Visual Stress in Migraine: Subjective and Psychophysiological Responses to Intense Visual Stimulation

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Abstract

This dissertation assesses whether intense visual stimulation can act as a stressor to migraine sufferers between attacks, and whether subjective and psychophysiological reactions to these stimuli can clarify how migraine attacks may be triggered.

The first study assessed thresholds of light-induced discomfort and pain in migraine sufferers and non-migrainous controls during a non-headache period. Two instruction sets were compared to assess whether information presented to participants would affect thresholds. The results showed that migraineurs had significantly lower thresholds for light-induced pain. However, this effect was most apparent in those who had heard the negatively biased instructions reinforcing the need to control contextual factors when assessing subjective phenomena such as visual discomfort.

The second study assessed subjective and psychophysiological responses of female migraine sufferers and female controls during exposure to visual stimuli incorporating spatial and temporal characteristics that are most likely to be bothersome to migraineurs. Two control stimuli were included to assess responses during similar, but theoretically less aversive conditions. Migraine sufferers had higher heart rate and more frequent electrodermal responses than controls at all points of the study, including baseline and recovery. However, while migraineurs reported higher anxiety during the intense conditions, and reported more visual and somatic complaints than controls during various viewing conditions, they did not show heart rate, heart rate variability or electrodermal changes that would suggest clear changes in autonomic function in response to aversive visual stimulation.

The third study assessed ambulatory electrocardiograms to investigate whether autonomic changes would be evident in the period leading up to, during or following a migraine. Three individuals were assessed on a day when they experienced a naturally occurring headache, and on a day when they were not. No obvious pattern of autonomic change was detected before or after headache, although there was some evidence that a pattern of increased heart rate and decreased vagal tone may accompany headache.

In summary, the results confirm that migraine sufferers are more sensitive to intense visual stimulation than controls, but do not support the contention that exposure results in widespread autonomic changes. Since interictal visual discomfort is a common in migraine, further research is needed to clarify how it can be incorporated into models of migraine pathophysiology.

Résumé

Trois études ont été effectuées afin d'évaluer si les stimulations visuelles intenses peuvent agir comme stresseurs chez les gens souffrant de migraine, et si les réactions subjectives et psychophysiologiques associées à ces stimuli peuvent clarifier la question à savoir comment les attaques de migraines sont engendrées.

Dans la première étude, nous avons évalué des seuils d'inconfort et de douleur provoqués par la lumière chez des gens souffrant de migraine et chez un groupe contrôle ne souffrant pas de migraine pendant une période dépourvue de maux de tête. Deux séries d'instructions ont été comparées afin d'évaluer si l'information présentée aux participants pourrait affecter les seuils. Les résultats démontrent que les gens souffrant de migraine avaient des seuils de douleur provoqués par la lumière significativement plus bas. Par contre, cet effet était plus marqué chez ceux qui avaient entendu des instructions biaisées négativement, renforçant le besoin de contrôle des facteurs contextuels lors de l'évaluation des phénomènes subjectifs tels que l'inconfort visuel.

Dans la deuxième étude, les réactions subjectives et psychophysiologiques de femmes souffrant de migraine et de femmes du groupe contrôle ont été évaluées durant leur exposition à des stimuli visuels qui incorporaient les charactéristiques spatiales et temporelles les plus probables à gêner les individus souffrant de migraine. Deux stimuli contrôle ont été inclus afin d'évaluer les réactions durant des conditions semblables mais théoriquement moins aversives. Les gens souffrant de migraine avaient un rythme cardiaque plus élevé et de plus fréquentes réponses électrodermales que ceux du groupe contrôle tout au cours de l'étude y compris la période entre le début et la fin des stimuli.

Par contre, alors que les gens souffrant de migraine rapportaient une plus grande anxiété pendant les conditions intenses et signalaient de façon plus fréquente des plaintes visuelles et somatiques que le groupe contrôle pendant diverses conditions d'observation, ces mêmes sujets, ne démontraient pas un rythme cardiaque, une variabilité dans celui-ci ou des changements électrodermales ce qui suggèrent clairement un changement en fonction autonomique en réponse à une stimulation visuelle aversive.

Dans la troisième étude, les électrocardiogrammes ambulatoires ont été évalués afin de déterminer si des changements autonomiques seraient évident lors de la période menant à, incluant, et suivant une migraine. Trois individus ont été évalués lors d'une journée pendant laquelle ils souffraient d'un mal de tête non-provoqué et lors d'une journée alors qu'ils ne souffraient pas de maux de tête. Aucune tendance de changements autonomiques n'a pu être discernée soit avant ou après le maux de tête bien que l'évidence indiquait qu'une tendance croissante du rythme cardiaque et décroissante de la tonicité vagale pourrait accompagner le maux de tête.

En résumé, les résultats confirment que les gens souffrant de migraine sont plus sensibles aux stimulations visuelles intenses que ceux du groupe contrôle. Mais les résultats ne supportent pas l'hypothèse que l'exposition provoque des changements autonomiques généralisés. Puisque l'inconfort visuel entre les maux de tête est commun dans le domaine de la migraine, d'autres études devront être effectuées afin de clarifier comment l'incorporer dans des modèles pathophysiologiques de la migraine.

Preface and Statement of Originality

The research presented in this dissertation provides original contributions to the study of subjective and psychophysiological responses that occur when migraine sufferers are exposed to intense visual stimulation. In particular, it evaluates whether aversive visual stimuli act as a stressor in the period between migraine attacks, and may contribute to pathophysiological changes that result in an episode. The presented studies build on an existing literature on visual sensitivity and autonomic function in migraine, and to a lesser extent a small number of studies that have combined these areas. However, each of the three studies presented addresses limitations of the previous research, further contributing to our understanding of these areas.

The first study assessed thresholds for photophobia in migraine sufferers and controls, adding to an existing literature that has investigated thresholds using different stimuli and threshold measures. However, this study also questioned whether information provided to participants prior to the measurement of thresholds would affect self-reported light sensitivity. While there was an existing literature to suggest that instructions can affect reports of pain, contextual factors had not been addressed in the study of visual discomfort in migraine.

The second study of this dissertation assessed whether exposure to intense visual stimulation could elicit subjective and physiological reactions that would clarify how these stimuli impact migraineurs between episodes, and how these responses may be involved in the initiation of a migraine episode. While migraineurs' reactions to intense visual stimuli had been referred to as "visual stress", there was little evidence to document whether migraineurs show subjective or widespread autonomic responses that

are more typical of traditional psychological stressors. The current study employed a more extensive assessment of subjective reactions and assessed heart rate variability and electrodermal responses, which had not previously been investigated in this context. It also incorporated a number of stimulus characteristics that have been shown to be particularly bothersome to migraineurs, thereby providing a more complete assessment of relevant visual triggers to discomfort.

The third study sought to determine the feasibility of using ambulatory recording to assess autonomic changes that accompany naturally occurring migraine episodes. Psychophysiological recording during migraine episodes has taken place in a laboratory setting, and ambulatory recording has been conducted during the interictal period. However, the two methods had thus far not been combined.

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List of Commonly Used Abbreviations

BDI	Beck Depression Inventory
BMI	Body Mass Index
ECG	Electrocardiogram
HCCIHS	Headache Classification Committee of the International Headache Society
HF	High frequency heart rate variability
HRV	Heart rate variability
Hz	Hertz (cycles or sample per second)
IBI	Interbeat interval in milliseconds (interval between R waves on ECG)
IG	Intense grating stimulus condition
I.H.S.	International Headache Society
IL	Intense light stimulus condition
LF	Low frequency heart rate variability
MA	Migraine with aura
MG	Mild grating stimulus condition
ML	Mild light stimulus condition
MO	Migraine without aura
RR	Respiratory rate in Hz (breaths per second)
STAI	State Trait Anxiety Inventory (Form X)
TH	Tension-type headache
VAS	Visual analogue scale

Chapter 1 – **General Introduction**

Migraine: background information

Clinical presentation and diagnostic criteria

Migraine is a condition that is typically associated with a throbbing headache of moderate to severe intensity. The headache is often unilateral or worse on one side, and sudden movements or exercise often worsen the pain or throbbing sensation. In addition to headache, other typical symptoms include nausea and sometimes vomiting, and an aversion to light (photophobia) and sound (phonophobia) at levels that would otherwise be considered normal. Some individuals also experience transient neurological symptoms, referred to as auras, which typically affect vision and can include flashing lights and blind spots in one visual hemifield. Auras can also affect other modalities such as touch and language.

While many of these symptoms have been associated with migraine for a long time, the combination of these symptoms required for a diagnosis of migraine has varied, making comparisons across research studies challenging. This is especially true since the diagnosis of migraine relies almost exclusively on the subjective description of headache characteristics and associated symptoms rather than on a laboratory test. Electrophysiological assessment and neuroimaging can be used to rule out other neurological conditions, but this is typically not done unless there are features of the presenting history that point towards other conditions (e.g. sudden onset of severe headaches). In order to facilitate the standard classification of headache disorders, the Headache Classification Committee of the International Headache Society (HCCIHS;

1988) established a set of diagnostic criteria that detail what symptoms are required for the diagnosis of migraine, other headache disorders, and facial pain. The diagnostic criteria for migraine with and without aura are presented in Appendix A. The criteria for tension-type headache are also provided, since together, migraine and tension-type headache are the most commonly diagnosed headache disorders. These criteria are most commonly referred to as the "I.H.S. criteria."

While not part of the diagnostic criteria, many other symptoms have been noted to present in association with migraine, some of which suggest autonomic disturbance. These symptoms include frequent urination, gastrointestinal disturbances (abdominal cramping, constipation, loose stools and sometimes diarrhea), blurry vision, enlarged pupils and tearing, nasal stuffiness, pallor and sweating (Silberstein, 1995; Silberstein, Lipton & Dalessio, 2001). Other associated symptoms include yawning, food cravings, anorexia, mood changes, social withdrawal, irritability, and vertigo. These symptoms may accompany the headache phase of a migraine attack, and may also occur in the hours or days before the onset of headache, in which case they would be considered part of the prodromal phase (Blau, 1992). While the aura phase typically does not last longer than one hour, the prodrome is considered a more vague and prolonged phase that precedes the migraine episode. Similarly, associated symptoms of migraine may outlast the headache phase, and often include fatigue, concentration difficulties, and feeling generally unwell. As such, any comprehensive psychophysiological theory of migraine must account for headache, but must also include explanations of how the neurological aura symptoms and more generalized symptoms that precede and follow an episode occur.

Epidemiology and impact of migraine

Migraine is a very common and often debilitating headache disorder that is more common in women than in men. A recent population-based telephone survey assessed the prevalence of migraine in Canadian adults and found that the lifetime prevalence of migraine with and without aura, as defined by the I.H.S. diagnostic criteria, was 24.9% among female respondents, and 7.8% among males (O'Brien, Goeree & Streiner, 1994). Prevalence rates of migraine episodes experienced in the past year were very similar (21.9% and 7.4% respectively). These rates resemble those from another Canadian study (Pryse-Phillips et al., 1992) and from a recent large-scale epidemiological survey conducted in the United States (Lipton, Stewart, Diamond, Diamond, & Reed, 2001). The latter study found prevalence rates of migraine experience within the previous year to be 18.2% of females, and 6.5% of males. These rates also correspond closely with those of population-based epidemiological studies in the United Kingdom, Denmark and France (see O'Brien et al, 1994 for review). The American Migraine Study II recently replicated an epidemiological study conducted 10 years earlier and revealed that migraine prevalence as defined by the I.H.S. criteria has remained very stable (Lipton et al, 2001).

The importance of understanding migraine in order to better treat and prevent this disorder is underscored by the significant impact migraine can have on the lives of those who suffer from it. In a study of Canadian adults with headache disorders, 50% of migraine sufferers reported being disabled to the point of canceling normal activities during an episode (Edmeads et al., 1993). In contrast, this level of disability was reported in only 18% of individuals with tension headache. Migraine episodes were reported to interfere with social plans and activities such as driving, and to have an adverse effect on

relationships with family, friends and colleagues. Of those with migraine, 11% reported that they sometimes did not report to work or had to leave early due to their headaches. This study also found that 64% of migraine sufferers reported having sought medical attention for their headaches. Of these, 41% had been further referred to a specialist (usually a neurologist) and 14% had used the emergency department for headache treatment. Other large studies in Canada (O'Brien et al, 1994) and the United States (Lipton, Diamond, Reed, Diamond & Stewart, 2001) have reported that approximately half of those who fit the I.H.S. criteria for migraine have seen and been diagnosed by a physician.

Together, the results of these studies highlight several important points. First, migraine is very prevalent in the general population. Second, migraine episodes cause pain and disability, often interfering with the normal activities of those who suffer from them, impacting family, social and work life. Third, migraine sufferers frequently seek medical consultation from primary care physicians, specialists and emergency departments, thereby incurring great cost to the Canadian health care system. Fourth, despite the fact that approximately half of migraine sufferers seek medical attention, half do not,which suggests that they do not have access to many of the currently available preventative and abortive treatments that could reduce disability. Finally, studies that include only clinic-referred samples may not be generalisable to the greater population of migraine sufferers.

Clearly, understanding more about migraine will contribute to better diagnosis, treatment and prevention, which will in turn impact a large percentage of the population. Despite several hypotheses that attempt to explain migraine etiology and

pathophysiology, some of which are discussed below, we still do not fully understand why migraine attacks occur, why some individuals are more vulnerable to migraine attacks than others, or what physiological processes occur to create the constellation of migraine symptoms. One important area of research needed to clarify some of these issues is the study of the cluster of visual symptoms that are common in migraine, as opposed to other headache disorders. This dissertation is focused on an examination of photophobia and visual discomfort, which are arguably the most common of these symptoms.

Visual involvement in migraine

Photophobia

General background on photophobia

Photophobia has been described as "an abnormal intolerance to light, usually associated with eye pain." (Martin & Corbett, 2001, p. 472). Others have added to the definition the idea that photophobia can take one of two forms: either a light-induced sense of glare or 'dazzle', or the worsening of pain in response to bright light (Drummond, 1997, p. 1857). According to Wolff (1963, Chapter 18), when it is not caused by physical damage to the eye, photophobia is characterized by both a motor component involving skeletal muscle, smooth muscle and the lacrimal glands, as well as a sensory component during which light is perceived as brighter and related to increased pain. The exact cause of photophobia in migraine is poorly understood, as are the mechanisms that underlie photophobia in general (Martin & Corbett, 2001). According to Martin and Corbett, several conditions that are associated with photophobia include:

1) disorders in which the anterior area of the eye is affected (e.g., corneal disorders, acute angle-closure glaucoma and cataracts), 2) vitreoretinal disorders and cancer-related retinopathy, 3) acquired optic neuropathies (e.g. optic neuritis), 4) intracranial diseases (e.g. meningitis, intracranial trauma), 5) central disorders (e.g. thalamic injury, trigeminal dysfunction), and 6) light deprivation. It is interesting to note that in their review, the authors imply that photophobia in migraine is linked to the intracranial aspect of the disorder. Another theory is presented by Drummond (1997), proposing that photophobia in migraine is caused by dysfunctional inhibitory subcortical processes. This theory is based on his finding that painful mechanical stimulation of the face and neck increased ratings of photophobia in migraineurs. More specifically, the hypothesis suggests that a link between trigeminal and visual inputs to the brainstem are involved in migraine, and that this process fails to inhibit sensations of glare and light-induced discomfort. Since the involvement of the visual system in migraine is complex and since the pathophysiology of migraine remains unclear, it is uncertain why photophobia is such a common symptom and how it is involved in the migraine process. Given the high prevalence of migraine, it is likely that this disorder is the most common cause of photophobia, especially since increased light-sensitivity is reported both during and between migraine episodes.

Photophobia during migraine episodes

As previously mentioned, increased sensitivity to light during a headache episode is one of the hallmark features of migraine and is included in the most widely accepted diagnostic criteria for the disorder (see Appendix A). While photophobia during a

migraine attack is not a necessary criterion for the diagnosis of migraine, several lines of evidence show that increased light sensitivity during migraine attacks is very common.

In one survey of migraine sufferers who had been diagnosed by physicians, 67% reported that they experienced photophobia with every migraine episode (Silberstein, 1995). Of those who did experience photophobia, the majority classified it as a severe symptom. Only 5% who experienced photophobia rated this symptom as mild in severity. Lab-based investigations have also demonstrated that during a migraine episode, migraine sufferers are more sensitive to light-induced discomfort than when they are headache-free, and also have lower thresholds than individuals who do not get migraines (Woodhouse & Drummond, 1993; Vanagaite et al., 1997).

Photophobia between migraine episodes

In addition to experiencing photophobia during headaches, migraine sufferers also describe being more sensitive to light between headaches. Migraine sufferers more often report being troubled by light on bright days and wearing sunglasses in normal daylight than non-migrainous controls (Mulleners, Aurora, et al., 2001). Laboratory studies have confirmed that in comparison to non-migraine controls, migraine sufferers have lower thresholds for light-induced discomfort and/or pain when they are headache-free (Drummond & Woodhouse, 1993; Main, Dowson & Gross, 1997; Woodhouse & Drummond, 1993; Vanagaite et al, 1997). The details of these studies are reviewed in the following chapter.

Martin and Corbett (2001) point out that while patients with photophobia may frequently wear sunglasses to cope with their sensitivity, this may in fact perpetuate the symptom since in the absence of disease processes or other disorders, light deprivation

alone can cause photophobia. Since migraineurs report wearing sunglasses even on cloudy days (Mulleners, Aurora, et al., 2001), attempting to avoid light seems to be a commonly used coping mechanism. A better understanding of photophobia in general, and more specifically how migraineurs react to light, would be beneficial in establishing whether avoidance is in fact adaptive.

Other types of visual sensitivity

In addition to experiencing sensitivity to bright lights, migraine sufferers report discomfort associated with a variety of other types of visual stimulation. Wilkins and colleagues (1984; see also Wilkins, 1995) conducted a series of studies to investigate the links between visual stimulus characteristics and reported illusions (e.g. motion, colors, and shapes), epileptogenic activity and headache. When pattern-sensitive epileptics were monitored by electroencephalograph (EEG), the stimulus characteristics that were most likely to result in epileptiform activity were also those that resulted in the most frequent reports of illusions and discomfort in individuals without epilepsy. According to this research, stimuli that are most likely to generate these consequences are striped patterns subtending a visual angle of at least three degrees. The patterns are most bothersome when viewed binocularly, and when the stripes are high in contrast (black and white as opposed to shades of gray), are of equal width and spacing, and when the stripes have a spatial frequency of approximately three cycles per degree of visual angle. Another characteristic that produces illusions and discomfort is flicker, particularly when temporal frequencies are in the range of approximately 10 to 20 Hertz.

According to research by Wilkins and colleagues (1984), there is a positive correlation between self-reported frequency of headaches and the number of illusions

reported when exposed to a striped pattern with the aforementioned stimulus characteristics. Also, those with unilateral headache, a prototypical feature of migraine, were most likely to report illusions and discomfort. While the Wilkins study did not formally classify headache diagnosis, more recent research has established a link between migraine and pattern-sensitivity. Marcus and Soso (1989) compared the behavioural responses of migraine sufferers and individuals with non-migrainous headache who were exposed to a series of cards displaying striped patterns. Testing was conducted when participants were headache-free. Eighty-eight percent of the migraineurs showed signs of aversion and visual discomfort such as looking away, grimacing and squinting when looking at the gratings, as opposed to 18 percent of the controls. Marcus and Soso (1989) did not use I.H.S. criteria for headache diagnosis, but a recent study that did employ these criteria found similar results (Mullneners, Aurora, et al., 2001). Mulleners and colleagues exposed migraine sufferers and controls to a series of striped patterns (spatial frequency: 3 to 4 cycles per degree) that increased in contrast and asked participants to indicate when the grating became visually stressful. Rather than using observations of participants' reactions, as Marcus and Soso (1989) had done, they asked individuals to report when they experienced visual stress which they defined as finding the grating bothersome, painful to look at, or irritating to the eyes. Migraine sufferers had lower thresholds than controls, needing less contrast before they were bothered by the grating. Thresholds of participants with migraine with and without aura were not statistically different.

Migraineurs may also experience prolonged or stronger after-effects and after-images, following exposure to intense visual stimulation. A recent study assessed

retrospective reports of the existence and duration of after-images following fundoscopy included as part of a general neurological outpatient clinic (de Silva, 2001). During fundoscopy, the bright light of an ophthalmoscope is shone into the eye for a matter of seconds. Of those who fit I.H.S. criteria for migraine, 62% reported experiencing an after-image, while only 25% of the non-migraineurs reported afterimages. While de Silva points out the need for further evaluation of this phenomenon using more standardized techniques and a variety of stimuli, this study provides strong support that increased susceptibility to afterimages is another indicator of heightened visual sensitivity in migraine sufferers. While afterimages are not necessarily aversive, this exaggerated or prolonged response to visual exposure may also reflect the hypersensitivity of the visual system in migraine.

The finding that migraine sufferers are sensitive to particular types of stimuli including high contrast stripes and flicker is important for at least two reasons. First, knowing what stimulus characteristics cause discomfort and can result in headache may provide guidance in creating environments that are less visually stressful for the relatively large proportion of the population that experiences migraines. Repetitive striped patterns are relatively abundant in modern industrialized settings. As Wilkins (1995) describes, escalator treads, horizontal blinds, wallpaper patterns and boldly patterned carpets are just a few examples of striped patterns in our every day environment. Flickering can be noted in fluorescent lights, computer monitors, strobe lights, and during naturally occurring situations such as driving along a tree-lined road while the sun is beginning to set. Clearly, not all of these items or conditions can be avoided. However, given that a variety of situations in the everyday environment can cause discomfort and possibly

trigger attacks in migraine sufferers, it worthwhile gaining a better understanding of this type of visual sensitivity. Research focused on establishing how migraineurs react to this stimulation and how this response interacts with the pathophysiology of migraine will improve both our understanding of migraine, as well as clarify how to reduce the impact of visual stress. Furthermore, by specifying the nature of visual stress, it will be easier to evaluate whether prophylactic treatments act on this symptom of migraine.

A second reason for investigating the nature of visual stress in migraine is to clarify how migraineurs are different from non-migraineurs between headache episodes and why they may be susceptible to light- and patterned-induced discomfort and headaches. Since the research on visual discomfort indicates that migraineurs are sensitive to specific spatial and temporal characteristics of visual stimulation, as are those with photosensitive epilepsy, this information may combine with our knowledge of human visual processing to tell us more about neurophysiological differences in migraine. While increased visual discomfort in migraine provides one source of evidence that the visual system functions differently in migraine, there are several other indicators that support this conclusion.

Other evidence for involvement of the visual system in migraine

Visual Aura

When asked to report symptoms experienced in association with a migraine attack, 73% of respondents in one study reported that they had had visual disturbances at least once, and 49 % indicated that they had visual problems with every episode (Silberstein, 1995). While visual disturbances can include many experiences, such as blurred vision during the attack, some migraineurs experience transient focal neurological

symptoms, referred to as aura, in association with their episodes. Typically auras occur before the onset of headache, although auras can occur during the headache as well. A recent epidemiological study found that 30% of the sample meeting I.H.S. criteria for migraine could be classified as having migraine with aura (Breslau et al., 2000). Auras can sometimes be the most prominent feature of a migraine episode, and for some individuals are only associated with a mild headache or no headache at all. In this case, the individual could be classified as having migraine with aura, without headache (HCCIHS, 1988).

Migraine auras can include a variety of neurological symptoms such as somatosensory sensations of numbness or tingling, and language or speech difficulties (see Olesen & Cutrer, 2000, for a more comprehensive review migraine aura variants), but they are most often visual in nature (Bana & Graham 1986; Manzoni, Farina, Lanfranchi & Solari, 1985). Visual symptoms can include both positive features such as sparkling lights and colors, and negative features such as blind or missing areas. The most prototypical type of visual aura involves arcs of scintillating zigzag lights and a scotoma or blind spot. The aura most commonly begins near the center of the visual field and gradually expands outwards into one hemifield, typically disappearing after 20 to 30 minutes. Aura episodes such as these have been described in some detail for more than a century (Airy, 1870; Alvarez, 1960; Hare, 1966; Lashley, 1941; Richards, 1971), often by scientists who have themselves experienced them. More recent studies have made systematic recordings of auras experienced by a larger number of individuals. These recordings, which ask migraineurs to draw, take note of, or take measurements of specific aspects of their auras as they occur, have improved our understanding of both the spatial

characteristics of aura (Jensen, Tfelt-Hansen, Lauritzen & Olesen, 1986; Russell, Iversen & Olesen, 1994; Wilkinson, Feindel, & Grivell, 1999) as well as the temporal aspects of flicker that many individuals perceive (Crotogino, Feindel & Wilkinson, 2001).

The systematic observations of the spatial and temporal characteristics of auras have provided support for the hypothesis that during visual aura, a wave of neuronal excitability followed by suppression travels through visual cortex. This spread of neural activation and suppression is typically referred to as cortical spreading depression, and is commonly included as a component in theories of migraine pathophysiology (e.g. Hardebo, 1992; Welch, 1998). Despite the common view that cortical spreading depression may be involved in migraine, how such a wave of activation is initiated or why migraine sufferers may be susceptible to such activity is unclear.

Our understanding of the mechanisms involved in migraine aura is the result of the careful investigation of a subjective symptom described by migraine sufferers for centuries. While understanding the aura is clearly an important step in elucidating the pathophysiology of migraine, the other symptoms of migraine must also be accounted for in a comprehensive model of the migraine process. Standardized assessment of other associated symptoms, such as visual sensitivity, will be needed before these symptoms can be adequately accounted for in a comprehensive model of migraine. This model will not only need to account for how symptoms occur during a migraine attack, but must also account for how migraineurs differ from controls between headache episodes.

Visual triggers

Increased visual sensitivity and visual aura both provide support for the notion that the visual system is involved in migraine. Another line of evidence supporting this

hypothesis is the finding that certain types of visual stimulation can trigger attacks. Specific triggers that have been reported include bright lights (Silberstein et al, 2001; Spierings, Ranke & Honkoop, 2001), and other environmental stimuli such as fluorescent lights, high contrast patterns, flicker, and alternating light and shade (Hay, Mortimer, Barker, Debney & Good, 1994). While the ability of visual stimulation to trigger attacks in some individuals may be due to subtle differences in the visual system of migraineurs between attacks, the mechanism by which visual triggers act is unclear. This is also true of other types of triggers, such as emotional stress or missing a meal, for which the link between the properties of the trigger, an individual's response, and the pathophysiology of migraine are unknown.

In order to understand the relationship between the visual system and migraine, research will need to move beyond simply evaluating the physical stimulus characteristics or properties of the purported trigger, and assess the broader context in which participants respond to the stimulus. For example, it is unclear what factors influence whether or not an individual with migraine is bothered by visual stimulation, or how exposure to certain visual stimuli can trigger pathophysiological events that initiate a migrainous episode. Martin and Teoh (1999) addressed some of these issues in an investigation of headache triggers. They found that while visual stimulation (a strobe light) induced headaches, the stimulation also led to higher ratings of negative affect drawing into question whether it is the visual characteristics or stress-inducing characteristics that cause headache. This study took a comprehensive approach, investigating both physiological and affective responses to visual exposure. However, for the majority of analyses that were reported, it grouped individuals according to their self-

reported triggers rather than headache diagnosis, thereby limiting the extent to which the findings can be applied specifically to the understanding of migraine.

Visual Evoked Potentials, Imaging and Transcranial Magnetic Stimulation

There are now several neurophysiological measures that allow researchers to investigate whether migraine sufferers show different neurological responses to visual stimulation, and whether visual areas of the brain show abnormal neurological responses either during headaches or between headaches.

Visual evoked potentials (VEP) assess an individual's EEG responses to repeated visual stimulation, averaged over many trials to extract a pattern of neurological reaction that directly follows stimulus exposure. While there have been many VEP studies of migraine sufferers, the results have been inconsistent. Some studies have found evidence that migraine sufferers' VEP responses show higher amplitudes and longer latencies of some components when exposed to flashes of light (Gawal et al., 1983), longer latencies to pattern-reversal stimuli (Mariani et al., 1990), and strong hemispheric response asymmetries to a flickering pattern (Nyrke, et al., 1990). However, it should be noted that other studies have failed to find statistically significant differences in VEP between migraine sufferers and controls (e.g. Raudino, 1988; Rossi et al, 1996).

In the study by Nyrke and colleagues, the stimulus flickered at six temporal frequencies, ranging from 10-24 Hz. Group differences emerged when the frequency ranged between 18-24 Hz, demonstrating that specific types of visual processing may be affected in migraine, rather than global differences. It is interesting to note that this frequency range is similar to the rate of flicker that is considered the most disturbing by headache sufferers (Wilkins et al., 1984), and is also the rate at which visual auras are

perceived to scintillate (Crotogino et al., 2001). Another interesting finding is that when exposed to pattern-reversal stimulation for an extended period, controls habituate, with their response amplitude diminishing over time. Migraine sufferers, on the other hand, either show no evidence of habituation (Afra et al, 2001) or show a potentiation of the response over time (Schoenen, Wand, Albert & Delwaide, 1995). Overall, the VEP literature in migraine seems to support the notion that the visual cortex of migraine is hyperexcitable in its response to visual stimulation, that the response may be specific to certain temporal frequencies, and that the response continues to occur when non-migraineurs would have habituated to it. Furthermore, studies have demonstrated that VEP differences are evident in childhood migraineurs (Marrelli et al., 2001), suggesting that differences in visual cortical function exist early in migraine history rather than developing only after years of experiencing headaches.

Brain imaging studies have provided evidence that the visual system is activated during attacks. Evidence demonstrating a wave of decreased blood flow moving through the cortex during episodes of migraine with aura has been noted for more than a decade (Olesen, 1987). Blood flow changes in migraine with aura continue to be investigated using newer imagine techniques. A recent study assessed blood oxygenation-dependent signals using functional magnetic resonance imaging (fMRI) in occipital cortex during an episode of migrainous visual aura (Hadijikani et al., 2001). This study found evidence of an increase in the signal, followed by a decrease in signal, spreading through striate and extrastriate cortex. The authors suggest that this activation may be due to a wave of vasodilation, followed by vasoconstriction. The activity followed a pattern and rate that is consistent with cortical spreading depression during aura.

In addition to the activation that occurs during aura, a phase that not all migraineurs experience, other studies have provided evidence there are alterations in activation in visual cortex during the headache phase of migraine without aura. Weiller and colleagues (1995) assessed regional cerebral blood flow during migraine using positron emission tomography (PET). The authors found evidence of increased blood flow in visual association cortices, as well as other areas, during spontaneously occurring episodes of migraine without aura. In this study, which showed activation of the parieto-occipital junction, participants were scanned within six hours of the onset of their attacks. Others (e.g. Woods, Iacobini & Mazziotta, 1994) have found evidence of decreased blood flow starting at the posterior of part of the brain, including the primary visual cortex, within the first two hours of one attack of migraine without aura. This study assessed one participant whose migraine episode was captured accidentally as she was participating in an unrelated study of visual function. Together, the results of these studies suggest that changes in regional cerebral blood flow occur during spontaneous attacks of migraine, and that the pattern of change may depend on what phase of the episode is assessed.

In addition to the imaging studies that have documented changes in activation occurring during migraine attacks, transcranial magnetic stimulation (TMS) has been used to study whether there are differences in neural activation thresholds between migraine episodes. In these studies TMS coils are positioned close to the scalp, over specific areas of cortex. The coils provide non-invasive stimulation of the cortical region beneath them, and participants are asked to report when they begin to experience evidence of neurological stimulation. When the coil is placed over visual cortical areas, flashes of light or patterns (phosphenes) are experienced. The amount of stimulation

needed before these visual phosphenes start is considered the threshold. Most TMS studies have found lower thresholds in migraineurs, supporting the hypothesis that the visual cortex is hyperexcitable between episodes when compared to non-migrainous controls (Aurora et al., 1998; Battelli, Black & Wray, 2002; Mulleners, Chronicle, Palmer, Koehler & Vredeveld, 2001a), although others have not found evidence for this pattern of results (Áfra et al. 1998). There is also preliminary evidence that lowered TMS thresholds are normalized when the participants with migraine with aura are treated with valproate, an anticonvulsant used in the prophylactic treatment of migraine (Mulleners, Chronicle, Vredeveld & Koehler, 2002). The motivation for this study was to test their hypothesis of reduced inhibition in the cortex, although it should be noted that valproate affects multiple neurochemical systems.

Visual psychophysics

Several research groups have tested specific visual functions using psychophysical methods. The strength of this approach is that most psychophysical tasks rely on forced choice judgment that greatly reduces the possibility of subjective bias. By using the methods of visual psychophysics, researchers assess visual functions that are known to involve particular pathways of neural activation that have been hypothesized to be play a role in migraine. One hypothesis that has received considerable attention is the theory that the visual cortex is hyper-excitable in migraineurs. One version of this theory was proposed by Chronicle and Mulleners (1994). They postulated that because episodes of migraine aura are associated with drops in regional cerebral blood flow in visual areas of the brain, repeated attacks of migraine might eventually lead to damage. More specifically, they suggested that inhibitory interneurons in layer IV of the primary visual

cortex would be most affected by the decreased blood flow, leading to a decrease in visual inhibition. Since then, the hypothesis that the visual cortex of migraineurs shows weaker inhibition than that of controls has been tested using psychophysical tasks that rely on cortical inhibition. Some researchers have found evidence for reduced inhibition using visual psychophysics (e.g. Mulleners, Chronicle, Palmer, Koehler & Vredeveld, 2001b; also see review in Chronicle & Mulleners, 1994). However, others have not found evidence of reduced inhibitory function in migraine sufferers when compared to non-migraine controls (Wilkinson and Crotogino, 2000), or found evidence that migraine sufferers show visual cortical hyperexcitability but do not show a loss of inihibition (McColl & Wilkinson, 2000). While the evidence for the hypothesis of reduced cortical inhibition may be inconclusive, there is an accumulating body of evidence demonstrating that migraineurs show many signs of visual system dysfunction (Chronicle & Mulleners, 1996). For example, when asked to detect a target letter against an intense grating pattern background, individuals with migraine with aura found it more difficult than those with migraine without aura and non-migraine controls (Chronicle, Wilkins, & Coleston, 1995). The authors suggest that this difficulty may be linked to the increased intensity of illusions that migraine sufferers experience and the visual processes that are responsible for this. A recent study also found that migraine sufferers have longer visual motion after-effects and tilt after-effects than controls (Shepherd, 2001), which may relate to the subjective impression of more intense or prolonged after-images that migraine sufferers sometimes report (Alvarez, 1960). A number of studies have also demonstrated differences in the processing of visual motion and other temporally modulated stimuli (e.g. Coleston & Kennard, 1995; McKendrick, Badock, Heywood & Vingrys, 1998).

While the methods of visual psychophysics allow investigation of a number of visual functions that may be affected in migraine, they do not assess subjective visual symptoms or complaints that commonly affect migraineurs.

Other interictal differences between migraineurs and controls

This dissertation focuses on the role of the visual system in migraine and how the nature of reactions to intense visual stimulation may inform comprehensive theories of migraine. However, a brief review of other proposed differences between migraine sufferers and controls is first discussed to provide a broader context for this topic.

Increased sensitivity to environmental factors and internal changes

In addition to being sensitive to visual stimulation between episodes, migraine sufferers have been found to have lower thresholds for noise-induced discomfort, or phonophobia, (Main et al, 1997), as well as lower thresholds for the detection of certain odours (Snyder & Drummond, 1997) compared to controls.

Migraineur sufferers also report that many factors, both exogenous and endogenous, can trigger episodes. Commonly listed migraine triggers include certain foods, weather patterns, alcohol, caffeine, stress, loss of sleep, hunger, hormonal fluctuations and physical exertion (Scharff, Turk & Marcus, 1995; Silberstein et al., 2001). However, several of the triggers reported to precipitate migraine episodes are also reported to trigger tension headache, including stress and tension, fatigue, lack of sleep and specific foods (Spierings, Ranke & Honkoop, 2001). While many triggers were common to both groups, precipitation of headache by light, smoke, smells and noise was reported significantly more often among migraine sufferers than participants with tension

headache. This pattern of results differs from another study that also compared migraine and tension headache triggers and found that stress, smoke and weather changes were reported more by tension headache sufferers than those with migraine (Rasmussen, 1993). It does not appear as though this study asked about visual triggers such as bright light. Presumably, if triggers are unique to one disorder, they may act through pathophysiological mechanisms that are also specific to that disorder. One methodological issue that hampers the identification of unique triggers is that this research relies on retrospective self-report, which may be one contributor to the inconsistencies in the literature.

By using prospective methods and placebo-controlled studies, some commonly reported migraine triggers have been confirmed, while others have failed to find support. For example, the hypothesis that weather changes are associated with an increase in migraine attacks received empirical support when diary recordings of headaches and weather report data were combined (Cooke, Rose and Becker, 2000). However, chocolate, which is often reported to trigger migraines, was not associated with an increased likelihood of having an episode when compared with carob, a substance that looks and tastes like chocolate and therefore used as a placebo (Marcus, Scharff, Turk & Gourley, 1997).

Triggers can be difficult to pinpoint as they are usually identified retrospectively and because factors such as stress, poor sleep, and changes in diet can co-occur. Even when studies try to compare triggers that seem to involve different processes, overlap may exist. The study by Martin & Teoh (1999), mentioned in the above review of visual triggers, is a good example of this. These authors compared reactions to a strobe light

(visual stressor) and to a negative affect induction, hypothesizing that the potential triggers may lead to different physiological responses in groups of headache sufferers. However, the subjective ratings of anxiety endorsed by the participants indicated that the visual stimulation was also associated with negative affect. A potential limitation of this study is that the instructions to participants referred to the goal of assessing headache triggers, possibly biasing participants' expectations and increasing the likelihood of headache reporting. A neutral condition was also included and, while it was not intended to trigger headaches, several participants reported that it did. Despite these potential limitations, this study highlights the point that when attempting to identify relationships between physical stimulus properties and physiological response patterns, the role of subjective reactions to the stimulus must also be considered.

Pain thresholds

It is clear that migraine sufferers are unusually sensitive to a variety of external factors, and that migraine sufferers can experience discomfort or painful sensations when exposed to some of these factors, such as intense visual stimulation. This elevated sensitivity is evident during the painful headache phase, but also exists between headaches. It is therefore logical to question whether migraine sufferers generally have lower thresholds for pain that may explain their lower thresholds for visual discomfort.

Pain thresholds and tolerance of pain induced by pressure to the fingers have been assessed in migraine sufferers and have not differed significantly from groups of individuals with tension headache, mixed headache, and non-headache controls (Feuerstein, Bush & Corbisiero, 1982). Furthermore, Feuerstein and colleagues (1982) did not find differences in how migraineurs responded to the painful stimulus, either in

their psychophysiological reaction or in their ratings of anxiety or use of cognitive coping strategies. Other studies have also failed to find differences between migraine sufferers, tension headache sufferers and controls on pressure-pain thresholds of the fingers (Drummond, 1987) or on pain thresholds and tolerance to the cold-pressor test, which induces acute pain by immersing a hand in very cold water (Bishop, Holm, Borowiak & Wilson, 2001). Together, these studies suggest that migraine sufferers do not have generally lower pain thresholds. It is therefore very unlikely that the lower pain thresholds can explain the increase in sensitivity to visual discomfort between migraine episodes.

Despite the failure to find general differences in pain sensitivity, there is evidence that differences in trigeminal function may be altered in a manner that is more specific to the experience of photophobia or to the migraine attack itself. Drummond (1997) compared the pain tolerance level of migraineurs and controls using spring-loaded forceps on the nasal ala and other locations on the face and neck. At baseline, there were no group differences in pain thresholds. During the same experiment, participants were asked to rate the light-induced pain and glare of an ophthalmoscope shone in their eyes. Both ratings were higher in migraineurs than in controls. When ratings of glare and light-induced pain ratings were evaluated during the pressure-pain induction, migraineurs gave higher ratings than when there was no pressure-pain added. Controls did not show this increase in glare and light-induced pain ratings. According to Drummond, these results suggest that while migraineurs are not generally less tolerant of pain, they do show signs that the visual system and trigeminal system interact leading to increased photophobia.

Another line of evidence suggests that migraineurs may experience a spread of pain sensitivity during a migraine episode. In addition to the perception of headache, individuals may experience pain in response to touching of skin, also referred to as cutaneous allodynia, in a number of areas on the face and scalp during migraine. They may also experience sensitivity to mechanical and cold stimulation, which can spread to other parts of the body during a migraine attack (Burstein, Cutrer & Yarnitsky, 2000). This is thought to provide evidence of central sensitization, a process by which a chain of trigeminovascular events in the pain pathway begins with localized pain and results in more generalized activation of peripheral pain mechanisms. According to the authors, this process involves interactions between pain sensitive neurons in the meninges and trigeminal neurons in the brainstem, with activation of the latter resulting in central sensitization.

Together, these studies on pain in migraine suggest that there are central and peripheral mechanisms that make migraine sufferers more prone to certain types of pain in response to specific types of stimulation. There has been speculation that the visual system and trigeminovascular system interact, possibly explaining some aspects of visual discomfort (Drummond, 1997). This may help to explain why migraine sufferers report increased sensitivity during painful headache episodes, but does not explain why in the absence of head pain, migraine sufferers are still more prone to visual discomfort.

Comorbidity with depression and anxiety

Since pain perception may be affected by psychological factors including affective and cognitive states, one may also hypothesize that finding visual stimulation more stressful or aversive may relate to psychological factors such as mood or anxiety.

Anecdotal reports have linked photophobic behaviour, or light-avoidance, to depressive episodes (Gerbaldo, 1988; Signer & Lapierre, 1989). Both involve case reports of clinically depressed individuals who became very intolerant of light during depressive episodes. In one case (Gerbaldo, 1988), the individual was particularly bothered by neon lights, which is a common complaint in migraine. While both cases rule out ophthalmological causes and seem to suggest that the photophobia was a symptom associated with severe depression, neither explicitly ruled out a diagnosis of migraine. It is unlikely that an association between psychiatric disturbances and migraine can account for increased photophobia that migraineurs experience; however, a brief review of associated mood and anxiety disorders seems warranted.

Epidemiological studies have demonstrated that migraine sufferers are at increased risk for both depressive disorders and anxiety disorders (see Schechter, Lipton & Silberstein, 2001, for review). The directionality of the relationship between depression and anxiety and migraine has been debated for many years. It is an open question whether being depressed or anxious makes one more likely to experience or be diagnosed with migraines, or whether having a chronic headache condition leads to an increase in depressive and anxious symptoms. In one recent study, migraine sufferers and a group with severe non-migrainous headache both had a lifetime prevalence of major depression that was three times higher than controls (Breslau et al., 2000). When anxiety disorders are also evaluated, epidemiological studies suggest that the most common order of occurrence is the anxiety disorder, followed by onset of migraine, and then depression (Merikangas & Rasmussen, 2000), although the onset of the conditions can occur in any order. The association among these disorders highlights the importance of taking

psychological factors into account when studying migraine. This is especially true when one is assessing variables that can be influenced by these factors, such as pain and discomfort.

Theories of migraine pathophysiology

There is extensive evidence that migraine sufferers show differences in visual sensitivity and function. One of these differences is that they are more bothered by bright lights, flicker and strongly patterned stimuli both during and between headaches. It is possible that this sensitivity is a function of abnormal visual function or activation that has been demonstrated using a variety of methods including neurophysiological techniques and visual psychophysics. However, the experience of visual discomfort involves a variety of factors in addition to visual processing, many of which may alter how the subjective phenomenon is perceived or the nature of the response. One such factor is pre-existing levels of anxiety. Theories of migraine etiology and pathophysiology often incorporate some of these interactions, but as of yet, do not explain why visual stimulation can act as a stressor in migraine.

Theories that attempt to explain migraine have evolved as our descriptions of migrainous phenomena have become more detailed and standardized, as our understanding of the central and peripheral nervous system has improved, and as the techniques used to investigate these systems have advanced. Earlier attempts to explain migraine often focused on the vascular aspects of the disorder and how changes in vasoconstriction and dilation that were evident during different phases of the migraine episode could explain the aura and head pain experienced during an episode (see Olesen,

1987 for review). Neural theories were also proposed, suggesting that the vascular changes were secondary to alterations in neural activation (e.g. Blau, 1984). While the vascular theories tended to focus on aura and head pain, Blau's version of the hypothesis that neural events preceded vascular changes also tried to account for prodromal symptoms and other associated symptoms during migraine. These symptoms included the gastrointestinal disturbances and changes in body temperature which have been associated with autonomic disturbances. Blau argued that migraine attacks could be initiated by neural events resulting from changes in the internal environment (e.g. sleep or lack of food), or external environment (e.g. light) that probably did not exert their effects through vascular changes. Furthermore, Blau suggested that areas of the sensory cortex and hypothalamus were sites that were likely involved in the initiation of attacks.

More recently, Welch (1998) extended the hypothesis that triggers set off neuronal events, possibly in a hyperexcitable central nervous system. According to Welch's theory, the resulting pattern of activation leads to vascular and neurochemical changes that cause the neurological manifestations of aura, changes in blood flow, the experience of pain, and associated symptoms such as nausea and vomiting. In this theory, it is proposed that the brainstem is activated by a cortical event, which then leads to the production of associated migraine symptoms. In Goadsby's (2001a) review of migraine pathophysiology, a very prominent role is attributed to connections with the brainstem, and in particular the trigeminovascular system. According to Goadsby (2001a), the sensitivity that migraineurs have to lights, sounds, smells and head movements during an attack may be attributed to the locus coeruleus, which is the source of major ascending noradrenegic projections to the forebrain. While these theories tie

migrainous symptoms to specific brain regions, further research is needed to clarify how the pathophysiological processes interact, and in which order they are initiated, as this will likely lead to improvements in both the prevention of episodes and aborting of attacks once they have started.

Various processes such as cortical spreading depression and the activation of the trigeminovascular system have been proposed. However, the order in which they occur and whether they are necessary parts of the migraine process continue to be debated (Goadsby, 2001b; Spierings, 2001). In one theory, sympathetic activation is said to follow rather than precede activation of pain processes and lead to sensory and autonomic symptoms (Spierings, 2001). From a clinical point of view, this timing of events is not consistent with the occurrence of prodromal symptoms that also suggest autonomic involvement and precede the onset of headache pain. In a review of migraine pathophysiology, Schoenen (1998) highlights the need for theories to address interictal differences in addition to the events associated with migraine episodes. Given the evidence that migraineurs fail to habituate to certain tasks as assessed by evoked potentials, Schoenen suggests that sensory stimulation may in some situations activate the cerebral cortex, which would in turn trigger the trigeminovascular system, resulting in a migraine episode.

Further research that investigates how migraineurs function in the period leading up to a migraine attacks, and the nature of their responses in reaction to stimuli to which they are sensitive or which can trigger attacks will lead to a better understanding migraine pathogenesis. This dissertation explores links between intense visual stimuli that may initiate or aggravate migraine episodes and the physiological responses that may

elucidate how migrainous psychophysiological events are initiated, as well as assessing some of the physiological patterns that precede, accompany and follow a migraine episode. The physiological responses assessed in this dissertation are measures of autonomic function that involve the activation of the brainstem.

Brain stem involvement

Many of the current theories of migraine highlight the role of the brainstem in migraine. The brainstem is involved in autonomic regulation (Mosqueda-Garcia, 1996), which includes various aspects of maintaining homeostasis in response to exogenous and endogeous stressors. The brainstem is involved in maintaining a balance between the sympathetic and parasympathetic divisions of the autonomic nervous system, affecting lacrimal and pupillary function, gastrointestinal function, peripheral vasculature, sweat glands, the cardiovascular system, and the kidneys and bladder (for review, see , Myer & Quezner, 1997, Chapter 4). The brainstem plays a role in gating the nervous system's responses to stimuli from the internal and external environments.

The activation of the brainstem during an attack of migraine without aura has been observed in PET recordings of induced (Bahra, Matharu, Buchel, Frackowiak & Goadsby, 2001) and spontaneously occurring (Weiller et al., 1995) attacks of migraine without aura. In both studies, brain stem activation persisted after treatment with sumatriptan, pain relief and a reduction in symptoms (e.g. photophobia and phonophobia). This suggests that while some components of the migraine process may be aborted with pharmacotherapy, most likely in trigeminal fibres of the dura, other aspects of the migraine process continue after treatment. Continuing brainstem activation

demonstrates that a fundamental part of the underlying pathophysiological process still needs to be accounted for in treating or preventing migraine episodes.

Another hypothesis is that persisting brainstem activation may result from neuronal changes or dysfunction caused by repeated migraine attacks. Studies using magnetic resonance imaging have also documented brainstem involvement during migraine attacks. In addition to activation of occipital areas, Welch and colleagues (1998) found activation of the red nucleus and substantia nigra during an episode of migraine with aura. This group has also investigated the involvement of the brainstem regions in migraine using high-resolution MRI techniques (Welch, Nagesh, Aurora & Gelman, 2001). In this study, they focused specifically on the periaqueductal gray matter, which the authors suggest may play an important role in migraine due to its involvement in antinocioceptive functions in connection with the autonomic nervous system and behavioural responses to threat. Results confirmed that participants who suffered from episodic migraine, and those with chronic daily headache that had started as migraine without aura, showed more periaqueductal gray matter activation than healthy controls, and that this activation was positively associated with the duration of their headache history. According to the authors, the differences in the periaqueductal region may reflect a pre-existing condition of migraine, and in addition may become progressively more affected during the duration of illness, possibly due to the neuronal and metabolic antecedents and consequences of repeated migraine attacks. They point to the periaqueductal region as a potential generator of migraine activity in migraine without aura, which may lead to dysfunction of the trigeminovascular nocioceptive system. If this brainstem area that is involved in autonomic function is central to the generation of

migraine attacks, then the impact of migraine triggers may be evident in a perturbation of autonomic indices.

Autonomic system deregulation in migraine

The autonomic nervous system serves to maintain homeostasis by regulating functions based on both the internal functioning of the body, and external influences in the environment. Aspects of homeostasis include maintaining balance in cardiovascular control, thermal regulation, gastrointestinal and urinary functions, and metabolic and endocrine functions (Hamill, 1996). It also responds to threat and stress with what is commonly referred to as "fight or flight" reactions. Since migraine episodes are often triggered by changes in both internal and external environments (e.g. changes in stress, weather, visual stimulation, certain foods), it is logical to question whether the autonomic system is involved in migraine etiology or pathophysiology prior to the onset of migraine pain.

There have been many investigations of autonomic function in migraine, using a number of different stressors, and a variety of psychophysiological indices. While a complete summary of this vast literature is beyond the scope of this chapter, Table 1.1. presents a review of several studies, highlighting the variety of methods used, and the differing patterns of results that have emerged. Some studies have assessed migraineurs' responses to traditional autonomic challenges, including orthostatic tests such as the tilt-test and isometric tests such as sustained hand-grip (e.g. Drummond, 1982; Havanka-Kannianen, Tolonen & Myllyla, 1986; Thomsen, Iversen, Boesen & Olesen, 1995). Another line of investigation has assessed autonomic reactivity to psychological and environmental stressors including mental arithmetic (e.g. Gannon, Haynes, Cuevas &

Chavez, 1987), exam stress (Passchier, Goudswaard & Orlebeke, 1993), stressful and relaxing imagery (Thompson & Adams, 1984), acute pain (e.g. Feuerstein, Bush & Corbisiero, 1982; Hassinger, Semenchuck & O'Brien, 1999), public speaking (Holm, Lamberty, McSherry, & Davis, 1997), noise (Rojahn & Gerhards, 1985; Kröner-Herwig, Diergarten, Diergarten & Seeger-Siewert, 1988) and strobe lights (Martin & Teoh, 1999) to examine whether migraineurs respond differently than non-migrainous controls. Finally, another group of studies have assessed migraineurs using ambulatory measures, to determine whether there is evidence of an autonomic dysfunction during normal routine activities (e.g. Appel et al, 1992; Tabata et al., 2000).

In addition to the varied challenges or conditions under which autonomic function in migraine has been tested, a variety of autonomic indicators have been assessed, including heart rate, blood pressure, temporal artery pulse amplitude, skin temperature, skin conductance, pupillary and electromyographic responses. In addition to traditional measures of heart rate, heart rate variability analysis has been used to assess parasympathetic and sympathetic influences on cardiac rhythm (e.g. Appel et al., 1992; Tabata et al., 2000). Since the parasympathetic and sympathetic branches of the nervous system interact to determine heart rate, systematic changes in temporal frequency can provide information about the balance of these two systems.

An examination of the studies presented in Table 1.1 demonstrates that there are many inconsistencies in the literature. There is evidence that suggests sympathetic hypo-function (e.g. Martin et al., 1992; Rubin et al., 1985), sympathetic hyper-function (e.g. Appel et al., 1992; Cortelli et al., 1991), parasympathetic hypo-function (e.g. Tabata et al., 2000; Thomsen et al., 1995), and combinations of sympathetic and parasympathetic

dysfunctions (e.g. Gotoh et al., 1984; Havanka-Kainniainen et al., 1988) in migraine. Other studies have found no significant signs of autonomic dysfunction or alteration in migraine (e.g. Piergangeli et al., 1997).

The rationale for testing autonomic function in migraine is clear. Migraineurs show activation of areas of the brain that regulate autonomic function during headache, and they show symptoms of autonomic disturbance both during and between attacks. Furthermore, migraine sufferers are sensitive to various internal and external changes which could point to a dysfunction of the autonomic mechanisms that attempt to maintain homeostasis. One might predict that alterations in autonomic variables would be most apparent in response to challenges that are especially relevant to migraine sufferers. Psychological stress is thought to be one of the factors that can trigger headaches.

One stressor that is particularly relevant to migraine is the intense visual stimulation reported to cause discomfort between headaches (Mulleners, Aurora et al., 2001). As reviewed above, the particular stimulus characteristics that are relevant and bothersome to migraine have been established (e.g. Marcus & Soso, 1989; Wilkins, 1995). This information can be used to create a stressor that may elicit autonomic responses that inform our understanding of how environmental stimuli can impact pathophysiological events that are relevant to the migraine process. While some studies have attempted to use environmental stressors to probe such differences, stimuli have not necessarily reflected aspects of the environment that migraineurs routinely complain of (e.g. white noise: Kröner-Herwig et al, 1988). A study by Martin & Teoh (1999) assessed responses to visually aversive stimulation and found that exposure was associated with both increased headache and negative affect. A clear pattern of

corresponding psychophysiological response was not evident. The central study of this dissertation builds on this research, incorporating a broader assessment of subjective measures and assessing different measures of autonomic function. Since there is also a possibility that the instructions used by Martin and Teoh (1999) influenced subjective symptom reporting, this dissertation addresses the potential for instructions to influence photophobia thresholds.

Goals and overview of this dissertation

This dissertation investigates whether intense visual stimulation can act as a stressor in migraine. It takes into account factors that have previously not received consideration, such as the impact of instructions and anxiety. It also measures the impact of intense visual stimulation using on a variety of subjective measures and on indicators of autonomic function that, if altered, would suggest that visual stress has a widespread effect on the peripheral nervous system of migraineurs. There is ample evidence that migraine sufferers find certain types of visual stimulation more aversive than non-migraineurs, and that their response to these types of stimulation has been referred to as "visual stress." It is likely that this stimulation does cause "stress" to a hyperexcitable visual system, however, there is little evidence that subjective anxiety varies with the intensity of visual stimulation, or that exposure results in alterations in autonomic indices that are typically associated with more traditional stressors. Studies that have assessed alterations in autonomic function in migraine have typically used physical challenges of the sympathetic or parasympathetic systems, or psychological stressors that are considered anxiety-provoking by both migraineurs and non-migraineurs. Little is known about whether aversive visual stimulation causes psychophysiological responses in

migraine that may help us to understand why it can, in some cases, trigger migraine attacks. It is currently unclear how common environmental stimuli such as intense visual stimulation can initiate a chain of pathophysiological events that leads to a migraine episode. This understanding is crucial to improving both preventative and abortive treatments for migraines that incorporate associated symptoms, such as visual sensitivity, in addition to head pain that has traditionally been the focus of intervention.

In summary, the purpose of this dissertation was to evaluate visual sensitivity in migraine, in a context that assesses both predisposing or pre-existing factors, as well as a broad response or reaction to exposure to visually aversive stimulation. Traditionally, visual sensitivity has been assessed using subjective outcomes such as discomfort thresholds. While we know that the individual perception and reporting of discomfort is influenced by situational, cognitive and affective factors, these factors have been largely ignored in the literature.

The following chapters detail three studies that were conducted to clarify the factors involved in the increased sensitivity to intense visual stimulation in migraine, and whether exposure to such stimulation triggers changes in autonomic function.

The central study of this dissertation, presented in chapter 3 compared the reactions of migraineurs and controls exposed to intense visual stimulation. It assessed several indicators of autonomic response, as well as the subjective complaints associated with viewing. While the focus of the investigation is on responses during exposure, differences at baseline and recovery were also evaluated.

In preparation for this study, chapter 2 details a study that assessed what light levels would generally be considered aversive by migraineurs and controls. While

several studies have assessed photophobia thresholds in migraine, lighting stimuli and threshold instructions had varied greatly, making extrapolation to our novel light stimulus set-up difficult. We were also concerned by the possibility that information provided to participants prior to testing and within testing instructions might influence photophobia thresholds. Since these thresholds are subjective in nature and likely influenced by cognitions and anxiety in the same way other types of pain measurements are, we tested thresholds using two different instruction sets. Both the threshold values and results of the instruction manipulation influenced the methodology of the central study that follows in chapter 3.

The final study, presented in chapter 4 of this dissertation, assessed ambulatory heart rate variability in a small sample of migraineurs who had participated in the previous study. Each of these participants was monitored both on a day when they did not experience headache, and on a day on which they recorded having a headache. This study sought to assess whether autonomic changes would be evident during or immediately before the onset of a migraine episode.

This dissertation ends with a general discussion that links findings from the three studies and integrates these results with our current understanding of migraine. While the study of migraine involves diverse fields including neurology, pharmacology, health psychology, vision research, epidemiology and electrophysiology, this discussion emphasizes the links between interictal sensitivity to aversive visual stimulation and theories that explain why migraineurs are vulnerable to such environmental factors.

Table 1.1

Summary of Psychophysiological Studies in Migraine

Study	Participants	Tasks	Measures	Significant psychophysiological differences in migraine group
Gannon et al., 1981	16 M 13 TH 15 NC	HR BVP EMG	Cognitive stress: (mental arithmetic) Physical stress (BP cuff)	More vasoconstriction at rest Higher HR and less change in HR than both TH and NC Elevated vasomotor response during recovery Conclude: M show different vasomotor response after stress, not during stress.
Drummond, 1982	20 M 20 NC	HR BP TPA RR Facial temperature	Isometric test Orthostatic test CO_2 rebreathing Cold pressor Radiant heat exposure Psychological stress: (mental arithmetic)	Higher DBP and HR at rest. Different vascular responses to psychological, orthostatic, isometric and physical stress: Increase in TPA and decrease in facial temperature to psychological stress, and increased RR during isometric test Conclude: extracranial vasomotor instability in response to stress, but normal general vasomotor reactivity.

Table continues on the following page.

Feuerstein et al, 1983	12 M (all female)	Temporal BVP Digital BVP EMG (frontal) BP Peripheral temperature State & trait anxiety	Assessed in lab on 5 days: Headache day and 4 consecutive days prior to it.	Higher anxiety on headache day. More variability of right temporal artery 3 days before headache, which was correlated with anxiety reported 4 days before the headache. Considerable individual variability in physiological responses. Conclude: No evidence of general ANS disturbance prior to migraine. Individual differences in temporal artery activity. Suggest need for ambulatory measures.
Gotoh et al, 1984	10 MA 11 MO 30 NC	BP Serum catecholamines (NE)	Orthostatic test Valsalva manoeuvre Aschner's test (pressure on eyeballs) Norepinephrine bolus Epinephrine eye drops	Less overshoot on Valsalva (MA only) Orthostatic hypotension (decreased SBP when standing) More reflex bradycardia to Aschner's test Lower plasma NE Greater dilation of pupils after eye drops Longer recovery from NE bolus Conclude: sympathetic hypofunction, parasympathetic hyperfunction, and hypersensivity of the iris and arterial blood vessels.

Table continues on following page

Thompson & Adams, 1984	8 M 8 TH 8 NC	EMG HR TPA EDA	5 imagery conditions: 2 stressful 2 relaxing 1 "typical day"	M did not differ in response from NC TH showed greater EMG response to stressful imagery. Conclude: results suggest different mechanisms for TH and M.
Arena et al, 1985	8 M 12 TH 8 MH Ictal & interictal	EMG HR VMR EDA Finger temperature	Self control imagery: (relax forehead, hand-warming) Cognitive stress: (mental arithmetic) Physical stress: (cold pressor)	No group differences at baseline. No difference between ictal and interictal responses at baseline. Increased vasodilation during first 2 minutes of recovery. M and MH took longer for finger temperature & VMR to return to normal than TH Conclude: no evidence of generalized psychophysiological dysfunction in M or TH. Poor homeostatic response in M & MH.
Rubin, Graham, Pasker & Calhoun, 1985	50 MO 86 NC	Pupillometry	Cold pressor (while dark-adapter and while light-adapted)	No differences at rest Defective pupillary dilation response to cold pressor Conclude: sympathetic hypofunction that is only evident during stress.

Table continues on following page

Havanka-Kanniainen, 1986	10 M 10 NC Ictal & Interictal	PRV BP	Deep breathing Valsalva Orthostatic stress Isometric test	No differences at rest During headache, M showed less response to the Valsalva, tilt test & isometric test. Conclude: No difference between headache. During headache, sympathetic hypofunction.
Havanka-Kainiainen et al., 1986	49 M 25 NC (ages 11-22 years)	PRV BP	Deep breathing Valsalva Orthostatic stress Isometric stress	No group differences Conclude: Normal interictal autonomic function in young M.
Gannon et al, 1987	8 M 8 CTH 8 NC	EMG BVP HR Self-reported headache ratings	Cognitive stressor: (mental arithmetic for 1 hour)	No differences in headache ratings Higher HR in CTH Higher neck EMG in M during stressor Sustained psychophysiological arousal preceded headache. Conclude: No group differences on vasomotor function.
Havanka-Kainniainen et al., 1988	114 MO 74 MA 85 NC	Pulse rate variability (similar to HRV)	Valsalva Isometric test Orthostatic test Deep breathing	Less BP variability during normal and deep breathing. Lower Valasalva ratio Less variability response to tilt test. Less BP response to hand grip Conclude: sympathetic hypofunction & mild parasympathetic hypofunction Differences greater in older M and longer M history.

Table continues on next page

Kröner-Herwig et al, 1988	37 M 44 NC	HR TPA DPA Skin temperature EDA BVP	2 stressors: Industrial noise Social discomfort (told they are being watched)	No difference in response to stressors. No difference during recovery Conclude: no major differences
Cortelli et al, 1991	13 MO 18 NC	HR BP	Valsalva Isometric Orthostatic Cold on face Sinus arrhythmia	Higher HR at rest Higher BP during cold face More HR and BP change to isometric challenge Conclude: mild sympathetic hyperactivity with normal control autonomic control of cardiovascular system.
Martin et al, 1992	75 M 78 NC	HR BP	Valsalva Deep breathing Isometric test	Decreased HR response to deep breathing Increased HR response and decreased BP response to standing. Conclude: normal parasympathetic function and sympathetic hypofunction.
Appel et al, 1992	10 M 8 TH 10 NC	HRV	24 hour ambulatory measure	No difference in HR Increased LF power (<.15 Hz), over 24 hour period Conclude: sympathetic hyperfunction.

Table continues on next page

Passchier, Goudswaard & Orlebeke, 1993	37 MO 37 NC	HR RR EMG TPA DPA Forehead temperature EDA	3 sessions: Rest (reading quietly) Real life stress (actual exam) Experimental stress (IQ test)	No differences at rest During real stress, M showed smaller TPA than NC, but self-reported anxiety was not higher than NC. During IQ test, M had higher forehead temperature than NC. Both groups showed higher HR and more EDA responses during exam. Conclude: Supports "symptom specificity", with M reacting to stress with the relevant physiological system
Thomsen et al, 1995	27 MO 23 MA 30 NC (10 M retested ictally)	HRV BP Transcranial Doppler	Deep breathing Valsalva Cold pressor Orthostatic test	No differences between ictal and interictal Less HR variability to Valsalva. No differences in response to other stressors. Conclude: Mild parasympathetic hypofunction. Normal sympathetic function.
Holm et al, 1997	30 M 39 CTH 35 NC	EMG Skin temperature PR	Speech stressor (3 feedback conditions: positive, negative & ambiguous)	No differences at rest No differences during stressor Slower recovery of PR after stressor Conclude: sustained cardiovascular reaction to stress.

Table continues on next page

Pierangeli et al., 1997	37 MO 19 MA 31 NC	HR (& HRV) BP RR	Valsalva Orthostatic test	No differences on Valsalva or tilt test No differences in HR, BP, RR or HRV Conclude: normal autonomic control of cardiovascular system.
Stronks et al., 1998	23 M 18 TH 22 NC	HR BP EMG TPA	Mental arithmetic	Higher frontalis EMG and SBP at rest. No differences in HR or TPA No differences in response to stressor. Conclude: increased cardiovascular activity, but not specifically in response to stress.
Martin & Teoh, 1999	46 M 29 TH 15 NC Classified according to reported trigger: NA (negative affect) &d VD (visual disturbance)	EMG (forehead) HR TPA RPI Self report: negative affect (NA), visual disturbance (VD), headache intensity (HI)	3 sessions: Stressor challenge: hard to solve anagrams Visual challenge: strobe light Control challenge: relax	No differences between M & TH, so headache vs controls compared. Stressor caused more NA than control challenge. Visual challenge caused more VD & NA than control. HI increased during all 3 sessions. Stressor: TPA & HR increased, RPI decreased. Visual challenge, RPI decreased. Conclude: stressor & visual challenges both induce NA & headaches, independently of reported triggers factors. Some differences in physiological reaction, but different trigger mechanisms are not clear.

Table continues on following page.

Hassinger et al, 1999	26 M 26 NC	HR BP CO TPR SV	Cognitive stressor: (mental arithmetic) Acute pain: (cold pressor)	No differences at rest At recovery, M had higher TPR and SV, and lower CO after cognitive stressor. Conclude: difference in homeostatic mechanism that regulates BP
Tabata et al., 2000	27 M 24 NC	HRV	48 hour ambulatory measure during normal daily routine	Evidence for cardiac parasympathetic hypofunction, as well as abnormal circadian rhythms in M compared to NC. Conclude: Parasympathetic hypofunction during normal daily routine.

Participants: M, migraine, undifferentiated subtype; NC, normal control; MO, migraine without aura (or common migraine); MA, migraine with aura (or classic migraine; TH, tension-type headache (or muscle contraction headache); MH, mixed headache (a combination of M and TH); CTH, chronic tension-type headache

Measures: HR, heart rate; BP, blood pressure (DBP and SBP, diastolic and systolic, respectively); RR, respiratory rate; TPA, temporal pulse amplitude, BVP, blood volume pulse; EMG, electromyography; NE, norepinephrine; EDA, electrodermal activity; VMR, vasomotor response; PR, Pulse rate; PRV, pulse rate variation; TPA, temporal pulse amplitude; DPA, digital pulse amplitude; RPI: R wave to pulse interval; CO, cardiac output; TPR, total peripheral resistance; SV, stroke volume; HRV, heart rate variability; LF, low-frequency heart rate variability; HF, high-frequency heart rate variability

Chapter 2 – A study of photophobia thresholds in migraine using a novel light stimulus and two instruction sets

Introduction

Several studies have assessed differences in photophobia between migraine sufferers and non-migraine controls using light of varying intensity as a test stimulus (Drummond, 1986; Drummond & Woodhouse, 1993; Main, Dowson & Gross, 1997; Vanagaite et al, 1997; Woodhouse & Drummond, 1993). While this research provides strong support for increased sensitivity to light in migraine sufferers, both during and between attacks, reported thresholds for discomfort and pain vary greatly between studies. This is not surprising given that very different light sources, testing environments and threshold measures have been used. A summary of the methods and corresponding results from these studies is provided in Table 2.1.

Another important consideration is the nature of the test instructions and background information given to participants. This has also varied in the aforementioned studies, although typically limited detail is provided in biomedical publications. Some studies specify what testing instructions were provided to participants (Main et al, 1997; Vanagaite et al, 1997), while other studies provide little or no information (e.g., Woodhouse & Drummond, 1993). Given the space limitations typical of publications, it is not surprising that information about what participants are told about a study prior to participating is not available. It is therefore difficult to assess whether such information could have influenced thresholds, and might account for some of the variability in thresholds reported in the literature. The threshold criterion used for photophobia studies has generally involved a judgement that the light has become uncomfortable or painful to

view (i.e., a sensory experience), and has sometimes added a behavioural descriptor (e.g., squinting eyes). It is now well accepted that pain is more than a sensory experience, also involving affective, cognitive and behavioural aspects (see Melzack & Wall, 1996, for review). Factors such as past pain experience, the meaning of a situation, anxiety and attention are general factors that influence how pain will be evaluated. It follows that the information provided to participants could influence pain thresholds by altering expectations about upcoming pain, either increasing or decreasing anticipatory anxiety.

The impact of instructions on photophobia thresholds has not been evaluated. The impact of biased instructions on other responses has however been assessed. Sternbach (1964) studied the impact of instruction sets on physiological responses to electric shock. Measures included cardiac rate, palmar skin resistance and relative finger pulse volume. A noise was paired with the shock, and participants received one of three instruction sets prior to the experiment. In the "neutral" group, participants were told that the experimenters were unsure of the effect of white noise on pain and that either a positive (analgesic) effect or negative (hyperalgesic) effect was possible. The "analgesic" group were told that the experimenters believed white noise deadens pain, and the "hyperalgesic" group heard that noise could increase perceived shock intensity. Surprisingly, all groups showed a significant decrease in physiological responses when the shock was paired with noise. However, this effect appeared strongest in the "analgesic" group and weakest in the "hyperalgesic" group, suggesting that expectations can bias the experience of pain. Sternbach (1964) also assessed the influence of three instruction sets on physiological responses to three gastrointestinal drugs (all were actually placebos). Instruction set had a significant effect on the gastric motility measure,

demonstrating that giving participants differing information about what to expect could alter physiological responses. Similarly, Cornwall and Donderi (1988) tested the impact of instructions provided to participants prior to the onset of a painful stimulus (pressure pain). Three instruction sets were compared: standard instructions, instructions that warned participants of upcoming pain, and instructions that warned participants about a stressor that was unrelated to pain. Participants in the latter two conditions that were designed to induce anxiety reported higher levels of pain and stress during the painful stimulus, and also demonstrated physiological differences when compared to the standard instructions (e.g. increased heart rate). Together, the results of these studies emphasize the impact that instructions can have on both subjective and physiological measures.

Providing participants with a model of what to expect also influences pain thresholds. In a study by Craig and Neidermayer (1974), autonomic responses to shock were evaluated following exposure to models who simulated different levels of discomfort and pain susceptibility. Participants exposed to the "tolerant" model tolerated higher levels of shock without an increase in autonomic response, which the authors used as an index of subjective discomfort. This study provides another example of how contextual factors (i.e., factors not relating directly to the stimulus characteristics or individual participant) influence the perception or expression of discomfort.

Thus, instructions provided to participants indicate the directions for a task, but also often provide a context and influence expectations. Suggesting that participants are likely to experience discomfort could create anticipatory anxiety. If this suggestion has more meaning or relevance to one of the groups being compared, differences in anxiety or expectation may affect the measure under comparison. For example, specifically

stating that a study is about visual discomfort in migraine implies several assumptions. The first is that discomfort can be expected. The second is that this effect is particularly relevant to those with migraine.

Given that the perception and expression of pain is open to influence by contextual factors such as those just described, using standardized and unbiased instructions would provide the best way to elucidate actual group differences. While providing no biasing information is ideal, in reality, ethical guidelines require that some information about the nature of the study be provided to participants. It is also essential that migraineurs be forewarned of the possibility that adverse effects (e.g., headache) may result from participating when there is reason to believe that this might be the case.

This study had two goals. The first was to determine thresholds for discomfort and pain in migraineurs and controls using a novel light stimulus and standardized instructions. This was needed in order to choose stimulus values for the central study of this dissertation which was designed to assess physiological and subjective responses during 5-minute exposures to an aversive, bright light and to a mild, dim light stimulus. By determining light sensitivity thresholds, a stimulus value for the aversive stimulus could be chosen such that it could be tolerated by the majority of subjects for several minutes while inducing sufficient discomfort to evaluate the psychophysiological correlates associated with photophobia.

The other goal of this study was to determine whether providing information about the nature of the study would have a biasing influence on the threshold measure, and whether this effect would be different in migraineurs when compared with controls. In order to test this, half of the participants in each group (migraine and controls) were

told that migraineurs are more likely to experience pain in response to bright light ("negative bias"), while the other half were told that bright light can be beneficial in the treatment of migraine ("positive bias"). The biasing statements, based on information already existing in the migraine literature, were chosen to produce different expectations about the effect bright light on people with migraine. It was predicted that thresholds would be higher for those hearing positive statements about the effect of light on migraine as compared to those who would anticipate negative effects. We anticipated that the migraine sufferers in the negative bias condition would be most sensitive to light (i.e., have the lowest thresholds), followed by the migraine sufferers in the positive bias condition. We anticipated that controls would have higher thresholds than migraine sufferers but were unsure whether the biasing statements would affect their sensitivity since the presented information was specific to migraineurs.

Methods

Participants

Participants were recruited through campus advertisements and through an undergraduate course that involved participation in psychology experiments. Migraine sufferers were also referred by local neurologists and general practitioners familiar with our ongoing research.

Potential participants were contacted by one of the two experimenters involved in this study. A semi-structured interview was administered to determine headache diagnosis according to I.H.S. (HCCIHS, 1988) criteria, and the presence of exclusionary criteria. The latter included a history of neurological problems (e.g., seizure disorder, cluster headache, multiple sclerosis, optic neuritis), other conditions that could affect

vision (e.g., diabetes, glaucoma), significant visual problems that were not corrected by glasses or contact lenses and medications such as beta-blockers and antidepressants that are used for migraine prophylaxis. The interview format is presented in Appendix B.

Twenty participants who fit I.H.S. (HCCIHS, 1988) criteria for migraine took part in the study (18 females, 2 males). Of these, 11 were classified as having migraine without aura (MO), and nine as migraine with aura (MA). Nine of these participants also met criteria for episodic tension-type headache (TH). This comorbidity of headache diagnoses is common and difficult to avoid given the high prevalence of both headache disorders. While the diagnostic criteria for migraine are based on subjective symptom description, whenever possible, we obtained written consent to contact the participant's general practitioner or neurologist for confirmation of diagnosis. We were able to obtain such confirmation in 14 of the migraine group participants. There were several reasons why we were unable to obtain confirmation in the remaining six participants. Two had been diagnosed several years earlier and their physicians were no longer practicing or had moved to an unknown location. One reported having discussed headache with their physician, although the reply indicated that the specifics required for I.H.S. (HCCIHS, 1988) diagnosis were not contained in the health record. One participant had never consulted with a physician because they experienced very classical aura symptoms that led them to self-diagnose migraine with aura. Two had been diagnosed informally by health professionals (one physician, one nurse) and did not think that the information would be contained in their health record. One form was sent but not returned by the physician.

The control group was composed of 20 individuals (17 females, 3 males) who did not suffer from migraines or other headache disorders, with the exception of mild tension headache. Participants in this group could not have more than two headaches per month. Fifteen of the participants met criteria for episodic tension-type headache. Only one participant indicated that they "never" had headaches, representing 5% of our control group. This is consistent with several epidemiological studies showing lifetime prevalence rates of headache in general population samples from industrialized countries ranging from 71-96% (see summary in Rasmussen & Lipton, 2000). The same exclusionary criteria used for the migraine group also applied to the control group.

Group characteristics are presented in Table 2.2. Information is presented as mean ± standard deviation, unless otherwise stated.

Apparatus and stimulus characteristics

Two boxes, each containing three 75-watt GE Halogen Fl 35 Beam light bulbs, were used to expose participants to light of increasing intensity. The front of each box measured 22.5 cm (width) by 47.5 cm (height) and was covered with frosted glass to diffuse the light. All six bulbs were connected to a single calibrated potentiometer so that the intensity of the lights could be simultaneously increased during testing. Illuminance was measured in lux for each dial position using a Gossen photographic light meter held at the participant's eye position and pointed towards the fixation point on the 17-inch computer monitor (between the boxes). Since halogen bulbs vary slightly in brightness according to temperature variations and running time, the threshold measure for each participant was derived from a mean of light measurements collected immediately before and after the testing session. The lights were warmed up for approximately 1 hour prior

to the testing session, at which point the lights consistently reached a maximum intensity of 3000 lux.

Procedure

Potential participants were first contacted by telephone. At the time of this initial telephone call, a standardized explanation of the study was provided to all potential participants, indicating that the purpose of the study was to take preliminary measures of their impressions of light exposure for an upcoming study on migraine and lights. After agreeing to be interviewed, the experimenter proceeded with a semi-structured interview to obtain the required information to classify headache status, as well as other relevant medical or neurological conditions or medication use that could exclude them from eligibility (see Participants section above for details). Those who met all inclusionary and exclusionary criteria received a 30-minute appointment time to visit the laboratory for the testing session. Participants were instructed that another experimenter would be conducting the testing, and that they should not to reveal whether or not they suffer from migraine to that person. Since the goal of the study was to record interictal thresholds (i.e., when participants were not experiencing or recovering from a headache episode), all participants were asked to reschedule if they had a headache on the day of or the day before their scheduled appointment.

On the day of testing, the experimenter who conducted the interview met with participants to review the informed consent form (see Appendix C). This allowed participants the opportunity to ask questions freely without divulging their headache diagnosis to the second experimenter who conducted the threshold testing. The consent form restated the general purpose of the study as presented earlier by telephone, and

indicated that participants could withdraw at any time, for any reason. It did not make specific mention of the risk that the lights could induce headache. This information was omitted to avoid priming participants with the idea that the stimulus could differentially affect individuals (i.e., those who get headaches versus those that do not). Since the stimulus used in this study involved bright lights of an intensity which occurs in the natural environment, and since participants were in control of asking that the stimulus to be shut off, we did not believe that this procedure would put individuals at risk of experiencing headache. After written consent was obtained, the experimenter assigned the participant to either the negative or positive bias condition. Conditions for the migraine group and control group followed an alternating schedule according to the order of appointments, thereby providing semi-randomised assignment and ensuring equal group sizes. The second experimenter then carried out the testing procedure.

Participants were seated comfortably in the dimly lit testing room, positioned 75 cm from a computer monitor that was flanked by the two light-boxes, described above. The experimenter then proceeded to read the negative or positive biasing statement, followed by a set of standardized instructions. The statements and instructions were as follows:

> "Recent research has revealed that people with migraine find bright light more uncomfortable to look at than people without migraines. Some may even find that viewing bright light is painful, even between migraines." (Negative bias)
>
> OR

"Recent research has revealed that people with migraine may benefit from regular exposure to bright light. This "light therapy", which you may have heard about for seasonal affective disorder, may in fact reduce the frequency of migraines." (Positive bias)

AND

"We are planning to investigate this phenomenon further, but need to pre-test some light levels before finalizing what we will use for the actual test condition. In order to do this, I will increase the intensity of these lights while you look at the centre of the computer screen. I would like you to indicate if or when the brightness of the light becomes uncomfortable to look at, by saying the word "discomfort". I will then keep increasing the light so that you can then indicate if or when you find the brightness painful to view, by saying the word "painful". At this point I will immediately shut off the light. If you do not feel any discomfort or pain, the light will continue to be increased to its maximum and then immediately shut off. This task will be repeated three separate times. You will have a two minute break between each test."

Following the standardized instructions, the experimenter then conducted the threshold measurements. The intensity of the lights was first set to 10 lux (1 log lux), and

was increased with a calibrated potentiometer in 25 steps, up to an intensity of 3000 lux (3.48 log lux). Each intensity level was maintained for 5 seconds to allow participants to respond before the level was increased. The threshold measurement was repeated three times, with a 2-minute rest period between trials.

A brief questionnaire followed the threshold measures to determine how strongly participants believed the information provided in the biasing statements. Participants were asked to read four statements about the effects of bright lights and to rate how strongly they believed each statement on a five-point scale (1 for "strongly disagree", 2 for "somewhat disagree", 3 for "no opinion", 4 for "somewhat agree" and 5 for "strongly agree"). The statements were:

Statement 1: " I believe that bright lights can be beneficial in the treatment of migraines."

Statement 2: " I believe that viewing bright lights can cause discomfort and pain."

Statement 3: "I believe that people with migraines are particularly sensitive to discomfort caused by bright lights."

Statement 4: "I believe that exposure to bright lights can be beneficial to your health and well-being."

The statements were designed to evaluate whether differences in beliefs existed according to bias condition and headache group. Statements included information about the effects of light on migraine sufferers (1 & 3) and the effects of light on people in general (2 & 4). It was assumed that responses to these statements would be influenced by a combination of factors including the recent exposure to bright light in the study, the biasing statement and other information provided in the instructions, and outside factors

such as previous experiences with photophobia (e.g., during headache), others reports of photophobia (e.g., family members with migraine) and information from physicians and the media.

Following testing, the experimenter who had conducted the testing read a standardized debriefing statement, which explained the general goals of the study. This included telling participants that their judgments about the light-induced discomfort and pain would be used in choosing light intensity levels for an upcoming study. They were also informed that while there is evidence for both positive and negative effects of light on migraine, we were assessing the impact of this information on thresholds. Participants were invited to ask questions, with both experimenters present.

Those who participated for course credit, which required a brief write-up about the experiment, were encouraged to contact the experimenter if they required further explanation of the methodology. Participants who were not obtaining course credit were entered in a $50 lottery as a way of thanking them for their time and involvement.

All procedures in this study were approved by the McGill University Research Ethics Board for Research Involving Humans.

Results

Thresholds

Since human perception of brightness bears a logarithmic relationship to light intensity (see Goldstein, 1989, Appendix A, for explanation) a log transformation was performed on the visual discomfort and pain threshold values prior to data analysis. Values are therefore presented in log lux.

Test-retest reliability:

Test-retest reliability of the three log-transformed threshold measures was assessed using paired Pearson correlations. Since several of the participants reported neither discomfort nor pain on some of the threshold measures, one set of correlations was calculated omitting these cases on a pairwise basis. Another set of correlations was conducted in which participants were assigned a value of 3.48 log lux (corresponding to maximum illumination possible, 3000 lux) in place of the missing data. For discomfort thresholds, reliability correlation coefficients between the three threshold measurement trials ranged from .78 to .92 when maximum values were not included ($\underline{n}$ = 32), and from .82 to .95 when maximum values were added ($\underline{n}$ = 40). Pain threshold reliability ranged from .77 to .92 ($\underline{n}$ = 20), and .88 to .95 ($\underline{n}$ = 40), respectively. These reliability coefficients indicate that participants were very consistent in reporting discomfort and pain thresholds over three separate threshold assessments. This was true whether or not ceiling values were included in the calculations. Table 2.3 shows how many participants in each group never reported discomfort or pain.

Effect of group and bias condition:

The transformed values for the three threshold measure replications were averaged so that each participant had one mean threshold value for discomfort, and one mean threshold value for pain in log lux units. As mentioned above, participants who did not report discomfort or pain were assigned a score of 3.48 log lux. Discomfort and pain thresholds are presented in Figures 2.1 and 2.2, respectively.

The threshold results indicate that our lighting stimulus was capable of inducing discomfort in the majority of participants. In this sample, 18 of the 20 migraineurs and 14 of the 20 controls reported light-induced discomfort. When bias groups were

combined, the mean discomfort threshold for the migraine group was 2.84 log lux (SD = 0.50) and 2.97 log lux (SD = 0.34) for controls. Twelve of the migraineurs and 9 of the controls reported light-induced pain. The mean pain threshold for the migraine group was 3.18 log lux (SD = 0.33) and 3.39 log lux (SD = 0.13) for controls. These mean threshold values include individuals who were assigned the maximum stimulus intensity because they did not report discomfort or pain.

Two-way factorial ANOVAs (group by bias condition) were conducted to assess thresholds for light-induced discomfort and pain. For the discomfort measure, there was no significant interaction between group and bias ($F(1, 36) = 2.52$, $p = .12$). While discomfort thresholds were lower in migraine sufferers than controls, this effect was not statistically significant ($F(1, 36) = 0.81$, $p = .37$). The main effect of bias for discomfort was also not statistically significant ($F(1, 36) = 0.20$, $p = .66$).

For the pain measure, there was a significant interaction between group and bias condition ($F(1, 36) = 4.24$, $p = .05$). In order to further explore the nature of this interaction, tests of simple main effects were conducted. One set of simple main effects was calculated to assess whether group differences existed within each of the bias conditions. In those who had received the positive bias, the difference in pain thresholds between migraine sufferers and controls was not statistically significant ($F(1, 18) = 0.16$, $p = .69$). Among individuals who had received the negative bias, there was a significant group difference ($F(1, 18) = 9.42$, $p = .007$) with migraine sufferers having lower thresholds for light-induced pain than controls. Another set of simple main effects was calculated to assess whether there were differences between those within a group according to which biasing statement they had heard (e.g. migraine, positive bias vs.

migraine, negative bias). Among controls, thresholds in the negative bias group were significantly higher than in the positive bias condition (F (1, 18) = 12.30, p = .003). It was the controls who had heard that light could cause discomfort in migraine that were less sensitive to light-induced pain than those who had heard that lights could have positive effects. Migraine sufferers showed the opposite direction of results, although the difference in thresholds between those who had heard the positive and negative bias was not statistically significant (F = (1, 18) = 1.11, p = .31).

While analysis of variance is relatively robust against violations of normality of the distribution and homogeneity of variance when group sizes are equal (Olson, 1987), there was an obvious ceiling effect in the measurement of pain thresholds. The ceiling effect was most apparent in the control group who had received the negative bias, in which nine out of ten participants never reported pain and were therefore assigned the maximum value. This greatly reduced variance and resulted in a significant violation in the assumption of homogeneity of variance (Bartlett's test: $p < .0001$). Pain thresholds were therefore re-assessed using non-parametric methods. Since there is no single non-parametric test that can replicate a two-way factorial analysis of variance, a comparison of the four groups was first conducted using the Kruskall-Wallis test (corrected for ties). A significant difference in pain thresholds was detected (H (3) = 9.87, p = .02). In order to further evaluate group differences in a manner that could be analogous to the assessment of the simple main effects described above, a series of paired comparisons using Mann-Whitney U tests were conducted. The results of these comparisons are presented in Table 2.4. The pattern of significance was the same as in the parametric analyses described above. Of those who had heard the negative bias, migraine sufferers

were more sensitive to light-induced pain than controls. Of the controls, those who had heard the negative bias were less sensitive to light-induced pain than those who had heard the positive bias.

Effect of migraine classification (MA vs. MO):

To test whether there were any significant differences in thresholds between participants with migraine with aura (n = 9) and migraine without aura (n = 11), unpaired t-tests were conducted. No significant differences for log discomfort thresholds (t (18) = 0.23, p = .82) or log pain thresholds (t (18) = 0.15, p = .89) were detected. The proportion of migraineurs with and without aura in both bias conditions was very similar (Positive bias: n = 5 MA & 5 MO. Negative bias: n = 4 MA & 6 MO).

Belief statement questionnaire

Means and standard deviations for the responses to the belief statement questionnaire are presented in Table 2.5. Two-way factorial ANOVAs (group crossed by bias) were conducted to assess whether differences in beliefs emerged on the post-threshold questionnaire.

For Statement 1(*" I believe that bright lights can be beneficial in the treatment of migraines"*), neither the interaction effect (F (1, 36) = 0.15, p = .71) nor the group effect (F (1, 36) = 0.15, p = .71) were significant. The bias effect approached significance (F (1,36) = 3.63, p = .065). Those in the positive bias condition (i.e., those who had heard that about the positive effects of light on migraine) agreed more with the statement than those who had heard the negative bias, although all group means centred around scores reflecting "no opinion" to "slightly disagree."

For Statement 2 (*"I believe that viewing bright lights can cause discomfort and pain"*), there were no significant interaction or main effects for group and bias condition (all $p > .05$). The means for all groups were above 4, suggesting that participants generally agreed with this statement independent of group.

For Statement 3 (*"I believe that people with migraines are particularly sensitive to discomfort caused by bright lights*"), neither the interaction effect and nor the bias effect were statistically significant (both $p > .05$). There was a significant group effect demonstrating that migraineurs agreed more strongly with this statement than controls ($F(1, 36) = 4.64$, $p = .04$). This suggests that regardless of what participants were told before the study, the migraine group believed more strongly that they were at risk of increased light sensitivity. While their scores were higher, it is interesting to note that the control group also agreed with this statement, regardless of what pre-test information was provided.

For Statement 4 (*"I believe that exposure to bright lights can be beneficial to your health and well-being*"), there were no statistically significant effects (all $p > .05$). Group means reflected neutral to somewhat positive belief in this statement.

In summary, beliefs on the effects of light differed according to migraine status. The biasing statements did not have a big impact on how participants responded to the statements.

Discussion

Visual Discomfort and Pain Thresholds

One of the main goals of this study was to test whether our lighting apparatus could elicit discomfort in a large proportion of the individuals tested. This was needed in

preparation for the central study of this dissertation, presented in Chapter 3, which required a light stimulus that could induce discomfort. Thresholds for both discomfort and pain were assessed in order to determine a stimulus intensity that would be considered aversive but tolerable for a 5-minute exposure. A stimulus intensity that would not induce discomfort was also required for a control condition that was intended to be milder and non-aversive. Since threshold values from previous studies had varied greatly and used a variety of light stimuli, this study assessed thresholds in a group of migraine sufferers and controls using our lighting apparatus.

The mean threshold values for light-induced discomfort and pain for both migraine sufferers and controls fell within the range of thresholds cited in the existing the literature (see Table 2.1). Thresholds measured using our apparatus and instructions proved to be very reliable over three trials. The assessment of pain was, however, limited by the maximum intensity value (3000 lux) that fell below the pain threshold for many individuals. This led to a ceiling effect that was particularly evident in the control group. While this ceiling effect might have been reduced by including higher light intensities, Vanagaite and colleagues (1997) tested thresholds for discomfort and pain using a procedure that was very similar to ours and a light stimulus that reached 23 000 lux (4.36 log lux). Their results showed that 22% of the control group and 4% of migraineurs did not report pain at the maximum value. Their results demonstrate that even at higher intensities, some individuals are still unlikely to experience or report light-induced pain.

Since the thresholds were required to generate appropriate stimulus intensity values for an intense, but not painful stimulus and a milder control stimulus for the central study of this dissertation, the intensity range provided by this lighting apparatus

was considered appropriate. Based on our results, values of 1000 lux (3 log lux) and 100 lux (2 log lux) were chosen for the intense (aversive) stimulus and mild (control) stimulus, respectively, for the upcoming study.

Effect of Biasing Statements on Thresholds

A second purpose of this study was to assess the impact of providing biased information about the purpose of the study on thresholds for light-induced discomfort and pain. Several aspects of the pattern of results were surprising. First, while we had predicted that migraineurs would be more sensitive than controls under both instruction sets, a significant difference only emerged when the negatively biased instructions were given, and only when pain and not discomfort was being assessed. Second, while we would have predicted that migraineurs would be more affected by the biased instructions, since they contain information that could be considered more relevant to them, it was in fact the control groups whose thresholds differed more according to bias condition. The thresholds of both groups of migraineurs were similar regardless of instructions, suggesting that pre-existing beliefs or experience with light-sensitivity were more powerful than the impact of information provided in the context of instruction. These results may reflect a tendency for controls to respond differently to a subjective task when they do not believe they are likely to be as affected as the clinical group under investigation. While the results of this study suggest that instructions should avoid biasing statements, the ability of instructions to affect visual discomfort thresholds should be further investigated. It would be interesting to further investigate this phenomenon by including a "neutral" group to assess thresholds when no information about the purpose of the study is provided. Also, while these data do support the impact of biased

instructions on subjective threshold measures, further investigation using a stimulus that can attain higher intensity values and larger sample size would be beneficial in confirming the findings of this study.

Beliefs about lights and migraine

As an additional measure of the effects of the biasing statements, participants were asked about their beliefs about light at the end of the study. Participants generally believed that lights could cause discomfort or pain, irrespective of diagnostic group or bias condition. While all groups also demonstrated a belief that migraine sufferers are more sensitive to light-induced discomfort, this belief was significantly stronger among migraine sufferers. Biasing information did not have an obvious impact on this belief, and it is likely that participants were aware of increased light sensitivity in migraines either from their own experience with it, the experience of migraineurs who they know, or information provided by other sources such as physicians or the media. With regards to the belief that light could be beneficial in treating migraine, an idea introduced in the positive bias condition, group means reflected neutral beliefs centered around "no opinion." There was a trend showing that those who had heard the positive bias were slightly more accepting of this statement, as would be expected. This was not true of the general statement about lights be beneficial to health and well-being, in which there was a general consensus around "no opinion" with no effect of group or bias. Based on these results, it would seem that the biasing statements were not strong enough to have a strong impact on stated beliefs assessed at the end of the study. While there is evidence for both the beneficial effects (Anderson, 1989) and the negative effects of light on migraine (e.g. Drummond, 1986; Hay et al., 1997; Silberstein et al, 2001; Vanagaite et al, 1997), there

is considerably more evidence for the latter, as was also reflected by beliefs about these phenomena.

While there is clearly an impetus for further investigation of the impact of instructions on photophobia thresholds and other subjective measures in migraine, the immediate value of this study was to provide a basis on which to refine the methodology of the following study.

Table 2.1

Photophobia Thresholds Previously Reported

(Note: Threshold values in the Results column all include log lux values to facilitate comparison among the studies since the majority used log-transformed values in their analyses)

Study	Stimulus	Threshold measure	Participants	Results
Drummond, 1986	Opaque white screen illuminated at 1 of 5 intensities (lux): 1.1 & 7.3 (dull), 36.3 (moderate) 153.5 & 500 (bright)	Subjects asked if light was "glarey" or caused pain (if yes, rate on 0-40 scale). 3 sets of the 5 stimuli (in random order) were tested.	54 H: 15 TH during headache, 18 M during a non-migraine headache, 21 M during migraine 20 C 24 H re-tested headache-free	- H: more glare at all intensities (during and between headaches) than C. - H: more pain during headache than when headache-free*. - H (headache-free): more pain than C at 500 lux* (2.7 log lux).
Drummond & Woodhouse, 1993	130 W halogen bulb, (35 steps from 1.5 – 2900 lux). On for 2 seconds, off for 2 seconds Steps of 5 – 500 lux.	Brightness increased to maximum, or until discomfort or request to stop increase. One trial per subject. Pain induction: thresholds re-measured during pain induction (ice on forehead).	30 MA 21 "features of MO" 27 C (<12 headaches /year of which ≤2 are severe)	- Thresholds: M<C, MO not different from MA - M thresholds decreased during pain (Cs did not)* - Threshold means (estimated from graphs): • C=3 log lux • M (no pain) = 2.7 log lux • M (pain) = 2.5 log lux

Woodhouse & Drummond, 1993	Same as Drummond & Woodhouse, 1993	Threshold measure same as Drummond & Woodhouse, 1993 No pain induction used.	16 M (9 MA, 7 MO) 16 C (<12 headaches /year, ≤2 are severe) M tested at home, once during headache, once between headaches. C tested twice in lab.	- Headache-free M < C* - M with headache < M headache-free, but C same at both times* - Threshold means (estimated from graphs): • C: 3 log lux • M headache-free: 2.5 log lux • M with headache: 2.0 log lux
Main, Dowson & Gross, 1997	2 200W halogen bulbs 25-1000 lux (steps or time not specified). Darkened room Participants to look midway and just below the two bulbs	"I am going to increase the brightness of the light and you must say when it is uncomfortably bright as though you want to look away or screw up your eyes."	52 M 48 C (≤1 non-migraine headache/month) No headache for past 72 hours	- M had lower thresholds for discomfort than C**** - Mean thresholds: • M = 95 lux (1.98 log lux) • C = 200 lux (2.3 log lux) - Does not specify how many did not report discomfort.

Vanagaite et al, 1997	800W halogen bulb behind grey glass 50-23 000 lux, in 33 steps controlled by computer. On for 2 seconds, off for 2 seconds	Asked to say "stop" when light became uncomfortable. Repeated 5 times. Last trial continued until pain or could not tolerate the light. 5 trials left eye, 5 right eye, 5 both eyes.	67 M (37 MA, 30 MO): 48 tested without headache, 19 during headache 67 C (no H diagnosis, ≤1 headache/month) Experimenters blind to diagnosis.	- 22% of C tolerated max without discomfort or pain. 4% of M tolerated max without discomfort or pain. - Thresholds: M < H (during and between attacks)***. M headache < M no headache. MO and MA not different. - Median discomfort: • 1.9-3.8 log lux - Median pain: • 2.3-4.4 log lux

*p <.05, **p <.001,*** p <.0005,****p <.0001

M= migraine, MO= migraine without aura, MA= migraine with aura, TH = tension-type headache, H= Headache, C=control

Table 2.2

Group Characteristics

		Migraine (n = 20)	Control (n = 20)
Sex ratio (female: male)		18:2	17:3
Age (years):	Mean ± SD	26.6 ± 6.1	23.9 ± 4.7
	Range	19 to 38	19 to 38
Headache diagnoses (n)			
Migraine without aura		11	
Migraine with aura		9	
Tension headache		9	1
Years of migraine*:	Mean ± SD	10.84 ± 6.65	N/A
	Range	3 to 23	
Episodes per year -			
Migraine:	Mean ± SD	22.2 ± 22.7	N/A
	Range	4 to 96	
Other headaches per year:	Mean ± SD	63.4 ± 65.5	8.2 ± 6.3
	Range	0 to 180	0 to 24
Typical episode severity -			
Migraine episode:	Mean ± SD	8.3 ± 1.4	N/A
	Range	6 to 10	
Typical other headaches:	Mean ± SD	3.1 ± 1.7	3.2 ± 1.6
	Range	1 to 7	1 to 7

* Data missing for one individual

** Severity was assessed using a 1-10 point scale, with 1 representing the least severe (no impairment in function), and 10 representing the worst possible headache (severely impaired ability to function).

Figure 2.1

Schematic of Testing Set-Up

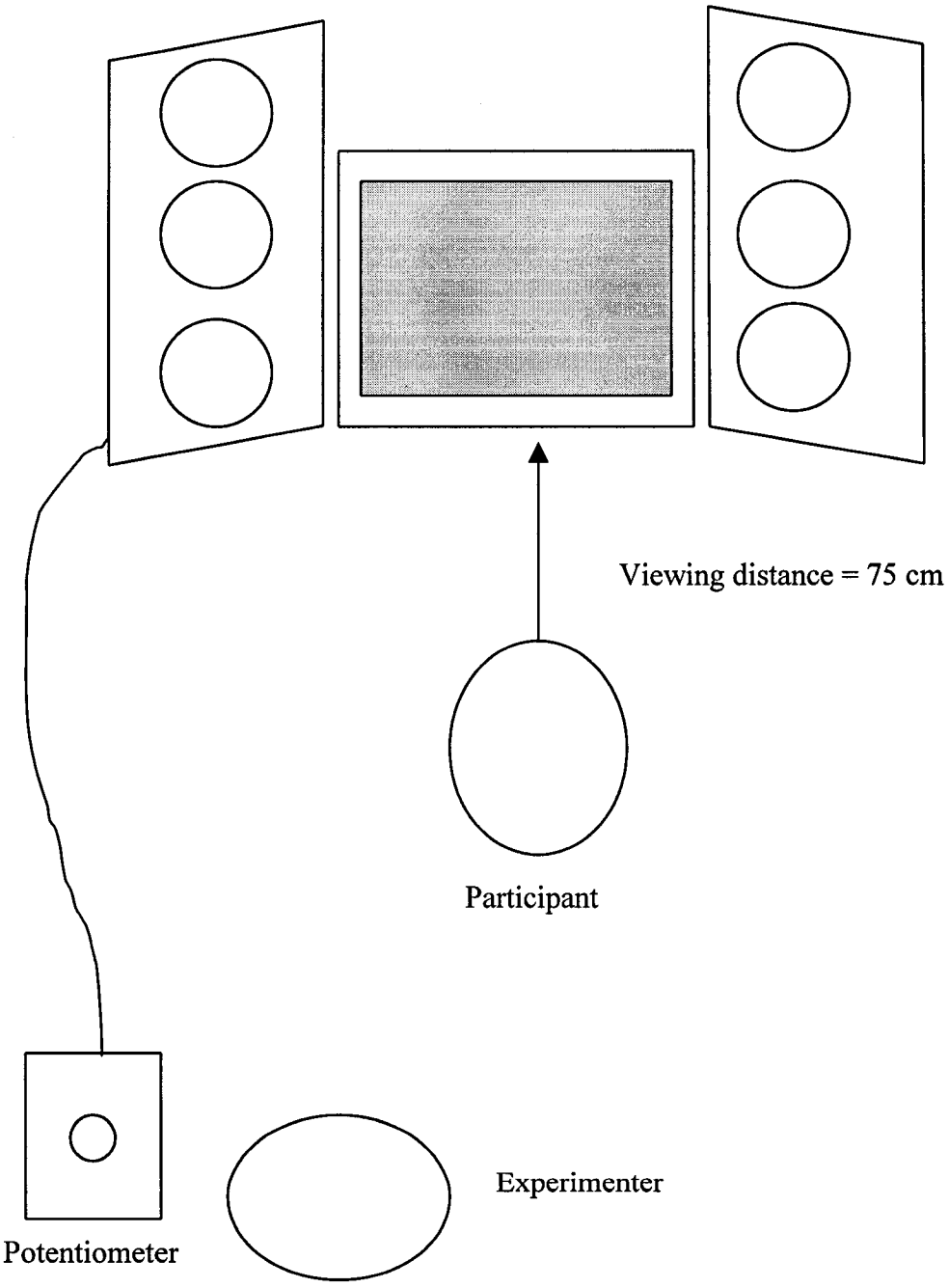


Figure 2.1

Mean Discomfort Thresholds According to Migraine Status and Bias Condition (Mean and Standard Error)

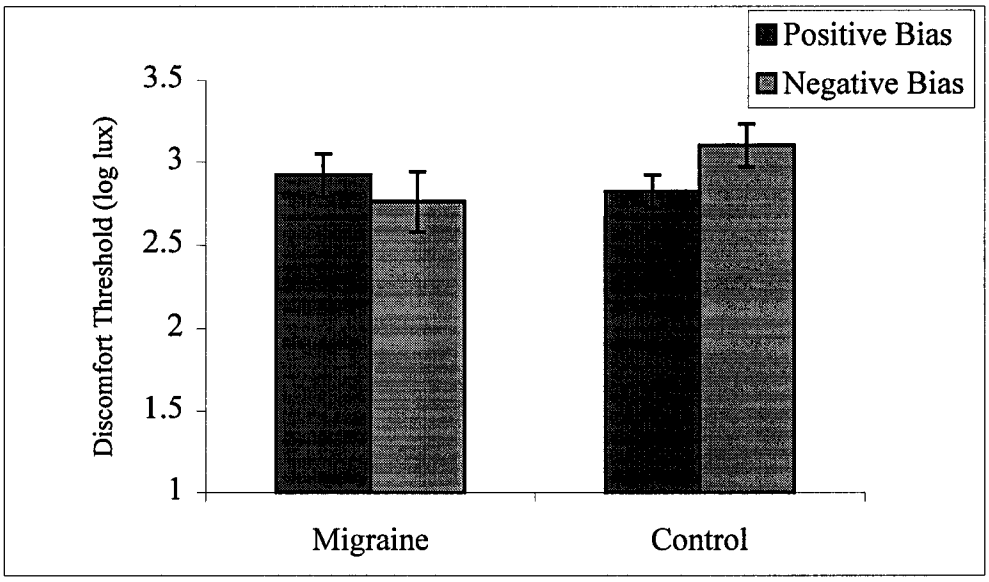


Figure 2.2

Pain Thresholds According to Migraine Status and Bias Condition (Mean and Standard Error)

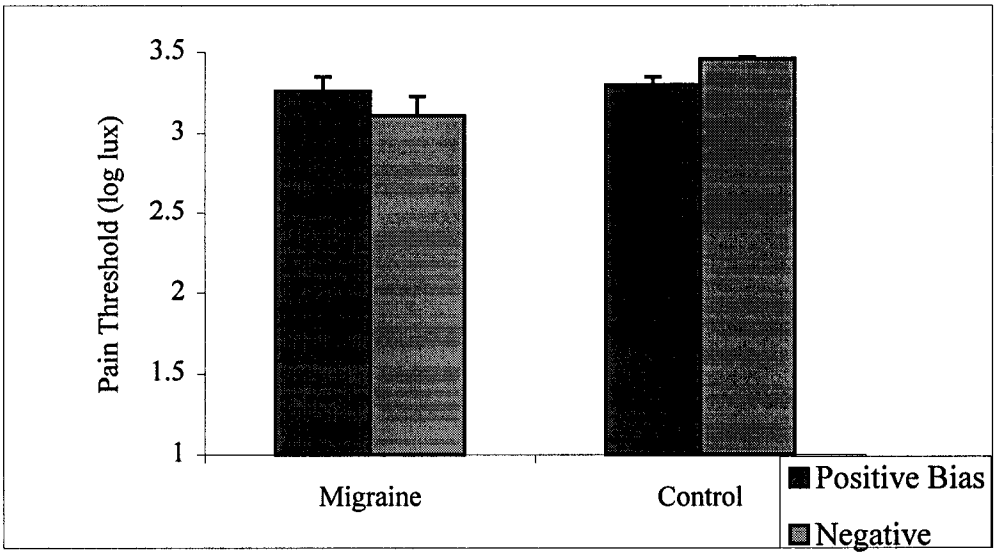


Table 2.3

Number of participants who never reported discomfort and pain during any of the three threshold measures.

	Migraine Negative Bias	Migraine Positive Bias	Control Negative Bias	Control Positive Bias
Never reported discomfort	2	0	2	0
Never reported pain	4	4	9	2

Table 2.4

Non-parametric comparisons of log pain thresholds (Mann-Whitney U test with values corrected for ties)

Comparison	Tied Z-value	Tied p-value
Migraine – Positive / Control – Positive	-0.306	.76
Migraine – Negative / Control – Negative	-2.218	.027
Control – Positive / Control – Negative	-3.144	.0017
Migraine – Positive / Migraine – Negative	-0.703	.48

Table 2.5

Endorsement of the Statements Presented Following Threshold Measurement According to Group (M ± SD, n = 10)

Group & Bias	**Statement 1** Light beneficial in treating migraine	**Statement 2** Bright lights can cause discomfort	**Statement 3** Migraineurs are more sensitive to light	**Statement 4** Bright lights can be beneficial to health and well-being
Migraine				
Negative	2.5 ± 1.2	4.1 ± 1.2	4.7 ± 0.5	3.6 ± 1.0
Positive	2.9 ± 0.6	4.6 ± 0.5	4.2 ± 0.8	4.2 ± 0.4
Control				
Negative	2.5 ± 0.9	4.3 ± 0.7	4.0 ± 0.7	3.8 ± 0.8
Positive	3.1 ± 0.6	4.2 ± 0.9	4.0 ± 0.7	3.5 ± 1.1

Response scale values: 1: strongly disagree, 2: somewhat disagree, 3: no opinion, 4: somewhat agree, 5: strongly agree

Chapter 3 – **A study of visual stress in migraine: subjective complaints and autonomic reactions to intense visual stimulation.**

Introduction

As summarized in the introductory chapter of this dissertation, there is considerable evidence that migraine sufferers describe bright lights and certain spatio-temporal patterns of visual stimulation as more aversive than non-migraineurs. The term "visual stress" has been introduced by Wilkins (1995) and used widely, yet it is unclear whether exposure to these types of visual stimuli results in physiological or affective responses that are associated with more commonly studied stressors in humans. Since intense visual stimulation can be aversive both during and between migraine attacks, and can sometimes trigger episodes, assessing the nature of psychophysiological response to this "stressor" may elucidate how normally benign environmental factors such as light can be involved in setting off a chain of events that results in migraine.

Migraineurs' responses to several types of stressors have been studied using a variety of autonomic measures (See Table 1.1 for overview). When commonly used psychological stressors, such as mental arithmetic or giving a speech, have been assessed, contradictory findings have emerged. Some studies have found that while migraineurs did not show altered autonomic function during the stressor, they showed differences in measures of blood pressure control during recovery, following the termination of the stressor (e.g. Gannon et al, 1981; Hassinger et al, 1999; Holm et al, 1997). Others have failed to find differences between the responses of migraineurs and controls to these traditional psychological stressors (e.g. Gannon et al., 1987; Kroner-Herwig et al, 1988; Stronks et al, 1998). The responses to physical stressors in migraine have also been the

focus of considerable study, but also show contradictory findings. For example, the blood pressure and heart rate responses to orthostatic tests (e.g. tilt test, or head-up tilt) have been used to assess sympathetic and parasympathetic function (Ravits, 1997). Using this technique, some studies have found evidence of sympathetic hypofunction in migraine (e.g. Gotoh et al, 1984; Havanka-Kainnianen, 1986; Havanka-Kainnianen et al., 1988), while others have found no differences between migraineurs and controls (e.g. Pierangeli et al., 1997; Thomsen et al., 1995). While these stressors elicit a characteristic autonomic response, and knowing whether these responses are different in migraine could be useful in understanding migraine pathophysiology, one could argue that the majority of these stressors are not specific to the migraine process and may therefore not result in a response that is as indicative of particular migraine processes. For example, while mental stress has been used in many studies, both tension headache and migraine sufferers report stress as a trigger factor (Spierings et al., 2001). Assessing autonomic function in response to a stressor that is particularly relevant to migraine should highlight unique responses that may not be evident during traditional challenges of autonomic function. Since there is considerable evidence that migraineurs are more sensitive to discomfort caused by intense visual stimulation (see Chapter 1 for review), and since migraine sufferers report visual triggers more commonly than tension headache sufferers (Spierings et al., 2001), it is logical that aversive visual stimulation could be considered a migraine-specific stressor.

The present study compared the reactions of migraine sufferers and non-migrainous controls to two types of visual stimulation that have been associated with visual stress: intense, diffuse illumination and a high contrast, square-wave grating that

phase-alternated at a moderate temporal frequency giving rise to a percept of flicker. Milder versions of these stimuli were also presented to assess reactions in conditions that reflected all other aspects of the testing situation to determine whether stimulus intensity affected the nature of responding. Each of the four stimuli was displayed for five minutes, during which physiological responses were recorded. Several physiological measures were recorded during this protocol in order to assess different aspects of autonomic function. These measures included heart rate, two indicators derived from heart rate variability analysis (vagal tone and sympathovagal balance), respiratory rate and electrodermal responses.

Psychophysiological measures assessed in this study

Heart rate is influenced both by the opposing influences of the sympathetic and parasympathetic branches of the autonomic system (see reviews by Berston et al., 1997; and Turner, 1994). According to these reviews, parasympathetic control of heart rate involves the activation of the vagus nerve, which when stimulated slows heart rate down. The sympathetic system increases heart rate, as well as influencing the vasculature. Under conditions of stress, the adrenal medulla is stimulated causing a release of adrenaline and noradrenaline. Adrenaline increases heart rate, and also increases contractile force that in turn increases blood pressure. The result of these responses is an increase in metabolism that prepares the individual for action, traditionally referred to as the fight or flight response.

Electrocardiograms (ECG) allow for non-invasive and reliable measurement of heart rate. Heart rate is traditionally reported in beats per minute. The ECG can also be used to derive interbeat interval (IBI), or the length of time between successive cardiac

beats. This time period, also referred to as heart period and RR interval, is typically reported in milliseconds. Both heart rate and heart period provide overall measures of how quickly the heart is beating and can be used to assess changes in this rate in response to stress. However, they do not provide an indication of whether the change is due to an alteration of sympathetic or parasympathetic function.

The analysis of different rhythmic influences that regularly increase and decrease heart rate provides an index of sympathetic and parasympathetic influence on cardiovascular control. To derive this information, a series of interbeat interval durations is analyzed to identify the extent to which different temporal frequencies are represented in the heart rhythm during a given period of time. In order to derive this measure, a number of mathematical and statistical methods, described in further detail below, can be used to quantify the degree of variation that exists. Variability within different ranges of temporal frequency is associated with parasympathetic and sympathetic influences on heart rate. Akselrod and colleagues (1981) demonstrated that pharmacological blockade in conscious dogs abolished fluctuations in specific frequency bands as assessed by power spectral analysis. More specifically, by blocking muscarinic parasympathetic transmission using glycopyrrolate, heart rate variability in the mid- and high-frequency bands (centered around 0.12 and 0.40 Hz, respectively) was abolished, and the amplitude of the low frequency band (centred around 0.04 Hz) was reduced. Propranolol was used to block sympathetic β-adrenergic receptors, which resulted in a reduction of the amplitude of the low frequency band peak. When the blockades were combined, the rhythmic variations in heart rate were abolished. This work demonstrated that heart rate variability is under the control of the sympathetic and parasympathetic branches of the

autonomic nervous system. The higher frequency fluctuations including those centered around respiratory rate, also known as respiratory sinus arrhythmia, rely on parasympathetic control. The low frequency fluctuations reflect both parasympathetic and sympathetic influences.

In more practical terms, the examination of temporal variability of heart period provides a non-invasive index of parasympathetic and sympathetic influences on heart rate. The influence of parasympathetic influence on cardiac rhythm is reflected by variability in the high frequency band (HF), centered around respiratory rate. When an individual inhales, heart rate increases, and when the individual exhales, heart rate decreases. The result is a rhythmic increase and decrease in heart rate that is referred to as respiratory sinus arrhythmia. This fluctuation, that is controlled by the vagus nerve, occurs at a temporal frequency of approximately 0.15 Hz.

Variation in the range of 0.05-0.15 Hz is typically referred to as low frequency (LF) heart rate variability, although this range is sometimes further subdivided into other components. While some consider variability in the LF range as an indicator of sympathetic function, the interpretation of this indicator is more controversial since the parasympathetic system also influences this frequency band. A ratio of LF to HF can therefore be used as an index of sympathovagal balance, or the relative contribution of sympathetic and vagal control (Berston et al, 1997).

There are a number of methods that are used to assess heart rate variability, including time domain measurements (e.g. the difference between longest and shortest RR intervals), statistical methods (e.g. variance of RR intervals) and temporal frequency analysis (e.g. fast-fourier transformation and autoregressive modeling). The present

study used a Vagal Tone Monitor, which combines these techniques (Delta-Biometronics, 1994). A more extensive explanation of the "moving polynomial method" used by Porges in designing the Vagal Tone Monitor is presented by Bernston and colleagues (1997). While a number of techniques are available to assess heart rate variability, the estimates they provide are highly correlated with each other because of mathematical reasons and because they are thought to be reflective of similar underlying physiological processes (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). There is no general consensus as to which is the best method for assessing heart rate variability (Berntson et al., 1997). In addition to recording ECG and the calculation of heart rate variability estimates, the present study also assessed respiratory rate. Respiratory rate can influence heart rate variability (Berntson et al., 1997) so including this measure ensured that any such association could be assessed.

While the high frequency heart rate variability, or vagal tone, is commonly thought to reflect parasympathetic function, the interpretation of the lower frequency band is more controversial (Bernston et al., 1997). Therefore, we also measured electrodermal activity, which is mediated exclusively by the sympathetic nervous system (Bellack & Hersen, 1998). Electrodermal responses reflect the activation of eccrine sweat glands, which are stimulated by the release of acetylcholine. According the Bellack and Hersen, when participants are well-matched on variables such as age and sex, and when external factors such as room temperature are well-controlled, electrodermal activity can provide a measure of anxiety-related phenomena such as fear responses. Several measures can be derived from the measure of electrodermal activity, including the

amplitude of the response that follows a particular stimulus, tonic level of skin conductance, or the number of electrodermal responses that occur in a given period of time. In the present study, the number of non-specific electrodermal responses that occurred during the various conditions was compared, since according to Bouscein (1992, Part 3), this measure is the best suited for continuous monitoring during stress-inducing conditions.

Subjective measures assessed in this study

Previous assessments of visual discomfort and photophobia have tended to focus on visual complaints of glare or light-induced discomfort and/or pain (see Table 2.1). Some have also included observational measures (Marcus & Soso, 1989; Wolff, 1963) or measures of headache or other pain (e.g. Drummond, 1997). An association between visual discomfort and somatic complaints has, however, also been suggested (Wilkins, 1995) but has been the source of relatively little quantitative assessment. Typically, these studies have used a single measure that is related directly to stimulus intensity. Visual discomfort may, however, involve a variety of visual and somatic complaints that are not captured by a unidimensional pain threshold. One of the goals of the present study was to assess a broader range of complaints that could be associated with visual stress and/or migraine, and to measure the intensity of these complaints in a standardized fashion that would allow comparison between participants and across different phases of the study. The list of complaints included a variety of visual symptoms (e.g. glare, squinting, visual discomfort) as well as somatic symptoms that could be relevant to migraine sufferers (e.g. headache, nausea, dizziness). Complaints were assessed before, during and after visual stimulation in order to determine whether intense visual stimulation was associated

with a pattern of increased migraine-related symptoms. Symptoms were measured using a visual analogue scale so that participants could report the intensity of complaints rather than just reporting their presence or absence.

In addition to the visual and somatic complaints, the present study also assessed anxiety using a visual analogue scale. While aversive visual stimulation is thought to act as a stressor to the visual system of migraineurs, subjective ratings of anxiety have not been assessed systematically. Martin and Teoh (1999) found that aversive visual stimulation was associated with higher ratings of negative affect. However, little is known about the relationship between visual stimulation and subjective ratings of anxiety. The present study therefore assessed subjective ratings of anxiety before, during and after visual stimulation to determine whether migraine sufferers found the visual stimulation more anxiety-provoking than controls, and more specifically, whether anxiety was greater during the intense viewing conditions as compared to the milder conditions.

Stimulus values for the light conditions in the present study were based on thresholds for discomfort and pain measured in the previous study. Since the present study used the same lighting apparatus, we assumed thresholds would be similar. Thresholds were, however, retested at the end of the protocol to verify this assumption.

Goals and hypotheses

In summary, the goal of this study was to measure psychophysiological responses and subjective complaints associated with intense visual stimulation, comparing the responses of a group of migraine sufferers with a group of non-migrainous controls. Responses to four viewing conditions (two intense stimuli and two mild stimuli) were evaluated. An attempt was made to reduce demand characteristics that could influence

the reporting of visual complaints or migraine-related symptoms. This was done by minimizing instructions and preamble that focused on visual discomfort, and by suggesting that the goal of the study was to assess basic visual performance and physiological responses during different viewing conditions.

We hypothesized that headache-free migraineurs would react to this stimulation with higher ratings of visual complaints, somatic complaints, and anxiety than the controls. Since light-induced discomfort and pattern-induced discomfort have not been compared, we used both types of stimuli to assess whether response patterns would be similar. Both intense and mild versions of each of these stimulus types were used, and it was predicted that complaints would be higher for the intense stimuli. We also predicted that migraine sufferers would show a different psychophysiological response to the intense stimuli than controls, reflecting the activation of autonomic responses outside of the ophthalmic division of the trigeminal nerve.

Methods

Participants

Participants were recruited using campus advertisements, information brochures placed in the waiting rooms of local university and college student health service clinics and other medical clinics, and by referral from local neurologists and general practitioners familiar with our studies. A small number of participants (4 M and 1 NC) had taken part in the previous study. In these cases, participants were not selected on the basis of their previous thresholds or on the basis of any other aspect of their past participation. Screening of potential participants was done by telephone using a semi-structured interview that assessed headache symptoms and screened for the presence of

exclusionary criteria. Only female participants were chosen for this study to reduce variability in the physiological measures introduced by sex differences.

Exclusionary criteria for both the migraine group and controls included a history of neurological disorders (e.g., seizure disorders, optic neuritis, multiple sclerosis, stroke, cluster headache), disorders that could affect visual function (e.g., diabetes), and significant visual problems that were not corrected by glasses or contact lenses (e.g., glaucoma). Participants could not be taking medications or herbal preparations that are used for migraine prophylaxis, cardiovascular conditions, mood disorders or anxiety disorders (e.g., beta-blockers, antidepressants, anxiolytics, feverfew) or any other daily medication with the exception of oral contraception. Participants who used other medications such as analgesics, anti-emetics or antihistamines for migraine or other conditions were accepted into the study but were required to be medication-free on the day of testing. Exclusion was also based on the presence of cardiovascular problems that would affect heart rate measures (e.g., high blood pressure).

Inclusion in the migraine group required that participants fit criteria for migraine without aura (MO) and/or migraine with aura (MA) as published by the I.H.S. (HCCIHS, 1988). These criteria are presented in Appendix A. Participants were required to have consulted with a neurologist or general practitioner about their migraines and be willing to provide contact information so that a request for confirmation of diagnosis could be sent by mail. This provided some assurance that a medical professional had ruled out other causes of headache, in accordance with the I.H.S. criteria. Participants had to experience at least one migraine attack per month and less than 15 headache days per month to be included. The latter criterion was necessary to facilitate the scheduling of an

appointment for testing on a headache-free day, as well to avoid participants who would meet criteria for chronic daily headache or transformed migraine. Participants could have an additional diagnosis of episodic tension-type headache (TH), but again, could not have more than a total of 15 headache days per month.

Inclusion in the non-migraine control group (NC) required that participants not fit criteria for a migraine disorder according to I.H.S. criteria (HCCIHS, 1988). If participants experienced headaches, headaches could not be described as severe in intensity and could not occur more than once per month. Typical headache disorders endorsed by NC participants included episodic tension-type headache (TH), acute sinus headache and occasional alcohol-withdrawal headaches. Control participants were age-matched to the migraine participants.

The migraine group (M) was composed of 24 women, and the non-migraine control group (NC) was composed of 23 women. Group characteristics are presented in Table 3.1.

All participants in the M group met I.H.S. criteria (HCCIHS, 1988) for migraine based on their interview data and reported having spoken to a doctor about their headaches. Confirmation of diagnosis was received in 17 patients, or 70% of our sample. In three cases, the forms were returned but the physician indicated that while the participant had been seen for headache, there was not enough information on file to specify a diagnosis. In three other cases, forms were sent to doctors but not returned to us. In one case, we were unable to obtain contact information for the physician. Two of the participants with unconfirmed diagnoses reported treating their headaches with migraine-specific prescription medications (e.g. sumatriptan).

Of the 24 migraineurs who met criteria for participation in this study, 14 learned about the study through campus advertisements, five from pamphlets placed at medical clinics, and three from friends who were aware of the study. Referral information was not noted for two participants. As mentioned earlier, four of these participants had taken part in the previous study. While several potential participants were referred by local general practitioners and specialists, none were suitable for this study due to the presence of exclusionary criteria such as prophylactic migraine medication use.

Viewing conditions and display

We assessed participants' reactions to four viewing conditions in this study. In two of the conditions, responses to diffuse light were assessed. Participants viewed a monochromatic grey computer screen flanked by two "light boxes", each containing three halogen bulbs. This apparatus was identical to the one used in the previous study, described in Chapter 2. Stimulus intensity values in this study were based on the findings of the previous study. The Intense Light (IL) condition had a stimulus intensity of 1000 lux, or 3 log lux. For the Mild Light (ML) condition, a low light intensity was chosen (100 lux, or 2 log lux). No participant in the previous study considered this level to be aversive. This condition was designed to provide a non-aversive yet otherwise similar comparison to the IL condition. Since the majority of participants in this study had not taken part in the previous study, thresholds for light-induced discomfort and pain were assessed at the end of this protocol. This was done in order to verify that the samples had comparable thresholds, which would further support our selection of light intensity stimulus values. Individualizing stimulus intensities according to participants' thresholds was not considered a feasible approach since this would have required

thresholds to be measured prior to the viewing conditions, introducing potential bias that we were attempting to avoid.

In order to maintain the participant's attention and to control the direction of gaze we asked participants to perform a simple computerized task that was displayed on a monitor between the light displays. A black circle was displayed at the centre of the computer monitor. Participants were instructed to indicate when this circle changed to a white square, using the mouse key to respond. If, after 2 seconds, participants had missed the change, a tone indicated their error and the stimulus reverted to the black circle. The stimulus change occurred every 30 +/- 5 seconds. Both the circle and square subtended a visual angle of approximately 1.6 degrees. In order to minimize the potential for inducing performance anxiety or stress, the computerized task was designed to be very easy to do. The task was identical for both the IL and ML conditions.

The two "grating" stimulus conditions involved a grating pattern displayed on the computer monitor. The spatial characteristics of these stimuli are represented in Figure 3.1. In the Intense Grating (IG) condition, the stimulus was a 100% contrast, square-wave grating with a spatial frequency of 3 c/deg of visual angle. The duty cycle was 50%. These characteristics create a black and white striped pattern with bars of equal width. The stripes alternated between black and white at a temporal frequency of 7.5 Hz, producing a flickering appearance. This stimulus was designed to incorporate the pattern characteristics that have been demonstrated to be aversive to headache sufferers (Wilkins et al., 1984) and migraine sufferers (Marcus & Soso, 1989). Pilot testing of a variety of temporal frequencies led us to choose a stimulus that was in the aversive range but avoided intolerable discomfort and the range most closely associated with photosensitive

epilepsy. The Mild Grating (MG) stimulus was designed to provide a less aversive version of the same pattern type. It was lower in contrast (5%), lower in spatial frequency (1 c/deg) and phase-alternated more slowly (0.5 Hz). Both stimuli subtended a visual angle of 21.6 by 16.2 degrees (width by height) at a viewing distance of 75 cm. Again, in order to maintain visual attention towards the stimulus, participants performed a simple computerized task that required them to indicate a change in the stimulus using the mouse key. Both grating stimuli were initially oriented horizontally. Participants were asked to respond when the pattern shifted briefly to a vertical orientation. As described above, the change took place every 30 +/-5 seconds, and a tone sounded when participants missed a change.

Computerized stimuli were created in Code Warrior © Pascal and displayed on a Macintosh 7100 computer with a 17-inch Apple monitor.

Physiological recording apparatus and data processing:

All physiological signals were recorded using BIOPAC Systems, Inc. hardware and Acknowledge© software (version 3.2.6), run on a 7200/90 Power Macintosh computer. A sampling frequency of 500 Hz was used for all variables. This sampling frequency is within the range recommended for acquiring acceptable resolution of inter-beat intervals for heart rate variability assessment (Bernston et al., 1997; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996), and is well above the sampling frequency required for the recording of respiratory rate and electrodermal signals.

Electrocardiogram and heart rate variables:

Electrocardiograms (ECG) were recorded using the BIOPAC Systems, Inc. ECG100B electrocardiogram amplifier module. Three Ag-AgCl leads with adhesive, disposable snap electrodes were placed on the torso such that one shielded electrode was positioned above and to the right of the heart, one shielded electrode below and to the left of the heart, and an unshielded ground positioned on the left collarbone. Satisfactory ECG signals with clearly identifiable R-waves and minimal background noise were obtained for all participants.

The ECG signal was processed off-line, using the Acknowledge software, to detect R-waves and generate an R-R interval tachogram (i.e., series of interbeat intervals in milliseconds). This information was saved in text format and then processed using the Vagal Tone Monitor (Delta-Biometrics Inc., 1994). R-R interval tachograms were edited to remove movement artifacts using software that accompanies the Vagal Tone Monitor. The editing program works by identifying R-R intervals that are either too short or too long to fall within an expected range. The user then determines whether to multiply or divide the interval value in question by judging how the result would fit within the preceding and following interval durations. The data files were then processed using the Vagal Tone Monitor's off-line analysis option to determine the variability of interbeat intervals within the high-frequency (0.12 – 0.40 Hz) and low-frequency (0.06 – 0.10 Hz) range. The high-frequency (HF) provides an index of vagal tone, or vagally mediated parasympathetic influence on cardiac rhythm (Porges, 1995), that is also referred to as respiratory sinus arrythmia. Since the interpretation of the low frequency (LF) range is more controversial, and is thought to be influenced by both parasympathetic and

sympathetic factors (Berston et al., 1997), we report the LF:HF ratio as an index of sympathovagal balance.

Respiratory rate:

Respiratory rate was recorded using the BIOPAC Systems, Inc. RSP100B pneumogram amplifier module and the TSD101B respiratory transducer. This transducer measures respiratory effort using a silicone rubber strain gauge attached to an adjustable nylon strap that fits around the participant's torso. For the purposes of obtaining simple respiratory rate, one strain gauge was used, positioned at mid chest level so as not to interfere with the ECG electrodes placed above and below it. Easily identifiable respiratory rate signals were obtained from all participants. While the Acknowledge software program has peak detection capabilities, variability in both the shape of respiratory waves and baseline level resulted in the inaccurate processing of the signal. Respiratory waves were therefore counted by visually scanning the five-minute signal records. Respiratory frequency was calculated by dividing the number of respirations by the file length in seconds, resulting in a mean respiratory rate for the recording period in Hertz (Hz). Portions of the signal that contained movement artifact that interfered with the identification of respiratory peaks were omitted from the calculation.

Electrodermal activity:

Electrodermal activity was recorded using the BIOPAC Systems, Inc. GSR100B amplifier module. Two Ag-AgCl finger electrodes filled with a non-irritating, conductive gel were attached to the third and forth digits of the non-dominant hands using Velcro® straps. Preparation of the electrode sites was done by firmly rubbing the areas with an alcohol-soaked cotton ball. If an adequate signal was not obtained, electrodes were

removed, the site re-prepared and the electrodes re-positioned and attached. Despite these attempts to correct poor signal acquisition, adequate signals were not obtained in one migraineur and two controls.

The analogue files containing the electrodermal signals were converted to text format and processed using a software program written for this data set by Mark Gross. This software was designed to detect electrodermal responses according to the waveform specifications cited by Boucsein (1992). Since the purpose of this study was to assess responding during relatively prolonged exposure, rather than specific event-related responses, the number of electrodermal responses detected during the 5-minute interval was analysed, rather than response latency or amplitude.

Other measures:

Depression and anxiety measures:

Migraine sufferers have higher rates of depression and anxiety disorders than the general population (see Merikangas & Rasmussen, 2000 for review). Participants were asked to complete the revised Beck Depression Inventory (BDI) (Beck, Ward, Mendelson, Mock & Erlbaugh, 1961) to assess the intensity of depressive symptoms. This 21-item scale asks participants to rate the presence of depressive symptoms in the past week, including the test day. Each item reflects a particular symptom or associated symptom of depression, such as feeling hopeless or lacking energy. For each of the 21 items, there are four statements that reflect varying degrees of the symptom, and each statement is numbered from 0 to 3. Participants are instructed to respond by choosing the statement that best reflects the way they have been feeling. A high score reflects a greater degree of depressive symptomology, and the maximum possible score for the BDI

is 63. Participants were also asked to complete the State-Trait Anxiety Inventory (STAI) (Spielberger, Gorush & Lushene, 1970). This scale is subdivided into two scales, each comprised of 20 items that participants rate from 1 ("not at all") to 4 ("very much so"). Total scores for each scale range from 20 to 80, with higher scores corresponding to higher ratings of anxiety. One scale assesses trait anxiety (STAI-Trait), which refers to anxiety proneness or the characteristic that makes individuals more likely to experience anxiety states. High scores on the trait anxiety scale may reflect both the likelihood that people will perceive situations as stressful, and a history of stressful experiences. The other scale measures state anxiety (STAI-State), or the intensity of perceived stress at the particular time that the questionnaire is being administered. The former is therefore considered a more stable attribute, while the latter is considered a transitory emotional state that is likely to change in response the situation at hand.

Subjective somatic and visual complaints:

At six points during the testing session, participants completed a questionnaire that asked them to rate a variety of complaints using a visual analogue scale (VAS). The items included somatic symptoms that are associated with migraine, and complaints that have been associated with aversive visual stimulation or stimuli similar to ours (e.g., Conlon, Lovegrove, Chekaluk & Pattison, 1999; Wilkins et al., 1984). Participants were also asked to rate the intensity of illusions and distortions following the grating stimuli. Illusions of movement, shimmering, colours or illusory shapes are often described when striped patterns are viewed, a phenomenon that has been found to be more intense in headache sufferers (Wilkins et al. 1984). For the light conditions, participants rated the intensity of afterimages that they had experienced, as there is some evidence that

migraine sufferers are more likely to report afterimages than non-migraineurs (de Silva, 2001). The complaints assessed at different points of the study are listed in Table 3.2.

Participants rated the symptoms from "none" to "extreme" along a 100 mm line. The baselineVAS immediately preceded the recording of the psychophysiological baseline period, the four viewing condition VAS measures immediately followed each of the 5-minute stimulus exposures and asked participants to rate their experience during the immediately preceding exposure condition, and the recovery VAS took place at the end of the testing session just before debriefing took place.

Visual discomfort and pain thresholds:

Thresholds for light-induced discomfort and pain were measured using the method described in the previous chapter. Thresholds were assessed after the viewing conditions and psychophysiological recording had ended. The standardized instructions differed slightly from the previous study and were as follows:

> "Now that we have finished all of the conditions, I would like to ask you to evaluate the lights as they increase in brightness. I will start with a dim level, and increase the brightness while you look at the centre of the computer screen. I would like you to tell me if the brightness of the lights becomes uncomfortable to look at, and as they continue to be increased, if you find them painful to look at. Just say, "discomfort" and "pain" to indicate if or when these first occur."

In the present study, only one threshold measure for each of discomfort and pain was recorded because of the good test-retest reliability demonstrated in the previous study.

Procedure

Potential participants were contacted by telephone and informed that the study would involve doing a computerized task under different viewing conditions while having physiological measures recorded. A semi-structured interview assessing headache symptoms and inclusionary/exclusionary criteria was then administered to those individuals who wanted to participate (see Appendix B). If the potential participant met criteria for inclusion in the migraine group, we asked whether we would have their permission to contact the physician with whom they had consulted about their headaches and requested contact information. An appointment time for a testing session lasting approximately 90 minutes was scheduled. Testing sessions were scheduled between 11:30am and 6:00pm, with the intention of reducing variability of autonomic measures due to circadian rhythms. Participants were instructed not to take medication on the day of testing, or to reschedule if they required medication for any reason. They were also asked to reschedule if they were experiencing a headache or had had one within 72 hours of the testing appointment, or were ill on the appointment day. Participants were asked to avoid caffeine and nicotine for at least one hour before testing and to wear clothing that allowed access to the torso for ECG electrode application.

On the day of their appointment, the experimenter welcomed the participant and read a standardized explanation of what the testing would entail (i.e., questionnaires, 5-minute exposures to four viewing conditions while performing a computerized task, 5-

minute rest intervals, making judgments about the viewing conditions, and physiological recording). Following the explanation, participants read and signed the consent form (see Appendix C). While the consent form made reference to the fact that some individuals might find the stimuli unpleasant and that there was a remote possibility that a headache could be triggered, risks were presented in a general manner rather than suggesting that the risk might be specific to the migraine group. The consent form also indicated that participants could discontinue the study at any time, for any reason, which was also restated verbally to all participants by the experimenter.

Participants in the migraine group also read and signed a form that included a letter to their physician and consent to release the requested medical information. This signed form was mailed to the physician along with another form that the physician was asked to fill out and return. On the latter form, the physician was asked to classify the participant's headache diagnosis/es according to medical chart information. Physicians were asked to classify patients according to the I.H.S. (HCCIHS, 1988) criteria. A copy of the criteria for migraine with and without aura was included with the forms.

Participants then filled out a questionnaire that asked when they last had a headache, when they last consumed medications, drugs or alcohol, caffeine and nicotine, if they were currently wearing glasses or contact lenses, and if there was anything unusual about how they were feeling that day (e.g., sick, over tired, etc.).

The experimenter then applied the physiological recording transducers to the participant (see Apparatus section for details). Participants completed a collection of questionnaires while the experimenter calibrated the signals and adjusted recording

equipment to obtain satisfactory signals. These questionnaires included the BDI, STAI, and baseline VAS.

Once participants had finished completing the questionnaires, physiological recording for the baseline period began. Instructions were provided to the participant by the experimenter at specific points during the protocol, using a standardized script. For the first 5-minute recording condition, referred to as the Baseline period, participants were asked to sit quietly and relax with their eyes open.

Following the baseline period, the first of the four 5-minute visual conditions began. The four conditions included a mild and an intense grating (MG and IG, respectively) and a mild and intense light (ML and IL, respectively), as described above. The presentation order of the visual conditions was counterbalanced and assigned to participants according to a list that contained all possible condition orders. The M and NC groups each had their own list to ensure equal counterbalancing between groups. During the viewing conditions, participants performed the computerized task as described above (see Viewing Conditions and Display for details).

Immediately following each viewing condition, participants completed the VAS questionnaire that asked participants to rate the degree of somatic and visual complaints experienced during exposure. Participants then sat quietly with their eyes open for a 5-minute rest period before the onset of the next viewing condition.

Following the fourth viewing condition, recording took place for another 5-minute period of rest. This will be referred to as the recovery period.

Thresholds for light-induced discomfort and pain were then assessed, as described above (see Methods – Other measures).

After the removal of the recording transducers, participants completed the recovery VAS. It was used to assess whether any symptoms remained after the stimulus exposure had ended.

Before leaving the testing session, participants were informed that they would be contacted by telephone within the next week to answer some follow-up questions. While participants were given the opportunity to ask questions at this point, information pertaining to the hypotheses of the study was not discussed until the follow-up telephone call. The purpose of the call was to assess whether headache, associated symptoms, visual problems or other related complaints (e.g., aura) had occurred following participation. At the end of the call, participants were debriefed about the general purpose of the study and provided with the opportunity to ask questions.

All procedures in this study were approved by the McGill University Research Ethics Board for Research Involving Humans.

Statistical analysis

Parametric statistical analyses were used for the majority of the analyses. These included t-tests and analyses of variance or covariance, followed by tests of simple main effects and/or Scheffé post-hoc comparisons where appropriate. All t-tests were two-tailed and unpaired, unless otherwise specified. When parametric analyses were inappropriate due to the violation of assumptions, non-parametric tests were used. The Mann-Whitney U-test was used for comparing two groups. The Kruskall Wallis test was used for comparing three or more groups. Chi-square analyses were used to compare categorical variables (e.g., the number of individuals endorsing a particular symptom). All analyses include a comparison of the 24 M participants and 23 NC participants,

unless otherwise specified. Statistical significance was determined using an alpha value equal or less than 0.05, unless otherwise specified.

The majority of statistical analyses were conducted using Statview (version 5.0.1) for MacIntosh. SPSS for Windows (version 10.0) was used to calculate the repeated-measures analyses of covariance.

Results

Participant characteristics

The migraine and control group were compared to determine whether they differed on a number of variables assessed prior to the onset of testing. No statistically significant differences between groups for age (t (45) = -0.02, p = .99) or body mass index (t (44) = -0.40, p = .69) were detected. See Table 3.1 for means and standard deviations.

Significant differences were detected for the depression and one of the anxiety measures. Migraineurs scored higher on the BDI than the control group (t (45) = 4.08, p = .0002). The BDI mean scores were 9.5 (SD = 5.9) for the migraine group and 3.9 (SD = 2.9) for controls. According to Beck's (1978) criteria for the 63-point measure, no participants fell in the severely depressed category (score of >30). A significant group difference was also detected on the STAI – Trait form, with migraineurs scoring higher than controls (t (45) = 2.50, p = .016). Mean STAI-T scores were 41.8 (SD = 10.7) for migraineurs and 35.2 (SD = 7.2) for controls. Migraineurs also scored higher on the STAI – State form, but this difference was not statistically significant (t (45) = 1.64, p = .107). Mean scores for the STAI-S were 32.5 (SD = 9.61) for migraineurs and 29.0 (SD = 5.9) for controls.

The frequency of subjective complaints

Before assessing whether group differences in the intensity of subjective complaints on the VAS measures existed, the number of participants in each group who endorsed the items was examined. This was done using chi-square analyses, comparing the number of individuals who endorsed a complaint at any point during the study (i.e., on one or more of the six VAS measures). The results of this analysis are presented in Table 3.3. Migraineurs were significantly more likely to endorse headache, motion sickness, visual discomfort and afterimages than controls. The increased number of migraineurs who endorsed glare and illusions and distortions approached statistical significance. Despite the more frequent endorsement of some complaints, migraineurs did not show a uniform pattern of reporting all complaints at a significantly higher frequency.

Since the reporting of headache complaints was more central to this study than many of the other somatic complaints, separate chi-square analyses were conducted to compare how many participants reported headache at each phase of the study: before, during and after the viewing conditions. These analyses revealed that significantly more migraineurs endorsed headache at all three phases of the study (Baseline: $\underline{X_2}$ (1) = 6.72, $\underline{p}$ = .01; During: $\underline{X_2}$ (1) = 6.30, $\underline{p}$ = .012; Recovery: $\underline{X_2}$ (1) = 5.56, $\underline{p}$ = .018). While we had hypothesized that migraineurs would endorse more headache than controls, we did not expect this finding at baseline, as all participants reported not having headache when they entered the testing situation. By this first VAS measure, recorded approximately 20 minutes after entering the testing room and before the visual conditions had started, 12 of the 47 participants (10 M and 2 NC) reported experiencing headache on the VAS.

Headache intensities were, however, most often relatively low on the 100 mm scale. Intensity values are presented in Figure 3.1. These intensity values indicate that while participants endorsed headache, the most intense headaches endorsed hovered around the midpoint between "none" and "extreme". In most cases, headache intensity was much closer to the "none" end (e.g. less than 10 mm on a 100 mm scale). Following testing, those who endorsed headache were questioned about the nature of the pain and accompanying symptoms in order to assess whether the episode fit criteria for a migraine episode. None of the headaches described were classified as migraine. It is also worth noting that no participant chose to discontinue the session due to headache (or any other reason). Many of those who endorsed very low headache values described feeling "headachy", or feeling as though a worse headache might occur.

The intensity of subjective complaints:

We were also interested in whether there were group differences in the intensity of reported complaints. When appropriate, parametric analyses were used to compare the intensity of complaints. For complaints that were assessed on all six VAS measures, a mixed design, two-way ANOVA assessed group (M vs NC) by condition (Baseline, IL, ML, IG, MG and Recovery) effects. For complaints that were not assessed at all points, such as the visual complaints assessed only following the viewing conditions, or tired and sore eyes assessed only at baseline and recovery, the repeated measures effect only included the relevant conditions. Significant interactions between group and condition were followed by tests of simple main effects and paired comparisons where appropriate. When significant violations of assumptions occurred, non-parametric analyses were conducted. The Mann-Whitney U Test was used for two-group comparisons, and the

Kruskall Wallis Test was used to compare three or more groups. In both cases, significance values that have been corrected for ties are reported.

Headache:

Means and standard errors for headache intensity according to condition are plotted in Figure 3.1. The distribution of the headache intensity values did not allow for further parametric analysis due to a very significant violation of the homogeneity of variance assumptions ($F_{max} = 49$). Group comparisons of headache intensity values were therefore conducted for each condition using the Mann Whitney U test. These analyses revealed that migraineurs had higher headache intensity scores at baseline ($U = 180.5$, $p = .008$) and recovery ($U = 168.0$, $p = .007$) than controls. They also had significantly higher scores during both intense stimulus conditions (IL: $U = 203.0$, $p = .05$ and IG: $U = 173.0$, $p = .01$). During the control conditions, there were trends showing that migraineurs also endorsed higher headache intensity values (ML: $p = .09$, MG: $p = .06$).

Anxiety

Mean and standard errors of anxiety levels according to group and condition are plotted in Figure 3.2. When the intensity of reported anxiety was compared according to group and condition, there was a significant interaction effect ($F(5, 45) = 3.10$, $p = .010$). The main effect of condition was also statistically significant ($F(5, 45) = 5.15$, $p = .0002$). Tests of simple main effects were conducted to assess whether the condition effect was present in both the M and NC groups separately. This analysis revealed that anxiety level did change significantly according to condition for the M group ($F(5, 23) = 6.08$, $p < .0001$), but not for NC ($F(5, 22) = 1.48$, $p = .20$). Scheffé post-hoc comparisons revealed that for migraineurs, anxiety during the intense grating condition was

significantly higher than during the mild light condition ($p = .01$) and during both the baseline and recovery periods (both $p < .005$). As Figure 3.2 indicates, anxiety was also higher during the intense light condition, but this difference did not reach statistical significance.

General fatigue

When ratings of fatigue, or the descriptor "tired", were assessed according to group and testing condition, there was a significant main effect of condition ($F(5, 45) = 3.93$, $p = .002$). The main effect of group, or interaction between group and condition were not statistically significant. Scheffé post hoc comparisons revealed that, for NC and M combined, fatigue was higher during the mild light condition than during baseline ($p = .01$). No other statistically significant differences emerged from this analysis.

Tired/Sore eyes

Ratings of tired/sore eyes were only included during baseline and recovery, since several more specific measures of eyestrain and other visual symptoms was included in the four VAS measures that followed the visual conditions.

A two-way, mixed design ANOVA (group [M, NC] by phase [Baseline, Recovery] revealed a significant interaction effect ($F(1, 45) = 4.66$, $p = .036$). Tests of simple main effects, assessing the condition effect for each group separately, confirmed that migraineurs showed a statistically significant increase in ratings of tired/sore eyes from baseline to recovery ($F(1,23) = 10.92$, $p = .003$), whereas controls did not.

Other somatic complaints

The intensity ratings of nausea, dizziness and motion sickness were not analyzed further since these symptoms were endorsed by a relatively small proportion of participants. (See Table 3.3).

Visual complaints

Participants were asked to rate a variety of visual complaints experienced during the viewing conditions on a VAS administered immediately following the termination of each 5-minute stimulus presentation (see Table 3.2 for a complete list of items). Overall, the majority of individuals in both groups endorsed visual complaints at some point during the study.

For both groups, the intensity of visual complaints was generally higher than the reported intensity of somatic complaints during the viewing conditions. To illustrate this point, the mean ratings of the various descriptors endorsed during the intense conditions (IG & IL combined) are presented in Figure 3.3.

Two-way, mixed design ANOVA's were conducted to assess the effects of group (M, NC) and stimulus condition (IL, ML, IG, MG), and the interaction between these variables. The results of these analyses are presented in Table 3.4a. In all cases, the interaction effect was not statistically significant. There were, however, significant main effects of both group and condition for several of the measures. Migraineurs' ratings of glare, squinting and visual discomfort were significantly higher across stimulus conditions than the controls' ratings (all $p<.05$). Migraineurs also rated higher levels of eyestrain than controls, although this difference did not attain statistical significance ($p = .08$). The intensity of these visual symptoms also varied significantly according to

stimulus condition (all p<.0001). The results of the Scheffé post-hoc comparisons comparing the four stimulus conditions are presented in Table 3.4b. Across both groups, ratings of glare and squinting were significantly higher during the intense light than during the three other viewing conditions (all p<.0001). The intense grating was also rated as causing more glare and squinting than the mild grating (both p<.05). Ratings of eyestrain and visual discomfort were significantly higher during the intense light as compared to both mild conditions, and during the intense grating as compared to both mild conditions (all p<.0001).

Afterimages and Illusions / Distortions

Participants completed a VAS measure of afterimage intensity following the two lighting conditions, and rated the intensity of illusions and distortions following the grating conditions. The means and standard errors of afterimages and illusions according to viewing condition and group are presented in Figure 3.4. The results of the two-way, mixed design ANOVA's assessing differences according to group (M vs NC) and intensity (intense vs mild) are presented in Table 3.5. Migraine sufferers endorsed significantly more intense afterimages than controls across both viewing conditions ($F = 16.33$, $p = .0002$). There was no statistically significant main effect of light intensity, and no interaction between group and light intensity (both $p > .05$).

The intensity of illusions and distortions was assessed following the two grating conditions (IG and MG). There was a significant interaction between group and grating intensity ($F(1, 45) = 5.11$, $p = .029$). In order to assess the nature of this interaction, simple main effects were calculated to compare migraineurs and controls during the intense and mild conditions separately. These analyses revealed that migraine sufferers

endorsed more intense illusions than controls during the intense grating condition (F (1, 45) = 11.84, p = .001), but not mild grating condition (F (1, 45) = 3.40, p = .072), although the latter did approach statistical significance.

Physiological responses:

Data analysis

All physiological variables were evaluated using parametric analyses. As with the subjective complaints described above, the physiological variables were assessed at six points of the study, so the sequence of analyses was similar. First, a two-way, mixed design ANOVA assessed the effects of group (M vs NC) and condition (Baseline, IL, ML, IG, MG, Recovery). Significant effects were further evaluated by assessing simple main effects and/or Scheffé post-hoc comparisons.

ECG Inter-beat interval (IBI):

Means and standard errors for IBI data are presented in Figure 3.5. Migraineurs had lower mean IBI (i.e., higher heart rate) across all conditions as compared to the controls (F = 8.46, p = .0056). There was also a significant main effect of condition (F = 4.11, p = .0014). In order to assess the nature of IBI differences at different points of the study, post hoc comparisons were conducted. For both groups, IBI was lower at baseline than during mild light and both grating conditions (all $p < .05$), indicating that heart rate decreased during these viewing conditions when compared to heart rate assessed before viewing started.

Given the consistent group difference in IBI and pre-existing group differences on the BDI and STAI, paired correlations were calculated to ensure that these differences

were not related. The correlations between mean IBI and the BDI (r = -.15), STAI-Trait (r = .05) and STAI-State (r = .18) were not statistically significant (all p >.05).

In summary, migraineurs had lower mean IBI values, corresponding to higher heart rate, at all points during the study when compared to controls.

Heart rate variability

Means and standard errors for both high frequency variability (vagal tone) and the ratio of low- to high-frequency variability (sympathovagal balance) are presented in figures 3.6 and 3.7, respectively. High frequency data are not available for one participant in the control group because of technical difficulties during the transformation of IBI values to variability values. This is also the case for low frequency data for two migraineurs. Data for one control subject was dropped from all analyses because she was a distinct outlier. Her mean vagal tone score was more than three standard deviations from the mean (Z score = -3.73). Despite having very clear ECG signals and appropriate IBI values, this participant's high frequency heart rate variability values were very low when compared with the range of values seen in both the migraine and control group. The following analyses of vagal tone therefore compare 24 M with 21 NC. The analyses of LF to HF ratio compare 22 M with 21 NC.

When high frequency variability was assessed according to group (M, NC) and condition (Baseline, IL, ML, IG, MG, Recovery), there was a statistically significant main effect of condition (F (5, 43) = 4.30, p = .0009). Neither the group effect or interaction were statistically significant. Scheffé post hoc analyses showed that high frequency variability was significantly lower during the two grating conditions than during the recovery phase (both p<.05). While it would appear that high frequency

variability was generally lower during the viewing conditions than during both baseline and recovery, especially for migraineurs, no other comparisons reached statistical significance. Similarly, when the ratio between low- and high-frequency variability (LF:HF) was assessed according to group and condition (Figure 3.7), there was also a significant main effect of condition ($F(5, 41) = 5.91$, $p < .0001$). Again, neither the group effect nor interaction was statistically significant. Scheffé post-hoc analyses of the condition effect across groups revealed that LF:HF increased during recovery when compared to all four viewing conditions and the initial baseline (all $p < .005$).

Respiratory rate

Mean respiratory rate values and standard errors are presented in Figure 3.8. When respiratory rates were compared according to group and condition, there was a statistically significant interaction effect ($F(5,45) = 2.93$, $p = .014$). There was also a statistically significant main effect of condition ($F(5, 45) = 29.79$, $p < .0001$). In order to clarify the nature of the interaction effect, simple main effects were used to evaluate the condition effect for both migraineurs and controls separately. For the migraine group, there was a statistically significant main effect of condition ($F(5, 23) = 26.37$, $p < .0001$), indicating that respiratory rate had fluctuated during the course of the study. Their respiratory rate was significantly higher during all of the viewing conditions than during both baseline and recovery (Scheffé: all $p < .0005$). For controls, the simple main effect of condition was also statistically significant ($F(5, 22) = 7.94$, $p < .0001$). The pattern of post-hoc comparison significance was also similar, but while all viewing conditions were associated with higher respiratory rates than recovery (all $p < .03$), only the intense grating was associated with higher respiratory than baseline ($p = .01$). Therefore, one

could say that while both groups showed increases in respiratory rate during the viewing conditions, this effect was more pronounced in the migraineurs. In order to clarify at which point migraineurs and controls differed with each other, unpaired t-tests were used to compare their respiratory rates during each condition. Migraineurs had significantly lower respiratory rate at baseline than controls (t (45) = -2.22, p = .03). The group difference at recovery approached statistical significance (t (45) = -1.78, p = .08). Respiratory rate group differences during each of the viewing conditions were not statistically significant (all p >.11).

Respiratory-heart rate variability interactions

Since respiratory rate can influence heart rate variability (Berntson et al., 1997), the interaction between these variables was explored. Paired correlations between respiratory rate and high frequency heart rate variability, which reflects the variability of interbeat interval at a frequency similar to respiratory rate, are presented in Table 3.6. In this study, the relationship between respiratory rate and high frequency variability was not statistically significant.

Since the relationship between respiratory rate and heart rate variability measures were not evident in this data set, no further analyses were done to explore how these measures co-varied.

Electrodermal responses

Despite repeated attempts to acquire adequate electrodermal signals, data was not available for four individuals (1 M and 3 NC). In these individuals, there was virtually no variability in the signal, likely reflecting an inability to achieve the necessary skin-to-electrode contact. The following statistical analyses will therefore compare 23

migraineurs with 20 controls. The means and standard errors of the number of electrodermal responses according to group and condition are presented in Figure 3.9.

When the number of electrodermal responses of migraineurs and controls were compared across the six conditions, a significant group main effect was detected (F (5,41) = 6.69, p = .013). Migraineurs had significantly more responses than controls. There was no statistically significant main effect of condition or interaction effect.

As expected, there was a significant correlation between the mean number of electrodermal responses recorded across all conditions and STAI-State, which measures state anxiety (r = .33, p = .03). Neither the BDI or STAI-Trait scores were significantly correlated with the mean number of electrodermal responses (r = .22 and r = .26, respectively. Both p >.05). In order to assess whether the group difference in electrodermal responses could be explained by difference on the STAI-State, an analysis of covariance (Group [M, NC; between subjects variable] by Condition [Baseline, 4 viewing conditions, Recovery; within subjects variable], with STAI-State score [covariate]) was conducted. This analysis revealed the significantly higher number of electrodermal responses in migraineurs remained even after the effect of state anxiety measured at the beginning of the study had been partialled out (F (1,40) = 4.49, p = .04).

Errors made during the visual attention task:

While assessing the ability to monitor stimulus changes was not actually a goal of the study, the number of errors made over the four stimulus conditions was assessed in order to evaluate whether there were overall group differences in the ability to perform the task or maintain attention towards the stimulus. The computer program generated 11 stimulus changes during each 5-minute viewing condition. The total number of errors

made by individuals ranged from 0 to 4 out of 44 possible stimulus changes, reflecting a relatively low error rate. However, more M participants made at least one error than NC (67% and 39%, respectively), with the difference between groups approaching significance (X^2 (1)= 3.58, p = .059).

Since this result was unexpected, further analysis was done to investigate whether the group difference was more evident during a particular viewing condition. While it would seem logical that more migraineurs would have made errors during the intense viewing conditions that were associated with more visual complaints, Chi-square analyses revealed that the group difference in the number of participants who made at least one error was only significant during the two mild conditions (ML: X^2 (1) = 3.95, p = .047, and MG: X^2 (1) = 4.81, p = .028).

Visual discomfort and pain thresholds:

Threshold values for discomfort and pain were converted to a log scale prior to data analysis (see Chapter 2 for explanation). Group means and standard errors for discomfort and pain are presented in Figure 3.10. Unpaired t-tests revealed that migraineurs had lower thresholds for both discomfort (t (45) = -2.17, p = 0.04) and pain (t (45) = -2.55, p = 0.014) as compared to controls. As in the previous study, there was a ceiling effect for the pain measure, such that 5 migraineurs and 14 controls had thresholds at the maximum level, or were assigned the maximum value because they did not endorse pain. As in the previous study, we therefore re-analyzed the pain thresholds using a non-parametric test (Mann-Whitney U test). The group effect remained significant using the non-parametric method (U = 161.0, tied p = .012).

Thresholds for MO (n = 17) and MA (n = 7) were also compared. No statistically significant differences between these groups were detected for discomfort or pain thresholds (t (22) = 0.70, p = 0.49 and t (22) = 0.34, p = 0.73, respectively).

Five participants in this study also took part in the previous study. Of these, three migraineurs and one control were from the negative bias condition, and one migraineur was from the positive bias condition. Since the debriefing statement from the previous study was designed to neutralize the biasing statements by telling participants that there was evidence for both positive and negative effects of light in migraine, we were not overly concerned about the impact of their previous participation. We were, however, interested in seeing whether their thresholds had remained relatively constant, and to check that these participants fell with the range of thresholds of the other participants in this study. Individual thresholds for discomfort and pain are presented in figure 3.11. There was no obvious pattern of increase or decrease in thresholds values for either measure. Paired Pearson correlations between the two discomfort and pain threshold measures were r = .86 and r = .89, respectively. Both sets of threshold values of the repeat participants fell within the range of scores reported by the other participants in this study.

Follow-up

Forty-four of the 47 participants were successfully contacted to obtain follow-up information. In two of these cases, the information was obtained later than one week after participation (at 8 and 14 days). Follow-up information was not available for one migraineur and two controls. Thirteen of the migraineurs and two controls reported experiencing headache within 24 hours of participation. It is not surprising that

significantly more of the migraine group reported headache (X^2 (1) = 10.79, p = .001) since inclusion criteria for the control group included not having headaches more than once per month. Based on the description of symptoms obtained at follow-up, only three of the thirteen headaches experienced by migraineurs could be considered migraine episodes (one MA, and two MO). In several other cases, the participants reported that the headache felt like a migraine but was either much less severe or did not have associated symptoms such as photophobia or nausea. When asked an open-ended question about possible triggers, five participants reported that they thought exposure to visual stimulation during the study may have precipitated or made the episode more likely. It is interesting to note that one of these individuals was a normal control who had reported in the initial screening interview that she almost never experienced headaches (less than one headache per year). She spontaneously reported believing that the intense grating pattern had triggered a headache, which she was very surprised by. Other suspected triggers mentioned by participants included fatigue, hunger, change in barometric pressure, nervousness about participating in the study and stress.

Discussion

This study compared the responses of migraine sufferers and non-migrainous controls exposed to intense visual stimulation. The goal of the study was to determine whether migraineurs who are not experiencing a migraine episode respond to this stimulation with a pattern general autonomic activation that could reflect a stress response, and/or the process by which normally benign environmental stimuli lead to the triggering of migraine-related physiological changes. The results of the current study can be classified into four main categories: 1) differences between migraine sufferers and

controls that were evident even at baseline, 2) general patterns of responses to our intense visual stimuli that occurred in both migraineurs and controls, 3) responses to visual stimulation that were specific to the migraine group, and 4) differences between the groups in their recovery following stimulation. These categories will be summarized below, along with the implications of these findings.

General differences between migraine sufferers and controls:

The migraine sufferers in this study reported higher levels of depressive symptomology and trait anxiety than controls, as assessed using the BDI and STAI-Trait, respectively. We made no attempt to exclude participants on the basis of mental health disorders, but did exclude potential participants who were being treated with antidepressants or anxiolytics, either for a mental health condition or for migraine. Given that migraine sufferers are at increased risk of suffering from depression and anxiety disorders (see review by Schechter et al, 2001), our finding is not surprising. However, this finding highlights the importance of taking pre-existing differences into account when comparing migraine sufferers to non-migrainous controls. This is especially important when assessing measures that can be associated with depressive or anxious symptoms, such as pain (Melzack & Wall, 1996).

When the results of the current study are compared with the results of two recent studies that assessed large samples of female headache sufferers, very similar levels of BDI, STAI-Trait and STAI-State scores are found (see Table 3.7). These samples included a group of 191 chronic tension-type headache sufferers, some of which also had migraines (Holroyd, Stensland, Lipchick, Hill, O'Donnell & Cordingly, 2000) and 195 individuals with a variety of headache disorders including migraine, tension-type

headache, and mixed headache (Marcus, 2001). These studies also reported significantly higher levels of self-reported depression and anxiety in headache sufferers as compared with controls. The similarity of these results suggests that the sample tested in the present study was not unusual in their level of depression or trait anxiety when compared with other female headache sufferers.

While trait anxiety was higher in migraine sufferers at baseline, evidence of an increase in state anxiety was less clear. On the STAI-State, migraineurs scored higher than controls, but the difference between groups did not achieve statistical significance. On the visual analogue scale measure which simply asked participants to rate their current level of anxiety by marking a line between the anchors of "none" and "extreme", migraineurs self-reported low levels of anxiety which were very comparable to the control group.

Another difference between migraine sufferers and controls was the frequency of self-reported headache. While it was predicted that migraine sufferers would report more headache during intense visual stimulation, and perhaps following stimulation, we did not expect migraine sufferers to report headache before the test conditions were initiated, especially since participants were asked to reschedule if they were experiencing headache on the test day. Furthermore, participants reported being headache-free when they first entered the testing situation. Despite this, 42% of the migraine group reported headache at baseline. Reported headache scores were, however, very low in intensity and not described as being migrainous. As such, the present study is more generalizable to an interictal state than a migrainous one. It is interesting to note that a recent study that assessed physiological responses to potential headache triggers found unexpectedly high

levels of reported headache during a control condition that was not intended to induce headache (Martin & Teoh, 1999). While their instructions specified that headache triggers were the focus of investigation, the present study deliberately attempted to avoid suggesting that participants were likely to experience headache. Even so, we found that headache was frequently endorsed, albeit in relatively low intensities.

In terms of physiological responses, migraine sufferers had shorter interbeat intervals, reflecting higher heart rate, at all points during the study including baseline and recovery. One possible explanation for this is that migraine sufferers have a deficiency in the parasympathetic mechanism that normally decreases heart rate via the vagus nerve. Since vagal tone was actually higher in migraine sufferers, albeit not significantly higher than controls, it is unlikely that the increase in heart rate could be accounted for by reduced parasympathetic control. Another possibility is that increased in sympathetic activity was associated with higher heart rate in the migraineurs. Migraineurs showed slightly higher vasovagal balance than controls during four of the six conditions. However, the interpretation of this latter measure involving low frequency heart rate variability is more controversial since both parasympathetic and sympathetic factors influence this frequency band (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). It is for this reason that an additional measure of sympathetic activity was included, namely electrodermal activity. On this measure, migraine sufferers also showed an increase in the number of electrodermal responses during all points of the study, including baseline and recovery. Together, the results suggest that elevated heart rate in migraine may be due to an increased sympathetic activity. While heart rate and the frequency of electrodermal

responses can both be associated with increased levels of stress or anxiety (Berntson et al., 1998; Bouscein, 1992; Ravits, 1997), pre-existing differences in anxiety between migraine sufferers and controls did not account for the psychophysiological group differences in this study.

Another way in which migraine sufferers differed from controls at baseline and recovery was respiratory rate. Despite faster heart rate, migraineurs breathed more slowly than controls at rest. One possible explanation for this result is that migraine sufferers were attempting to self-regulate increased arousal by slowing their breathing at a time when they were asked to relax. This hypothesis is, however, purely speculative.

In summary, migraineurs showed differences on several psychophysiological measures at rest, when compared with controls. Many of the studies of autonomic function in migraine have not found group differences at baseline on psychophysiological measures (see Table 1.1). However, like the present study, some researchers have found migraine sufferers to have higher heart rate at baseline (Drummond, 1982; Cortelli et al, 1991). Baseline differences in migraine sufferers have also been found using other measures. For example, migraineurs have been found to have higher blood pressure at baseline than controls (Drummond, 1982; Stronks et al, 1998). Details of several studies are presented in Table 1.1. In reviewing these studies, it is unclear what factors or sample characteristics differentiate those studies that have found baseline differences between migraineurs and controls, from those that have not. This inconsistency in findings is not, however, unique to the study of migraine. Research on autonomic function in individuals with anxiety disorders has also provided mixed results which have

been attributed to differences in testing environments, test situations and the group characteristics (Berntson et al., 1998).

General responses to intense visual stimulation:

The central purpose of this study was to examine the impact of intense visual stimulation on the psychophsyiological responses of migraineurs and on their subjective complaints. Before addressing this question, it is necessary to assess whether the stimuli used in the present study were in fact considered intense or aversive and whether they induced a general pattern of response that was not specific to migraine sufferers. Both groups reported higher levels of visual discomfort and eyestrain during the intense conditions. Furthermore, both groups had significantly higher ratings of glare and squinting during the intense light as compared to the other viewing conditions, and during the intense grating as compared to the mild grating. These findings suggest that the intense and mild stimuli were evaluated differently by participants and the intense stimuli were associated with more complaints.

Thresholds measured at the end of the test session provide further confirmation that the intense light stimulus was bright enough to be considered aversive. Mean thresholds for light-induced discomfort were above 2 log lux, which was the intensity of the mild light condition. Pain thresholds were close to 3 log lux for migraine sufferers, and somewhat higher for controls. The intense light stimulus in the present study was 3 log lux, and would therefore have been considered uncomfortable for the majority of participants.

While subjective responses supported the contention that the intense stimuli were associated with more complaints, psychophysiological responses tended to vary more

according to the phase of the study than according to the intensity of the stimuli. For example, both groups showed a significant drop in heart rate during viewing of three of the four stimulus conditions as compared to baseline. Both groups also showed an increase in respiratory rate during viewing. Respiratory rate was included as a measure in this study for two main reasons. First, to determine whether the high frequency heart rate variability range used to assess vagal tone was in fact centered around the respiratory rate of participants, which it was. Second, to ensure that if significant effects in heart rate variability were detected, they were not simply a function of respiratory rate differences, which they were not. Stimulus- or task-specific changes in respiratory rate were not predicted. In fact, respiratory rate is often not a central measure in psychophysiological studies since it is under the influence of both voluntary and involuntary control, making changes in the variable more difficult to interpret (Wientjes & Grossman, 1998). As a result, it is sometimes recommended that researchers attempt to minimize the impact of respiratory rate changes by requiring participants to breath at a fixed frequency (see Berntson et al., 1997). This did not seem like a feasible option in the present study since participants were already involved in attending to a visual task. Nonetheless, it is interesting that both heart rate and respiratory rate changed during viewing conditions in comparison with baseline. Since this pattern was evident during all viewing conditions and did not show an obvious difference between mild and intense stimuli, it is possible that this change in respiratory rate was related to the task requirements, rather than to stimulus characteristics. Participants were required to focus on the computer monitor and remain vigilant for changes in the stimulus. This likely resulted in a reduction in

movement which may account for the drop in heart rate and respiratory rate (Obrist, 1976).

Migraine-specific responses to visual stimulation:

The central question of this study was whether migraine sufferers would show unique subjective and physiological responses to intense visual stimulation as compared to non-migraineurs. According to self-report, migraineurs did not generally report higher levels of anxiety than controls. However, during the intense viewing conditions, migraineurs showed an increase in anxiety that the controls did not. This increase was highest during the intense grating condition. This finding suggests that for migraineurs, intense visual stimulation can be anxiety provoking. Despite this increase in anxiety, overall levels of anxiety were relatively low. While the intensity of the intense light stimulus was later rated as, on average, falling between the thresholds for discomfort and pain, a 5-minute exposure did not generally lead to high levels of anxiety in most migraineurs. Likewise, the patterned stimulus was designed to incorporate characteristics that are typically considered bothersome to headache sufferers (Wilkins, 1995). Therefore, while intense visual stimulation elicited a number of subjective responses that demonstrate that migraine sufferers were more bothered by it, this stimulation was not associated with very high levels of anxiety that may be associated with more traditional, but less migraine-specific stressors such as the cold pressor task or mental arithmetic.

Migraine sufferers also reported headache and motion sickness more frequently than controls. However, the severity of these symptoms was, on average, very mild and parametric comparisons of intensity were not conducted. At follow-up, a relatively large proportion of our migraine group and some of our controls reported experiencing

headache. Martin & Teoh (1999) also exposed participants to a visual stressor (looking at a word on a computer monitor while a strobe light flashed at 5 Hz) and cognitive stressor (hard to solve anagrams) and found that many individuals reported the triggering of headache episodes. Martin & Teoh found that both stimuli acted as headache triggers and that both were associated with higher ratings of negative affect than a control condition. Participants in Martin & Teoh's study were told that, "the study was an investigation of the role of factors suggested to be capable of triggering headaches." (p. 709). This may have lead to an expectation that headache would result from participating. However, the results of the present study confirm that exposure to intense visual stimulation can result in headache, even when instructions intentionally avoid inducing an expectation that headaches will be triggered. The majority of headaches described in the present study could not be classified as migraine episodes. It is possible that in order for a migraine to be triggered, other internal or external factors that heighten the risk of an episode must co-occur.

In comparison with the somatic complaints endorsed during the course of the viewing conditions, visual symptoms were much more frequently endorsed by both groups and tended to receive higher intensity ratings. Migraine sufferers reported more intense visual complaints, including glare, squinting and visual discomfort, than controls. Again, both groups reported more intense visual symptoms during the stronger viewing conditions as compared to the mild conditions. There were no interactions between group and intensity, demonstrating that while intense stimuli were associated with more symptoms, migraine sufferers were more bothered by even the milder forms of visual stimulation. This may explain why migraine sufferers are more likely to wear sunglasses

even on cloudy days (Mulleners, Aurora, et al., 2001). It is also interesting to note that while the visual complaints occurred at mild levels of stimulation, anxiety only showed a relative increase in migraine sufferers during the intense conditions.

The current study also assessed afterimages and illusions and distortions. Both visual phenomena have been reported to be more severe in migraine sufferers, although little standardized measurement of these experiences has been conducted. The results of the present study confirm that migraine sufferers report more intense afterimages than controls during exposure to both mild and intense light. Migraine sufferers also reported more intense illusions and distortions than controls, however, this effect was only significant during the intense grating condition.

The above findings demonstrate that migraine sufferers report more anxiety, visual complaints, afterimages and distortions when exposed to certain types of visual stimulation. Despite this relatively strong subjective reaction to the stimuli, migraineurs did not show a pattern of corresponding psychophysiological differences that would support widespread autonomic reactivity. Migraine sufferers did not show evidence that the intense stimuli caused an alteration in parasympathetic or sympathetic influence on heart rate, general heart rate, respiratory rate or electrodermal responses. The results therefore suggest that "visual stress" does not lead to a migraine-specific perturbation in overall autonomic function. There are several possible explanations for this finding. First, it is possible that despite the increased level of anxiety reported by migraine sufferers, anxiety was at no point intense enough to result in significant shifts in sympathetic or parasympathetic function. Second, the effects of visual stress may have been evident in other branches of the autonomic system. For example interactions

between the visual and trigeminal systems may cause localized changes in vasculature that are relevant to migraine. However, widespread activation of the autonomic system that would be evident in cardiovascular changes or electrodermal activity may not accompany these changes. Drummond (1997) investigated the interactions between the trigeminal system and visual system in migraine by assessing whether changes in photophobia threshold or temporal pulse amplitude and lacrimation (both autonomic indices) occurred when painful stimulation was applied to the face and neck. In one condition that combined pain and visual stimulation, migraine sufferers did not show a lacrimal response on the side of the head that they typically reported migraines. Drummond interpreted this as an indication of a local parasympathetic deficit, and more generally suggested that a loss of inhibitory subcortical processes that might normally suppress photophobia are not functioning normally in migraine. Therefore, it is possible that while a localized parasympathetic deficit is involved in the visual sensitivity of migraine, it is not associated with a more widespread deficit of autonomic function.

Differences in recovery to testing

Several studies have found that psychophysiological recovery from stress was altered in headache sufferers (Arena et al, 1985; Hassinger et al, 1999; Holm et al, 1997). In the present study, we did not find evidence that the physiological responses of migraine sufferers differed from those of controls during recovery. As mentioned previously, they did show faster heart rate and more electrodermal responses, but these increases were evident at all times. Migraine sufferers did, however, report an increase in some somatic complaints following the termination of the viewing conditions. They reported an increase in tired and sore eyes during recovery in comparison to baseline

measures. Migraine sufferers were also more likely to endorse the presence of headache during recovery, although this was also true during baseline and during testing. These ratings were generally very minimal in intensity and were not described as migrainous. Migraine sufferers were also more likely to report the onset of headache within the 24 hours following participation than controls. While the majority of these episodes were not described as full-blown migraine attacks, several participants attributed their headaches to the intense visual stimuli. It is therefore possible that physiological changes may have occurred following the end of the recording session, in closer proximity to the onset of more severe headache symptoms.

Summary and conclusions.

The results of this study confirm that migraine sufferers associate exposure to bright light and high contrast, flickering gratings with increased discomfort and visual complaints when compared to non-migrainous controls. Milder forms of these stimuli are also associated with an increase in reported complaints. In addition to visual complaints, migraineurs showed an increase in anxiety that was evident during the intense grating, and to a lesser extent during the intense light, suggesting that these stimuli can be associated with affective changes. Despite the lengthy and intense viewing conditions, there was a relatively small increase in somatic complaints, which were expected to be more prominent in the migraine sufferers. Complaints of tired and sore eyes persisted in the migraine group following viewing, which may explain why migraineurs sometimes are bothered by visual aspects of the normal environment (e.g. fluorescent lights, computer monitors, etc.). However, symptoms such as nausea and headache were generally quite low.

Migraine sufferers had higher heart rate and more spontaneous electrodermal responses than controls at all times. This may reflect a hyperarousal of the sympathetic system that is generally present, or it may reflect an increase in activation that is specific to the laboratory environment. However, the increase in these variables was not accounted for by self-reported anxiety. Also, the migraineurs in this study did not react to the intense visual stimulation with a clear pattern of autonomic response. While self-reported complaints and anxiety were higher in migraineurs, cardiovascular and electrodermal indicators of autonomic reaction were not strongly affected.

The results of the present study do not support a pattern of generalized autonomic perturbation that results when an aversive visual stimulus is presented to migraine sufferers. However, if an interactive model is considered, it is possible that migraine sufferers are more likely to be bothered by visual stimulation, but only react physiologically to this stimulation when other pathophysiological events associated with migraine are already involved. As such, a shift in autonomic activity may only be evident in the period leading up to an actual migraine episode. In order to study this hypothesis, more research will need to be conducted to assess the pattern of autonomic activity before, during, and following migraine episodes. The following chapter presents data to address this issue.

Table 3.1

Participant Characteristics According to Diagnostic Group

		Migraine (n = 24)	Control (n = 23)
Age (years):	Mean ± SD	24.71 ± 6.36	24.74 ± 6.33
	Range	18 to 43	18 to 41
Headache diagnoses (n)*			
Migraine without aura		20	
Migraine with aura		5	
Migraine with aura without headache		2	
Tension headache		14	10
Age of migraine onset (years)**:	Mean ± SD	13.8 ± 5.3	
	Range	5 to 26	
Years of migraine*:	Mean ± SD	10.1 ± 6.1	
	Range	2 to 25	
Episodes per year -			
Migraine:	Mean ± SD	41.4 ± 32.3	N/A
	Range	12 to 120	
Other headaches per year:	Mean ± SD	28.6 ± 43.4	3.8 ± 3.3
	Range	0 to 156	0 to 12
Typical episode severity **-			
Migraine episode:	Mean ± SD	8.1 ± 1.6	N/A
	Range	5 to 10	
Typical other headaches:	Mean ± SD	3.9 ± 1.8	3.2 ± 1.6
	Range	1 to 7	1 to 7
Body mass index***:	Mean ± SD	22.0 ± 2.5	22.3 ±3.0
	Range	17.8 to 26.6	18.4 to 30.3

* Data missing for two individuals

** Severity was assessed using a 1-10 point scale (1: no impairment in function, and 10: worst possible headache, severely impaired).

***Body mass index (BMI) = weight (kg) / height $(m)^2$, no data available for one NC

Figure Legend for Figure 3.1

When held at a viewing distance of 85 cm, these patterns demonstrate the spatial characteristics of the intense grating stimulus (top) and mild grating stimulus (bottom). The overall size of the actual stimuli was larger.

Figure 3.1

Spatial Stimulus Characteristics of the Intense Grating (top) and Mild Grating (bottom).

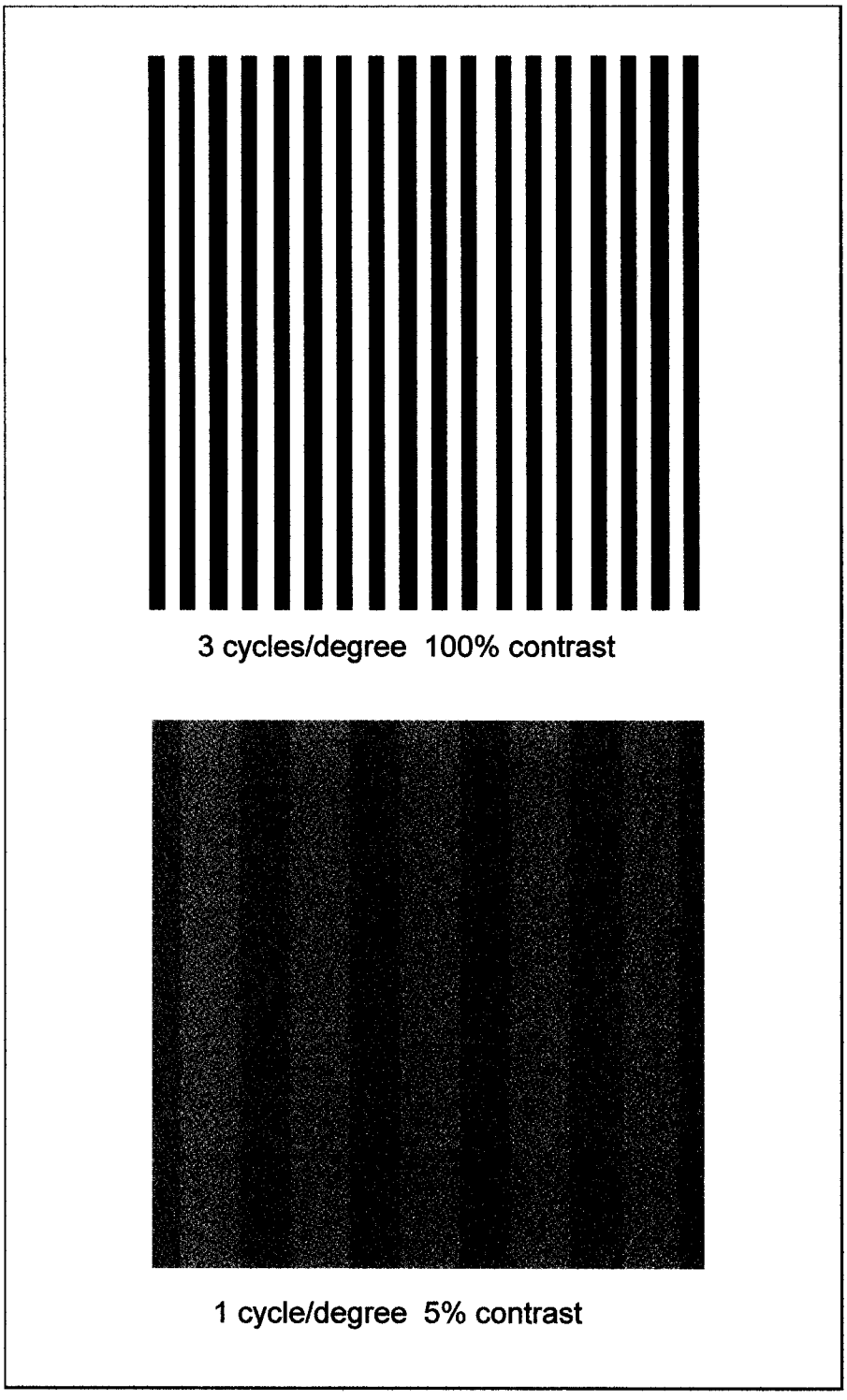


Table 3.2

Symptoms assessed using a visual analogue scale at different times during the study.

Complaint	Pre-test	Viewing conditions	Post-test
Nausea	X	X	X
Headache	X	X	X
Dizziness	X	X	X
Motion sickness	X	X	X
Anxiety	X	X	X
Tired	X	X	X
Tired/sore eyes	X		X
Glare		X	
Visual discomfort		X	
Eyestrain		X	
Squinting		X	
Illusions and distortions		Grating stimuli	
Afterimages		Light stimuli	

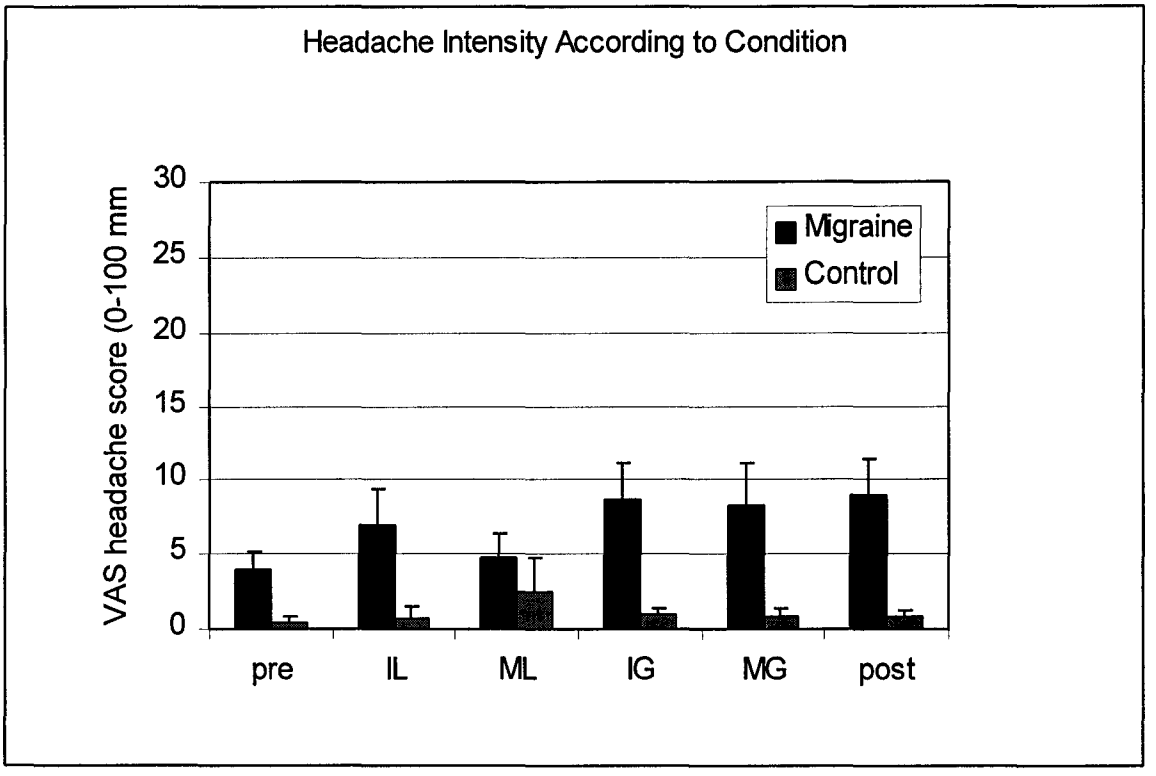
Table 3.3

Percentage of participants in each group who endorsed the VAS items on at least one occasion.

Item	Migraine	Control	Chi-square (1 df), p-value
Nausea	21	26	NS
Headache	71	30	7.67, p=.006
Dizziness	67	48	NS
Motion sickness	46	13	6.04, p=.014
Anxiety	83	65	NS
Tired	96	96	NS
Tired/sore eyes	79	70	NS
Glare	100	87	NS (trend: 3.34, p=.068)
Visual discomfort	100	83	4.56, p=.033
Eyestrain	96	87	NS
Squinting	96	87	NS
Illusions & Distortions	96	78	NS (trend: 3.26, p =.071)
Afterimages	83	52	5.25, p = .022

Figure 3.1

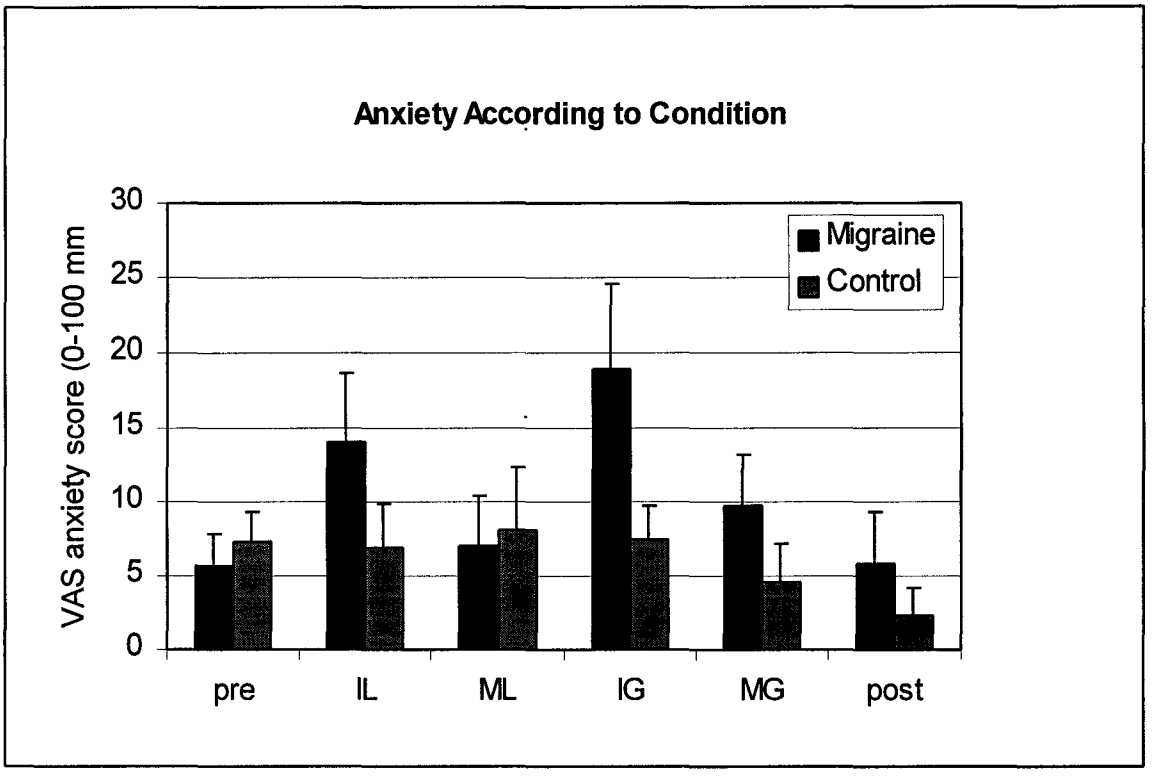
Headache Intensity Ratings According to Condition



Means and standard errors of headache intensity ratings measured on the visual analogue scale (0-100 mm).

Figure 3.2

Subjective rating of anxiety according to group and condition



Means and standard errors of anxiety intensity ratings recorded using the VAS.

Figure 3.3.

Mean (and SE) Visual Analogue Scale Ratings of Somatic and Visual Complaints During Two Intense Viewing Conditions.

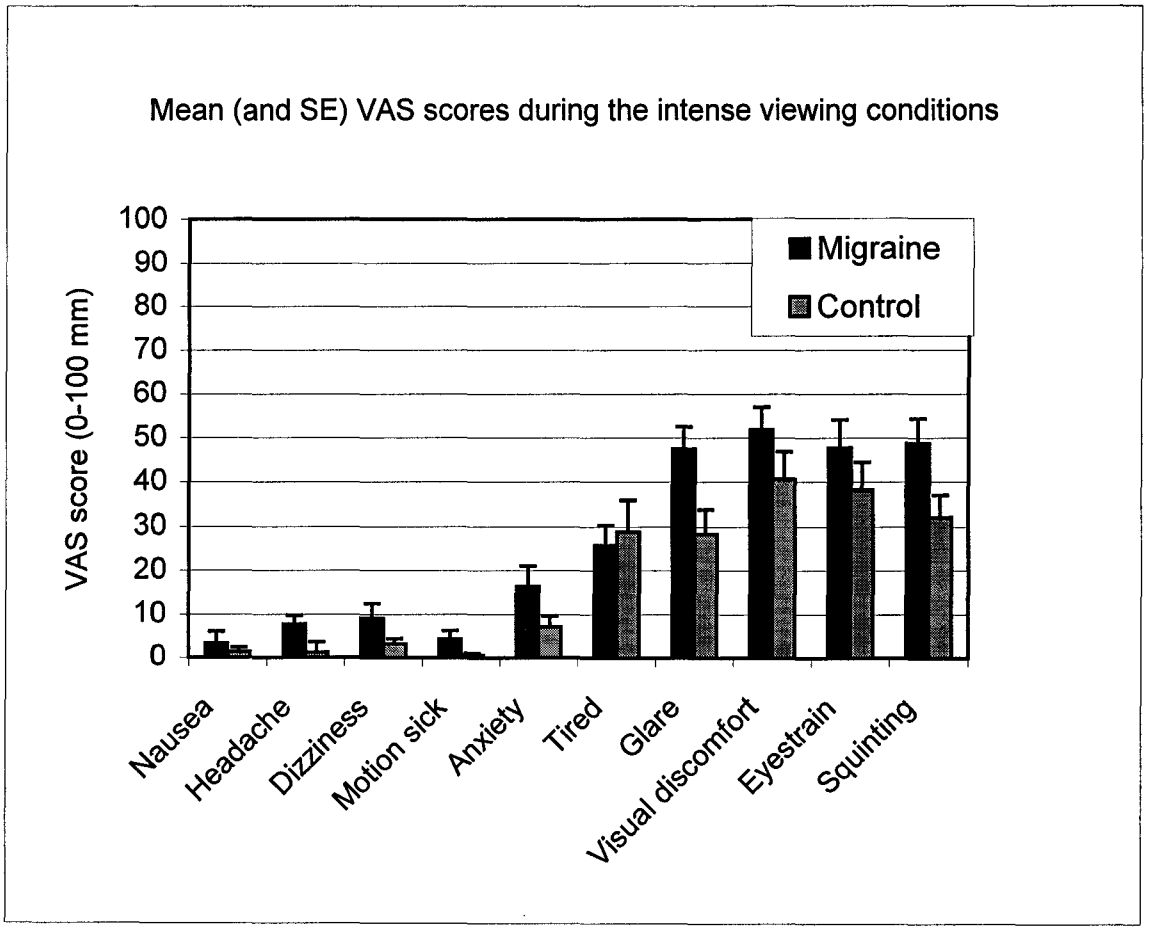


Table 3.4 a

Results of the ANOVAs comparing visual complaints according to group and stimulus intensity (F statistic values).

	DF	Glare	Eyestrain	Squinting	Visual Discomfort
Group	1, 45	7.79 *	3.15 ~	5.87 *	4.44 *
Condition	3, 45	28.72 **	32.27 **	51.79 **	41.27 **
Group x Condition	3, 45	0.57	0.51	0.17	0.42

*: p <.05, **: p<.0001, ~: p <.10 & >.05

Table 3.4 b

P-Values of Scheffé Post-hoc Comparisons of Stimulus Conditions (Across Groups)

Comparison*	Glare	Eyestrain	Squinting	Visual Discomfort
IL, ML	<.0001	<.0001	<.0001	<.0001
IL, IG	<.0001	.18	<.0001	.62
IL, MG	<.0001	<.0001	<.0001	<.0001
ML, IG	.62	<.0001	.17	<.0001
ML, MG	.35	.97	.73	.98
IG, MG	.022	<.0001	.012	<.0001

* Groups: IL: Intense Light IG: Intense Grating

ML: Mild Light MG: Mild Grating

Figure 3.4

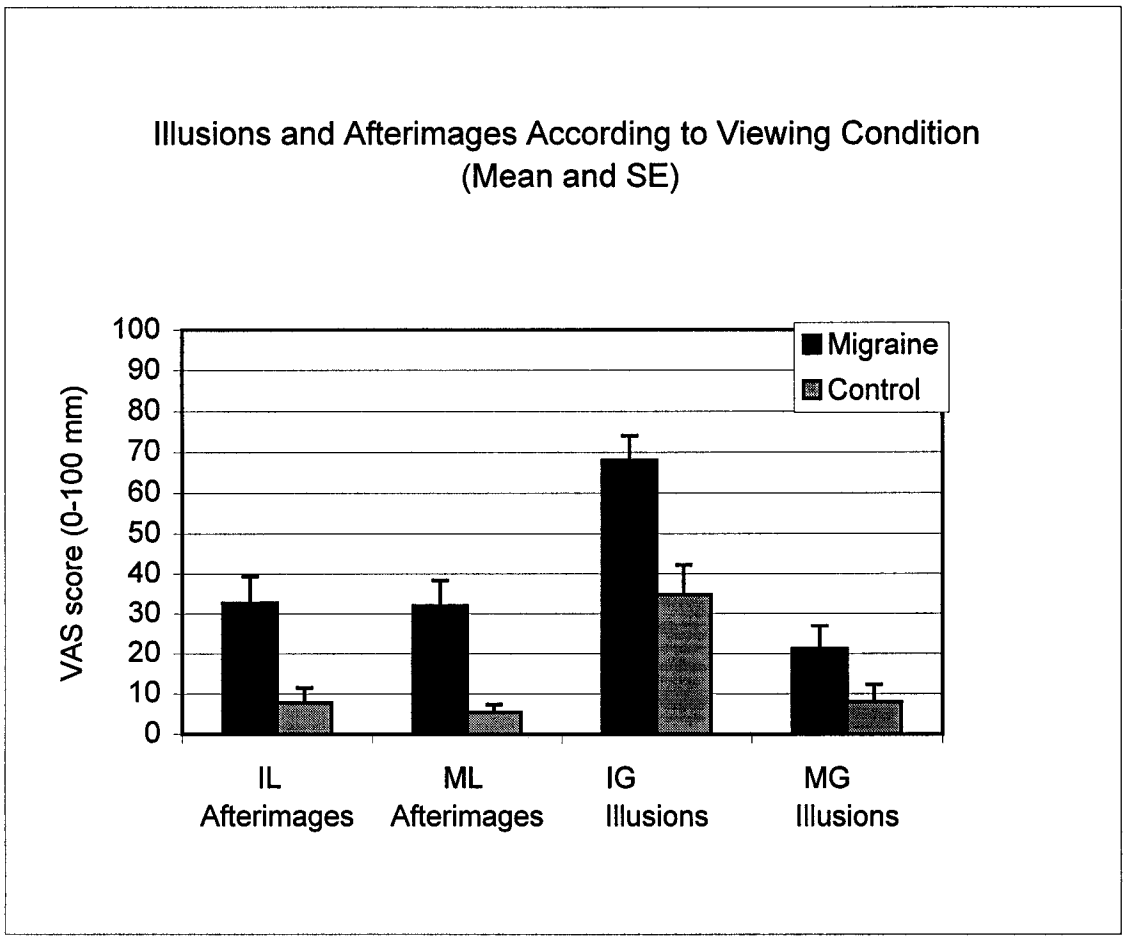

Illusions and Afterimages According to Viewing Condition
(Mean and SE)
VAS score (0-100 mm)
100
90
80
70
60
50
40
30
20
10
0
Migraine
Control
IL
Afterimages
ML
Afterimages
IG
Illusions
MG
Illusions

Table 3.5

Results of ANOVAs comparing the intensity of afterimages and illusions /distortions according to group and stimulus intensity.

	Afterimages (During Light Conditions)	Illusions & Distortions (During Grating Conditions)
Group	16.327 ***	10.26 **
Intensity	0.20	69.71 ****
Group X Intensity	0.82	5.112 *

*: $p < .05$, **: $p < .005$, ***: $p < .0005$, ****: $p < .0001$

Figure 3.5

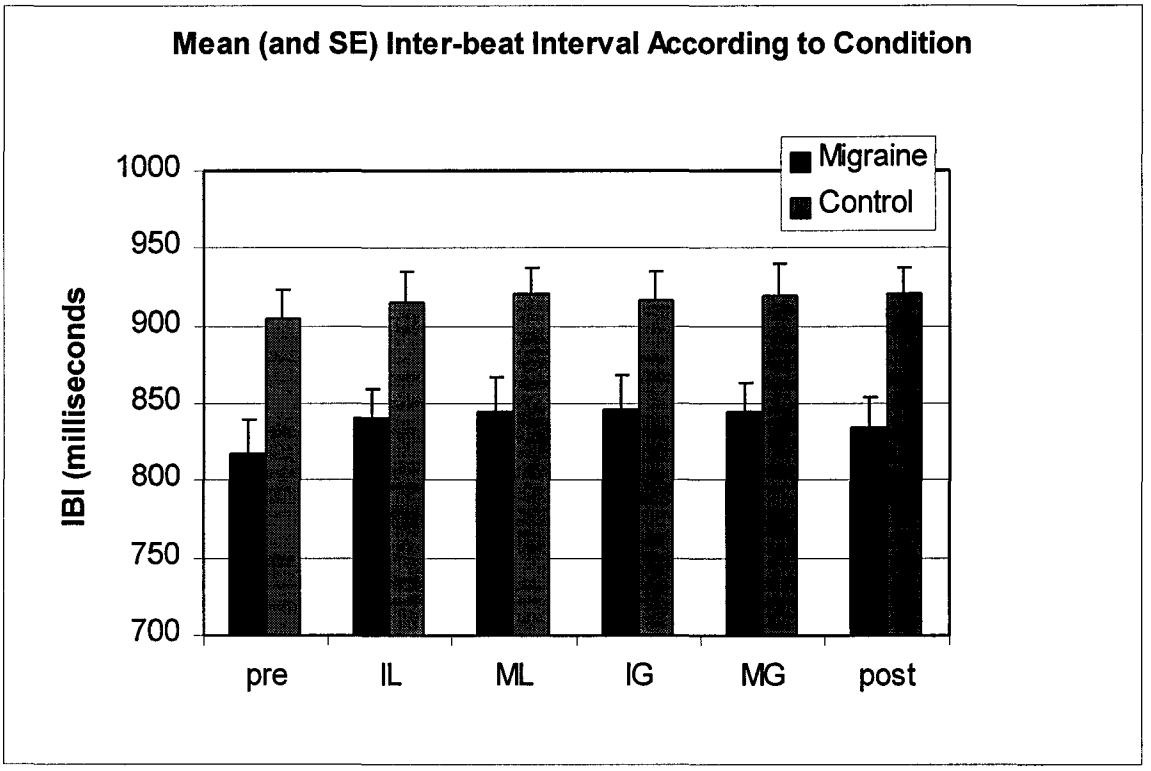

Mean (and SE) Inter-beat Interval According to Condition
IBI (milliseconds
1000
950
900
850
800
750
700
Migraine
Control
pre
IL
ML
IG
MG
post

Figure 3.6

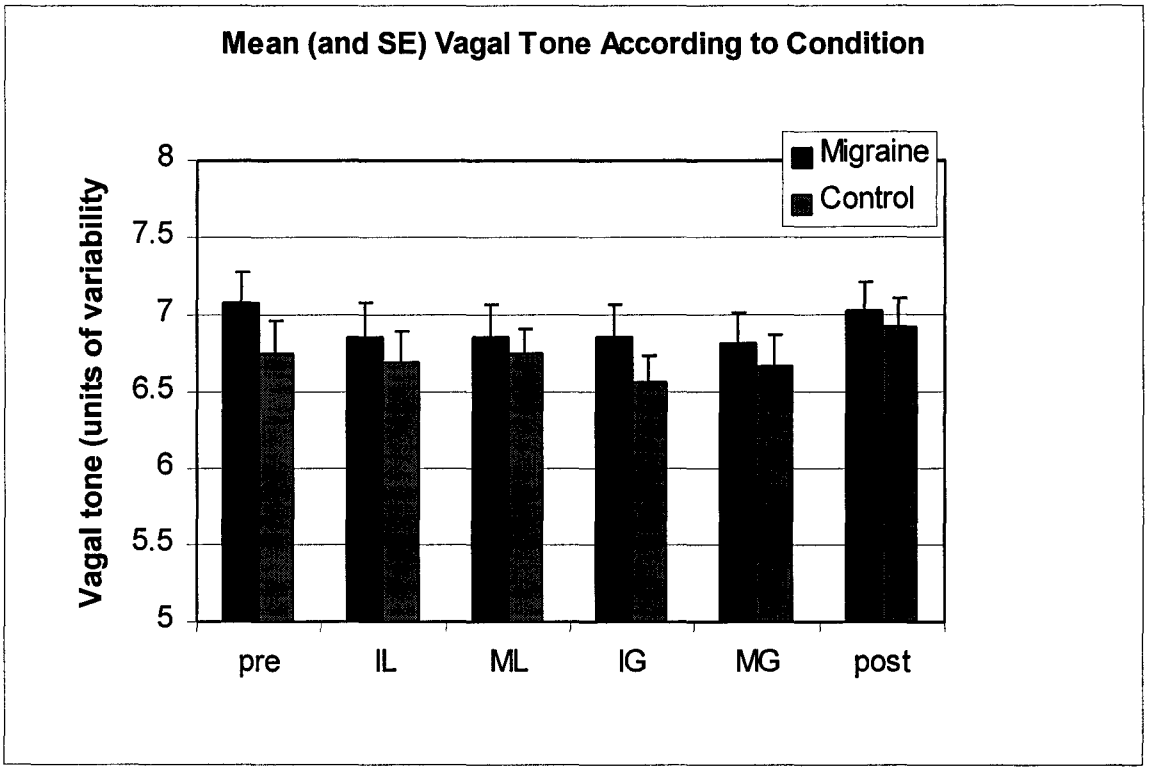

Mean (and SE) Vagal Tone According to Condition
Migraine
Control
Vagal tone (units of variability
8
7.5
7
6.5
6
5.5
5
pre
IL
ML
IG
MG
post

Figure 3.7

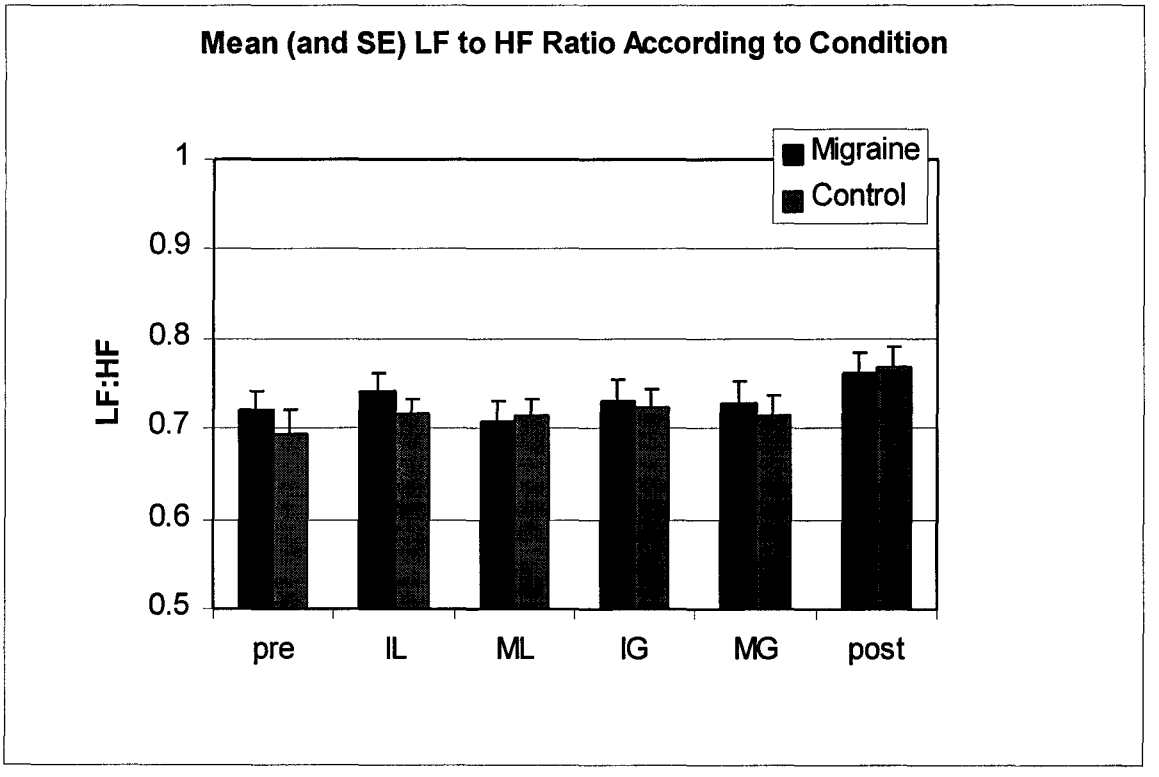

Mean (and SE) LF to HF Ratio According to Condition
Migraine
Control
LF:HF
1
0.9
0.8
0.7
0.6
0.5
pre
IL
ML
IG
MG
post

Figure 3.8

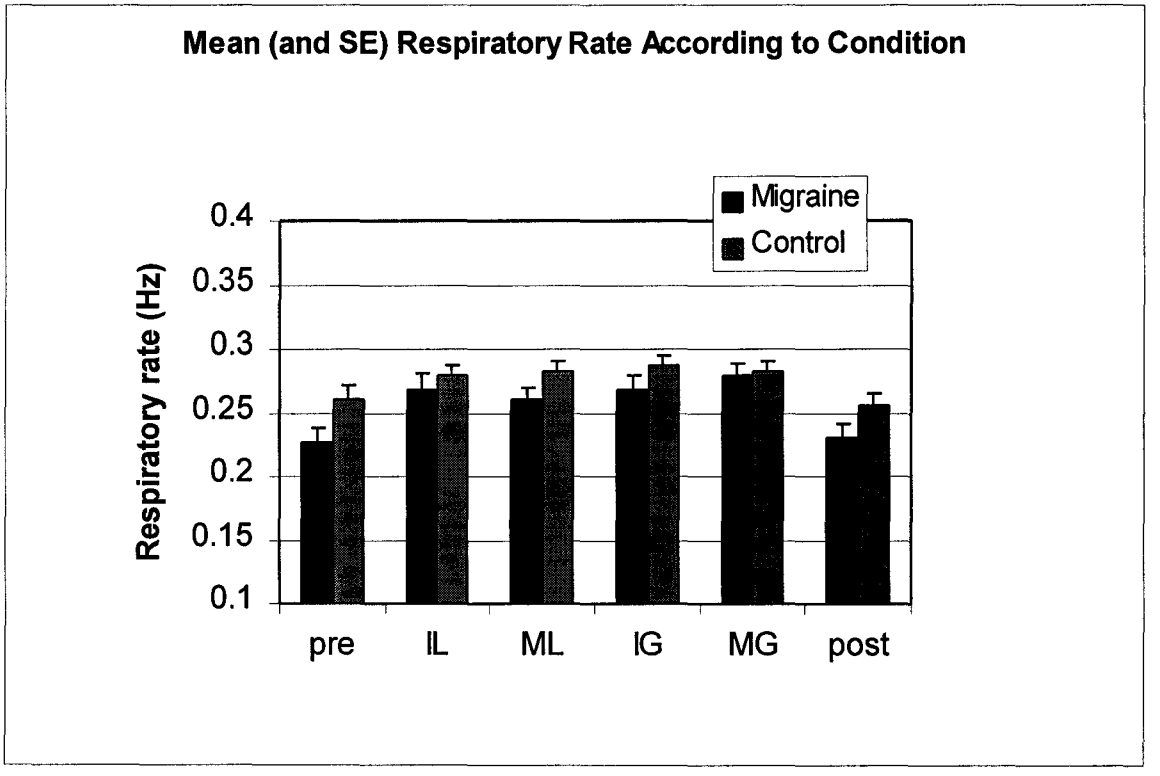

Mean (and SE) Respiratory Rate According to Condition
Migraine
Control
Respiratory rate (Hz)
0.4
0.35
0.3
0.25
0.2
0.15
0.1
pre
IL
ML
IG
MG
post

Table 3.6

The Relevant Paired Correlations Between Measures of Respiratory Rate (Resp) and Vagal Tone (HF) (n= 45 and 46, depending on measure)

	Resp Pre	Resp During	Resp Post	HF Pre	HF During	HF Post
Resp - Pre	1.0	--	--	--	--	--
Resp - During	.87*	1.0	--	--	--	--
Resp - Post	.71*	.71*	1.0	--	--	--
HF – Pre	-.21	--	--	1.0	--	--
HF - During	--	-.14	--	.91*	1.0	--
HF – Post	--	--	-.15	.85*	.88*	1.0

*: $p<.0001$

Figure 3.9

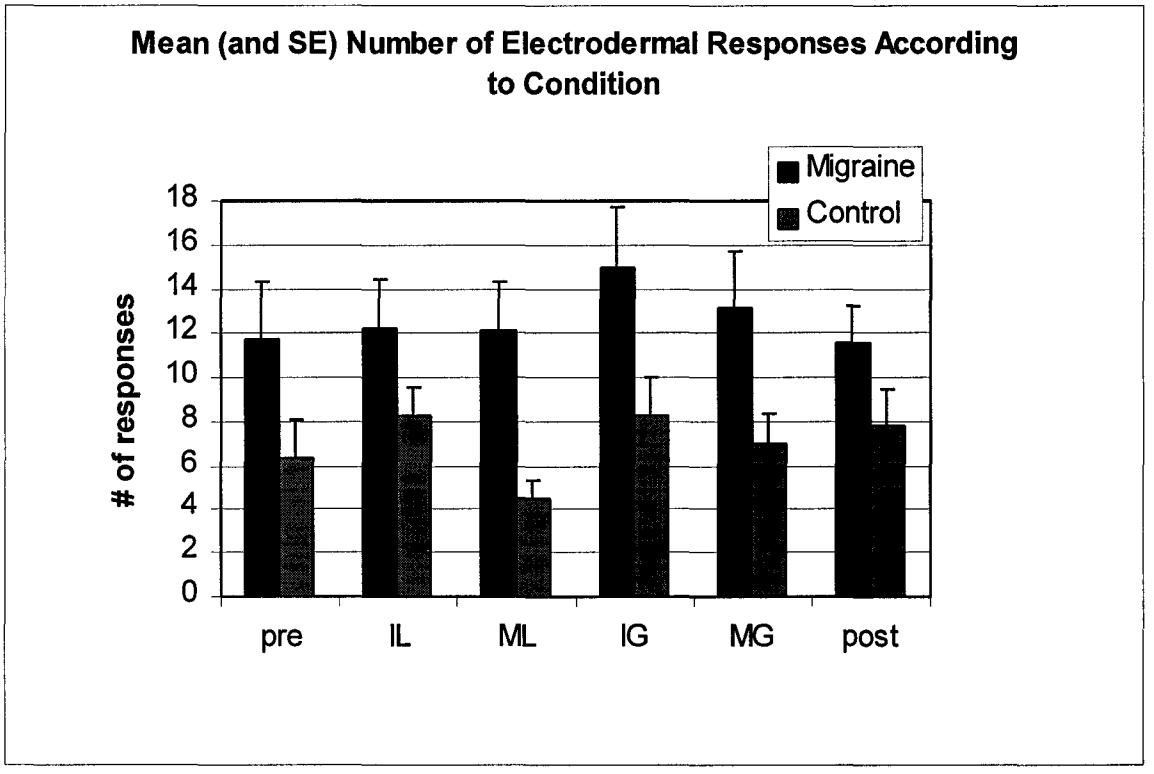

Mean (and SE) Number of Electrodermal Responses According to Condition
Migraine
Control
# of responses
18
16
14
12
10
8
6
4
2
0
pre
IL
ML
IG
MG
post

Figure 3.10

Thresholds For Light-induced Discomfort and Pain

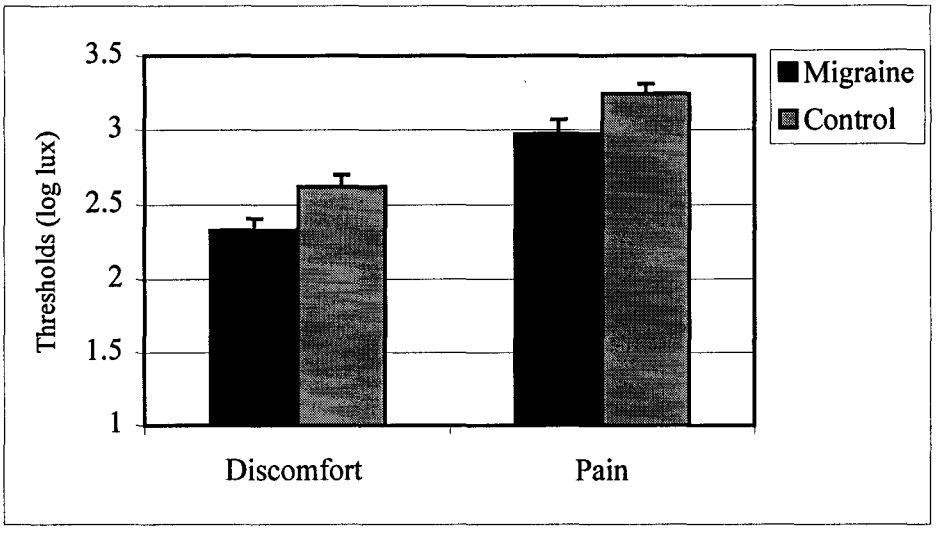
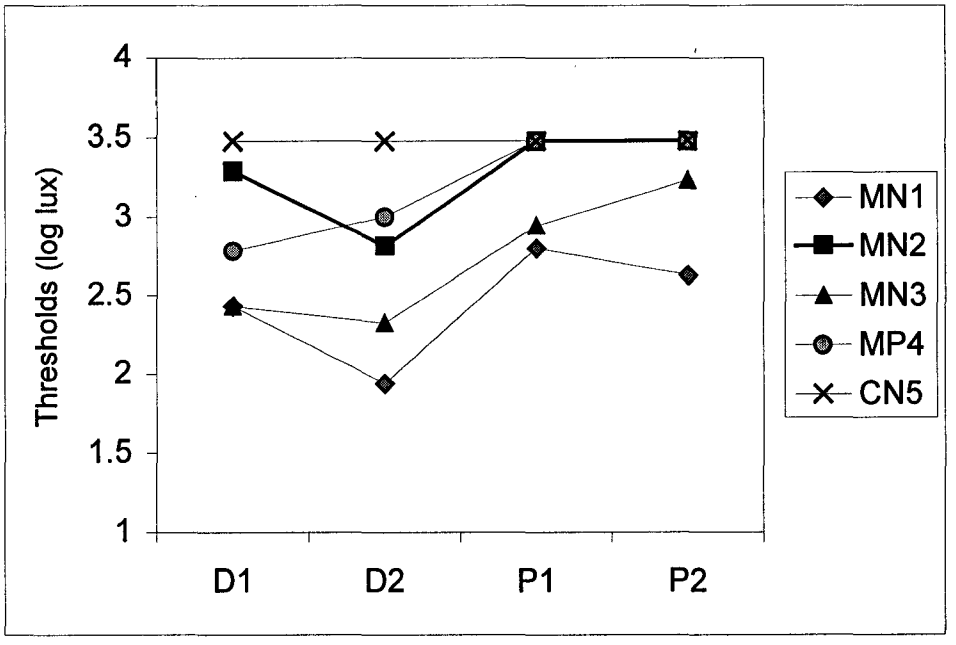


Figure 3.11

Thresholds of Participants Who Took Part in Both Studies



Threshold values for discomfort (D) and pain (P) according to study (1 and 2). Participants are coded by migraine status (migraine = M, control = C), bias conditions from the previous study (positive = P, negative = N). Lines between D1 and D2, and between P1 and P2 show the direction of change in individual threshold scores.

Table 3.7.

A comparison of BDI and STAI scores from other female samples of headache sufferers

	Current study	Marcus, 2001	Holroyd et al, 2000
Sample	n = 24 (M, some with TTH)	n = 195 (31% M, 18% TTH, 29% M + TTH, 12% post-traumatic, 10% other)	n = 191 (CTTH, some with M)
BDI	9.5 (5.9)	10.1 (9.9)	9.6
STAI-T	41.8 (10.7)	39.5 (12.5)	42.7
STAI-S	32.5 (9.6)	39.1 (12.5)	

Means and standard deviations (where available) of BDI and STAI scores in groups of female participants with headache. While the primary headache diagnosis varies between studies, all three samples include participants with multiple diagnoses.

Chapter 4 – Ambulatory heart rate variability of three migraine sufferers during and between headache episodes

Introduction

The results of the previous study found evidence that migraine sufferers had higher heart rate and more electrodermal responses. These differences were evident at all times of the study, including baseline and recovery. Migraineurs did not respond to visual stimulation that they associated with increased anxiety and visual complaints in a psychophsyiological pattern that would reflect a change in autonomic balance. While it has been postulated that autonomic activation is associated with actual migraine attacks, it is unclear at what point these changes would begin. Some have speculated that sympathetic activation would follow the onset of pain processes (Spierings, 2001). However, the presence of prodromal symptoms in some individuals would suggest that the autonomic imbalance begins prior to the onset of headache. The goal of the following study was to assess the degree to which autonomic function during the period leading up to, during, and following naturally occurring migraine episodes could be evaluated using ambulatory ECG monitoring. The ECG signal was used to generate heart rate and vagal tone.

Several studies have assessed ambulatory heart rate variability in migraine sufferers between episodes. Appel and colleagues (1992) studied ten migraine sufferers, ten healthy volunteers, and eight individuals with tension headache, admitting them to a hospital setting for 24-hour ambulatory ECG rate monitoring. All participants were female. In this setting, heart rate between groups was very similar, but enhanced low

frequency variability was detected in the migraine group, suggesting sympathetic imbalance. This increase in low frequency variability was apparent at all times of the day, but even more evident at night. Migraine sufferers also showed a small reduction in high frequency variability, reflecting mild parasympathetic hypofunction. The heart rate variability profile of tension headache sufferers resembled that of the healthy controls. The authors conclude that because low frequency variability is associated with vasomotor control, the results suggest that migraine is associated with lability in the system that maintains vascular tone. The same research group has reported similar findings in a study that assessed the effects of propranolol on ambulatory heart rate variability (Zigelman, et al., 1992). Again, migraineurs showed increased low frequency variability, which was then normalized with propranolol. However, it is difficult to ascertain whether the increase in low frequency variability was replicated in a new group of individuals, or if the same group of migraineurs was tested in both studies. In a third study by this group (Zigelman et al., 1994), which assessed the influence of verapamil, a calcium antagonist used in the prophylactic treatment of migraine, the authors make reference to the fact that participants were selected on the basis on showing increased low frequency heart rate variability. So, while it would seem that several studies have found increased low frequency fluctuation in small groups of migraine sufferers, it is unclear how consistent this effect is across different groups of individuals.

In addition to the above studies that use similar methodology and emerge from the same group of researchers, Tabata and colleagues (2000) have also assessed ambulatory heart rate variability in migraine. They studied larger groups of individuals, comparing 27 migraine sufferers and 24 controls. In this study, ambulatory recording took place

over a 48-hour period during normal routine activity, while migraine sufferers were free of headache. Low and high frequency heart rate variability was assessed in this study. Cosinor rhythm analysis was also conducted to assess circadian rhythms in autonomic function. Under normal circumstances, these authors indicate that sympathetic activity generally increases from morning to afternoon, and parasympathetic activity increases during the night. Tabata and colleagues suggest that their results provide evidence for cardiac parasympathetic hypofunction, as well as abnormal circadian rhythms in migraine.

The aforementioned studies highlight differences in autonomic function between migraine episodes. However, the results do not provide an indication of how the differences in autonomic function would change as a result of a migraine episode. Laboratory-based studies have compared the autonomic responses of migraine sufferers during and between attacks. Havanka-Kanniainen (1986) measured a number of psychophysiological indicators during cardiovascular stressors such as deep breathing and orthostatic and isometric challenges. The results of this study indicated that during a migraine episode, migraineurs had less a reduced autonomic response to tasks that typically activate a sympathetic response, such as the isometric hand grip test. The author concluded that during migraine there is evidence of sympathetic hypofunction that is not apparent between headaches. Others have, however, not found differences in responses between migraineurs tested during headache and while headache-free (e.g. Thomsen et al., 1995). One possible explanation for this discrepancy in findings is that the timing of assessment during headaches differed between the studies. For example, Havanka-Kanniainen (1986) took recordings for "six hours from the beginning of the

migraine attack" (p. 443). This is a relatively long period of recording, so it is possible that the differences found by Havanka-Kannianen represent a period of autonomic dysfunction that is not present throughout the migraine episode and may therefore not be captured during shorter sessions. Alternatively, headache characteristics such as severity or accompanying symptoms may have differed between studies. Both Havanka-Kanniainen (1986) and Thomsen and colleagues (1995) provide some details of the nature of headaches that occurred during testing. While both indicate that the attacks were migraines, as opposed to another type of headache, 5 of the 10 participants were vomiting during the former study, while 1out of 10 vomited in the latter. This could either reflect more severe migraines, or episodes that are associated with a different pattern of autonomic involvement. Differences in the symptoms and timing of attacks may be especially important to note when conclusions are based on the relatively small samples which are typical of this type of research, since naturally occurring migraine episodes are logistically difficult to capture. In summary, the question of whether migraine episodes are preceded, accompanied or followed by autonomic alterations remains unclear.

The goal of the present study was to assess whether ambulatory recording during naturally occurring migraines can address these issues. Ambulatory heart rate and heart rate variability (vagal tone) during naturally occurring migraine episodes was evaluated. A small number of individuals with frequent or predictable migraines were tested. Data for each participant were collected on two separate days: one day on which the participant experienced headache, and one non-headache day. In doing so, we hoped to determine whether changes in autonomic function were evident in the period leading up

to a migraine attack, or if a distinct pattern of autonomic activity was evident during migraine.

Methods

Participants

The goal of participant selection for this study was to find migraine sufferers who had relatively predictable and/or frequent migraineurs. These participants were chosen in order maximize the likelihood of scheduling ambulatory monitoring on a day when a migraine episode would occur. The list of migraine participants from the previous study was screened to select individuals who met at least one of the following criteria: 1) reported migraines that were temporally linked to their menstrual cycle, thereby making episodes somewhat predictable, 2) had one or more migraine episodes per week, increasing the likelihood that a migraine attack would occur on one of the testing days and 3) indicated that the onset of their migraine episodes was often predictable because of premonitory symptoms such as increased sensitivity to light or gastrointestinal upset. Of the 24 participants in the previous study, 15 met one or more of these criteria. After attempting to make contact via telephone and e-mail addresses provided at their last interview, 7 of the 15 participants were successfully contacted.

The seven potential participants were all contacted by telephone and told about the nature of the study. They were informed that the study involved ambulatory heart rate monitoring on two or three days during routine activity, and required the completion of regular diary-type recording. Those who were interested were re-interviewed to assess changes in health or headache condition since their last interview and to verify that they still had frequent and/or predictable migraines. Participants were required to be free of

medication when tested, with the exception of oral contraception, so changes in medications were also verified. Of the seven individuals who were contacted, three individuals met inclusion criteria and were interested and able to participate.

The following case descriptions provide the relevant background on these individuals.

Participant #1(P1): This 20-year-old female had a diagnosis of migraine without aura, as confirmed by a general practitioner. At the time of the previous study, she had been experiencing approximately two migraine episodes per week. At the time of re-interview, she was experiencing approximately one migraine episode per week. She reported that the episodes were not linked to predictable triggers, such as menstruation, but that she could identify when a migraine episode was about to begin because they were typically preceded by approximately 30 minutes of pressure in her head. This participant had been experiencing migraines for approximately seven years. She also met criteria for episodic tension-type headache, which she experienced approximately two times per month.

Participants #2 (P2): This 29-year-old female had a diagnosis of migraine without aura, confirmed by a neurologist. She experienced approximately 3 episodes of migraine without aura per month, which was similar to the frequency reported at her original interview. Episodes of migraine without aura were linked to her menstrual cycle, occurring typically three to four days before the onset of menstruation. She had been experiencing migraines for approximately twenty years.

Participant #3(P3): This 22-year-old female indicated that she experienced episodes of migraine without aura that were not predictable, but were frequent enough to

suggest that a migraine episode would occur by chance on one of the three potential recording days. At the original interview, P3 reported experiencing two to three migraine episodes per week. At the time of re-interview, she reported a frequency of approximately 1 episode per week. While her headache description fit I.H.S. criteria (HCCIHS, 1988) for this headache condition, her general practitioner had returned the confirmation of diagnosis form indicating that they had seen this participant for headaches, but that a diagnosis could not be specified. The physician did rule out other neurological or medical conditions as a cause of the headaches (Criterion E, see Appendix A). Since the rest of the criteria are based on subjective symptom description, and she reported more than the minimum requirement of migraine characteristics, we felt comfortable with the diagnosis of migraine without aura. Her typical migraines were described as unilateral, throbbing, accompanied by photophobia, phonophobia and nausea, became more intense with exercise and lasted up to an entire day. She had been experiencing migraine for approximately eight years. She reported that she did not experience headaches other than migraines on a regular basis.

Apparatus and heart rate measures

Interbeat interval recordings and conversion to vagal tone:

Ambulatory heart rate was recorded using a Polar R-R Recorder. This lightweight heart rate monitor is worn on the participant's waist and receives input from two disposable, self-adhesive electrodes worn on either side of the chest. Hypoallergenic paste was applied to the electrodes. Sequential interbeat intervals were recorded for a period of approximately 24 hours.

Data files containing the cardiac interbeat interval files were processed using the off-line analysis option on the Vagal Tone Monitor II (Delta-Biometrics, Bethesda, MD). Using this method, estimates of high frequency variability (0.12 - 0.40 Hz) and heart rate were derived for sequential 30-second windows of data. In order to reduce the extensive amount of data collected over the 24-hour period, means for each hour of data collected were calculated. This data reduction process is similar to that described by Appel and colleagues (2000). In the current study, heart rate and high frequency variability are presented. Again, the latter measure is used as an index of vagal tone or respiratory sinus arrhythmia.

Diary recordings

During ambulatory recording, participants were asked to make regular entries into a pocket-diary that assessed a number of variables including headache, associated symptoms, activity and mood. This diary is presented in Appendix D. Participants were asked to make entries every three hours that they were awake. Given the small number of individuals tested using this protocol, the diary information was intended to provide a descriptive account of the participants' activities and symptoms, rather than providing the basis for quantitative statistical comparisons.

Procedures

Following the telephone interviewing process, described above, participants scheduled an appointment for ambulatory recording. The scheduling of this appointment was based on when participants believed they would be most likely to experience an attack (e.g. on a day of their menstrual cycle on which migraine typically occurs). At this meeting, the participant reviewed the consent form and provided written consent. The

experimenter attached the ambulatory heart rate monitor and reviewed the pocket-diary with the participant. Participants were encouraged not to remove the recording equipment unless they needed to perform an activity, such as showering, that would damage the recording device. A meeting was then scheduled, approximately 24 hours later, to remove the recording equipment and collect the diary information. If participants did not experience a headache on the day of testing, another appointment was to be scheduled on a day when an episode would be likely to occur. If migraine had not occurred, the day of recording could be used for the control day. If migraine had occurred, another recording day was scheduled in an attempt to measure 24-hour ambulatory heart rate on a non-migrainous day.

Participants received $50 as compensation for their time and the inconvenience of taking part in the study. All procedures in this study were approved by the McGill University Research Ethics Board for Research Involving Humans.

Data analysis

Since this study involved a very small sample, no statistical comparisons were made between participants or across recording days. Instead, hourly means were calculated and are presented graphically to illustrate the pattern of recorded heart rate and heart rate variability (See Figures 4.1, 4.2 and 4.3 for individual data).

Results

Headaches were reported on one of the days of ambulatory monitoring for all three participants. The characteristics of these episodes are described in Table 4.1. Participants P1 and P2 described headaches and associated symptoms that met I.H.S. criteria for a migraine episode (HCCIHS, 1988). The episode described by P3 would not

be classified as a migraine since it lacked enough accompanying symptoms. This episode could be classified as a tension-type headache (See Appendix A) because, despite meeting several criteria for migraine, such as unilateral location, it was not accompanied by enough migrainous symptoms. Furthermore, the reported pain of this episode was relatively low in intensity.

Our attempt to measure ECG in the periods preceding and following the migraine episodes was successful in P1. For P2, the migraine occurred just as recording began, so the preceding period is not captured. For P3, the recording period ended just after the headache.

Comparison of headache and non-headache recordings

Ambulatory heart rate and vagal tone data for each participant are presented in Figures 4.1, 4.2, and 4.3. Both the control day (a) and headache day (b) are illustrated. The arrow indicated on the headache day graphs represents the time frame during which headache was reported.

On all ambulatory recordings, both headache and non-headache days, participants show a pattern of decrease in heart rate and increase in vagal tone during the night. Morning was associated with a reversal of this pattern, likely reflecting an increase in sympathetic activity as the morning routine unfolds and activity levels increase. This pattern of change is considered typical (Tabata et al, 2000).

When headache and non-headache days are compared, there is no striking pattern of differences that precedes, accompanies or follows headache. Of the three headaches recorded, two (P2 and P3) show a pattern in which there is a simultaneous increase in heart rate and decrease in vagal tone. Since one of these headaches could not be

classified as a migraine, it is possible that this pattern reflects a response to headache pain, rather than a migraine-specific process. However, P1, who described having a more intense headache than P3, did not show this pattern of activity. Instead, there is a gradual decline in heart rate. Another possibility is that that the drop in heart rate and increase in parasympathetic activity occurring at the end of these episodes is a function of a decrease in activity that results from headache-related disability. As this change occurred, P1's diary recordings indicate a change from working on her computer at 21:00 hrs, to attempting to relax at midnight. The diary records of P2 and P3 document periods of activity during the initial stages of their headaches when heart rate is increasing, however, no recordings were made as heart rate decreased.

In addition to comparing the pattern of heart rate and heart rate variability, reported anxiety levels between non-headache and headache days were compared. Anxiety level was measured on a 5-point scale. The item was labeled "anxious/tense", and participants circled a number between 0 and 5. Anchors were "not at all" (0) and "very much" (5). For P1 and P3, reported anxiety/tension was slightly higher on the headache day than on the non-headache day (means for P1: 2.2 and 1.6, respectively; P3: 2.6 and 1.9, respectively). Anxiety/tension levels fluctuated considerably during the period of time associated with the headache. Participant 2 did not report experiencing any anxiety at any of the reporting times of the non-headache or headache day. Statistical comparisons were not conducted because of the small sample size.

Discussion

The results of this study document the ambulatory ECG recordings taken during naturally occurring headaches. The recordings also capture periods of normal daily

activity preceding and/or following these episodes. The data highlight some possible patterns of autonomic activity that may accompany migraine, but do not show dramatic changes that precede the migraine episode. One pattern that was evident in two cases was a sharp increase in heart rate and decrease vagal tone during the headache phase. While Spierings (2001) suggested that sympathetic activation may follow the onset of migrainous pain, the results of these two individuals are more suggestive of a period of parasympathetic hypofunction, during which the vagus is not exerting its normal influence in slowing heart rate. A drop in vagal tone has also been found during ambulatory recording in a subgroup of women with irritable bowel disorder that experienced severe pain that was not postprandial (Burr, Heitkemper, Jarrett & Cain, 2000). This suggests that a drop in vagal tone may be implicated during painful episodes of a number of chronic pain disorders. Further research is needed to evaluate the possibility that changes in heart rate variability accompany migraine.

While this study explored the feasibility of using ambulatory recording to study to assess the pattern of autonomic change that precedes, accompanies or follows migraine, this approach has some notable limitations. First, most migraine sufferers do not have predictable migraine episodes, which makes acquiring a large enough sample challenging. While attempting to trigger attacks would result in more episodes, it is possible that triggered episodes would not reflect gradual changes in function that may precede naturally occurring episodes. Furthermore, since there is speculation that repeated migraine attacks may actually lead to changes in the central nervous system (Chronicle & Mulleners, 1990), attempting to trigger migraine episodes may present an ethical challenge.

The results of this study also highlight the variability within ambulatory recordings that will make finding distinct patterns of change related to migraine episodes a considerable challenge. Patterns may be more evident if measurements are repeated across several episodes within the same individuals. This would require a sample of highly motivated individuals who would be willing to undergo a considerable amount of ambulatory measurement. Furthermore, these individuals would need to be well-trained to clearly document the onset and offset of symptoms. Studying individuals with migraine with aura may be particularly fruitful as they typically experience clear indications that a headache is about to occur. This would also clarify whether episodes are migrainous or not, since in the present study, this distinction was somewhat ambiguous.

In summary, while this study was successful in recording ambulatory ECG during naturally occurring migraines, the results of this study did not document any clear changes in heart rate or heart rate variability that precede the onset of headache. Furthermore, this study highlights the challenges involved in using ambulatory measures to assess autonomic changes related to migraine episodes. It is unclear whether changes in autonomic activity reflect a process that is specific to migraine pathophysiology, the pain process, or behavioural changes that accompany headache episodes.

Table 4.1

Characteristics of headache episodes according to diary records

Migraine characteristic	P1	P2	P3
Unilateral headache	Yes	--	Yes
Throbbing pain quality	--	Yes	--
Worsening of pain with exercise	Yes	Yes	--
Nausea	--	--	--
Vomiting	--	--	--
Photophobia	Yes	Yes	Yes
Phonophobia	Yes	Yes	--
Other symptoms noted	Dizzy	Weak, tired, unsteady balance upon standing	--
Mean intensity*	38 (30-46)	30 (28-33)	9 (8-12)
Onset of headache	Between 5:00 pm and 9:00 pm	Woke up with it	10:30 am
End of headache	After 12:30 am, before 10:30 am	After 2:00 pm, before 8:30 pm	After 4:00 pm, before 7:00 pm
Duration	> 3 hours	> 5 hours	> 5 hours
Medication**	Mersyndol® at 12:20 am	Fiorinal® at 9:15 am	--

*VAS score on 100 point scale – "Mild" to "severe"

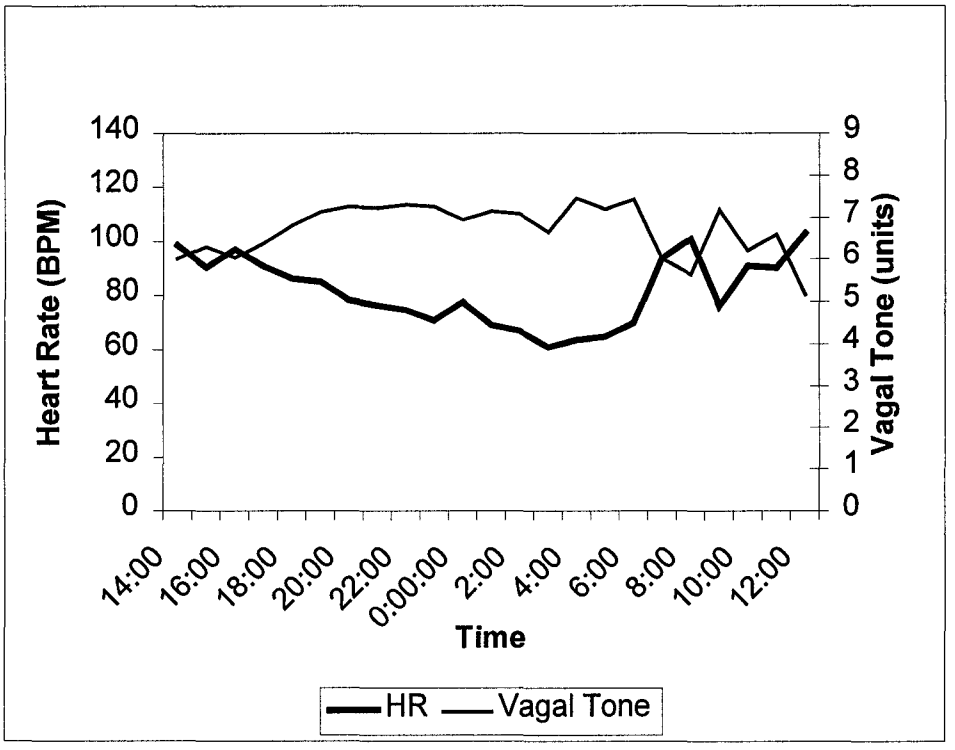
** Mersyndol: acetaminophen, codeine & doxylamine succinate (antihistamine/sedative), Fiorinal: ASA, caffeine, butalbital (possibly with codeine) (Canadian Pharmacists Association ,1999)

Figure Legend For Figures 4.1 – 4.3

Figure a) and b) show hourly means of ambulatory heart rate (HR) and low-frequency variability (Vagal Tone) for the control day and headache day, respectively. A break in the plotting of these variables indicates periods when data was unavailable, either due to the temporary removal of the heart rate monitor or a problem with the acquisition of ECG signals. The arrow indicated on the headache days represents the time frame during which headache was reported.

Figure 4.1

a) Participant 1 – Control Day



b) Participant 1 – Headache Day

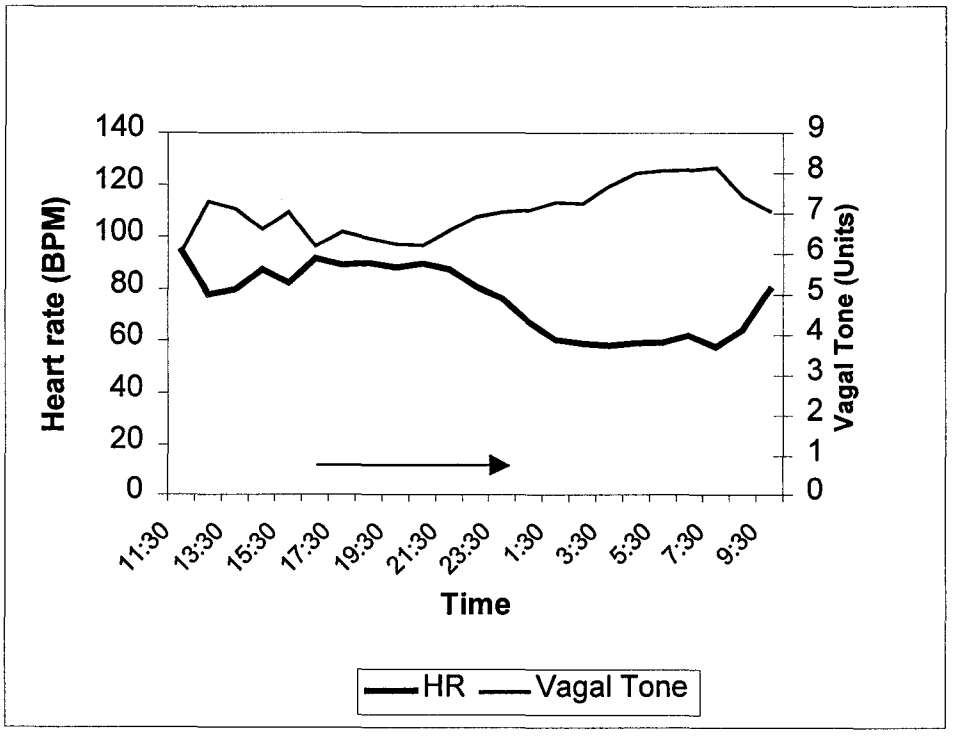
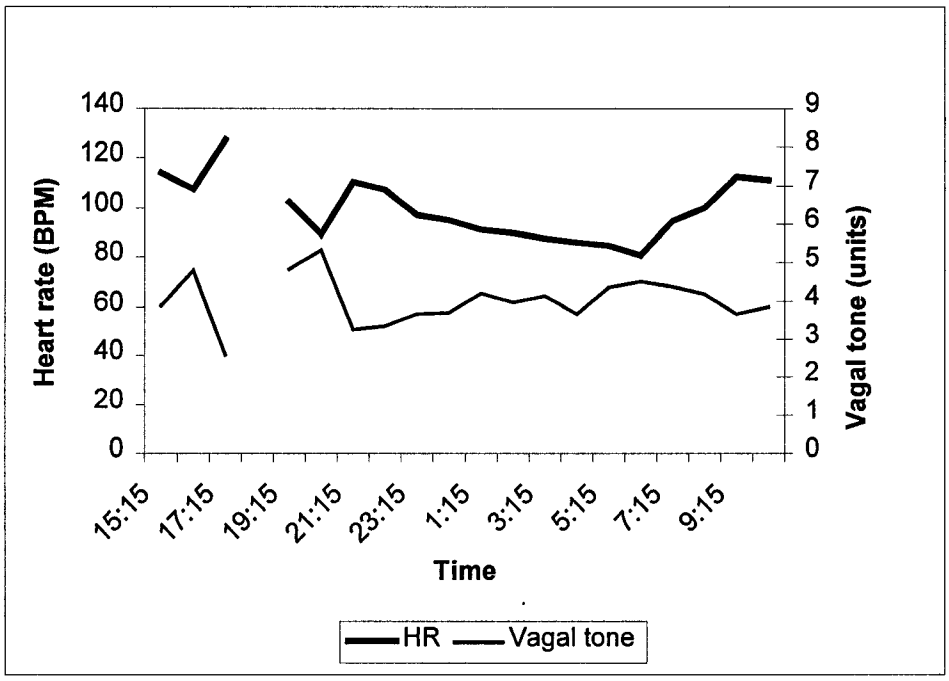


Figure 4.2

a) Participant 2 – Control Day



b) Participant 2 – Headache Day

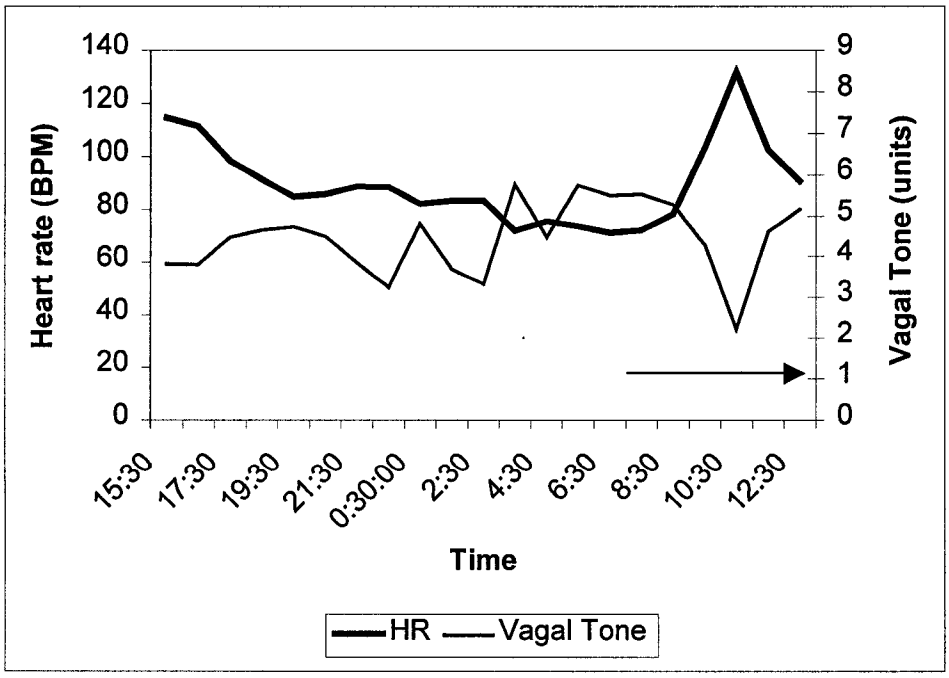
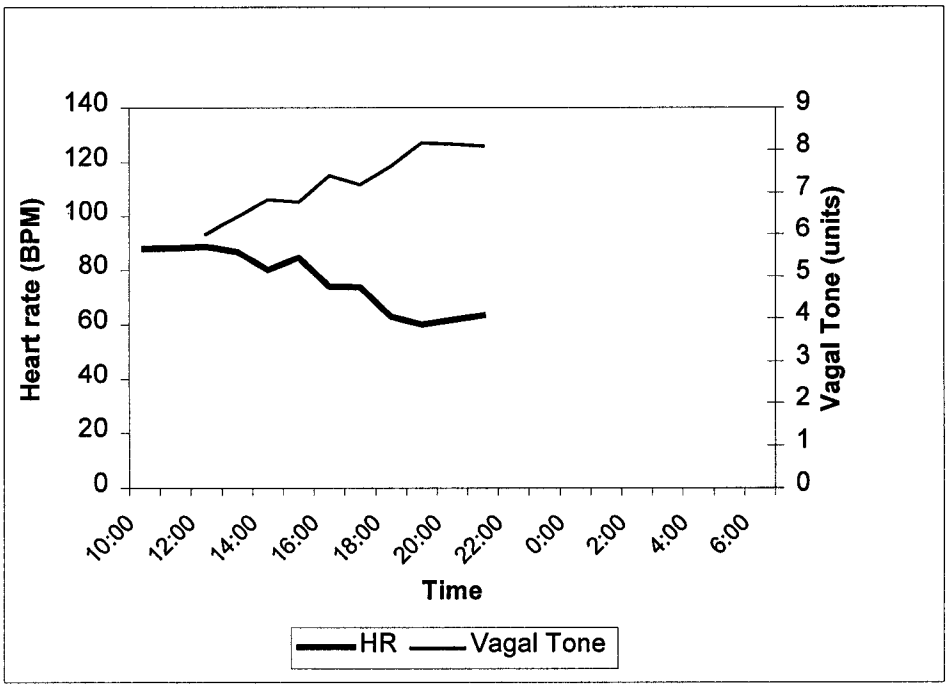
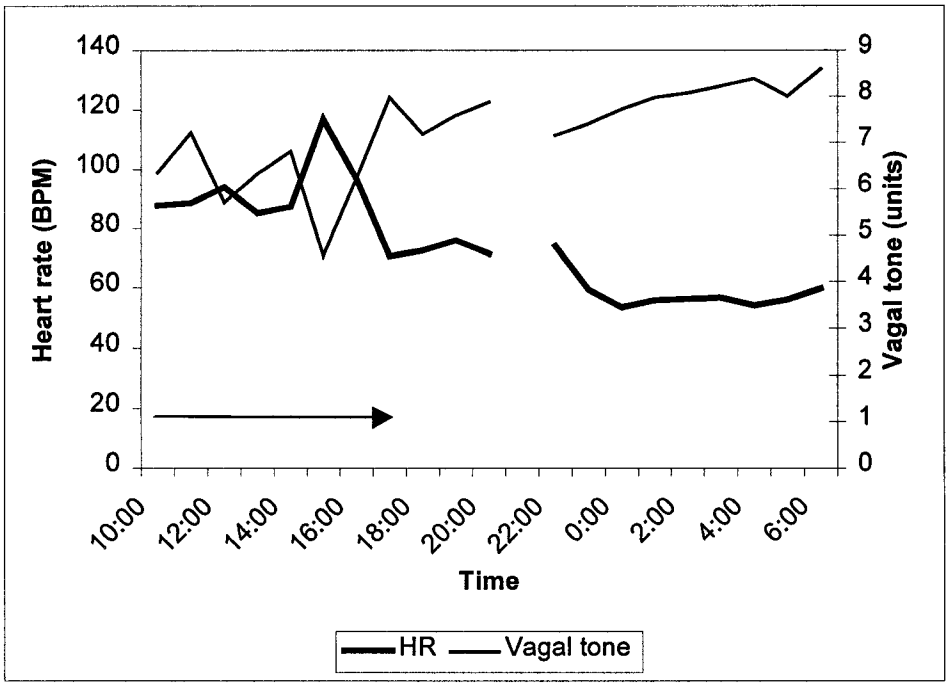


Figure 4.3

a) Participant 3 – Control Day



b) Participant 3 – Headache Day



Chapter 5 - **General Discussion**

Summary of findings and theoretical implications

The objective of this dissertation was to assess subjective and psychophysiological responses that occur when migraineurs are exposed to aversive visual stimulation, and whether these responses support its role as a stressor between episodes. One of the central questions of this dissertation was whether exposure to intense visual stimulation would elicit widespread autonomic changes in migraine. Currently, pathophysiological models of migraine tend to emphasize explanations of the aura and headache phase, as these are the symptoms that have been most widely studied. However, sensitivity to visual stimulation is a common symptom that occurs both during and between attacks and should therefore be included in such models. In order to do so, the nature of this symptom and interactions with other migrainous symptoms needs to be clarified.

The results of this dissertation did not support a widespread reaction of the autonomic system of migraineurs to intense visual stimulation. Instead, migraineurs showed elevated heart rate and electrodermal responding at all times, suggesting an increase in sympathetic activation that was generalized, rather than specific to the aversive stimulation. While elevated psychophysiological responses were not associated with the visual stimuli, migraineurs subjectively described increased levels of anxiety and subjective complaints in response to visual stimulation. This finding confirms similar findings by Martin and Teoh (1999) who also found that while visually aversive stimuli could trigger attacks, they did not result in a clear pattern of autonomic perturbation. Our work extended this previous research by including a broader range of subjective

measures, reinforcing the finding that the behavioural response to intense visual stimulation is very evident in migraine. We also used instructions and a methodology that minimized the likelihood that participants would expect to experience discomfort or headaches. The results of the first study of this dissertation reinforced the need for controlling this type of contextual influence. Finally, the central study of this dissertation employed a wider range of stimulus characteristics that are known to be aversive to migraineurs, increasing the likelihood that they would induce discomfort and any clinically relevant psychophysiological reactions. Together, these results suggest that intense visual stimuli do not produce an immediate and general activation of autonomic indicators that are commonly affected by more traditional laboratory stressors. Since both studies showed that headaches were commonly reported at follow-up shortly after the experiment, it is possible that autonomic changes occurred in closer temporal proximity to the onset of headache.

The possibility that autonomic changes would be evident in the period leading up to, during, or following headache was addressed by the final study of this dissertation. This study was successful in conducting ambulatory recording during naturally occurring headaches. The need for this approach was suggested by Feuerstein and colleagues (1983) assessed autonomic activity in a laboratory setting for several days leading up to a migraine attack, and on the day of the episode, and did not find evidence of a general autonomic disturbance. The results of the third study of this dissertation suggest that a pattern of autonomic change may occur during the headache (increased heart rate, decreased vagal tone), but that comparing the ambulatory recordings of individuals experiencing naturally occurring headaches is unlikely to be the best approach to confirm

these findings. Considerable variability across individuals and time of day would make finding clear patterns of change extremely difficult. Furthermore, even in individuals who report frequent or predictable migraines, precise and frequent diary recordings would be needed to clarify that the pattern is related to migraine rather than headache in general. An alternative approach would combine the methods of the second and third study of this dissertation. Since intense visual stimulation was reported to trigger headaches following the termination of the testing session, it would be interesting to assess ambulatory recordings after intense visual stimulation to address whether autonomic changes occurred in closer proximity to headache. Using laboratory stimulation to increase the likelihood of headache activity would eliminate the need to find individuals with predictable headaches. However, this does raise again the fundamental dilemma in migraine research of to what extent it is ethical to trigger migraines in order to study them.

The results of the studies presented confirm that visual discomfort is a very common experience of migraine sufferers between attacks. While aversive visual stimulation is associated with a broad range of subjective complaints, the lack of widespread autonomic activation further supports the need to investigate how other systems are involved in this common symptom of migraine. Given Drummond's (1997) finding that a facial pain stimulus can exacerbate photophobia in migraine, interactions between the visual system and trigeminal system may provide some of these answers. There is also considerable evidence that the visual cortex is hyperexcitable in migraine, lending support to the theory that migraine involves interictal cortical excitability or reactivity (Schoenen, 1998). This increase in cortical sensitivity may make migraineurs

more vulnerable to environmental factors such as intense visual stimulation. However, recent emphasis on the role of the brainstem in migraine (e.g. Weiller et al., 1995; Welch et al., 2001) also reinforces that importance of the trigeminovascular system and autonomic system in migraine pathophysiology. Thus far, theories of migraine have tended to focus on explanations of migraine aura and headache. Visual discomfort is another very common feature of migraine and should also be incorporated into comprehensive pathophysiological theories of migraine.

The presented results also demonstrate that while visual discomfort is more common in migraine than controls, there are some migraineurs who do not experience high levels of it, while there are controls who do. The studies in this dissertation did not assess self-reported levels of visual discomfort in the natural environment, or the degree to which individuals believed they were susceptible to visual triggers. Following the initiation of the central study of this dissertation, The Visual Discomfort Scale was published (Conlon, Lovegrove, Chekaluk & Pattison, 1999). This measure asks participants to rate how frequently symptoms of visual discomfort occur. These include the experience of blurring and distortions while reading, eye strain when viewing striped patterns, and experiencing headache when working under fluorescent lighting. High scores on this scale were associated with increased perceptual disturbances and ratings of unpleasantness during the viewing of striped patterns similar to the ones used in this dissertation. Furthermore, Conlon & Hine (2000) found that while differences on a visual search task were not detected between groups suffering from different headache disorders, when participants were classified according to severity interictal visual discomfort, those in the high visual discomfort group performed more slowly than those

with low visual discomfort. It would be useful to incorporate a measure of interictal visual discomfort, such as the one presented by Conlon and colleagues, in future research on visual sensitivity. While migraineurs are often subdivided according to whether or not they experience aura, classifying groups according to whether or not they are vulnerable to visual discomfort may demonstrate that this phenomenon is relevant to migraine pathophysiology in some migraineurs but not others.

There are several aspects of our results and the results of a previous study that suggest that the role of cognitive factors and anxiety should be the focus of further investigation in migraine. In both the current study and Martin and Teoh's (1999) study, exposure to intense visual stimulation was associated with an increase in negative affect or anxiety. Despite an increase in anxiety, clear patterns of associated autonomic disturbance were not evident. Anxiety may nonetheless have an impact on how migraineurs respond when confronted with intense visual stimulation. An interesting line of future research would examine whether cognitive and emotional factors such as perceived locus of control or anticipatory anxiety plays a role in determining how migraineurs respond when confronted with potential triggers. If these factors do play a role, it is possible that for those who are anxious in the presence of potential triggers, attention is directed towards somatic sensations that would otherwise not be attended to. This is not to say that the headache itself is not "real." Rather, the threshold at which a headache will be perceived as disabling or extremely painful may be altered by the cognitive and emotional factors that influence the perception of pain (Melzack & Wall, 1996).

Clinical implications

The results of this dissertation confirm that migraineurs between episodes are more sensitive to discomfort caused by intense visual stimuli, and may also be bothered by visual stimulation at milder levels than controls. Currently, there are several approaches to treating and preventing migraines, both pharmacological and non-pharmacological (see reviews by Goadsby, Lipton & Ferrari, 2002; Silberstein, 2000). The effectiveness of these medications is typically judged by whether abortive medications can reduce head pain once it is initiated, or whether prophylactic medications can reduce the frequency of migraine episodes. In some cases, the ability of a treatment to affect aura or associated symptoms during the attack is also considered.

A number of recent studies have assessed the impact that prophylactic medications have on interictal differences in migraine. For example, beta-blockers are commonly used in an attempt to reduce the frequency of migraines. Propranolol, one of the beta-blockers that is often used, is proposed to act by interfering with the vigilance-enhancing adrenergic pathways by inhibiting central beta-receptors, or by interacting with serotonergic function (Silberstein, Saper & Freitag, 2001). It is thought to block the vasodilating properties of beta-receptors, making it easier for vasoconstriction to occur (Freeman, 1996). Despite this theory, the mode of action of beta-blockers in migraine prophylaxis remains unclear (Tfelt-Hanson & Shanks, 2002). We do, however, know that prophylaxis with beta-blockers reduces a number of the differences that have been found to exist between migraineurs and controls when they are headache-free. This includes a decrease in auditory evoked potentials, an effect that is correlated with clinical improvement (Sandor, Afra, Ambrosini & Schoenen, 2000), a normalization of

contingent-negative variation, another cerebral potential that is altered in migraine (Schoenen, Maertens de Noordhout, Timsit-Berthier & Timsit, 1986), and a reduction in sympathetic control of heart rate which has otherwise been found to be increased in migraineurs during ambulatory ECG recording (Zigelman et al., 1992). Given migraine prophylaxis can reduce a number of interictal differences, it would be interesting to assess whether subjective visual discomfort and increases in photophobia could also be reduced with appropriate pharmacotherapy. Knowing the how these functions are impacted by pharmacological interventions is useful for theories that try to explain how they can be incorporated into pathophysiological theories of migraine. Future research is needed to understand whether increased visual sensitivity can be affected by prophylactic medications. This would improve our understanding of how this bothersome symptom originates and how it can be reduced. This emphasis on migraine prophylaxis is especially important if, as some have proposed, repeated migraine attacks may eventually lead to changes in the central nervous system (Chronicle & Mulleners, 1994; Welch et al, 2001). As of yet, we are not aware of research that has evaluated the impact of prophylactic treatments on ictal or interictal visual discomfort. Since this symptom is relatively common and associated with discomfort and anxiety, knowing how to reduce it would improve our understanding of migraine, but would also be helpful in reducing an associated symptom that may exacerbate migraine-related disability.

While it is possible that pharmacological interventions could reduce visual discomfort, non-pharmacological interventions may also be helpful. There is considerable empirical support for using relaxation, biofeedback and cognitive behavioural therapy in the treatment of migraine (see reviews by Holroyd, Penzien &

Lipchik, 2001; McGrath, Holroyd, & Sorbi, 2000; and Silberstein, 2000). For example, the results of a meta-analysis by Holroyd and Penzien (1990) concluded that propranolol and a combination of relaxation and thermal biofeedback training were equally effective in reducing migraine activity and both were superior to placebos. As with propranolol, the method of action of psychological interventions remains unclear. Therapeutic goals of behavioural and cognitive interventions can include a reduction in headache severity or frequency, and an improvement in associated psychological symptoms, somatic complaints and the ability to cope. The data from the second study of this dissertation reinforce the need for anxious and depressive symptoms to be considered even in individuals who are not disabled to the point of seeking specialized services. Despite the fact that the majority of our migraine sample was recruited from campus, rather than through headache clinics or neurologists, they reported high levels of depressive and anxious symptoms. This dissertation also demonstrated that exposure to intense visual stimulation can be associated with an increase in anxiety and a number of subjective complaints. While visual discomfort is likely based on physiological interactions of the visual system and trigeminal system, current models of pain continue to emphasize the important role that psychological factors can have in modulating the intensity or expression of pain (Drummond & Holroyd, 2000). These factors include beliefs and attitudes about pain, depression, anxiety and distress. Behavioural and cognitive-behavioural treatments that are aimed at influencing these factors may therefore reduce the impact of discomfort associated with visual stimulation, and in turn reduce migraine-associated disability. An empirical investigation of this hypothesis would be an interesting area for future research.

While it would be interesting to know how pharmacological and non-pharmacological treatments impact visual sensitivity from a theoretical standpoint, from a practical standpoint it is unlikely that all patients will require intervention aimed at reducing visual discomfort. However, it is clear that many individuals with migraine are bothered by visual stimulation in their every day environments and make attempts to cope with it using behaviours such as wearing sunglasses in normal light (Mulleners, Aurora, et al., 2001). In extreme cases, the avoidance of visual triggers may be extreme and debilitating enough to be classified as a phobic disorder (Spierings, Reinders, Cornelis & Hoogduin, 1989). At an individual level, it would be relatively easy to ask patients whether they are bothered by visual stimulation and to incorporate a discussion of how the visual environment can be altered without requiring dramatic efforts to avoid all potentially aversive stimulation. For example, advising patients on how to make simple choices to avoid excessive exposure to the spatio-temporal characteristics that are particularly bothersome may be helpful in reducing visual discomfort during and between headaches (e.g. avoiding boldly striped patterns in their décor, choosing lighting that does not flicker, etc.). However, patients are commonly advised to avoid triggers in the hopes that this will prevent migraine episodes (Diamond, 2001). It has been suggested that attempting to avoid bright light by frequently wearing sunglasses may in fact exacerbate this symptom since light deprivation can worsen photophobia (Martin & Corbett, 2001). It is likely that there is an appropriate balance between advising patients to avoid excessive amounts of visual stimulation while finding treatments, either pharmacological or psychological, that can reduce visual discomfort in those who are bothered by it. Knowing how best to achieve this will require further research. On the other hand,

spatially and temporally periodic patterns such as gratings are known to particularly bothersome, so simple advice on how to change their environment could be very helpful.

Summary

In summary, this dissertation supports and extends an existing literature that shows migraine sufferers are more bothered by various types of visual stimulation than non-migraineurs. It also demonstrates that elevated sensitivity between migraine attacks is associated with a number of subjective complaints and anxiety. Despite this, we did not find evidence that intense visual stimulation causes widespread autonomic reactivity that is typical of more traditional psychological stressors. More research is needed to clarify how increased visual sensitivity can be incorporated into pathophysiological models of migraine, and how this symptom, which is associated with discomfort and anxiety, can be treated.

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Appendix A -

International Headache Society Diagnostic Criteria For Migraine Without Aura, Migraine With Aura, and Tension-Type Headache (CCIHS, 1988)

Migraine without aura (MO)

(Previously used terms: common migraine, hemicrania simplex)

A. At least 5 attacks fulfilling B-D.

B. Headache attacks lasting 4-72 hours* (untreated or unsuccessfully treated)

C. Headache has at least two of the following characteristics:

1. Unilateral location
2. Pulsating quality
3. Moderate or severe intensity (inhibits or prohibits daily activities)
4. Aggravation by walking stairs or similar routine physical activity

D. During headache at least one of the following:

1. Nausea and/or vomiting
2. Photophobia and phonophobia

E. At least one of the following:

1. History, physical- and neurological examinations do not suggest one of the disorders listed in groups 5-11**
2. History and/or physical- and/or neurological examinations do suggest such a disorder, but it is ruled out by appropriate investigations
3. Such disorder is present, but migraine attacks do not occur for the first time in close temporal relation to the disorder.

Migraine with aura (MA):

(Previously used terms: Classic migraine, classical migraine, ophthalmic-, hemiparesthetic-, hemiplegic- or aphasic migraine, migraine accompangée)

A. At least 2 attacks fulfilling B.

B. At least 3 of the following 4 characteristics:

1. One or more fully reversible aura symptoms indicating focal cerebral cortical and/or brain stem dysfunction.
2. At least one aura symptom develops gradually over more than 4 minutes or, 2 or more symptoms occur in succession.
3. No aura symptom lasts more than 60 minutes. If more than one aura symptom is present, accepted duration is proportionally increased.
4. Headache follows aura with a free interval of less than 60 minutes. (It may also begin before or simultaneously with the aura).

C. At least one of the following:

1. History, physical- and neurological examinations do not suggest one of the disorders listed in groups 5-11**
2. History and/or physical- and/or neurological examinations do suggest such a disorder, but it is ruled out by appropriate investigations
3. Such disorder is present, but migraine attacks do not occur for the first time in close temporal relation to the disorder.

Episodic Tension Type Headache (TH):

(Previously used terms: tension headache, muscle contraction headache, psychomyogenic headache, stress headache, ordinary headache, essential headache, idiopathic headache and psychogenic headache.)

A. At least 10 previous headache episodes fulfilling criteria B-D listed below. Number of days with such headache < 180/year (< 15/month)

B. Headache lasting from 30 minutes to 7 days

C. At least 2 of the following pain characteristics:

1. Pressing/tightening (non-pulsating) quality
2. Mild or moderate intensity (may inhibit, but does not prohibit activities)
3. Bilateral location
4. No aggravation by walking up stairs or similar routine physical activity

D. Both of the following:

1. No nausea or vomiting (anorexia may occur)
2. Photophobia and phonophobia are absent, or one but not the other is present

E. At least one of the following:

1. History, physical- and neurological examinations do not suggest one of the disorders listed in groups 5-11**

2. History and/or physical- and/or neurological examinations do suggest such a disorder, but it is ruled out by appropriate investigations
3. Such disorder is present, but tension-type headache does not occur for the first time in close temporal relation to the disorder.

* In children below age 15, attacks may last 2-48 hours. If the patient falls asleep and wakes up without migraine, duration of attack is until time of awakening.

** Disorders in this group include headache associated with head trauma, headache associated with vascular disorders (e.g. transient ischemic attack), headache associated with non-vascular intracranial disorder (e.g. high cerebrospinal fluid pressure), headache associated with substances or their withdrawal, headache associated with non-cephalic infection, headache associated with metabolic disorder (e.g. high altitude headache), and headache or facial pain associated with disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cranial structures.

Appendix B

Migraine Screening Interview For - Subject Information

(Italicized items were not included when participants were screened for the study presented in Chapter 2).

Date: Language: Subject #:

Name:

Telephone: (Home) (Work)

Permanent Telephone #:

Address:

E-mail address:

Age: Date of Birth:

Sex:

Height: *Weight:*

Can you come to McGill?

How did you find out about the study?

Have you ever been diagnosed or treated for any of the following:
Epilepsy, cluster headache, multiple sclerosis, optic neuritis, *cardiovascular problems*, *high blood pressure*, diabetes, glaucoma, previous head or neck injury, other neurological disorder or any condition that could affect your vision, *asthma, allergies*?

Do you get headaches?

Have you ever been diagnosed as having migraine?

If so, by a GP or neurologist? Can you bring in your doctor's address?

Doctor's address:

Onset of migraine (age):

Do you get more than one type of headache or migraine? (If so, record how participants refer to them and ask the following questions for each type separately):

Describe your headaches briefly:

How frequently do you get headaches/migraines? (excluding headaches from hangovers or illnesses such as the flu)

*Please specify:

Never

Less than once a year

More than once a year but less than once a month (specify)

Once a month

More than once a month (specify)

Rate the severity of your typical headache on a scale of 1 to 10, with a score of 1 being the least severe (mildly uncomfortable) and 10 being the most severe (impedes daily activity):

*Where are your headaches/migraines located?

On the left side

On the right side

On both sides

Other

* How would you describe the pain?:

Throbbing

Pulsating

Sharp

Tight

Other

*Do you experience any other symptoms with your headache?

Photophobia (sensitivity to light)

Phonophobia (sensitivity to sound)

Nausea

Vomiting

Other

When you do routine exercise (e.g. climbing stairs) during a headache, do you notice a change in your headache? (*Does it make it worse or better?)

How long do your headaches last if not treated with medication?

Are you taking any medications? (including herbal remedies)

We are particularly interested if you have taken anything for migraine, antidepressants, anti-anxiety medication, or any heart/blood pressure medications in the past year?
Are you taking any contraceptives or estrogens?

Do you ever experience any visual symptoms with your headache/migraine?
Describe what you see, as best you can:

Gradual onset?

Have you ever had any other sensations? (* numbness or tingling, speech difficulties, etc.)

Have you ever been diagnosed by a doctor as having visual aura?

Onset of aura (age):

How frequently do you experience aura?:

*Specify:

Never

Less than once a year

More than once a year but less than once a month (specify)

Once a month

More than once a month (specify)

Does the aura come before, during or after your headache?

Where in space are the visual symptoms located?

How long do your visual symptoms last?

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* When response options are given, the question was first asked in an open-ended fashion, noting the participant's response. If the participant did not understand the question or had difficulty answering, response options were read.

Appendix C - Consent Forms

A) Consent form used in the study presented in Chapter 2

CONSENT FORM

You are invited to participate in a study that will help us to clarify what stimulus values to use in an upcoming investigation of exposure to light in people with migraine headache.

The test we will carry out will be done over one session of approximately 15 minutes. During this session we will ask you to make some judgements about a light stimulus. Standardized instructions will be read to you, informing you about the judgements you will be asked to make. Following the testing, you will be asked to fill out a brief questionnaire.

If for any reason you wish to discontinue, you may do so at any time.

All personal information collected in this study will remain confidential. Your test results, if presented individually in published material, will be identified by your subject identification code only.

I acknowledge that my participation in this study is voluntary. I understand that the study will involve looking at visual displays intermittently for a period of approximately 15 minutes and that I may withdraw from the study at any time. If I have any questions about the study I can contact Dr. Frances Wilkinson at 398-6085 or 398-1399.

Participant: ....

(signature) (block letters)

....

Witness Date

B) Consent form for the study presented in Chapter 3

CONSENT FORM

You are invited to participate in a study investigating visual sensitivity in people with migraine headache. Many migraine sufferers experience visual disturbances associated with their headaches; the purpose of this project is investigate the basis of these disturbances by determining whether individuals with migraine are unusually sensitive to particular types of visual stimulation. While this information will not provide any immediate medical benefit in the treatment of migraine, it will contribute to our understanding of the neurological processes underlying migraine. It will also clarify how certain environmental features influence migraine.

The tests we will carry out will be done over one session of approximately 90 minutes. During this session we will record certain physiological measures (heart rate, respiratory rate and electrodermal activity) while you view and make decisions about visual stimuli. At the beginning of testing and after each viewing condition (approximately 5 minutes each) you will be asked to evaluate the stimulus and how you are feeling on a brief questionnaire. Various rest breaks will be given between viewing conditions, at which point you will be asked to remain seated and relax for several minutes.

Some individuals find the type of stimuli you will see unpleasant, and very rarely, find that they trigger headaches. The goal of this study is not to trigger headaches, but in the unlikely situation that this does occur, you will be given the option to continue testing or terminate the session immediately. If you have any reason to believe that you have epilepsy, you should not participate in this study.

If for any reason you wish to discontinue, you may do so at any time. At the end of the session, you will be reimbursed $25 for your time and inconvenience. If you withdraw from the study before testing is completed, this amount will be prorated.

After today's testing session, you will receive a short follow-up telephone call within 48 hours. At this point we will ask you a few questions about your testing experience, as well as answer any questions that you may have about the study.

All personal information collected in this study will remain confidential. Your test results, if presented individually in published material, will be identified by your subject identification code only.

I acknowledge that my participation in this study is voluntary. I understand that the study will involve looking at visual displays intermittently for a period of approximately 1.5 hours and that I may withdraw from the study at any time. If I have any questions about the study I can contact Dr. Frances Wilkinson at 398-6085 or 398-1399.

Participant: ....

(signature) (block letters)

....

Witness Date

C) Consent form for the study presented in Chapter 4

Informed Consent Form

The purpose of this study is to examine the relationship among daily activities, physiological functioning, and headaches. If you agree to participate, you will be asked to wear a small "fanny pack" containing a recording device that measures you heart rate for a maximum of three 24-hour periods. One of these will be during a period in which you are unlikely to experience a headache. The other(s) will be during a period in which you are likely to experience a headache, based on your own self-observations. If you experience a headache on the first day of recording during this period, we will do no further recording. However, if a headache is not experienced on that day, we will ask you to wear the monitor for one more day. The monitor uses disposable electrodes with hypoallergenic paste. The monitor is small and lightweight – about the size of a pager. It can be easily removed by the research assistant or yourself if need be. You can withdraw from the study or parts of it (e.g. wearing the monitor) at any time.

In addition to wearing the heart rate monitor, you will be asked to complete a brief diary every three hours while awake. It asks questions concerning your current activities, mood, and headache symptoms. All information we obtain from you in this study is completely confidential and will be coded using an arbitrarily determined subject number.

If you agree to participate in this study, please sign below.

Name:

Date:

Signature:

Witness:

If you have any questions, please do not hesitate to ask the research assistant. You may also contact the director of the study, Dr. Blaine Ditto of the Department of Psychology at 398-6097 either before or after participating in the study.

Appendix D

Diary Completed by Participants During Ambulatory Recording (Chapter 4)

This diary at to be completed at around 8am, 11am, 2pm, 5pm, and 8pm.

Time at which you completed this diary:_____

Where are you? (e.g. home, work)_____

What are you doing? (e.g. working on a computer, eating)

_____

How much mental effort is involved?

None Great effort

0 1 2 4 5

How much physical effort is involved?

None Great effort

0 1 2 4 5

How anticipated/expected was the activity when it began?

Expected Very unexpected

0 1 2 4 5

While doing this activity were you

	Not at all					Very much
Angry/irritated	0	1	2	3	4	5
Anxious/tense	0	1	2	3	4	5
Sad	0	1	2	3	4	5
Happy	0	1	2	3	4	5

Interested/involved	0	1	2	3	4	5
Feeling in control	0	1	2	3	4	5

Are you having ANY headache right now?

Yes ☐ No ☐

If yes, is it

☐ Sharp?

☐ Tight?

☐ Pulsating/Throbbing?

☐ Other _____.

Is it

☐ Both sides equally bad?

☐ Left side only?

☐ Right side only?

☐ Both, but worse on left?

☐ Both, but worse on right?

How intense is the pain? – Mark the line

Mild _____ Severe

Does routine physical activity make the pain

☐ Worse?

☐ Better?

☐ Or it makes no difference?

When did the pain start?_____.

If you get auras, did you have one? (Describe)

_____

_____

Have you taken any medication?

Yes ☐ No ☐

If yes, what? _____ **When?** _____.

At the moment, are you

- ☐ More sensitive to light than normal?
- ☐ More sensitive to sound/noise than normal?
- ☐ Nauseous?
- ☐ Have you vomited?
- ☐ Other _____.