p = 0.347$.

Table 5:5: Mean (SD) peak-to-peak difference for each level of contrast.

Pattern contrast	Control	MA
5%	5.90 (1.31)	5.38 (1.77)
20%	8.67 (2.99)	7.89 (2.11)
80%	8.77 (5.29)	9.56 (2.79)

The latency and amplitude of P1 and N2 components were examined using a 3x2x2 mixed ANOVA, separately, to ascertain any contrast, group or hemisphere differences.

The latency of P1 revealed no significant effect of contrast, $F(2, 46) = 1.309$, $p = 0.280$, $\eta^2 = 0.05$, and no significant interaction between contrast and group, $F(2, 46) = 0.132$, $p = 0.877$, $\eta^2 = 0.0005$. The main effect of hemisphere was not significant, $F(1, 23) = 1.080$, $p = 0.309$, $\eta^2 = 0.05$, nor was the interaction between hemisphere and group, $F(1, 23) = 0.005$, $p = 0.946$, $\eta^2 = 0.00002$. The interaction between contrast and hemisphere was not significant, $F(2, 46) = 1.836$, $p = 0.171$, $\eta^2 = 0.07$, neither was the interaction between contrast, hemisphere and group, $F(2, 46) = 0.000$, $p = 1.000$, $\eta^2 = 0.000001$. The main effect of group,

although not significant, $F(1, 23) = 3.056$, $p = 0.094$, $\eta^2 = 0.12$ suggested the P1 component was slower in the control group.

A significant main effect of contrast was found for the amplitude of the P1 component, $F(2, 46) = 47.03$, $p < 0.001$, $\eta^2 = 0.67$. P1 amplitude was lower for both groups for the grating of 5% contrast. The main effect of hemisphere was not significant, $F(1, 23) = 0.894$, $p = 0.354$, $\eta^2 = 0.03$, neither was participant group, $F(1, 23) = 0.164$, $p = 0.690$, $\eta^2 = 0.0007$. A quadratic trend that approached significance was found between level of contrast, hemisphere and group, $F(1, 23) = 2.971$, $p = 0.098$.

A significant main effect of contrast was also found for the latency of N2, $F(2, 46) = 4.702$, $p = 0.014$, $\eta^2 = 0.16$. There was a significant interaction between hemisphere and group, $F(1, 23) = 9.517$, $p = 0.005$, $\eta^2 = 0.09$. A quadratic trend that approached significance was found between contrast and group, $F(1, 23) = 3.071$, $p = 0.093$ and between contrast and hemisphere, $F(1, 23) = 3.499$, $p = 0.074$.

A significant main effect of hemisphere was found for the amplitude of N2, $F(1, 23) = 11.3$, $p = 0.003$, $\eta^2 = 0.32$. There was a significant interaction between contrast and hemisphere, $F(2, 46) = 7.32$, $p = 0.002$, $\eta^2 = 0.24$.

Three participants in the MA group experienced unilateral migraine pain: 2 on the left side of the head and 1 on the right. A reduction in the amplitude of the VEP in the hemisphere affected by unilateral pain has been shown previously (Tagliati, Sabbadini, Bernardi, & Silvestrini, 1995; Tsounis, Milonas, & Gilliam, 1993). Unilateral pain may reflect lateralised oligemia in the brain (Lance, 1993), which may result in a reduction of the VEP response in the affected hemisphere. For this reason unilateral pain rather than unilateral aura was investigated in the current study. Asymmetry of the VEP was investigated in the MA and control groups to establish whether this effect is unique to individuals with unilateral migraine pain or whether an asymmetry of the evoked potential exists in other groups. As discussed previously, a significant effect of hemisphere was found for the amplitude of N2 and a significant interaction was obtained between hemisphere and group for the latency of N2. The mean latency of N2 decreased with contrast in both hemispheres for the MA group but the latency of N2 decreased in the control group then increased for the patterns of 80% contrast. The amplitude and latency of the N2 component was plotted individually for the 3 participants who experienced unilateral migraine pain (see Figure 5:4).

The absolute difference between the amplitude of the left and right hemispheres was calculated for the MA group and controls in order to examine any differences in asymmetry. The average values for each level of contrast are presented in Table 5:6. Independent samples t-tests were conducted separately for each level of contrast but no significant differences were found between groups.

Table 5:6: Mean absolute difference between the amplitude of the left and right hemisphere for the N2 component.

Group	Contrast		
	5%	**20%**	**80%**
Control	1.31	2.06	3.09
MA	1.49	1.67	3.59

The absolute difference was calculated for the latency of the N2 component in the left and right hemispheres for the two groups (see Table 5:7). Again, independent-samples t-tests were conducted separately for each level of contrast but no significant differences were found.

Table 5:7: Mean absolute difference between the left and right hemisphere for the latency of the N2 component.

Group	Contrast		
	5%	**20%**	**80%**
Control	20.0	9.86	12.0
MA	11.45	9.27	17.45

No significant effects of asymmetry were found for the latency and amplitude of the N2 component for the MA group or controls. There was a trend for lower amplitude and shorter latency of the N2 component in those individuals who experience lateralised migraine pain but a larger sample will be required to further investigate the effect.

All participants reported the number of visual illusions experienced whilst viewing Pattern 2 of the Pattern Glare Test (i.O.O Sales, London, England). The average (SD) number of illusions for the control group was 2.3 (1.06) and for the MA group 2.9 (1.91). Participants also completed the contrast threshold for discomfort task described in Chapter 3. This result contrasts with previous reports that individuals with migraine are more sensitive to distortions from strong patterns (Harle et al., 2006; Marcus & Soso, 1989; Wilkins et al., 1984). Harle et al. (2006) recruited participants with a formal diagnosis of migraine in accordance with IHS criteria, which may account for some of the discrepancy of results concerning the current study. The average contrast threshold for discomfort for the control group was 71.6% and was 66% for the MA group, $t(25) = 1.21$, $p = 0.238$. A Spearman's correlation was conducted across participant groups to examine whether a lower contrast threshold for discomfort was associated with the experience of more illusions. There was not a significant correlation between contrast threshold for discomfort and the experience of illusions, $r_s = -0.091$, $N = 20$, $p = 0.702$.
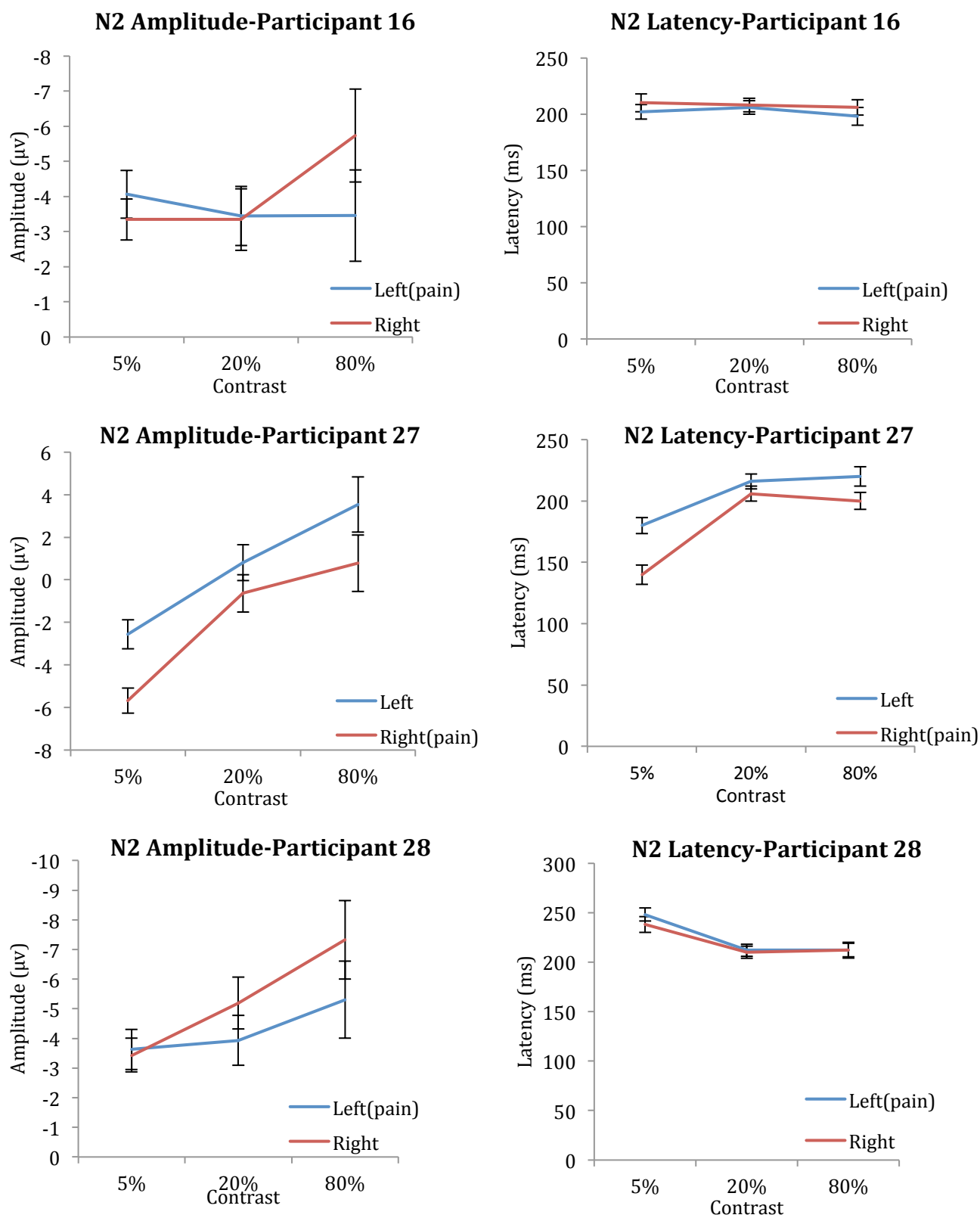
Figure 5:4: Amplitude and latency of N2 for individuals who experienced unilateral migraine pain. Error bars denote 1SE.

5.4   Discussion

The physiological response to striped patterns was measured using NIRS and EEG. The haemodynamic response, measured using NIRS, did not increase with contrast and there were no between-group differences. There were also no differences in the MA group for the slope of the 'onset' and 'offset' of the response. There was a trend for the P1N2 peak-peak amplitude to continue to increase with contrast in the MA group but not controls, but this was not significant. A significant effect of contrast on the amplitude of the P1 component was found for the VEP response. A significant effect of contrast was also found for the latency of the N2 component, but overall there were no significant group differences. Four individuals experienced consistently lateralised migraine pain and the latency and amplitude of the N2 response tended to be smaller in the hemisphere affected by pain. A larger sample of individuals who experience lateralised pain will be needed to draw conclusions as to the mechanism of these effects.

The origin of the P1 component of the VEP has been attributed to the parvocellular pathway and the N2 component has been linked to the magnocellular pathway (Kubová et al., 1995). Both the magnocellular and parvocellular pathways are thought to be affected by migraine (Diener et al., 1989). It would therefore be expected that the amplitude of the P1 component would increase with contrast. If the visual cortex is indeed hyperexcitable in migraine then a P1 component of greater amplitude than controls would be expected for high contrast stimuli. The patterns presented in the current experiment may not have activated the magnocellular pathway sufficiently as only mid-range spatial frequency static

patterns were presented. Large patterns of low spatial frequency may help reveal any abnormalities of the magnocellular system in migraine. Grating patterns of mid-range spatial frequency were presented in the current study because these stimuli are known to evoke visual discomfort in individuals who experience migraine.

Asymmetry of the VEP has been reported previously (Shibata, Osawa, & Iwata, 1997b; Tagliati et al., 1995; Tsounis et al., 1993). Tagliati et al. (1995) found no overall differences in VEP amplitude (N70, P100) or latency between individuals with MA, those with MO and controls. Individuals who experienced visual aura showed a marked reduction in VEP amplitude in the hemisphere ipsilateral to the aura. The participants in that study also underwent perimetry, which did not identify any visual field asymmetries associated with the aura. Tsounis et al. (1993) measured the latency of the P100 component in individuals with MA and those with MO who experienced lateralised migraine pain. The P100 latency was significantly shorter in the hemisphere affected by the pain in a subgroup of participants who experienced constantly lateralised pain during attacks of migraine. Nyrke, Kangasniemi, and Lang (1990) reported strong asymmetry of steady-state VEP's in participants with MA but lateralisation of pain or aura was not clear enough for comparison. A reduction of regional cerebral blood flow (rCBF) has been shown during the early phase of migraine but the reduction is not of sufficient magnitude to cause the symptoms of migraine (Olesen et al., 1981). The reduction of rCBF is usually present on the same side as a unilateral headache and migraine aura (Olesen et al., 1990). A local reduction of rCBF (hypoperfusion) preceded the headache in all of the participants in that study. The relationship between lateralised migraine pain and visual aura is still unclear. One hypothesis proposed to explain the mechanism of unilateral pain is instability of

neuronal control of cerebral vascular supply, which would predispose an individual to episodes of lateralised cortical oligemia (Lance, 1993). Asymmetry of the rCBF has also been investigated in the inter-ictal period in individuals with migraine. Asymmetry of rCBF has been shown to be significantly greater in individuals with MA when compared to controls (Levine, Welch, Ewing, & Robertson, 1987). Ramadan, Levine, & Welch (1991) also found interictal CBF asymmetries in individuals with MA. The posterior regions had more significant flow asymmetries, which may reflect the origin of the aura symptoms.

The results of the current study suggest that the P1N2 peak-peak amplitude continues to increase with contrast in migraine and to stabilise in controls but this will require further investigation. For those individuals who experience consistently unilateral migraine pain, there is a tendency for the latency and amplitude of the N2 component to be lower in the hemisphere affected by pain. This finding is in agreement with the previous literature and a large sample of individuals who experience consistently lateralised migraine pain will be required for conclusive results. The current study sampled only individuals who experience MA, however the effect of lateralised pain on the VEP appears to be consistent irrespective of migraine diagnosis (MA or MO) (Tsounis et al., 1993).

Chapter 6 The use of Coloured Filters in Schools

Abstract

Children who experience visual discomfort often report an improvement in their symptoms when wearing glasses with lenses of individually selected colour. Twenty-two participants aged 9-30 who routinely used coloured overlays to read, underwent a standard colorimetry test to identify a colour of light that reduced perceptual distortion and improved comfort. This colour was reproduced under conventional white light using coloured lenses (active lenses). A second set of lenses with CIE 1976 UCS chromaticity differing by approximately 0.06 were identified using a computer algorithm and were as near as possible to the colour of the participant's overlay (placebo lenses). During a separate testing session 7 days after the colorimetry assessment, participants were given the Wilkins Rate of Reading Test whilst wearing each set of lenses. The number of words read whilst wearing the 'active' and 'placebo' lenses did not differ significantly. An assessment of the suitability of these participants to use coloured filters was not conducted by the researchers. The participants in this study may not have demonstrated a significant increase in an assessment of reading speed with overlays; therefore a benefit from the use of precision spectral filters would not be expected.

6.1   Introduction

Reading speed can be affected by many factors, including the semantic content and syntactic complexity of the words. Reading difficulties are often attributed to these factors, which can mask the contribution of visual distortions and discomfort from text. As was shown in Chapter 1, visual stress is a condition characterized by perceptual distortions from strong stimuli, usually patterns of striped lines, and the distortions can be alleviated with the use of a coloured filter.

Printed words can cause glare and discomfort because the successive vertical letter strokes, and lines of text, resemble a striped pattern (Wilkins et al., 2007). Olive Meares (1980) described the problematic visual effects, caused by text, on children learning to read. Meares (1980) identified the maximum contrast black on white printed text as impeding progress in children who experienced anomalous visual distortions. Classrooms are generally over lit with a combination of fluorescent lighting and natural daylight and high luminance levels can cause glare when reading (Winterbottom & Wilkins, 2009). Conlon, Lovegrove, Chekaluk, & Pattison, Philippa (1999) showed that participants who reported high visual discomfort scores on a Rasch scale rated a pattern of letters as more perceptually distorted and unpleasant than individuals who reported low discomfort scores. Reading comprehension has been shown to be impaired when the text is distorted (Dickinson & Rabbitt, 1991). Children make more reading errors on smaller texts; this is particularly the case for young children suggesting that reading materials use text that is

too small (Hughes & Wilkins, 2000). This may help explain why reading presents difficulty to some individuals of average intelligence.

As described in Chapter 1, a test of reading speed called the Wilkins Rate of Reading Test (WRRT) (i.O.O Marketing, London, England) was developed to assess the influence of visual discomfort, rather than comprehension, on reading speed (Wilkins et al., 1996). The test consists of closely spaced, random words, so as not to provide any semantic cues to the participant. The WRRT is commonly used as an adjunct to the diagnosis of visual stress and the assessment of suitability for coloured filters.

Scotopic Sensitivity Syndrome, similar to visual stress, has been described as the distortions experienced by some individuals when reading and is more common in individuals who experience dyslexia (Irlen, 1997). Kriss & Evans (2005) found a significant improvement in reading speed in dyslexic participants who chose a coloured overlay. Historically, one of the accepted diagnostic criteria for visual stress is a >5% increase in reading speed for the WRRT with the use of an overlay. Of the participants in Kriss & Evans (2005) study, 47% of the dyslexic group met the above criterion, as did 25% of the randomly selected control group. The criterion appears fairly easy to meet, which indicates a need for more stringent diagnostic criteria. Kriss & Evans (2005) were the first to suggest that a 5% increase is reading speed is not a difficult criterion to meet and that strict guidelines are necessary. Dyslexia and visual stress are distinct clinical disorders, but combined, the impact of the conditions on reading ability may explain the improved response of dyslexic individuals with the use of coloured filters (Singleton & Trotter, 2005).

There exists an overlap between the symptoms of visual stress and those of specific learning difficulties, such as dyslexia. Diagnostic criteria, specifically for visual stress, are used when the contribution of learning difficulties and optometric problems has already been established. A recent Delphi study conducted by Evans, Allen, & Wilkins (2017) established the symptoms and signs of visual stress that best predict the patients who will go on to use coloured filters (see Table 6:1). An increase in reading speed of ≥15% with the use of an overlay is now necessary to meet the diagnostic criteria for visual stress (Evans et al., 2017; Wilkins et al., 2016).

Table 6:1: Delphi diagnostic indicators of visual stress reproduced from Evans *et al.* (2017).

At least three of the following six typical symptoms:

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1. Words move

2. Words merge

3. Patterns or shadows in text (e.g. 'rivers')

4. Text seems to stand out in 3-D above the page

5. Words or letters fade or darken

6. Discomfort with certain artificial lights and flicker

And

At least two of the following three signs from investigations:

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1. Voluntary unprompted use of an overlay for 3 months or more

2. Overlay improves performance on the WRRT by ≥15%

3. A pattern glare test result of >3 distortions for the mid-range frequency grating

---

Several systems for the prescription of coloured filters have been developed and a small body of research has compared their efficacy. The effect of the Intuitive overlays (i.O.O Marketing, London, England) on reading speed was compared with that of the Crossbow Reading Rulers (Crossbow Education Ltd., Stafford, England) (Smith & Wilkins, 2007). The Crossbow Reading Rulers are coloured sheets of plastic, smaller than overlays, which only cover approximately four lines of text at a time. In that study the Intuitive overlays increased the reading speed of individuals with visual stress, whereas the Crossbow Reading Rulers did not. Colour specificity may need to be greater than that afforded by the 5 colours then available in the Crossbow system. The Irlen system for prescribing coloured overlays has also been investigated under double-masked conditions (Ritchie, Della Sala, & McIntosh, 2011). In this study, children of poor reading ability and those with a diagnosis of Irlen syndrome (scotopic sensitivity syndrome), completed the WRRT under three masked conditions: an overlay of prescribed colour, an overlay of non-prescribed colour and no overlay. No improvement of reading speed was found with the Irlen overlays. A wide choice of coloured overlays are available for schools that wish to provide them to students. Coloured overlays, generally, are a cost-effective way of helping students with reading problems and this may lead to over-use in schools. It is likely that only small minorities of students for whom overlays are provided receive a benefit. This raises important ethical considerations when prescribing coloured overlays. Griffiths, Taylor, Henderson, and Barrett (2016) conducted a systematic review of the literature regarding the use of coloured filters. The authors conclude that reported benefits from the use of coloured filters are the result of placebo, Hawthorne and novelty effects. Elliott (2016) reviewed the ethical implications of providing a placebo treatment. The author suggests that future studies into the efficacy of coloured lenses should openly acknowledge that an

improvement in symptoms may be the result of a placebo effect and to investigate whether this influences the results.

Overlays and precision spectral filters are likely to differ in colour due to colour adaptation when spectral filters are worn (Lightstone, Lightstone & Wilkins, 1999). Participants may expect to benefit from the set of lenses most similar to their overlay colour, thus maintaining the double-mask. Wilkins et al. (1994) suggest the improvement of symptoms with the use of 'active' lenses could be better observed if the colour difference between 'active' and 'placebo' was increased. Several days passed between the two stages of testing during the current study. This permitted an increase in colour difference, as participants were less likely to recognise the 'active' lenses as the colour that had been chosen during the first stage of testing. The increase in colour difference permitted the approximate matching of 'placebo' lenses with the individual's overlay but both pairs of experimental lenses were of the same transmission. It would therefore be expected that participants would read faster when wearing the 'active' lenses because reproducing the colour of an individual's overlay as lenses should diminish any perceptual benefit (Lightstone, Lightstone, & Wilkins, 1999).

6.2   Method

Participants

Twenty-two participants (14 female, 8 male, aged 9-30) were recruited from a secondary school in Norfolk. One participant, aged 30, was a parent of one of the children and also used an overlay to read. Selection was based on the school's identification of reading problems and assessment of the need for coloured overlays using the procedure described by Crossbow (Crossbow Education, Stafford, England). Those individuals who had been given a coloured overlay and continued to use it were selected. At the time of first appointment the average age of participants was 14 years 3 months (SD 3 years 9 months). Written consent was obtained from all parents prior to data collection. One participant was excluded from the study due to inconsistency during the colorimetry assessment. The participant could not reliably identify one colour that was of benefit from a small range of colours. Because of this, no follow-up tests were conducted. Twenty-one participants provided data for analysis all of whom had normal colour vision assessed using the Ishihara Tests for Colour-Blindness 38 plates edition (Kanehara Shuppan Co., Ltd., Tokyo, Japan) and the City University Colour Vision Test 3rd Edition (Keeler, Windsor, England). All methods were approved by the University of Essex ethics committee.

Procedure

Participants answered questions regarding their use of coloured overlays and a refractive correction. The Ishihara Tests For Colour-Blindness were completed by all participants (Kanehara Shuppan Co., Ltd., Tokyo, Japan). Participants who made several errors during the Ishihara test were tested again using The City University Colour Vision Test (Keeler, Windsor, England). The Ishihara test does not assess tritanopia but the prevalence of this form of deficit is estimated between 1:13,000 and 1:65,000 individuals (Wright, 1952). The likelihood of an S-cone deficit in one of the participants in this experiment is therefore extremely low.

Participants completed a colorimetry assessment during the first stage of testing. The procedure for colorimetry was the same as that described in Chapter 3.

The second stage of testing was completed 7 days after the first by a different examiner who was unaware of the identity of the lenses. Participants completed the WRRT (i.O.O Sales, London, England) whilst wearing one of two sets of coloured lenses one after the other. The 'active' set of lenses produced the colour identified using the Intuitive Colorimeter. The 'placebo' lenses produced a colour that differed by 0.06 from the 'active' lenses and as similar as possible to the colour of the participant's overlay. 'Active' and 'placebo' lenses were of the same photopic transmission under CIE Type F3 lighting. Both the participant and experimenter conducting the WRRT were unaware of the identity of the lenses. The 'active' and 'placebo' lenses were given a code and presented in random order. Passages of random words A and D were viewed with one set of lenses and passages B and

C with the other (see Appendix C for example text from the WRRT). The letters had an x-height of 1.6mm. The number of words read by the participant in one minute was measured with both sets of lenses.

6.3   Results

The mean (SD) number of words read in one minute for the 'active' and 'placebo' lenses was calculated; 86.62 (27.36), 86.17 (28.15) respectively. A paired-samples t-test revealed no significant difference between the number of words read using the 'active' and 'placebo' lenses, $t(20) = 0.13$, $p = 0.897$. The number of words read whilst wearing the active and placebo lenses were plotted (see Figure 6:1). Points on the line indicate the same number of words were read for the 'active' and 'placebo' condition. For those participants for whom the lenses increased the number of words read by 5 or more, 5 were wearing the 'placebo' lenses and 10 were wearing the 'active' lenses. The Delphi criteria outlined in Table 6:1 state that a 15% increase in reading speed is indicative of a benefit from the use of colour. Using the WRRT this would equate to an increase of 22.5 words per minute. The increase in reading speed did not reach this threshold in any of the participants for whom the 'active' lenses were of benefit and reached the threshold for 3 participants for whom the 'placebo' lenses were of benefit.

WRRT Results
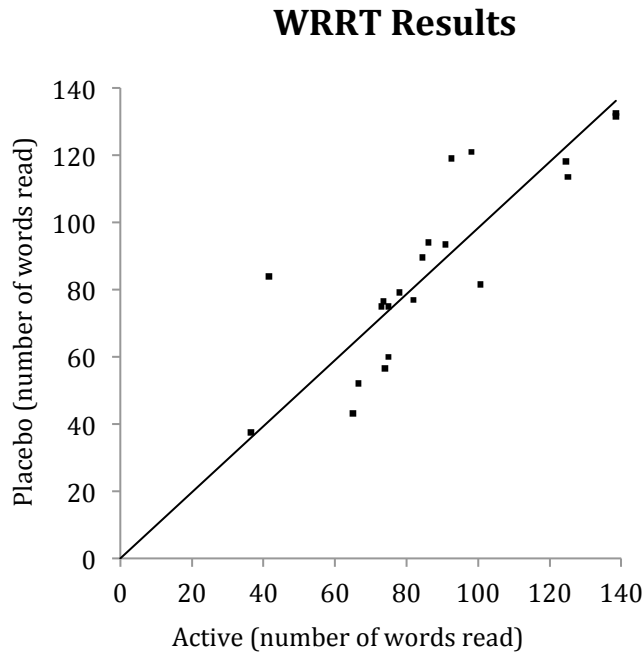
Figure 6:1: Mean number of words read whilst wearing the 'active' and 'placebo' lenses. Each symbol represents a participant and the position is determined by the number of words read when using the 'active' (abscissa) or 'placebo' (ordinate) lenses.

The mean (SD) Pythagorean distance was calculated between the chromaticity of the overlay (see Figure 6:2 and Figure 6:3) and 'active' lenses 0.102 (0.041) and between the overlay and 'placebo' lenses 0.070 (0.029). The mean (SD) Pythagorean distance was also calculated between the 'active' and 'placebo' lenses, 0.104 (0.040). A previous study conducted by Huang *et al* (2011) controlled the chromaticity difference (0.07 in the CIE 1976 UCS diagram) between 'active' and 'placebo' lenses. The difference between the chromaticity of the 'active' and 'placebo' lenses varied as 'placebo' lenses were required to resemble the chromaticity of the participants overlay. A paired samples t-test revealed a significant difference between the Pythagorean distance from the overlay to 'active' and to 'placebo' *t*(20) = 4.15, *p*<0.001. The colour of the 'placebo' lenses was nearer to that of the overlay than the 'active' lenses.
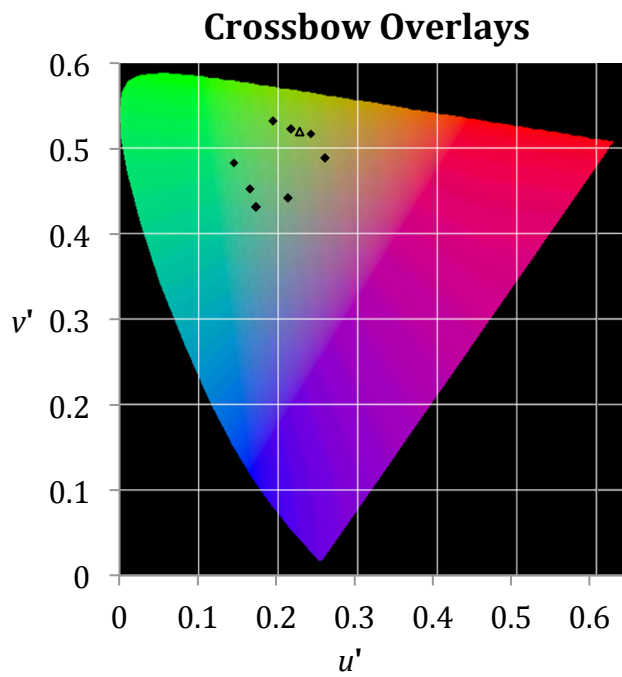
Crossbow Overlays

Figure 6:2: CIE 1976 UCS diagram showing the chromaticities of Crossbow overlays (Crossbow Education Ltd, Stafford, England) used by participants for reading. The triangular point denotes a yellow Intuitive overlay (i.O.O Sales) used by one participant.

Cromaticity of Lenses
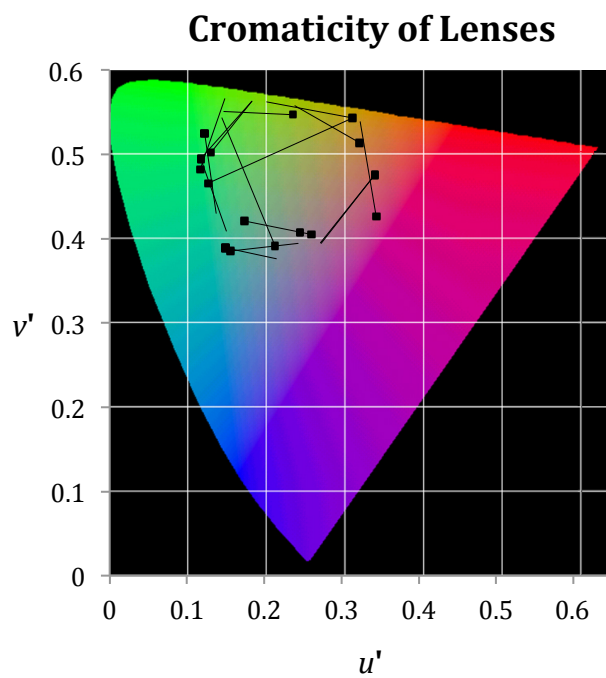
Figure 6:3: CIE 1976 UCS diagram showing the Pythagorean distance between 'active' lenses (black points) connected to 'placebo' via a black line.

The mean (SD) number of perceptual distortions measured using the three colorimeter questions (see the section 3.2.1 of Chapter 3) was 2.33 (0.67). Twenty participants reported that the text hurt their eyes.

6.4   Discussion

In the absence of a baseline measure of reading speed, it is difficult to ascertain whether the participants were gaining a benefit from the everyday use of an overlay. Participants had previously undergone an overlay assessment, which was not conducted by the researchers and the Delphi criteria of diagnostic indicators for visual stress had not yet been published (Evans et al., 2017). The finding that 'placebo' lenses produced a ≥15% increase in reading speed for 3 participants may indicate that the individuals sampled in the current study were not good candidates for overlays. It is difficult to speculate whether participants recognised the colour of the 'placebo' lenses as being similar to that of their overlay. Participants would not have known that the optimal chromaticity of an overlay differs to that of precision tinted lenses. If participants did recognise the colour of the 'placebo' lenses this may have produced a change in motivation and a belief in the effectiveness of the 'placebo' lenses.

The use of precision spectral filters (PSF) and overlays is controversial, as the treatment is prone to placebo and Hawthorne effects. Precision spectral filters may produce a placebo effect because of the participant's belief in the treatment. Participants who have experienced visual discomfort for many years may have a strong desire for the treatment to work and have researched the possible beneficial effects. The Hawthorne effect refers to

a temporary change in behaviour as a result of being observed. The colorimetry assessment resembles a clinical procedure, which may affect a participant's motivation and behaviour by being closely observed. Figure 6:4 illustrates the many factors that can contribute to the need for a coloured filter in addition to the placebo effect (Evans & Allen, 2016). Factors relevant to the current research in a school setting include the overlay as an excuse for under-achieving and optometric factors that were not investigated prior to an overlay assessment.
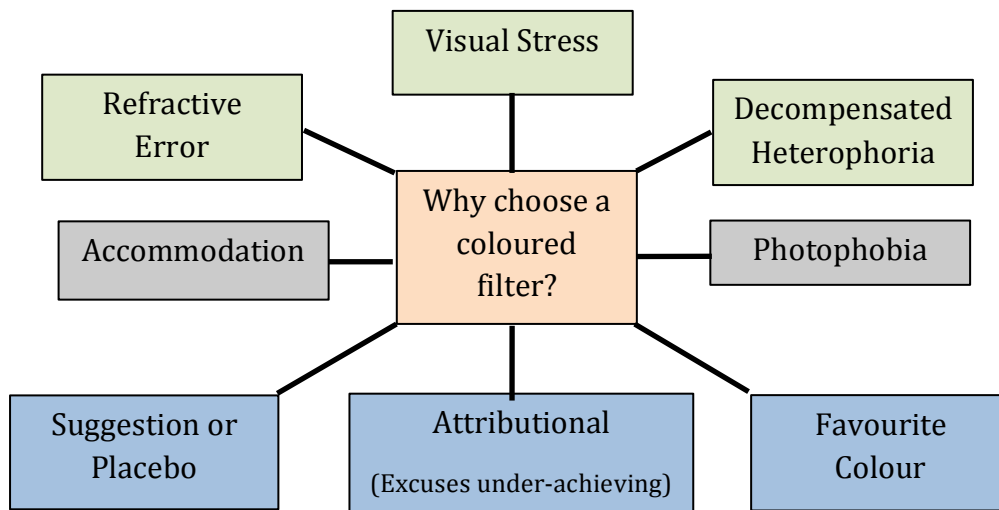
Figure 6:4: Factors that may influence the choice of a coloured filter based on a figure by Evans & Allen, (2016).

An increase in reading speed of ≥15% and sustained use is necessary to demonstrate a beneficial effect from the use of an overlay that exceeds chance (Evans et al., 2017). Participants who were 'poor' candidates for overlays and did not experience a marked benefit from their use may be particularly susceptible to the placebo and Hawthorne effects afforded by the lenses.

Colour adaptation has previously been shown to play a role in the identification of a coloured filter because the optimal chromaticity of a precision tint and overlay differs (Lightstone, Lightstone & Wilkins, 1999). The chromaticity of the 'placebo' lenses, in the current study, approximated the colour of the participants' overlays. It was therefore unlikely that participants would gain the same perceptual benefit from precision tints of chromaticity similar to that of the overlay.

The need for colour specificity has been demonstrated previously and it has been suggested that changes in hue with illumination may reduce but not extinguish the beneficial effects of the tints (Wilkins, Sihra, & Smith, 2005). Most studies investigating the efficacy of coloured overlays have utilised a sample that habitually uses overlays, suggesting beneficial effects from doing so. It may be the case that colour specificity is not as important for individuals for whom the overlay only makes a small difference. Schools may provide overlays to the majority of children who experience reading difficulty without investigating whether the problems are of visual origin. The use of overlays on a large scale in schools does create a financial burden and some children may experience social stigma whilst using their overlay in school. It may therefore be of benefit for schools to implement the Delphi Criteria (Evans et al., 2017) for visual stress when assessing students. These stringent criteria will ensure that students who are experiencing visual stress and for whom an overlay will provide a marked difference are provided with one.

Chapter 7   The use of Coloured Filters in Optometry

Abstract

The purpose of this study was to assess the effect of coloured filters on reading speed in individuals who had been screened for visual stress and to assess the repeatability of clinical assessments with the Intuitive Colorimeter. Patients underwent two assessments with the Intuitive Colorimeter conducted by two different examiners. The first examination was conducted by students of optometry under the supervision of the clinic leader (RLP). The second examination was conducted using a different colorimeter by a researcher who did not know the result of the first assessment (AA). Lenses of comfortable colour significantly increased reading speed. In participants with visual stress, assessment with the Intuitive Colorimeter was repeatable. The visual stress clinic provided the necessary screening of participants to explore the effects of colour on reading speed in those for whom colour is of benefit.

The study described in Chapter 7 was published in May 2018 in the journal *Neuro-Ophthalmology and Visual Neuroscience*. See Appendix D for the published version of the study.

7.1   Introduction

As discussed in Chapter 1, coloured sheets of plastic called overlays have been used in the treatment of visual discomfort and have been shown to improve reading speed when an appropriate colour is selected (e.g. Jeanes et al., 1997). Various tinting systems exist for the provision of coloured lenses, including Irlen, Intuitive and ChromaGen, which differ in diagnostic method and available chromaticities. Coloured filters have been associated with placebo effects; so coloured filters are often compared with control filters that differ in chromaticity. Children with reading difficulties have been shown to read on average 4% faster with an individually chosen Intuitive overlay than with a control that was ultraviolet blocking (Bouldoukian, Wilkins, & Evans, 2002). Robinson & Foreman (1999), conducted a trial of Irlen filters by providing three groups of participants with either placebo, blue or optimal filters. Reading accuracy and comprehension increased more quickly than a control group who did not use coloured filters. The greatest improvement was observed when participants were using the optimal filters.

The use of the Intuitive Colorimeter for the identification of a comfortable colour of light was described in Chapter 3. For any given individual the chromaticity that produces improvements in perception is constrained within a limited range (Wilkins et al., 1992). Participants can be masked as to the identity of a 'beneficial' active tint by the selection of a placebo that is outside the range of improvement. Under these conditions, Wilkins *et al* (1994) report participants experienced significantly fewer adverse symptoms (eye-strain, headache) when the 'beneficial' active tints were worn and participants were not aware of the identities of tints. Suttle, Barbur, & Conway, (2017) conducted an initial colorimetry

and overlay assessment and a second colorimetry and overlay assessment on a separate occasion. The author's report 11 of 21 individuals with visual stress identified different overlay colours on the first and second assessment. For those participants who identified two different overlays, the chromaticity difference between the two-colorimetry assessments was 11.4 JND's. A JND in that study was based on mean detection ellipses measured by Jennings and Barbur, (2010). The chromaticities of illumination obtained in the Intuitive Colorimeter could then be compared with the chromaticity shift associated with a just noticeable difference, thus providing an estimate of whether two colours of illumination would be perceived as different. For the 10 participants who identified the same or similar overlay, the chromaticity difference between the two-colorimetry assessments was 8.0 JND's. This finding raises important questions concerning the need for precision in colorimetry and overlay assessments. The study conducted by Suttle et al., (2017), has several limitations, most notably the statistical analyses of chromatic difference. The data are positively skewed, resulting in an enlarged mean separation between the two assessments. When median separation is calculated for individuals who chose the same or similar colour during both assessments, the colour remained within the necessary separation to be of benefit (Wilkins, Sihra, & Myers, 2005). The number of JND's as a measure of chromaticity difference may not be the most appropriate measure of the colour difference between the two-colorimetry assessments. The colorimetry assessment requires adaptation to each colour and memory for previous colours, which increases variability. Chromaticity difference measured in CIE 1976 UCS colour-space, however, is a physical measure that is directly related to the relative energy captured by the three classes of cones. Chromaticity difference is calculated in the current study and used in much of the previous literature.

For the current study, participants read a passage of closely spaced random words whilst wearing one of two sets of coloured lenses. One combination of trial lenses was 'active' (a colour identified as alleviating visual discomfort) and the remaining combination was a placebo, which differed in chromaticity by an average of 0.078. Both the participants and examiners conducting colorimetry were masked as to the identities of the lenses. The examiner conducting the rate of reading test did not know which lenses were 'active' and which were 'placebo'. Individuals underwent two sessions of colorimetry enabling an assessment of reliability by the examiners. The 'active' set of lenses may afford an increase in reading speed for those individuals who were reliable in their choice of colour.

7.2   Method

Participants

Participants were 20 individuals who were attending the Anglia Ruskin University eye clinic for assessment regarding the use of precision spectral filters. Written consent was obtained from the individual or a parent. All methods were approved by the Anglia Ruskin University ethics committee. The details of the participants are given in Table 7:1. The extent to which each participant conformed to the criteria for visual stress recently introduced by Evans, Allen, and Wilkins (2017) can be judged from Table 7:2. Fifteen participants had used an overlay for >3 months. All read more quickly with an overlay but only in 16/20 was the increase in reading speed greater than 15%; 15/20 had Pattern Glare scores of more than 3; 17/20 had 3 or more symptoms. Overall, 16 participants satisfied the criteria.

Table 7:1: Patients' details, reason for referral, colorimetry results, consistency ratings and rate of reading.

Participant	Age	Sex	Reason for Referral (VS = Visual Stress)	1st Colorimetry (u',v')	2nd Colorimetry (AA) (u',v')	1st Reliability Rating	2nd Reliability Rating (AA)	WRRT Active lenses (wpm)	WRRT Placebo lenses (wpm)
1	13	F	VS	0.156, 0.504	0.123, 0.525	Good	Moderate	136	113.5
2	11	F	Dyslexia	0.275, 0.491	0.275, 0.491	Good	Moderate	76.5	51
3	17	F	Dyslexia	0.157, 0.497	0.144, 0.496	Good	Good	216.9	216.2
4	17	F	Headaches/Dyslexia	0.235, 0.512	0.255, 0.529	Good	Good	119	117
5	13	F	Headaches	0.163, 0.478	0.297, 0.479	Poor	Poor	101.5	94.5
6	71	M	VS	0.285, 0.473	0.236, 0.394	Moderate	Good	114.5	104
7	58	M	VS	0.181, 0.487	0.262, 0.438	Poor	Poor	147.5	143.5
8	9	F	VS	0.222, 0.513	0.279, 0.541	Good	Moderate	70	84.5
9	9	M	VS/Dyslexia	0.158, 0.504	0.134, 0.516	Poor	Good	92.5	83.5
10	8	M	VS/Dyslexia	0.223, 0.425	0.236, 0.394	Good	Good	102.5	96
11	14	M	VS/Dyslexia	0.155, 0.483	0.158, 0.407	Good	Good	118.5	78
12	18	M	VS	0.223, 0.425	0.282, 0.423	Good	Good	123	131
13	38	F	VS/Dyslexia	0.155, 0.483	0.117, 0.464	Good	Good	149.5	124
14	27	F	VS	0.275, 0.491	0.307, 0.516	Good	Good	165.5	158.8
15	14	M	VS/Dyslexia	0.21, 0.421	0.15, 0.389	Poor	Poor	78.5	73.5
16	31	M	VS/Dyslexia	0.185, 0.419	0.185, 0.419	Good	Good	100	74.5
17	12	M	VS/Concussion	0.188, 0.508	0.123, 0.525	Good	Good	187.5	183.7
18	23	F	Dyslexia	0.18, 0.504	0.262, 0.519	Good	Moderate	275.7	270.6
19	19	M	VS/Photosensitivity	0.158, 0.504	0.13, 0.487	Good	Good	91	85.5
20	23	F	VS	0.144, 0.487	0.134, 0.516	Good	Good	163.5	181.5

Table 7:2: Delphi criteria for visual stress. Participants whose reliability was rated as poor by bo... highlighted in bold.

	Delphi criteria for visual stress				
Participant	3 month overlay use	Increase in WRRT >15%	Pattern Glare >3	Symptoms from text	Pass Crite
1	0	1	1	4	1
2	1	1	1	3	1
3	1	1	1	3	1
4	0	1	1	3	1
5	**1**	**0**	**1**	**0**	**0**
6	1	1	1	4	1
7	**0**	**0**	**1**	**5**	**0**
8	1	1	1	3	1
9	1	1	0	3	1
10	0	0	0	1	0
11	1	1	0	3	1
12	1	1	1	3	1
13	1	1	1	3	1
14	1	1	1	3	1
15	**0**	**0**	**0**	**0**	**0**
16	1	1	1	3	1
17	1	1	1	3	1
18	1	1	1	4	1
19	1	1	0	3	1
20	1	1	1	6	1

Procedure

Each participant underwent an extended eye examination and colorimeter assessment that was conducted by optometry students in the clinic under the supervision of the clinic leader Rupal Lovell-Patel (RLP). An Intuitive Colorimeter Mk. 3 (Cerium Visual Technologies, Tenterden, Kent) was used to identify a colour of illumination that maximized comfort and reduced perceptual abnormalities. The first colorimetry assessment followed the practice at Anglia Ruskin of restricting the saturation to 30. The assessment is thereby simplified for students, and avoids the provision of hues that are too dark; the final assessment is reviewed by the supervisor, and revised if necessary.

Two lens stacks were prepared using the trial lenses supplied with the colorimeter and worn in a lens holder mounted on a headband. One stack was *active* (matching under office lighting the chromaticity selected by the participants as optimal) and one *placebo* having CIE 1976 UCS chromaticity that differed by an average of 0.078 (SD = 0.02). The placebo was selected by a spreadsheet that chose a similar combination of lenses but with different dyes. There are seven dyes in the colorimeter system that can be arranged in a hue circle. The placebo lenses differed by two steps on this circle and had a transmission similar to that of the active lenses.

A second examiner (AA) who did not know the identity of the two lens stacks administered the Wilkins Rate of Reading Test four times, A-D. One set of lenses, chosen at random, was used for passages A and D and the second set for B and C.

The participant was then debriefed to allow them to leave if they wished. All consented to remain and underwent a second colorimeter assessment conducted about one hour after the first by examiner AA. The second assessment used an Intuitive Colorimeter Mk. 2. This machine has the same filters as the Mk. 3, but has a very different appearance. The second examiner had no knowledge of the results of the first examination. The second colorimetry assessment did not restrict the saturation and followed the procedure described in the Colorimeter Manual (Cerium Visual Technologies) (Wilkins, 2002a). The difference in the colorimetry procedure will have increased the difference in the chromaticities obtained, but the central concern in this experiment was to study the repeatability of colorimetry under the conditions that currently obtain in clinical practice, including differences in procedures and instruments.

Both the examiners who undertook the colorimeter examination gave a rating reflecting their assessment of the certainty with which patients were able to choose their optimal chromaticity. Individuals, who identified an optimal colour and did not deviate, were given a consistency rating of "good"; those who were unsure or for whom the colour was repeatedly adjusted were rated "poor." Those participants who identified a colour with only minimal adjustment were rated "moderate." The examiners gave their ratings independently without knowledge of the rating given by the other examiner.

After the second colorimetry assessment, participants were asked the following questions:

- Which pair of lenses did you benefit from?

- Would you like either of these pairs of glasses for reading?

- Which glasses made the page the same colour as the one you chose in the box (Colorimeter) earlier?

7.3   Results

Participants read faster with the 'active' set of lenses, 132 words per minute compared to 123 words per minute with 'placebo', $t(19)$ = 2.61, p = 0.017. Figure 7:1 illustrates the number of words read per minute with the WRRT. Points along the line represent individuals for whom there was no effect of colour.

WRRT
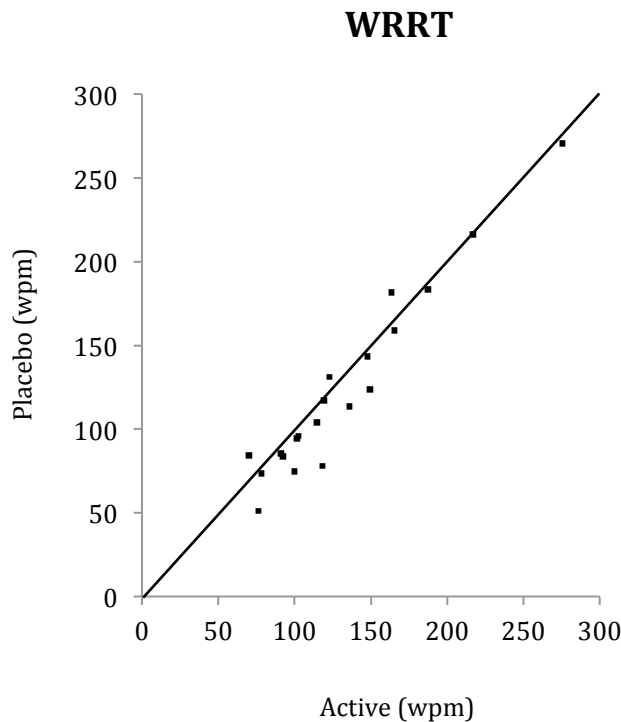
Figure 7:1: Number of words read per minute. Points below the line represent participants who read faster with the 'active' lenses and points above the line represent participants who read faster with the 'placebo' lenses.

Of the 20 participants, 16 were rated as 'good' or 'moderate' by both examiners. Three were rated as 'poor' by both examiners. Only one was rated 'good' by one examiner and 'poor' by the other. For the purposes of this analysis, the ratings were scored as follows: 'good' was given a score of 2, 'moderate' was given a score of 1 and 'poor' was given a score of 0. A 3x3 Chi-square test revealed a significant association between the ratings, X^2 (4, $N =$ 20) = 14.7, p = 0.005.

The rating was significantly related to criteria for the diagnosis of visual stress proposed in a Delphi study by Evans et al. (2017). The examiners who carried out the colorimetry assessments were masked to participant's Delphi criteria results. To pass the criteria participants needed two of the following three signs: 3 months' use of overlays, an increase

in reading speed of 15% or more with an overlay, a Pattern Glare score of more than 3 with a mid spatial frequency grating. They also needed 3 of 6 typical symptoms. The signs are shown as present (1) or absent (0) in Table 7:2. The three participants rated "poor" by both examiners did not meet the Delphi criteria for visual stress and are highlighted in bold text in Table 7:2. To analyse this contingency statistically, the examiners' rating was converted to a numerical value by summing a score of 2 for "Good", 1 for "Moderate" and 0 for "Poor" across both examiners. The mean rating score for the individuals who passed the criteria for visual stress was 3.56 and for those who failed 1.0, $t(18) = 4.59$, $p = 0.0002$.

Overall, the mean difference in chromaticity between the two colorimetry assessments was 0.043 (SD 0.027), median 0.037. The difference was smaller for the 16 participants who were rated by both examiners as either "good" or "moderate": 0.037 (SD 0.022), median 0.033. For the three participants rated "poor" by both examiners (omitting the one participant who was rated "good" by one examiner and "poor" by the other) the difference in the chromaticity of the two colorimeter assessments averaged 0.083 (SD 0.011), median 0.086. The similarity between the two colorimeter assessments was significantly greater in the participants rated as "good" or "moderate" by both examiners than those rated as "poor" by both $t(17) = 3.42$, $p = 0.003$, $d=1.79$). However, the number of "poor" participants was small. The chromaticities are shown in Figure 7:2. Because of the difference in colorimetry procedure, on average, the second assessment gave chromaticities of greater saturation. The cross of Figure 7:2 represents equal energy white.
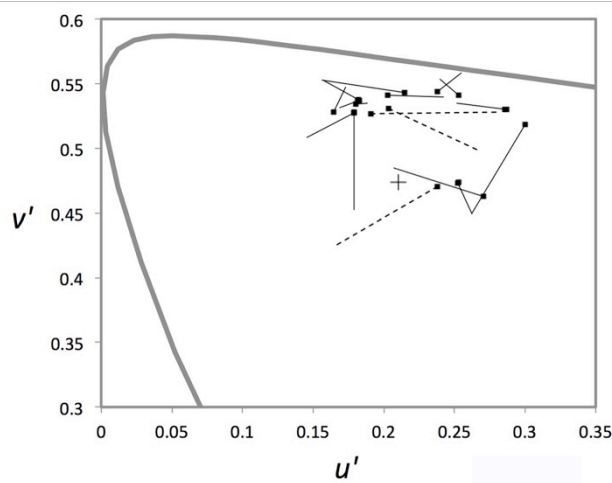
Figure 7:2: The chromaticities obtained during the first colorimetry assessment are marked by a point. They are connected by a line to the chromaticities from the second assessment. The broken lines denote participants who were rated as 'poor' by both examiners.

Following the WRRT, participants were asked: 'which of the two lens stacks did you benefit from?' Seven individuals reported either the placebo lenses or neither of the two lens stacks to be of benefit. The mean number of words read for the 'active' and 'placebo' lenses were, 139 and 141 respectively. Two individuals in this group were rated 'good' for reliability by both examiners. Examiner 1 or Examiner 2 rated the remaining participants in this group as 'moderate' or 'poor' for reliability. The remaining 13 participants reported that the 'active' lenses were of benefit, reading an average of 127 words compared to 114 with the 'placebo' lenses, $t(12) = 4.031$, $p = 0.002$.

Individuals were asked: 'Which pair of lenses would you prefer for reading?' Data were collected from 18 individuals, 11 participants chose the 'active' lenses and 7 chose 'placebo' or expressed no preference. Participants were then asked: 'which pair of lenses made the page the same colour as the one you chose in the box (Colorimeter) earlier? Eleven participants chose the 'active' lenses and 7 chose 'placebo.'

7.4   Discussion

Under double-masked conditions, individuals read more quickly with lenses tinted to match their colorimeter setting than with lenses that differed in chromaticity by 0.078. Fourteen participants did not have prior experience with trial lenses. Those participants who were rated as reliable in their choice of colour read faster than those who were rated unreliable by two independent examiners. Ratings predicted reliability as assessed by a second colorimetry examination. The participants who passed the Delphi criteria for visual stress received higher ratings of reliability, which supports the use of the criteria as an assessment for the suitability of treatment with coloured filters (Evans et al., 2017).

The chromaticities of the two lens stacks varied by only 0.078 and the colour of the 'active' lenses was selected in an environment in which the participant was colour-adapted. Participants were not informed that one set of lenses was less effective, nor was the identity of the 'active' lenses revealed. Participants were not fully masked to the identity of the 'active' lenses as the majority of individuals reported that these lenses were of benefit. The experimenter conducting the WRRT was masked until data collection for each participant was complete.

The current study has confirmed the chromaticity of effective coloured tints is individual and constrained within a small range (Wilkins et al., 1994, 2002). In a study of children with reading difficulty, Wilkins et al. (1994) report a difference in chromaticity between

'experimental' and 'control' lenses of 0.065 in CIE 1976 UCS colour space, which equates to approximately 6 times the just noticeable difference in colour. Symptoms of eye-strain and headache were less frequent on days when the 'experimental' lenses were worn. Wilkins et al. (2002) report a similar difference (0.078 or 6 JND's) between 'active' and 'placebo' lenses in a study of the effects of precision tinted lenses in adults with migraine. A difference in colour of 6 JND's between an optimal tint and a placebo is sufficient to reduce the beneficial effects of the lenses. Suttle et al. (2017) suggest that 'the use of colour in the treatment of visual discomfort is not a valid approach or that the use of colour is valid but the colour does not need to be precise.' For the "consistent" observers in the study conducted by Suttle et al. (2017) i.e. those who chose the same or similar overlays, the colour difference averaged 0.035. The colour difference averaged 0.053 for the "inconsistent" participants. The findings in the present study were similar: the colour difference for participants rated as "good" or "moderate" by both assessors averaged 0.037, as compared with 0.067 for the remaining four participants. The mean chromaticity difference for the consistent participants was averaged for the two studies and was 0.036. The standard error of this mean was estimated from the standard deviation of data from both studies and was $0.026/ \sqrt{40} = 0.0041$. The colour difference observed between the two colorimetry assessments reported by Suttle *et al*. (2017) is within the limits for which both sets of lenses will be of benefit, even for the inconsistent participants.

The current research measured reading speed under visually stressful conditions using the WRRT. Although previous studies utilising the WRRT have shown an increase in reading speed with the use of coloured overlays (Jeanes et al., 1997; Wilkins, Lewis, Smith, Rowland, & Tweedie, 2001; Wilkins & Lewis, 1999), the current research is the first study of this kind to demonstrate an effect with PSF's.

Reliability in the choice of colour is predictive of a benefit from PSF's and an increase in reading speed. Two independent examiners rated the reliability of participants during colorimetry, the rating predicted reliability measured by a second colorimetry assessment. Reliability in the choice of colour has been demonstrated with coloured overlays: 47% of the children tested chose the same coloured overlay during a second assessment (Wilkins et al., 2001). Hollis & Allen (2006), assessed two screening methods to predict those for whom a coloured overlay would increase reading speed, a pattern-glare assessment immediately before testing provided the most reliable measure. Objective tests to predict improvement in reading speed with a coloured overlay may be particularly effective in the assessment of younger populations for whom standard methods are too complex (Singleton & Henderson, 2007). The results of the current study suggest ratings of reliability by examiners are sufficient to predict: (a) participants who are consistent in their choice of colour, and (b) individuals who will demonstrate an improvement in reading speed with the appropriate colour. Choice of colour is consistent between examiners and with two models of the Intuitive Colorimeter.

Under double-masked conditions, an increase in reading speed was demonstrated when the 'active' set of lenses were worn. The present results support experimental and anecdotal reports of the benefits of PSF's with an appropriate colour that is specific to the individual. Ratings of reliability predict those for whom colour is likely to be of benefit. A rating given by the examiner does not expose the patient to further visual discomfort, such as that experienced during the pattern-glare test, and does not increase the time needed for

an assessment. This may be particularly useful in the testing of children and patients who

may not be able to give a detailed description of their symptoms.

Chapter 8 General Discussion

The experiments described in this thesis were designed to examine visual function, visual distortions and visual discomfort in individuals who experience migraine and those who experience difficulty when reading. The effects of coloured filters were also examined in these two groups of particpants. Here we have examined visual function in the form of contrast discrimination and the discomfort experienced from viewing patterns of striped lines.

Individuals with migraine often show impairment when completing psychophysical tasks, however several studies have shown superior performance in migraine or no difference between individuals with migraine and controls (Karanovic et al., 2011; Palmer et al., 2000; Shepherd et al., 2011). Individuals with migraine are known to be particularly susceptible to discomfort from high contrast patterns of striped lines (Wilkins et al., 1984). Coloured filters have been used as a non-invasive treatment for visual discomfort and visual distortions in individuals with migraine and those who experience discomfort from printed text (Evans et al., 2002; Wilkins, Sihra, & Myers, 2005). Comparing the visual function of individuals with migraine and controls can help explore the effects of migraine aura on the visual sytem and examine the underlying physiological mechanisms. The use of coloured filters remains controversial but they have been shown to be of benefit in the treatment of visual discomfort.

8.1   Summary of Results

In Chapter 2, contrast discrimination thresholds were measured in individuals who experience migraine, and controls, at two pedestal contrasts. There were no between-group differences for contrast discrimination threshold but individuals who experienced a consistently unilateral visual migraine aura were more sensitive in the field affected by the aura. There was some evidence that contrast discrimination was supranormal in the affected field of individuals with unilateral migraine aura (compared to healthy controls) but this effect will require further investigation.

Contrast threshold for discomfort was measured in Chapter 3 in individuals who experienced migraine and controls. Gratings were presented until the participant experienced visual discomfort. The gratings were illuminated by a colour of light that was comfortable for viewing text and a second colour that was uncomfortable. Individuals in the MA group had the lowest contrast threshold for discomfort but the comfortable colour of illumination significantly raised the threshold in all participant groups. Participants in the MA group chose as comfortable, colours of significantly greater saturation than those in the MO group or controls.

The effects of coloured filters on contrast discrimination thresholds were examined in Chapter 4. It may be the case that the superior performance in the field affected by aura in

Chapter 2 is the result of a cortical hyperexcitability. Coloured filters may reduce the excitability of neurones and thus normalise contrast discrimination threshold. This will be discussed in detail in section 8.4. Contrast discrimination was again measured in individuals who experience a unilateral visual migraine aura and controls. Individuals wore two sets of coloured lenses to complete the task: (1) a colour identified as comfortable for viewing text and (2) grey lenses of matched transmission. The lenses of comfortable colour significantly raised (worsened) the discrimination threshold of individuals in the migraine group.

The NIRS and VEP response to three grating patterns of low, mid and high contrast was explored in Chapter 5. Individuals with MA and controls showed no between-group differences in the amplitude or offset of the NIRS response. There was an effect of contrast for the P1 and N2 components of the VEP response but no between-group differences.

Chapters 6 and 7 formed two double-masked trials of the effects of coloured filters on reading speed. The participants in Chapter 6 were children who used an overlay to read. A colour of illumination was identified that was comfortable for viewing text and a second colour that differed by 0.06 was used as placebo. No differences in reading speed were found. In Chapter 7, participants were individuals attending a visual stress clinic in an optometry practice. Again, a comfortable colour of illumination was identified and a placebo that differed in colour by 0.078 was provided. Participants read significantly faster when wearing the lenses of comfortable colour.

8.2   Contrast discrimination and hyperexcitability of the visual cortex

As was previously shown in Chapter 1 individuals with migraine demonstrate impairment in psychophysical and electrophysiological tasks but are particularly susceptible to discomfort from patterns of striped lines. There is also growing evidence for a hyperexcitability of the visual cortex in individuals with migraine. As mentioned previously, hyperexcitability may predispose the individual to the neuronal discharge associated with cortical spreading depression (Aurora & Wilkinson, 2007; Welch et al., 1990). The hyperexcitability observed in migraine may share some similarity with that found in individuals with epilepsy because anti-epileptic drugs are effective in both conditions (Welch, 2005). Hyperexcitability of the visual cortex may be non-uniform as is the case in epilepsy (Binnie et al., 1981). Small regions of hyperexcitability may be responsible for a lateralised visual migraine aura. Migraine aura is predominantly visual in the form of positive hallucinations (Wilkinson, 2004) that have been linked to cortical spreading depression using fMRI (Hadjikhani et al., 2001). A computational model of cortical spreading depression has been used to show that the pattern of neuronal activity breaks-up into small highly active elements (Reggia & Montgomery, 1996). This may help to explain the wide variation of patterns seen during the aura phase of migraine. In Chapter 2 it was shown that individuals who experience a unilateral visual migraine aura are more sensitive at discriminating contrast in the affected field. A consistently unilateral visual migraine aura may represent a specific hyperexcitable region in the visual cortex. The region of hyperexcitability may *increase* sensitivity in the corresponding visual field. Only eight individuals in the MA group experienced a unilateral aura and 16 experienced bilateral visual aura. The difference in contrast discrimination threshold between fields

was significantly greater in the unilateral aura group. No difference was found between controls and the bilateral aura group. In Chapter 4 individuals in the MA group were not more sensitive at discriminating contrast in the affected field, however there was a trend for lower discrimination thresholds in the field affected by lateralised aura. Precision tinted lenses and control grey lenses were used in Chapter 4 but no lenses were used in Chapter 2. The control grey lenses may also have raised the contrast discrimination threshold in Chapter 4, thus reducing the difference between the affected and unaffected fields. A future experiment could include a baseline condition with no lenses, which could be compared with performance when precision tinted lenses and control grey lenses are worn.

Few studies have demonstrated greater sensitivity in individuals with migraine (Karanovic et al., 2011; Palmer et al., 2000; Shepherd et al., 2011; Wray et al., 1995). The experiment conducted in Chapter 2 revealed greater sensitivity, selectively, in the visual field affected by migraine aura relative to the unaffected field and a non-significant trend in the same direction was found in Chapter 4. Studies that have reported greater visual sensitivity and losses of sensitivity were reviewed in Chapter 2 (Table 2.6 and Table 2.7). Because of the differences in the tasks used it is difficult to directly compare results.

Khalil (1991) reported worse performance in the affected field of individuals who experience a unilateral aura when completing a hemi-field contrast discrimination task. Worse performance was related to a long duration of disease. It may be the case that the related vascular changes during an attack of MA cause damage over a period of many years. The participants in the study reported in Chapter 2 were non-neurological patients and

were therefore less severe cases. One might speculate that a region of hyperexcitability in the cortex would produce a heightened neuronal response (greater sensitivity) but also a predisposition to CSD. Hypoperfusion of the regional cerebral blood flow has been shown to accompany the aura phase of migraine, which is followed by hyperperfusion during the headache phase (Olesen et al., 1990). In this study the headache began whilst rCBF was reduced. Trigeminovascular nerve activation has been demonstrated in response to a period of ischemia (Moskowitz et al., 1989). This activation may cause the associated hyperperfusion and contribute to the pain of migraine. Over time this process may damage the susceptible GABA-ergic cells of the visual cortex and result in a loss of sensitivity to visual stimuli, which is not inconsistent with the hypothesis proposed by Chronicle and Mulleners (1994).

8.3   Colours for comfort in migraine

The experiment described in Chapter 3 revealed differences in the colours chosen as comfortable by individuals who experience MA and those who experience MO. Mulleners, Aurora, et al. (2001) used a self-report questionnaire and a measure of threshold for visual discomfort to show that individuals with MA were more photophobic than those with MO or controls. Participants in the MA group were also more likely to have a migraine attack triggered by visual stimuli. The authors describe the measures of photophobia used in this study as accurately predicting diagnostic category. Individuals who experience migraine are known to find certain grating patterns aversive and headache provoking (Wilkins et al., 1984) but the colour of light used to illuminate a high contrast pattern can moderate these effects (Chronicle & Wilkins, 1991). Chronicle and Wilkins (1991) presented a high-

contrast passage of text inside the Intuitive Colorimeter and asked participants with migraine (MA and MO) and controls to identify a colour of illumination that made the text (a) comfortable to view and (b) uncomfortable to view. Individuals in the migraine groups were more likely to report red hues as uncomfortable and the angular variance of the hues selected was significantly lower, which indicates that the colours were constrained within a smaller region of the CIE 1976 UCS diagram. Chronicle et al. (1995) presented a target letter on a background grating, which was illuminated by (a) the mean hue identified as uncomfortable by the migraine group (red), (b) the mean hue identified as comfortable by the migraine group (blue) and (c) a neutral illuminant. Individuals with MA, those with MO and controls viewed the target letter, which increased in luminance until the participant had correctly identified the orientation at four successive luminance levels. Threshold for the detection of the probe letter was significantly higher in the MA group, which indicates the worst performance, but the MO and control groups did not differ. There was also a significant effect of the colour of illumination in the MA and MO groups. Red and neutral hues significantly raised the threshold in relation to the blue condition. These findings are in agreement with those reported by Chronicle and Wilkins (1991). Monger et al. (2015) presented grating patterns of increasing contrast until discomfort was reported by individuals who experienced visual stress and controls. The gratings were tinted (a) grey, (b) a comfortable colour identified previously and (c) an uncomfortable colour identified previously. Individuals who had previously reported that a coloured tint made reading more comfortable had a significantly lower contrast threshold for discomfort when viewing the gratings with the grey tint and the uncomfortable tint.

Relatively little is known about hyperexcitability of the visual cortex in individuals who experience MO, possibly because of the interesting links between hyperexcitability, CSD and the migraine aura. A transcranial magnetic stimulation (TMS) technique called magnetic suppression of perceptual accuracy has been used to show little or no suppression of responses in participants with MA but normal profiles of suppression in MO and controls (Chronicle, Pearson, & Mulleners, 2006). In this study, letter trigrams were presented and a TMS pulse was administered such that participants were unable to correctly identify two out of the three letters correctly and in the right order. Further differences have been observed between MA and MO. The threshold for eliciting phosphenes is lower in individuals who experience MA, which has been used as evidence of a cortical hyperexcitability (Aurora et al., 2003; Young et al., 2004). Pattern-reversal VEP's have been shown to be of increased amplitude in individuals with MA when compared to controls (Shibata et al., 1997a).

The experiment conducted in Chapter 3 revealed important differences between the two forms of migraine. Individuals in the MA group chose as comfortable colours of significantly higher saturation than the MO group. The control and MO groups chose colours of illumination that were close to white on the CIE 1976 UCS diagram. No trends in the chromaticity of colours identified as uncomfortable emerged, which differs from the results of Chronicle et al. (1995) and Chronicle & Wilkins (1991). In these studies, red hues were identified as uncomfortable by individuals with migraine. The measure of contrast threshold for discomfort used in Chapter 3 is an objective test of visual discomfort that predicts diagnostic category. Chronicle and Wilkins (1991) suggest that the visual discomfort reported by some individuals when viewing a grating pattern may be

dependent on the colour used to illuminate the stimulus. The results of the experiment conducted in Chapter 3 are in agreement with the above statement as contrast threshold for discomfort was significantly raised in all three participant groups when the stimuli were illuminated by a comfortable colour. It may be the case that the underlying pathophysiology of MA differs from that of MO or that MA is a more severe form of the condition. Because of the absence of aura in individuals with MO, the brain may not be subject to the electrical and chemical changes associated with cortical spreading depression. This would result in less damage to inhibitory networks and the suggested damage from near-ischaemic conditions in the brain during the aura phase. There is evidence to suggest that hyperbaric oxygen, that is oxygen under a pressure of more than one atmosphere, relieves the pain of an attack of MA (Wilson, Foresman, Gamber, & Wright, 1998). The authors suggest that the vasoconstriction caused by 100% oxygen was responsible for the relief of pain and tenderness.

The effects of visual migraine aura on the brain have been measured extensively and revealed shared mechanisms with epilepsy. The study conducted in Chapter 3 has revealed important differences between the two forms of migraine. Further investigation of the experience of photosensitivity in MA may help reveal the underlying differences between MA and MO.

8.4   Contrast discrimination and the effects of Colour

In Chapter 2 it was shown that individuals who experienced unilateral visual aura had superior contrast discrimination thresholds in the affected field relative to the unaffected field. The same task was used in Chapter 4 to investigate the effects of colour on contrast discrimination in individuals who experienced a consistently unilateral visual migraine aura. Lenses of comfortable colour significantly raised the contrast discrimination threshold in the migraine group.

As was discussed in section 8.2, small regions of hyperexcitability in the visual cortex may be responsible for triggering a unilateral migraine aura. One might speculate that lenses of comfortable colour may act selectively on these areas of hyperexcitability and reduce the neuronal activation to a normal level.

Coloured filters have been shown to be effective in a number of applications, including the treatment of migraine, epilepsy and reading difficulty (Wilkins, 2002c; Wilkins et al., 1999, 2002). There is fMRI evidence to suggest cortical activation is reduced in individuals with migraine (MA and MO) when coloured lenses of a comfortable colour are worn (Huang et al., 2011). Individuals in that study viewed both visually stressful and comfortable grating patterns whilst wearing lenses of comfortable colour, control grey lenses or control coloured lenses. Cortical activation was greater in the migraine group when viewing the visually stressful pattern with the grey lenses or the control-coloured lenses that differed from the comfortable colour by 0.07 in CIE 1976 UCS colour space. That study supports the hypothesis that precision is necessary when prescribing coloured glasses to relieve visual

discomfort. Coloured lenses have also been used as a non-invasive treatment for photosensitive epilepsy. Wilkins et al. (1999) conducted a longitudinal study in which individuals who experienced visually induced seizures were prescribed lenses of comfortable colour. Follow-up tests were conducted on average 2.4 years after the lenses were prescribed. Six participants reported a reduction in unpleasant symptoms such as dizziness caused by fluorescent lighting. Three of the seventeen participants available at follow-up reported a reduction in the number of seizures but the majority of the group reported changes to their anti-epileptic medication. Coloured overlays have been shown to increase reading speed in around 5% of school children who read 25% faster with an appropriately coloured overlay (Wilkins et al., 2001). The authors suggest that coloured filters alter the distribution of cortical activation in the brain and that a comfortable colour acts on hyperexcitable regions to reduce excessive activation and the perceptual distortions that it causes. The results of the study conducted in Chapter 2 support the hypothesis of a non-uniform distribution of hyperexcitable regions in the cortex, which is discussed below.

As was discussed in Chapter 2, the distribution of hyperexcitable regions in the visual cortex may be non-uniform. Small hyperexcitable regions may be responsible for unilateral migraine aura. Lenses of comfortable colour have been shown to reduce excessive neuronal activation when viewing uncomfortable pattern gratings (Huang et al., 2011). In reducing the neuronal activity, tinted lenses may 'normalise' the response. This would result in the increased contrast discrimination thresholds observed in the MA group when the lenses of comfortable colour were worn. An increase in contrast discrimination threshold appears to be dependent on the colour of the lenses. Grey lenses did not raise the contrast

discrimination threshold but lenses of comfortable colour may alter the distribution of cortical activation in such a way that discomfort and perceptual distortions are reduced. Coloured filters may reduce and re-distribute the excessive neuronal activation in hyperexcitable regions and thus equate the level of activation to that in non-hyperexcitable regions.

8.5   Physiological correlates of Visual Discomfort

The similarities between migraine and photosensitive epilepsy were described in Chapter 1. An attack of migraine is visually triggered in the majority of patients and the stimuli that induce a migraine attack can usually also trigger a seizure in patients with photosensitive epilepsy. The VEP response to gratings of high contrast has been shown to be of increased amplitude in individuals with photosensitive epilepsy (Porciatti et al., 2000). The shape of the haemodynamic response has been shown to change when stimuli that are known to be aversive are viewed (Haigh et al., 2015).

In Chapter 5 the NIRS and VEP response to striped patterns was measured. In Chapter 3, patterns of mid-range spatial frequency at high contrast were shown to be particularly uncomfortable for individuals who experienced MA. The VEP response revealed that the amplitude of the P1 component increased with contrast, as did the latency of N2. There was also a significant interaction between hemisphere and group for the latency of N2 and an interaction between contrast and hemisphere for the amplitude of N2. Because of these hemisphere differences, asymmetry of the VEP was investigated in both participant groups. No significant asymmetries were found in either group, however there was a trend of lower

amplitudes and shorter latencies in the hemisphere affected by unilateral migraine pain. Only three individuals in this study experienced consistently lateralised pain and a larger sample of these individuals will be necessary to further examine these effects.

Unilateral migraine aura has been shown previously to affect the amplitude of the VEP (Tagliati et al., 1995). In that study the VEP was of lower amplitude in the hemisphere affected by unilateral aura. The effects of unilateral pain have also been observed in cluster headache. Boiardi et al. (1986) reported VEP amplitude reduction in the hemisphere affected by the pain of cluster headache. Regional cerebral blood flow has been shown to be reduced in the hemisphere affected by migraine pain in the inter-ictal period (Levine et al., 1987). Significant asymmetry of CBF in the posterior regions of the brain may reflect the origin of unilateral migraine pain and aura. A reduction of the amplitude of the N2 component was found in the affected hemisphere of individuals with unilateral pain. This finding is consistent with the previous literature, however a larger sample of these participants will be required to investigate the underlying mechanisms.

In Chapter 5, no differences were found in the shape of the haemodynamic response when participants viewed uncomfortable grating patterns, contrary to the report by Coutts et al. (2012) mentioned earlier. The relationship between neuronal excitation and the haemodynamic response is related to local field potentials (Logothetis et al., 2001). The haemodynamic response can therefore be used to measure neuronal excitation. Individuals who experience MA are known to be particularly susceptible to the uncomfortable stimuli presented in Chapter 5. The haemodynamic response was not significantly larger for the

high contrast gratings. On average, participants in the control group had fewer channels acceptable for analysis and the signal was of poorer quality. The shape of the haemodynamic response has been shown to vary with the level of visual discomfort as uncomfortable stimuli produced a steeper offset of the response (Haigh et al., 2015). No differences in the shape of the haemodynamic response were found in the current study. Coutts et al. (2012) found no difference between individuals with migraine (15 MA and 5 MO) and controls in the amplitude of the haemodynamic response to pattern gratings of low and high spatial frequency and a checkerboard pattern. The time-course varied however, as the response occurred earlier in the migraine group. The largest amplitude response was for the checkerboard pattern, which had a Michelson contrast of 98% and flashed at a frequency of 1Hz. For the experiment conducted in Chapter 5 the pattern grating of highest contrast was 80%. This should have been sufficient to induce measurable differences between participant groups. Stimuli were presented in intervals of 1s, which is in agreement with previous literature and limits the possibility of inducing an attack of migraine. The literature reviewed in this thesis that has utilised NIRS has typically presented stimuli with different characteristics such as, static and moving gratings (Haigh et al., 2015) or patterns of striped lines and checkerboard stimuli (Coutts et al., 2012). The only stimulus parameter that was varied in Chapter 5 was contrast. It may be necessary to increase the number of stimulus presentations in order to observe differences in the shape of the haemodynamic response to static achromatic pattern gratings.

8.6   Double-masked trials of precision spectral filters

In Chapters 6 and 7 the effects of coloured filters on reading speed were examined. In Chapter 6, participants were children who used an overlay to read. A comfortable colour of illumination was identified and produced as lenses. Control lenses differed by 0.06 in CIE 1976 UCS colour space. No differences in reading speed were found between the lenses of comfortable colour and the control lenses. In Chapter 7 participants were patients attending a visual stress clinic at Anglia Ruskin University. Participants read more quickly when wearing lenses of a comfortable colour. It may be the case that coloured overlays are over-used in schools and that the visual stress clinic provided the screening necessary to reveal a difference in reading speed.

As discussed in Chapter 1, the theory of a magnocellular deficit in dyslexia remains controversial. Some individuals experience visual discomfort and illusions in the absence of any ocular abnormality (Evans, 2005). Printed text resembles a pattern of striped lines and individuals with visual discomfort can experience glare and discomfort when reading (Wilkins, 1995, page 66). The visual illusions experienced by these individuals when reading may be the result of cortical hyperexcitability. Coloured filters may reduce the response to a more 'normal' level.

The participants sampled in Chapter 6 may have experienced a reduction of visual discomfort when using their overlay, but the difference in reading speed between the 'active' and 'placebo' conditions was not sufficient to meet the current guidelines for the diagnosis of visual stress (Evans et al., 2017). A diagnosis of visual stress requires an

increase in reading speed of ≥15%, which is based on reading with an overlay and reading without an overlay. The experiment described in Chapter 6 did not include a no-overlay condition. Schools may give overlays to all students with reading difficulty without assessing whether reading problems stem from visual discomfort and perceptual distortion of the text. A reduction in the contrast of text with the use of the 'placebo' lenses may have provided some relief from visual distortion. In a future experiment, the nature of visual symptoms could be measured (a) without precision tinted lenses (b) with precision tinted lenses and (c) with coloured 'placebo' lenses. A change in the nature of visual distortions in response to a reduction in contrast with the 'placebo' lenses can then be measured.

In Chapter 7 participants were attending a visual stress clinic, which provided screening of their suitability for the use of an overlay. Sixteen participants met the Delphi criteria for visual stress in this study and reliably identified a colour that improved comfort and clarity. Participants read significantly faster when wearing lenses of comfortable colour compared to lenses that differed by 0.078 in CIE 1976 UCS colour space. Again this study highlights the need for precision when identifying lenses to alleviate the symptoms of visual stress. An increase in reading speed of ≥15% provides a good measure of those who will experience a benefit with the use of colour because it is >2 SD's outside the range for intra-subject variability (Evans et al., 2017). As discussed in Chapter 1, visual discomfort and illusions when reading may arise from a hyperexcitability of the visual cortex. The illusions experienced during reading interfere with reading speed, which was increased when individually selected lenses were worn during the experiment conducted in Chapter 7. If hyperexcitability of the cortex is non-uniform and different in each individual, this may help explain why precision is necessary when prescribing a coloured tint.

8.7   Limitations and Future Directions

Participants of the studies described in this thesis were not given a full eye-examination because the diagnostic criteria defined by the International Headache Society do not specify this as a requirement for diagnosis of migraine (IHS, 2013). It may be the case that some participants had undiagnosed optical abnormalities but screening was conducted for conditions that would have affected results such as, colour-vision anomalies and reduced contrast sensitivity (Cambridge Low Contrast Gratings).

Due to the specialised groups that were sampled in the experiments reported here, it was not possible to accurately match the age groups of the migraine participants and controls. In Chapter 2 (Experiment 1) the mean contrast discrimination threshold of the MA group was lower than controls indicating better performance even though the MA group had a greater mean age. Contrast sensitivity has been shown to decline with age (Elliott, 1987), therefore it would be anticipated that contrast discrimination would be negatively affected by age. This was not the case in the experiment described in Chapter 2. It may be the case that the greater mean age of the MA group in Chapter 4 reduced the proposed benefit from hyperexcitablilty of the cortex.

In Chapter 3 (Experiment 2) participants completed the contrast threshold for discomfort task under the light of the Intuitive Colorimeter mk.2 (Cerium Visual Technologies, Tenterden, Kent) rather that under normal office lighting conditions whilst wearing trial

lenses, as is the procedure in clinical practice. This procedure enabled all participants to complete the task under the same lighting conditions (11-$17cd/m^2$). Individuals who participated in the experiment described in Chapter 3 were not asked to assess whether the selected colour of illumination would be beneficial under normal conditions, rather individuals were asked to complete a novel psychophysical task. The procedure used in Chapter 3 did differ from that used in clinical practice, however presentation of the task in the Intuitive Colorimeter enabled greater control in an experimental setting.

No between-group differences were found for the pattern-glare test results obtained in Study 4 (Chapter 5). This is in contrast to previous reports and indicates that the MA group sampled in this experiment was not a representative sample of the migraine population. The cause of this result is not clear, as the MA group were sampled in the same manner as Experiments 1, 2 and 3. It may be the case that some participants in the control group experienced high levels of visual-stress when undertaking the pattern-glare test but these individuals did not experience migraines. Only a small number of MA participants in Study 4 experienced unilateral pain or unilateral visual aura. Between-group comparison of results was therefore difficult. Illustrative graphs are provided in Chapter 5 to demonstrate the possible effect of unilateral migraine pain on the amplitude and latency of the VEP. Due to the small group numbers no analysis was conducted on the results for participants who experienced unilateral aura. Future research could investigate the effect of unilateral migraine aura on the amplitude of P1 and N2 components.

8.8   Main Findings

Increased sensitivity to visual stimuli has been demonstrated in the visual field affected by a unilateral aura relative to the unaffected field. These results are consistent with the hypothesis of a hyperexcitability of the visual cortex in migraine. A consistently unilateral visual aura may indicate a region of the cortex that is particularly susceptible to cortical spreading depression. A susceptibility to CSD at a particular site may reflect hyperexcitability in this region. The results described in Chapter 2 are not inconsistent with a model of hyperexcitability in which there is a greater neuronal response without an increase in the level of background noise (Shepherd, 2007). Contrast discrimination threshold was lower for both migraine groups in Chapter 2 although not significantly so. The within-subject differences observed for individuals who experience unilateral aura may indicate an increased neuronal firing rate of a small population of neurones, relative to the average, at the affected site in the cortex. This would produce a greater response in the affected field relative to the unaffected field. Hyperexcitability may therefore be non-uniform in the visual cortex. One might speculate that there are important differences in visual processing in individuals who experience aura at different sites within the visual field. Differences between individuals who experience aura at a consistent site in the visual field and those for whom the aura varies in location may also help reveal the effects of hyperexcitability on visual processing.

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Appendices

Appendix A

Question 1: Have you ever experienced a headache attack that lasts between 4 and 72 hours when left untreated or unsuccessfully treated by pain medication?

(Please tick the appropriate box)

□ YES

□ NO

Question 2: During an attack, do you experience any of the following symptoms:

(Please tick the appropriate boxes)

□1. Headache occurs in only part of the head, for example only on the left or right side.

□2. Headache has a pulsating or pounding quality.

□3. Headache is of moderate or severe pain intensity.

□4. Headache symptoms are aggravated by routine physical movements or cause avoidance of normal daily activities.

Question 3: Have you experienced an attack that is associated with one or both of the following two symptoms?

□a. Nausea and/or vomiting.

□b. Strong urge to avoid light or sound.

Question 4: Please estimate the total number of headache attacks you have experienced with the qualities mentioned in the previous 3 questions.

□ 1-2 in my lifetime

□ 2-4 in my lifetime

□ 5 (or more) in my lifetime

Question 5:Please estimate the monthly frequency of headache attacks you experience characterized by the qualities mentioned in questions 1-3.

□ Less than 1 per month

□ 1-3 per month

□ 3-10 per month

□ More than 10 per month

Question 6: Do you have a history of the following:

□ Severe head and/or neck trauma

□ Stroke and/or other vascular disorders (Transient Ischemic Attack)

□ Brain disease or infection

□ Seizures

□ None of the above

Any other brain or neck-related medical event (Please specify below).

Question 7: Have you ever been prescribed glasses or contact lenses? If yes, what was the prescription for (long or short-sightedness)?

Question 8: Have you ever been prescribed coloured glasses by an optometrist or medical professional?

□YES

□NO

Question 9:Do you have normal colour vision?

□YES

□NO

Question 10: I have been told by a medical professional that I have:

□ Migraine with aura

□ Migraine without aura

□ A headache disorder

□ I have not been diagnosed with migraine or any other headache disorder

Question 11: If you experience aura that is associated with your migraines please specify the symptoms below:

□ Temporary visual disruptions such as flickering lights, patterns or spots and/or loss of all or some vision.

□ Temporary sensory disruptions such as pins and needles or feelings of numbness.

□ Difficulty in speaking or understanding speech.

How soon after the aura starts does the headache begin?

Question 12: Current migraine status:

Are you currently experiencing a headache or migraine attack?

□YES □NO

Do you believe that you are likely to have a migraine in the next 1-3

days?

□YES □NO

Have you experienced a headache within the last 3 days?

□YES □NO

Are you currently on any medication?

□YES □NO

If your medication is a treatment for migraine, please specify the name and dose of the drug.

Question 12: Current migraine status:

How often do you take medication for your migraines?

□ Everyday to prevent a migraine

□ Only to relieve the pain once started

Please indicate how this medication is administered.

□ Orally (tablets or liquid)

□ Injection

For how many years have you been experiencing migraines?

Question 13: Please indicate the length of time since your most recent migraine attack.

Question 14: Food-related triggers:

(Please tick all that apply.)

□ Certain foods (e.g. chocolate, dairy products, citrus, etc.)

□ Missing meals

□ Dehydration

□ Alcohol

□ Caffeine

Question 15:Environmental triggers:

(Please tick all that apply.)

□ Light

□ Computer screens

□ Pollen

□ Mould

□ Loud Noise

□ Cigarette smoke

□ Fumes from cars, paint etc.

□ Menstruation

Question 16: If you always experience pain on one side of the head is it:

□ Always left side of head

□ Both sides of head

□ Always right side of head

OR does the pain vary in location?

□ Sometimes left side of head

□ Sometimes both sides of head

□ Sometimes right side of head

Question 17: Do the visual phenomena you see before the headache vary in location:

☐ Sometimes left side of vision

☐ Sometimes right side of vision

☐ Sometimes both sides of vision
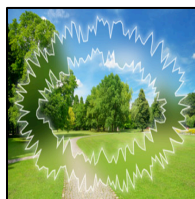
OR are they always the same

☐ Left side of vision

☐ Right side of vision

☐ Both sides of vision

Approximately how many headaches do you have in a year?

Appendix B

Equations for the approximation of the Planckian locus reported in Chapters 3 and 4.

The Planckian locus can be approximated from a colour temperature of 1667K to 8000K.

$$
x_c = \begin{cases} -0.2661239 \dfrac{10^9}{T^3} - 0.2343580 \dfrac{10^6}{T^2} + 0.8776956 \dfrac{10^3}{T} + 0.179910 \quad 1667K \leq T \leq 4000K \\[2ex] -3.0258469 \dfrac{10^9}{T^3} + 2.1070379 \dfrac{10^6}{T^2} + 0.2226347 \dfrac{10^3}{T} + 0.240390 \quad 4000K \leq T \leq 25000K \end{cases}
$$

$$
y^c = \begin{cases} -1.1063814 x_c^3 - 1.34811020 x_c^2 + 2.18555832 x_c - 0.20219683 \quad 1667K \leq T \leq 2222K \\ -0.9549476 x_c^3 - 1.37418593 x_c^2 + 2.09137015 x_c - 0.16748867 \quad 2222K \leq T \leq 4000K \\ +3.0817580 x_c^3 - 5.87338670 x_c^2 + 3.75112997 x_c - 0.37001483 \quad 4000K \leq T \leq 25000K \end{cases}
$$

$$
u' = \frac{4X}{X + 15Y + 3Z} = \frac{4x}{-2x + 12y + 3}
$$

$$
v' = \frac{9Y}{X + 15Y + 3Z} = \frac{9y}{-2x + 12y + 3}
$$

Appendix C

An example passage from the Wilkins Rate of Reading Test.

come see the play look up is cat not my and dog for you to

the cat up dog and is play come you see for not to look my

you for the and not see my play come is look dog cat to up

dog to you and play cat up is my not come for the look see

play come see cat not look dog is my up the for to and you

to not cat for look is my and up come play you see the dog

my play see to for you is the look up cat not dog come and

look to for my come play the dog see you not cat up and is

up come look for the not dog cat you to see is and my play

is you dog for not cat my look come and up to play see the

see the look dog and not is you come up to my for cat play

not up play my is dog you come look for see and to the cat

look up come and is my cat not dog you see for to play the

my you is look the dog play see not come and to cat for up

for the to and you cat is look up my not dog play see come

you look see and play to the is cat not come for my up dog

come not to play look the and dog see is cat up you for my

and is for dog come see the cat up look you play my not to

dog you cat to and play for not come up the see look my is

the come to up cat my see dog you not look is play and for

Appendix D

The repeatability of colorimetry is precise(ly) as expected

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Abstract

The purpose of the study was to assess the repeatability of clinical assessments with the Intuitive Colorimeter, a repeatability classified as "poor" in a previous study. Patients underwent assessments with the Intuitive Colorimeter in two studies. In each study, one published by Suttle et al[1] and the other described herein, assessments were undertaken on two occasions. The studies differ in respect of the models of colorimeter used, the methods employed, the interval between examinations, and the masking of examiners. The repeatability was assessed using the methods currently used in clinical practice, which differ according to examiner. Both studies show a similar repeatability of the assessments. This repeatability is consistent with previous literature. We estimate the standard deviation of u' and v' coordinates each to be 0.020 and thereby obtain an estimate of the number of tinted trial lenses necessary when prescribing coloured filters. In patients with visual stress assessment with the Intuitive Colorimeter is repeatable. The minimum number of tints necessary for assessment is estimated to be 77.

Introduction

A technical note in Ophthalmic and Physiological Optics has suggested that the repeatability in choosing coloured overlays and lenses is "poor"[1]. It is shown here that the repeatability of colorimetry is consistent with previous literature, and a study is reported that confirms the repeatability under masked conditions.

The Intuitive Colorimeter is an instrument that is used to obtain a tint that reduces visual stress. It illuminates text with coloured light and permits the separate manipulation of hue and saturation without an associated change in luminance. In the first such instrument[3], light from three coloured filters was mixed in different proportions. In a subsequent design[4], seven coloured filters were used to ensure that the spectral power distribution of the light in the instrument closely resembled that obtained when coloured spectacle lenses were worn under typical office lighting.

The process of tint selection is subjective. The text is illuminated by light of one hue and the saturation increased and decreased at that hue in order to assess all shades of this hue in comparison with white. The hue is then changed and the process repeated for 12 hues. Having short-listed those of the 12 associated with an improvement in visual comfort, the hue and saturation are alternately adjusted by small amounts so as to evaluate hues that lie between those originally examined. The best overall combination of hue and saturation is thus obtained under conditions in which the eyes remain colour adapted. Combinations of tinted trial lenses are then offered that match the chosen chromaticity under office lighting. From seven dyes are chosen two with neighbouring chromaticity. Each dye has five lenses with a geometric progression of dye deposition. By combining the lenses $2^5 - 1 = 31$ levels

of deposition are available for each dye. When the two dyes are combined the 31*32=992 combinations of lenses sample the appropriate chromaticities so as to provide a visible match to any colorimeter setting.

The Intuitive Colorimeter described above was initially designed as a research tool to investigate the improvement in visual comfort with different colours[5] but has subsequently found clinical use in eye-care practice.

Suttle et al classify colorimetry as having "poor" repeatability because the number of Just Noticeable Differences (JNDs) between two measurements is large. JND refers here to the difference that is just noticeable when two coloured surfaces are observed side by side, as is the case with coloured overlays. JNDs have previously been used[2] as an adjunct to the unfamiliar concept of chromaticity difference, with the McAdam ellipses as a guide. When two surfaces are simultaneously visible, very small differences in chromaticity are discernible, partly as a result of opponent processes. It is not clear from the paper by Suttle et al how the JNDs were derived, but it could be argued that the use of JNDs is inappropriate in the context of colorimetry. During colorimetry coloured lights are presented successively. Any comparison involves not only adaptation to the colour but memory for colours previously shown. This inevitably increases variability.   JND is a subjective measure, whereas chromaticity difference is a physical measure that is directly related to the relative energy captured by the three classes of cones. For this reason only chromaticity difference is used in this paper. It is shown that the repeatability of assessment with the Intuitive Colorimeter is as would be anticipated from previous literature.

Some idea of the likely repeatability of the colorimetry assessment can be obtained in various ways, as will now be described.

The first method of estimating the likely repeatability is from studies that presented text under coloured light and repeatedly required observers to report any reduction of perceptual distortion, recording the chromaticities associated with such reduction. The paper that first described the device also described such a study[6]. A small sample of three children reported a reduction of perceptual distortion with light of particular chromaticities. From the graphs provided for each individual, the average separation between all pairwise combinations of chromaticities has been obtained, and the average (SD) was 0.046 (0.026) for participant A, 0.064 (0.03) for participant B and 0.052 (0.032) for participant CD (a participant who was examined on two occasions, C and D).

A second method of judging the likely repeatability involves describing the boundary in the chromaticity diagram within which perceptual distortions abate. This method was used in a subsequent paper[2] that reported a double-masked study. Twenty-three participants were asked to select a chromaticity that reduced their perceptual distortions. The hue was then altered progressively until the distortions returned. The average difference in chromaticity between the two settings was 0.065[2].

A third method of judging the likely repeatability is more objective and involves measuring the effect of the tint on reading speed. Five individuals who used coloured lenses were asked to read randomly ordered common words aloud rapidly, without their lenses, under light of randomly chosen chromaticities[7]. The reading speed was plotted as a function of the chromaticity difference between the colour used for reading and that selected as

optimal for clear perception of the text. It can be seen from Figures 1 and 2 in reference 7, which show the variability of the observations, and from Table 1 in reference 7, which shows the parameters of the curve fitting, that for all individuals, there was a progressive decrease in reading speed with chromaticity difference. Little beneficial effect of the colour was apparent when the chromaticity difference reached 0.07 (ΔE^* = 91, see Appendix of reference 7).

From the above studies, involving 3, 23 and 5 individuals respectively, it appears that the beneficial effects of the colour are lost when the chromaticity of a light differs by 0.07 from that selected as optimal for the perception of the text as "clear and comfortable". This inference is supported in four studies involving more than 80 participants in which active and placebo lenses differed in chromaticity by 0.065 - 0.07. Two were masked studies of symptoms that improved with active lenses more than with the control[2,8]. Two involved measurement of the characteristics of the cortical haemodynamic response to uncomfortable patterns, and showed a normalization only with the active tint and not the control[9,10]. In all four studies, both those with and without high rates of attrition, the effects of the optimal tint were greater than those of the placebo. This indicates that a chromaticity difference of 0.07 is sufficient to reduce the clinical efficacy, and sets limits on the effective chromaticity.

In the paper by Suttle et al.[1] participants were considered to have visual stress if they reported one or more symptoms of visual discomfort or distortion while reading, and they reported alleviation of symptom(s) with a coloured overlay. This selection process is possibly more lenient than implied by the practical diagnostic guidelines suggested recently[11] but the study was conducted before these were available. Participants were

asked to view text and to report any symptoms experienced. If any symptoms were reported, participants were then asked to observe the text through each of the ten Intuitive Overlays (starting with Rose), individually and then in combinations of two, following the procedure previously described[12].

This was followed by assessment with the Intuitive Colorimeter[13] in a darkened room, following the procedure described earlier. The assessment was repeated at a second appointment between 2 and 57 days after the first. Only four individuals in the sample of 20 showed a difference in colorimeter measurements that was greater than 0.07. All four had poor consistency in the choice of overlay.

Numerical methods were used to estimate the probability of chance occurrence of colorimeter settings as close as those obtained. The first settings were re-paired with the second settings randomly across participants, and the average chromaticity difference calculated. This was done 1000 times and 34 such re-pairings gave a chromaticity difference less than that obtained from the correct pairing. On this basis the chance occurrence of the chromaticity difference obtained may be estimated to be 0.034.

Given the above, the repeatability of colorimetry judgments was as might have been expected from the previous literature. It was also somewhat better than might have been expected had observers simply memorised the hue. D'Ath et al[14] required healthy observers to reproduce a previously displayed screen colour in a darkened room by varying hue (h_{uv}) with saturation constrained to lie on a circle radius 0.060, centred on the chromaticity of D65. The average difference between the original hue (h_{uv}) and that reproduced one hour later was 48 degrees; a difference in chromaticity of 0.049. This

difference may be compared with the difference of 0.035 in the previous paper[1] with the "consistent" participants (those who chose overlays of the same or similar colour).

In the following study colorimetry was undertaken twice on the same day by two independent masked examiners using different instruments and the procedures in current clinical practice, so as to assess the repeatability in typical use.

Method

Participants

Twenty participants were recruited from patients attending the Anglia Ruskin University Eye Clinic for assessment of visual stress. (See Table 1). Written consent was obtained from the individual or a parent. All methods were approved by the Anglia Ruskin University Faculty of Science and Technology Research Ethics Panel. The details of the patients and their results are given in Table_1. The extent to which the patient selection conformed to the criteria for visual stress recently introduced by Evans et al[11] can be judged from Table 1. 15 participants had used an overlay for >3 months. All read more quickly with an overlay but only in 16/20 was the increase in reading speed greater than 15%; 15/20 had Pattern Glare scores of more than 3; 17/20 had 3 or more symptoms. Overall, 16 patients satisfied the criteria[11].

Procedure

Participants underwent an extended eye examination and colorimeter assessment that was conducted by optometry students in the clinic under the supervision of RLP. An Intuitive Colorimeter Mk. 3 (Cerium Visual Technologies, Tenterden, Kent) was used to identify a colour of illumination that maximized comfort and reduced perceptual abnormalities.

The colorimetry assessment followed the practice at Anglia Ruskin of restricting the saturation to 30. The assessment is thereby simplified for students, and avoids the provision of hues that are too dark; the final assessment is reviewed by the supervisor, and revised if necessary. The second assessment did not restrict the saturation and followed the procedure described in the Colorimeter Manual (Cerium Visual Technologies)[13]. The difference in the colorimetry procedure will have increased the difference in the chromaticities obtained, but the central concern in this paper was to study the repeatability of colorimetry under the conditions that currently obtain in clinical practice, including differences in procedures and instruments.

Two lens stacks were prepared using the trial lenses supplied with the colorimeter and worn in a lens holder mounted on a headband. One stack was *active* (matching under office lighting the chromaticity selected by the participants as optimal) and one *placebo* having CIE 1976 UCS chromaticity that differed by an average of 0.078 (SD = 0.02). The placebo was selected by a spreadsheet that chose a similar combination of lenses but with different dyes. There are seven dyes in the colorimeter system that can be arranged in a hue circle. The placebo lenses differed by two steps on this circle and had a transmission similar to that of the active lenses.

A second examiner (AA) who was not party to the identity of the two lens stacks administered the Wilkins Rate of Reading Test four times, A-D. One set of lenses, chosen at random, was used for passages A and D and the second set for B and C.

The patient was then debriefed to allow them to leave if they wished. All consented to remain and underwent a second colorimeter assessment conducted about one hour after the first by examiner AA. (In normal observers, memory for coloured lights after one hour is similar to that after one week[14]). The second assessment used an Intuitive Colorimeter Mk. 2. This machine has the same filters as the Mark 3, but has a very different appearance. The second examiner had no knowledge of the results of the first examination.

Both the examiners who undertook the colorimeter examination gave a rating reflecting their assessment of the certainty with which patients were able to choose their optimal chromaticity. Individuals who identified an optimal colour and did not deviate, were given a consistency rating of "good"; those who were unsure or for whom the colour was repeatedly adjusted were rated "poor." Those participants who identified a colour with only minimal adjustment were rated "moderate." The examiners gave their ratings independently without knowledge of the rating given by the other examiner.

Results

Participants as a group read more quickly with the 'active' set of lenses: 132 words per minute compared to 123 words per minute with 'placebo', one-tailed $t(19)$ = 2.61, p = 0.0086, d=0.16. Note that a one-tailed test was used because the hypothesis is directional. The two-tailed test was also significant (p=0.017).

Of the 20 participants, 16 were rated as "good" or "moderate" by both examiners. Three were rated as "poor" by both examiners. Only one was rated "good" by one examiner and "poor" by the other. Cohen's Kappa was 0.0365, and the association between the ratings expressed in a 3x3 contingency table was significant by Fisher's exact test, p=.011.

The rating was significantly related to criteria for the diagnosis of visual stress proposed in a Delphi study by Evans et al[11] (see Table 4 of reference 11). To pass the criteria participants needed two of the following three signs: 3 months' use of overlays, an increase in reading speed of 15% or more with an overlay, a Pattern Glare score of more than 3 with a mid spatial frequency grating. They also needed 3 of 6 typical symptoms. The signs are shown as present (1) or absent (0) in columns 4-6 of Table 1. The number of symptoms is listed in column 7. The three patients rated "poor" by both examiners did not meet the Delphi criteria for visual stress[11]. To analyse this contingency statistically, the examiners' rating was converted to a numerical value by summing a score of 2 for "Good", 1 for "Moderate" and 0 for "Poor" across both raters. The mean rating score for the individuals who passed the criteria for visual stress was 3.56 and for those who failed 1.0, two-tailed $t(18)$=4.59, p=.0002, d=1.73.

Overall, the mean difference in chromaticity between the two colorimetry assessments was 0.043 (SD 0.027), median 0.037. The difference was smaller for the 16 participants who were rated by both examiners as either "good" or "moderate": 0.037 (SD 0.022), median 0.033. For the three participants rated "poor" by both examiners (omitting the one participant who was rated "good" by one examiner and "poor" by the other) the difference in the chromaticity of the two colorimeter assessments averaged 0.083 (SD 0.011), median 0.086. The similarity between the two colorimeter assessments was significantly greater in the participants rated as "good" or "moderate" by both examiners than those rated as "poor" by both (two-tailed $t(17)=3.42$, $p=.003$, $d=1.79$). However, the number of "poor" participants was small. The chromaticities are shown in Figure 1.

Given that the first colorimetry assessment was non-standard and restricted the saturation to 30, the two assessments are perhaps best compared in terms of the hue chosen rather than the combination of hue and saturation and associated chromaticity. The hue was identical in 7 of the 20 participants and differed by 30 degrees or less in 16 of the 20. The probability of the agreement occurring by chance was estimated numerically as follows. The pairing of one hue setting with another was randomised across the 20 participants, and the difference in hue angle squared (to remove the effects of the sign of the difference) and summed. The process was repeated 1000 times and only six of the 1000 repetitions gave a sum lower than that obtained from the correct pairing. A similar analysis of the chromaticity differences was also undertaken. The Euclidian distance in UCS between the two colorimetry assessments was obtained (by Pythagoras) when the pairing was randomised across participants 1000 times. None of the chromaticity differences obtained from such randomisation was as small as that obtained from the correct pairing.
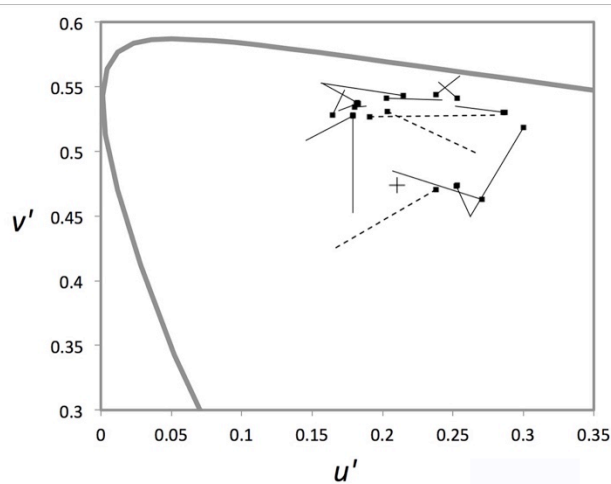
Figure 1. The chromaticities obtained in the first colorimeter assessments are marked by a point. They are connected by a line to the chromaticities from the second assessment. Broken lines represent the participants whose consistency was rated as poor by both examiners. In the first assessment saturation was constrained to 30, so the second assessment usually gave chromaticities that were more saturated (i.e. further from equal energy white, shown by the cross).

Discussion

Under conditions in which the examiner was masked, the patients read randomly ordered common words more quickly with lenses tinted to match their colorimeter setting than with lenses that differed by 0.078 in chromaticity. Fourteen patients had not had prior experience with trial lenses. None had had experience with the particular lenses associated with their colorimeter setting. Reading randomly ordered words is artificial, and the numerical difference in reading speed is small, but the task has validity in predicting benefit from the use of coloured filters[5].

The examiners concurred in their assessment of the quality of the judgements given by their patients: 14/20 of the assessments were identical and 19 (all but one) were similar. The patients who passed the criteria for visual stress received higher ratings, supporting the criteria proposed by Evans et al[11]. The ratings predicted both the repeatability of the two assessments and the benefit from the tint. This suggests that examiners can infer the likely repeatability of patients' judgements during one colorimetry session. These

judgements are likely to be of clinical use. It has been shown that the benefits of a coloured filter in increasing reading speed are greater in patients who give consistent results[16].

The repeatability of the two colorimeter examinations was similar to that obtained earlier by Suttle et al,[1] notwithstanding (1) the masked protocol; (2) the use of different models of colorimeter; (3) different assessment procedures, one restricting saturation; (4) a shorter but consistent interval between the two assessments. The similarity between the two studies is encouraging. For the "consistent" observers in the earlier study[1] i.e. those who chose the same or similar overlays, the colour difference averaged 0.035. It averaged 0.053 for the "inconsistent" participants. The findings in the present study were similar: the colour difference for participants rated as "good" or "moderate" by both assessors averaged 0.037, as compared with 0.067 for the remaining four participants.

The mean chromaticity difference for the consistent participants was averaged for the two studies (the present study and the previous study[1]) and was 0.036. The standard error of this mean was estimated from the standard deviation of data from both studies and was $0.026/ \sqrt{40} = 0.0041$.

The cluster of points in a chromaticity diagram that are associated with improved clarity can be modelled most simply as a bivariate normal distribution in which the distribution of points is centred on an optimal chromaticity; i.e. their u' and v' coordinates are independently and normally distributed, see Figure 2.
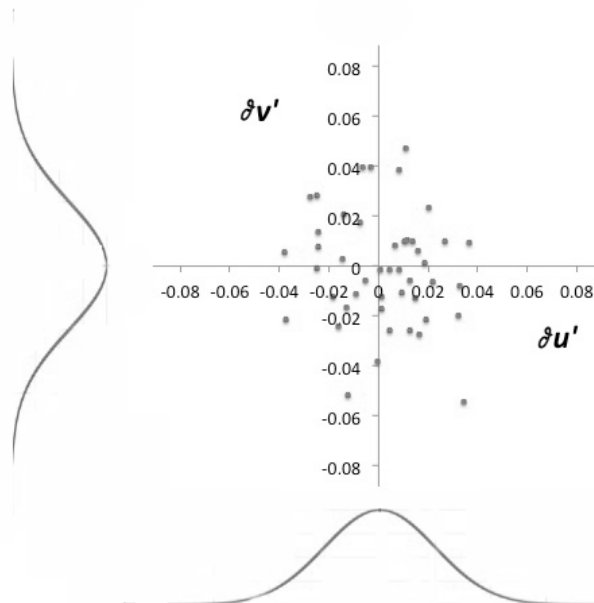
Figure 2. Distribution of hypothetical colorimeter adjustments centred on a single optimal chromaticity with a bivariate normal probability density. The optimal chromaticity is at the origin and the axes show the departure from optimum in units of u' and v'. The separation of any two points averages 0.036. The standard deviation of the points, σ, is therefore $0.036/\sqrt{\pi} = 0.020$.

The average difference between two points in a bivariate normal distribution is the square root of pi times the standard deviation. The standard deviation of the u' and v' coordinates can therefore be estimated to be $0.036/\sqrt{p} = 0.020$ with lower and upper confidence limits (estimated from the standard error of the mean given earlier) of 0.016 and 0.025 respectively. In the introduction reference was made to a chromaticity difference at which little benefit remains. The difference was 0.07 and this corresponds to more than three standard deviations.

The standard deviation of the u' and v' coordinates permits an estimate of the number of tints needed for a tinting system that will offer patients a sufficient range of tints. The chromaticity diagram can be most efficiently tessellated by hexagons, the centre of each hexagon representing the chromaticity of a trial lens. For a system to have a sufficient

number of trial lenses, there should always be a lens available that is no more than (say)

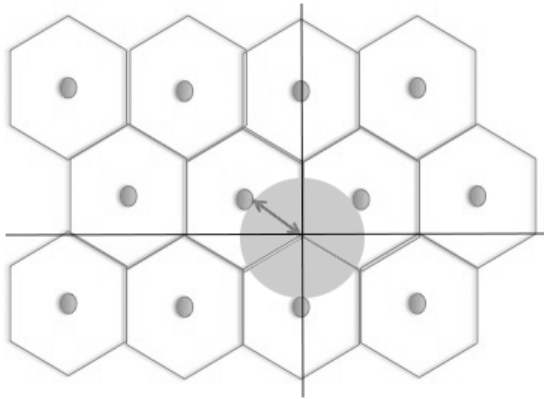one standard deviation distant from the chosen chromaticity, as in Figure 3.

Figure 3. A UCS surface tessellated by hexagons. At the centre of each hexagon is the chromaticity of a trial lens. The scatter of chosen chromaticites is represented by the grey circle with its centre at the intersection of the horizontal and vertical axes, as in Figure 2. The chromaticities of the trial lenses closest in colour are one standard deviation from the centre of the scatter, as represented by the arrow.

This will occur when the side of the hexagons is equal to one standard deviation and the

area of each hexagon is therefore 3/2 x $\sqrt{3}$ x 0.020^2 = 0.00104. The area of the gamut

available for use with conventional CR39 dyes that transmit more than 5% is given as 0.08

in reference 17. Therefore 0.08/0.00104 = 77 tints are required to cover this gamut with a

resolution of 1s. The estimate of s given above has confidence limits that may be estimated

from the mean +/- 2 standard errors of the mean. The lower and upper confidence limits of

the estimate of the number of tints required are thus 39 and 222 respectively. The

estimates are similar to those from a previous study based on different methods and data[17].

Although a system with hexagonally tesselated tint chromaticites would be efficient, it

might be difficult to maintain the necessary accuracy of each tint. It is therefore more

realistic to use a larger number of trial lenses with greater tolerance. The chromaticities of

the trial lenses in the Intuitive Colorimeter system show no gaps in the distribution of chromaticities that are larger than 0.020[6,7].

The above analyses have used the CIE UCS diagram rather than a cone-opponent diagram. This use maintains continuity with previous reports of colorimetry. The approach is supported theoretically by the observation that both discomfort and its physiological correlate, the amplitude of the cortical haemodynamic response[9,18], are both affected strongly by the difference in CIE UCS chromaticity, and not so strongly with other measures of colour difference based upon cone contrasts, see Table 2 of reference 19.

Suttle et al[1] use their findings to suggest that either "the use of colour to alleviate discomfort or difficulty reading is not a valid approach, or that the use of colour is valid but the colour does not need to be precise." The first inference is not valid and the second depends on what is meant by precision. The findings presented here are entirely consistent with previous literature. They show that when colour improves reading speed it does so optimally only if within about 0.020 of the CIE 1976 UCS chromaticity chosen as providing "clarity and comfort" of vision.

Acknowledgements

Dr Kalvis Jansons provided useful comments.

Declaration of interest

The last author (AW) invented the Intuitive Colorimeter when he was employed by the UK Medical Research Council. He receives emoluments from the Council, and from Essex University based upon sales of the colorimeter and the Wilkins Rate of Reading Test, but not for the sale of coloured lenses. AW and PA have received honoraria for lectures on the use of coloured lenses in eye care practice. The other authors have no conflicts of interest to declare.

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