UNDERSTANDING THE MIGRAINE AURA: COMBINING VISUAL DISCOMFORT WITH STRESS

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Chairperson
Dedication

This thesis is dedicated to Edward P. Chronicle, a professor who saw promise in me, an advisor who guided me, and a friend who is always with me. May you rest in peace.
Acknowledgements

It is often said that in life we meet a few people that will have such an impact on us that we are better people after having met them. Dr. Edward P. Chronicle was definitely one of those people. He took me in at a time when I thought I was on my way out. He guided me as a true advisor of life. This body of work would not have materialized had it not been for his keen intelligence and patient heart.

I thank my parents, who have always believed in me. My mom persistently reminded me that I have a degree to finish and always reminded me that she cared even though I often was irritated in the moment. My dad gave me his quiet encouragement.

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Abstract

Migraine is a headache disorder of unknown origin that is characterized by severe to very severe head pain, localization on one side of the head, sensitivity to light and/or sound, and gastrointestinal disturbance. In previous studies, stripe-induced visual discomfort has been shown to be aversive to migraine patients. Stress has been strongly implicated as a migraine trigger. This study is an investigation of the effect that a cognitive stressor may have on the migraineous brain when presented in combination with grating patterns known to induce visual discomfort. Experimentation consisted of the presentation of two grating patterns, 3.0 CPD (cycles per degree) and 0.5 CPD, to subjects in the presence and absence of a cognitive stressor. The subjects within this study included a group diagnosed as having migraine with aura and a group of non-headache control subjects. The study used a novel computerized method for presenting the patterns which incorporated two new measures of visual discomfort: escape and viewing duration. Subjects with migraine aura found the 3.0 CPD pattern to be significantly more aversive to view than the 0.5 CPD pattern and reported significantly more illusions than control subjects. The cognitive stressor, however, did not cause a significant increase or decrease in visual discomfort. The results of this experiment do corroborate the findings of previous studies examining visual discomfort in the migraine population, using a more standardized presentation procedure and more objective measures of visual discomfort. The absence of the stress effect has implications for future work on migraine triggers.
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<tr>
<td>C</td>
<td>Control</td>
</tr>
<tr>
<td>CBF</td>
<td>Cerebral Blood Flow</td>
</tr>
<tr>
<td>CGRP</td>
<td>Calciton Gene-Related Peptide</td>
</tr>
<tr>
<td>CPD</td>
<td>Cycles Per Degree</td>
</tr>
<tr>
<td>CSD</td>
<td>Cortical Spreading Depression</td>
</tr>
<tr>
<td>IHS</td>
<td>International Headache Society</td>
</tr>
<tr>
<td>ICHD-2</td>
<td>International Classification of Headache Disorders, Second Edition</td>
</tr>
<tr>
<td>NV</td>
<td>Cranial Nerve V</td>
</tr>
<tr>
<td>MA</td>
<td>Migraine with Aura</td>
</tr>
<tr>
<td>TMS</td>
<td>Transcranial Magnetic Stimulation</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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Introduction

Ancient Egyptian records, dating back to 1500 B.C., are believed to be the first to describe the debilitating effects of migraine as well as the crude methods of treating the disorder (Martin-Araguz, Bustamante-Martinez, Emam-Mansour, & Moreno-Martinez, 2002; Karenberg & Leitz, 2001). Migraine aura has been described in medical literature for thousands of years (Sacks, 1992). Hippocrates first described the aura symptoms of migraine in 400 B.C. as a shining light that usually occurs in the right eye and is then followed by violent pain (Edmeads, 1991; Rapoport & Edmeads, 2000). Today, it is estimated that migraine affects nearly 12% of the world’s adult population. In a recent epidemiological study from the United States, it was estimated that approximately 6% of men and 18% of women experience migraine headaches (Lipton, Bigal, Diamond, Freitag, Reed, & Stewart, 2007). Migraine has also been ranked among the top 20 most debilitating diseases, ahead of diseases such as asthma and diabetes, by the World Health Organization (Deiner, Stepper, & Tepper, 2006; Menken, Munsat, & Toole, 2000). However, despite this high incidence, the fundamental cause of migraine is unknown and there has been relatively little research on migraine.

Clinical Features

Migraine is classified as a primary headache disorder and can be divided into two major sub-types, migraine without aura (formerly classified as common migraine) and migraine with aura (formerly classified as classical migraine). Both types of migraine are characterized by special features and associated symptoms. Migraine without aura is described by a recurrent headache that lasts between 4 to 72 hours.
According to the International Headache Society's (IHS) International Classification of Headache Disorders 2nd Edition (ICHD-2), the typical migraine headache is unilateral, of moderate to severe intensity, and is pulsating in nature. Migraine without aura is often associated with nausea and/or photophobia (light sensitivity) and phonophobia (sound sensitivity). This type of migraine may be aggravated by routine physical activity. Although most patients with migraine experience the attack exclusively without aura, approximately 30% of patients report one or more characteristic neurological symptoms that usually occur in advance of the head pain (Swanson, 2004). The neurological symptoms are collectively termed the migraine aura and are comprised of positive and negative symptoms. Positive symptoms can be thought of as "true hallucinations", or something that is perceived but is not present in the external world, whereas, negative symptoms refer to a loss in sensation (Wilkinson, 2004). The aura can be manifested in different ways, specifically through sensory and/or speech symptoms. Positive symptoms typically appear first (e.g. flickering lights, spots, zig-zag lines, prickling paresthesias) and are then followed by the negative symptoms, such as decreased, or loss of, vision (scotoma) or loss of sensation (Olesen, 1993; Cutrer & Huerter, 2007). According to Russell and Olsen (1996), the visual aura is the most common type of aura experienced, with nearly 99% of aura patients reporting visual aura. Patients with migraine aura may sometimes experience symptoms in other parts of the body such as the extremities. Sensory aura, symptoms that involve numbness or tingling in the extremities, have been reported as occurring in 30% to 54 % patients with migraine aura (Manzoni, Farina, Lanfranchi, & Solari, 1985; Eriksen, Thomsen, & Russell, 2004; Wilkinson, 2004). Speech disturbance, such as dysphasia, is the least
common form of migraine aura, occurring in 9% to 31% of cases (Eriksen et al., 2004). It is typical for individuals with aura to also experience attacks without aura (Cutrer & Huerter, 2007).

The defining feature of migraine with aura is the focal neurological event that usually precedes the headache or sometimes accompanies it. The neurological symptoms typically develop over 5-20 minutes and last for less than 60 minutes. Visual auras classically manifest themselves as spreading scintillations and transient blind spots in the left or right visual field (Lashley, 1941). Visual aura is considered to be unique to migraine and is characterized by a paracentral scotoma that gradually expands into a C-shape with the convex edge of the scotoma containing zigzag patterns (Richards, 1971). These symptoms are collectively known as the fortification pattern. It is generally restricted to either the right or left visual field and can vary in size (Lashley, 1941). The fortification pattern typically moves from the interior toward the visual periphery and usually lasts for about 20 to 25 minutes (Richards, 1971). The disruption and partial loss in vision is not permanent and vision continues as normal once the fortification pattern disappears, however, in rare cases, a second consecutive fortification may occur (Poppel, 1973). Zigzag patterns comprised of lines and shapes are often described as being located on the edge of the scotoma (Lashley, 1941; Richards, 1971).

*Theories of Migraine*

Although the cause of migraine is not fully understood, current research suggests that changes in neuronal events are most likely responsible for this neurovascular disorder (Buzzi & Moskowitz, 2005; Sanchez-del-Rio & Reuter, 2004). The literature
suggests three major theories of migraine: the vascular theory, the neurogenic theory and the neurological theory. Both the vascular and neurogenic theory account for the pain associated with the migraine attack, whereas the neurological theory focuses on the prodromal (onset) aspects of the migraine with aura attack.

**The Vascular Theory.** The vascular theory originated from work done by Harold Wolff, who, during the 1930s found that patients suffering from migraine had dilated extracranial (temporal) arteries (Graham and Wolff, 1938). According to the vascular theory, increased vascular pulsation in migraineurs is thought to lead to the activation of stretch receptors, thereby activating perivascular nerves that cause the pain associated with migraine (De Vries, Willems, Heiligers, Villalon, & Saxena, 1999).

**The Neurogenic Theory.** This theory asserts that migraine pain stems from the inflammation and dilation of the meninges, the membrane (dura) that surrounds the brain (Arulmozhi, Veeranjaneyulu, & Bodhankar, 2005; Bussone, 2004). Inflammation of the dura membrane is believed to be caused by neuropeptides that are released from primary sensory nerve terminals innervating the dural vessels (Bussone, 2004). The anatomy of the trigeminovascular system provides compelling evidence that trigeminal innervation is a key factor in migraine pathophysiology. The trigeminal nerve (NV) contains both sensory and motor neurons and consists of three branches, the ophthalmic, maxillary and mandibular branches (Martini, Timmons, & Tallitsch, 2006). The ophthalmic division of the trigeminal nerve is the origin of unmyelinated nerve fibers of the trigeminovascular system. These nerve fibers contain various neuropeptides such as calciton gene-related peptide (CGRP), neurokinin A and substance P. Recent work with CGRP has demonstrated that levels of CGRP are increased in individuals with migraine.
during a migraine attack. This suggests that CGRP may be involved in the vasodilation and increased cerebral blood flow (CBF) observed during a migraine attack (Goadsby, Edvinsson, & Ekman, 1990). The pain pathway for the trigeminovascular system begins in the caudal brain stem and high cervical spinal cord and is then relayed to the thalamus via the quintothalamic tract. The thalamus is known to be a major relay station of both sensory and motor tracts, and is known to process vascular pain. The cortical aspect in this process is currently being investigated (Martini et al., 2006). The serotonergic system is one of four modulatory systems that originate in the raphe nuclei along the brain stem midline and have nuclei that project to the lower nuclei of the spinal cord and the upper nuclei of the brain (Silverthorn, 2007). This system is believed to have a major impact on the events that occur during a migraine. Specifically, serotonin plays a key role in the neurotransmission of the trigeminovascular system (Mulleners, Chronicle, Palmer, Koehler, & Vredeveld, 2001).

The Neurological Theory. The neurological theory suggests that abnormal neural activation (i.e. abnormal neuronal firing and neurotransmitter release due to cortical hyperexcitability) is responsible for certain prodromal aspects of the migraine attack, which the vascular theory and neurogenic theory have difficulty explaining. Pearce (1984) suggests that the neurological basis of migraine is supported by the fact that migraine attacks develop slowly and can be enhanced by factors such as stress and hunger which is a notable characteristic in other neuronal disorders. Cortical spreading depression (CSD) is thought to be the cause of the sensory and motor symptoms associated with the migraine aura (Lauritzen, 1994; Parsons, 1998).
Aristedes Leao (1944), a Brazilian neurophysiologist, first discovered the CSD phenomenon in 1943 while investigating cortical epilepsy in animals. This early research led to Milner and Lashley's hypothesis that CSD is the underlying pathophysiological phenomenon of the migraine aura (Milner, 1958; Lashley, 1941). CSD is the process of the expanding depolarization of cortical neurons and glial cells and can be described as a wave-like propagation of depression of electrical activity across the cortex with a speed of 2-8 μm per minute (Arulmozhi et al., 2005). Essentially, CSD can be described simply as a burst of neuronal activity that is then followed by the prolonged depression of neuronal activity that spreads along the cortical surface. Arulmozhi et al. (2005) demonstrated that CSD is simultaneously accompanied by an increase in regional CBF that is short-lasting followed by a long-lasting CBF hypoperfusion (decreased blood flow). CBF typically begins posteriorly and then spreads anteriorly. Recent functional magnetic resonance imaging (fMRI) studies strongly support the occurrence of CSD during visual migraine aura (Hadjikhani et al., 2001).

Functional hyperexcitability of the visual cortex has been implicated as a major factor in why the migrainous brain is more susceptible to CSD. Previous research has produced compelling convergent evidence that the visual cortex of the human brain is hyperexcitable to stimulation in those with migraine (Chronicle, Wilkins, & Coleston, 1995; Chronicle & Mulleners, 1996; Palmer & Chronicle, 1998; Palmer, Chronicle, Rolan, & Mulleners, 2000; Mulleners, et al., 2001; Mulleners, Chronicle, Palmer, Koehler & Vredeveld, 2001). Migraine patients have been shown to be more susceptible to visual discomfort when viewing square-wave grating patterns (Wilkins, Nimmo-
Smith, Tait, McManus, Della Sala, Trilley, Arnold, Barrie, & Scott, 1984; Marcus & Soso, 1989; Mulleners et al., 2001). A later study by Chronicle, Wilkins, & Coleston (1995) placed more focus on controlling for the possibility of the over-emphasizing of symptoms by migraineurs. They utilized a target-detection method to compare migraineurs with controls. The target-detection method focused on the detection of the presence or absence of a target stimulus, presented on a background of stripes (similar to those that cause illusions and discomfort). Results from the Chronicle et al. (1995) study demonstrated increased target threshold detection by migraine with aura patients as compared to migraine without aura patients.

Work with transcranial magnetic stimulation (TMS) provides further supporting evidence for hyperexcitability in migraine patients. TMS utilizes powerful magnetic fields to induce electrical fields in the brain by electromagnetic induction in a non-invasive manner. A number of researchers have shown that the threshold for elicitation of visual phosphenes by single-pulse TMS over the posterior portion of the head (i.e. occipital lobe of the brain) is significantly lower in migraine (Aurora, 1998; Mulleners et al., 2001). Furthermore, Palmer et al. (2000) used metachronist masking, a psychophysical technique in which a target is superimposed upon a patterned background thereby causing it to become difficult to see. Palmer demonstrated that migraine patients showed significantly less masking than controls. It should be noted that a few studies suggest the opposite, hypoxcitability in the migraine patient, although the consensus in the literature seems to support the notion that the visual cortex is hyperexcitable in migraine (Afra, Cecchini, De Pasqua, Albert, & Schoenen, 1998;
Both the vascular and neurogenic theories of migraine focus on the origin of the pain associated with the migraine attack, whereas the neurological theory accounts for the onset symptoms (i.e. the migraine aura). However, there has been no theory of migraine that explains both the occurrence of the migraine aura and the pain that follows. Recent progress in understanding the role of cortical spreading depression in migraine (Parsons, 1998) permits the emergence of a unifying hypothesis (E.P. Chronicle, personal communication, 2006). The brain is hyperexcitable in migraine, which is probably genetically predetermined. In response to psychological or physiological stress, excessive sensory stimulation, or a combination of these, inhibitory processes in the cortex fail to maintain an equilibrium, and CSD may result. The widespread physiological disruption that follows can then potentially cause the pain and autonomic features of the attack to occur as an aftereffect.

Visual Correlates of Migraine

One question that has been relatively under-researched relates to the onset of each migraine attack. It has been well documented in the literature that the visual system is implicated in migraine (Chronicle & Mulleners, 1996). The visual cortex has been shown to be hyperexcitable in migraineurs by a wide array of electrophysiological, psychophysical, and TMS studies (Chronicle et al., 1995; Chronicle & Mulleners, 1996; Palmer & Chronicle, 1998; Palmer et al., 2000; Mulleners et al., 2001; Mulleners et al., 2001).
Grating Patterns as Visual Stimuli. Since Lashley (1941) first reported his findings, there have been numerous psychophysiological studies that have focused on the primary visual cortex in migraine, specifically, examining visual discomfort in migraine patients using a variety of psychophysiological methods (Wilkins et al., 1984; Marcus & Soso, 1989; Khalil, 1991; Coleston & Kennard, 1995). Many of these studies involved the use of high-contrast square-wave grating patterns varying in spatial frequency, that is, the number of pairs of bars within a given distance on the retina (Wilkins et al., 1984; Marcus & Soso, 1989; Khalil, 1991). These investigators examined the unpleasantness of striped patterns, the spatial properties of these patterns, the specificity of these properties and the extent to which they produced visual discomfort. Wilkins et al. (1984) noted that individuals with frequent headaches were more likely to experience discomfort when viewing the striped grating patterns compared to individuals without headaches. They found that patients with unilateral headaches were more likely to report illusions in a 3-4 cycles per degree (CPD) grating pattern. Their findings suggested that certain grating patterns can induce significant discomfort in individuals with headaches. Marcus and Soso (1989) published a similar study in which they examined visual discomfort among three groups (migraine, non-migraine, and non-headache subjects) by recording and analyzing behavioral responses such as grimacing with eye narrowing, turning away, or refusal to look at the stimuli. Subjects with migraine found certain grating patterns to be significantly more aversive to view compared to the non-migraine headache groups and the non-headache group. The results of Khalil (1991) added to the findings of Wilkins et al. (1984) and Marcus and Soso (1989) by showing that headache patients overall saw more illusions than
controls when shown grating patterns of various sizes and experienced more discomfort in response to these patterns. Furthermore, illusions and discomfort were more frequent in migraine aura patients than those without the aura. In a later study, Coleston and Kennard (1995) required that subjects not only rate the presence or absence of an illusion, but also the intensity of the illusion seen in a grating pattern. They also varied the fundamental spatial frequency of the stimulus grating and observed the effects on the intensity of the illusion. Overall, migraine patients experienced more intense illusions than did controls. Furthermore, those with migraine aura reported the most intense illusions among the three groups (migraine with aura, migraine without aura, and non-headache controls).

There is ample evidence supporting the notion that visual discomfort can be induced by the presentation of grating patterns. Furthermore, the visual discomfort as measured by ratings or behavioral reactions appears to be greater in migraine than non-migraine subjects. These results also indicate that migraine subjects experience more illusions when viewing these patterns. However, simple viewing of a striped pattern, while uncomfortable and occasionally aversive for migraine subjects, does not automatically induce an aura (Wilkins et al., 1984).

**Migraine Triggers**

The pathogenesis of migraine has been reasonably well understood for many years (see above for a review of migraine theories), however, it is still unclear how migraine attacks are triggered. A variety of factors have been implicated as migraine trigger factors, including menstruation, sleep disturbances, fatigue, alcohol consumption
and nutrition. Environmental and psychological factors have also been mentioned as trigger factors to migraine (Wober, Holzhammer, Zeithofer, Wessel, & Wober-Bingol, 2006). Sensory stimuli, such as flickering light and glare, are particularly related to migraine with aura and less often to migraine without aura (Scharff, Turk, & Marcus 1995; Spierings, Ranke, & Honkoop 2001; Chabriat, Danchot, Joire, & Henry, 1999; Russel, Rasmussen, Fenger, & Olsen, 1996; Ulrich, Olesen, Gervil, & Russell, 2000). Although visual stimuli sometimes trigger migraine, it is a more common clinical observation that combinations of events (e.g. "I had a really bad day in the office, then I drove home with the sun low on the horizon") are potent triggers.

Stress and Migraine

Psychological factors, such as stress, have long been thought to be facilitating factors in migraine attacks (Wang, Timsit-Berthier, & Schoenen, 1996; Kropp, Siniatchkin, & Gerber, 2002; Fanciullacci, Alessandri, & Fanciullacci, 1998). Specifically, mental stressors have been considered to be a major precipitant of migraine (Chabriat et al., 1999) and have been found to do so in controlled studies (Holm, Lokken, & Myers, 1997; De Benedittis & Lorenzetti, 1992). Although stress is considered a common trigger of migraine, there are no experimental data to directly relate the possible interaction between stress and visual discomfort in the precipitation of migraine attacks (Schoonman, Evers, Ballieux, de Geus, de Kloet, Terwindt, van Dijk, & Ferrari, 2006). The experiment reported here examines how two factors, psychological stress and visual stimulation, may interact in migraine subjects.
According to Hassinger, Semenchuk and O'Brien (1999), there have been a number of studies that have examined the vascular responses of migraineurs to a variety of laboratory stressors. The results of these studies, however, have been inconclusive and inconsistent. Arena, Blanchard, Andrasik, Appelbaum, & Myers (1985), Drummond (1982), Drummond (1985) and Rojahn & Gerhards (1986) each found support for vasodilation in response to stress while Ahles, Martin, Gaulier, Cassens, Andres, & Shariff (1988), Morley (1985), and Passchier, Goudswaard, & Orlebeke (1993) reported vasoconstriction in response to stress. Numerous other investigators have reported no difference in vascular response in migraine and control subjects as a function of stress. Some investigators have focused on the cardiovascular system based on the hypothesis that there is a heightened level of autonomic arousal in response to stress. However, like the research examining vascular response, results have been inconsistent. Some researchers have reported greater heart-rate reactivity to stress (Cohen, Williamson, Monguillot, Hutchinson, Gottlieb, & Waters, 1983; Gannon, Haynes, Safranek, & Hamilton, 1981) while the majority have reported no difference between migraine and control subjects. Although these studies are inconsistent, Hassinger et al. (1999) suggests that the cause for the inconsistency is due to the fact that these studies essentially measure just two responses, heart rate (HR) and blood pressure (BP). Hassinger et al. (1999) looked beyond just HR and BP and instead looked at individual difference in hemodynamic response to stressors since subjects may exhibit reliable differences in hemodynamic response even when both their HR and BP are similar. The measurement of multiple cardiovascular components was accomplished by using impedance cardiography. The results of the Hassinger et al. (1999) study supported the
hypothesis that individuals with migraine have physiologically different responses to stress than control subjects.

Psychophysiological studies examining stress in migraineous individuals typically utilize a physiological, cognitive or mental stressor (Hassinger, et al., 1999). According to de Kloet, Joels, & Holsboer (2005) mental stressors are psychological events that threaten the homeostasis of a living organism. It has been suggested that migraineurs experience heightened reactivity when exposed to stressful stimuli (Passchier, 1994). Physiological stress can involve auditory stimulation, acute pain (i.e. the cold pressure test or the radiant heat test), or visual stimulation (i.e. stressful imagery). Typical cognitive stressors include intelligence tests, time estimation tasks and mathematical stressors. Mathematical stressors often used include mental arithmetic problems where subjects are given a series of mathematical problems and are asked to verbally solve them out loud or serial subtraction where they are asked to subtract continuously from a starting number verbally out loud.

In a serial subtraction problem reported by Hassinger et al. (1999) migraine subjects had a different physiological response from control subjects. The task was found to be an effective stressor, producing significant changes in cardiovascular reactivity as measured by systolic blood pressure, diastolic blood pressure, heart rate, stroke volume, total peripheral resistance, and cardiac output. Migraineurs showed increased heart rate reactivity to stress, and, furthermore, migraineurs have differences in cardiovascular reactivity in response to cognitive stressors. Thus, it is plausible that the pairing of heightened reactivity to stressful stimuli and cortical hyperexcitability may serve as a trigger to a migraine attack.
Although there has been considerable research done to examine the physiological role of cardiovascular reactivity to stress in migraineurs, there has been a no research to explore the interactions between stress and striped grating patterns known to induce significant visual discomfort in migraineurs. It seems likely that psychological factors interact to generate a migraine attack; for example, it is possible that visual stimuli (e.g. striped patterns, flickering light, etc.) may only trigger a migraine attack if the subject is already experiencing psychological stress. Debney (1984) supports this notion with a catastrophe model of the initiation of an attack, in which various environmental factors may sum to exceed the critical threshold of brain stimulation for the onset of an attack.

By investigating the effect of combining grating patterns known to induce visual discomfort with a potential stressor, it may be possible to gain some insight into how a migraine with aura attack might be initiated. Here, grating patterns of varying cycles per degree (3.0 CPD vs. 0.5 CPD) were paired with a cognitive stressor (mathematical task) designed to induce a stressful state.

The aim of the experiment reported here was to demonstrate that combining grating patterns known to induce visual discomfort with a cognitive stressor will increase the aversiveness of viewing the grating pattern. A secondary aim of this work is to increase the methodological precision of this kind of study by: 1) using computer-generated stimuli presented on a computer monitor instead of the usual paper format; 2) providing subjects with an escape response; and 3) measuring the actual viewing durations in addition to pleasantness ratings.
Method

Design

The independent variables of this experiment are the diagnosis of the subject (migraine with aura [MA] or control [C]), the presence or absence of a psychological stressor and the spatial frequency of the grating patterns, 3.0 CPD or 0.5 CPD. The dependent measure is the level of discomfort experienced by the subjects to the grating pattern presented. Each subject was presented with each grating pattern an equal number of times in both the stress and no stress conditions. The order of the stress and no stress conditions was counterbalanced across subjects.

Subjects

Subjects were recruited through advertisements posted on the University of Hawaii at Manoa campus (Appendix A and Appendix B). All potential subjects were sent a packet containing a cover letter (Appendix C), study information sheet (Appendix D), expression of interest form (Appendix E) and migraine questionnaire that asked about headache symptoms (Appendix F). The questionnaire had been used previously in studies involving migraine (Chronicle, 1993) and had been formulated in accordance with the diagnostic criteria for migraine set out by the Headache Classification Committee of the International Headache Society (ICHD-2). It has been suggested, however, that diagnosis based on questionnaire responses may not correspond well with those made by clinicians (Rasmussen et al, 1991). Therefore, the questionnaire was used as a screening tool for those who probably had migraine. After review of the migraine questionnaire, potential subjects not fulfilling inclusion criteria were mailed an exclusion letter (Appendix G) indicating why they were not suitable for participation.
Before participating in the experiment, all subjects were interviewed by the experimenter to assess headache and aura symptoms and to verify that their symptoms fulfilled the diagnostic criteria. During the interview, subjects were further screened for exclusionary criteria, such as history of neurological pathology or neurosurgery. Individuals with a history of epilepsy were excluded as were those on drugs such as antidepressants, tranquilizers, lithium, anti-epileptic drugs, anti-parkinsonian drugs, muscle relaxants, systemic anticholinergics, migraine prophylactics, Ca-entry blockers, anti-emetics, beta-histamine, cinnarizine, piracetam and hormone replacement therapy. All subjects were tested for visual acuity using the Snellen Eye Chart #2867-1264 (Graham-Field, Atlanta, Georgia) and had normal visual acuity after correction. All subjects fulfilling participation criteria completed a written informed consent form (Appendix H).

37 subjects took part in the experiment. In one group, there were 20 subjects (7 men and 13 women) diagnosed with migraine with aura (MA). The age range of subjects in the MA group was 18-41 years with a mean of 24. All migraineurs took medication for their migraines only during an attack, because potential subjects on migraine prophylactics had been excluded from the study. 17 control subjects (5 men and 12 women) completed the same questionnaire as the MA group and none gave responses to the questions that were indicative of any headache disorder, and none had any history indicative of migraine at the interview. The age range of subjects in the control group was 18 – 34 years with a mean of 24. Controls were approximately age and sex matched to the MA subjects.
Apparatus and Stimuli

The striped grating patterns (see Figures 1, 3, 5, and 7) were generated in Adobe Photoshop CS (Adobe Systems Incorporated, San Jose, California). Calculations for how these images were derived can be found in Figures 2, 4, 6, and 8. The striped grating patterns were presented to subjects via Super Lab Pro (Cedrus Corporation, San Pedro, California), an experiment management software application designed for the presentation of experimental stimuli. Stimuli were presented on a 19” digital flat panel computer monitor (Dell Computer Corporation, Round Rock, Texas) with a DPI of 86, a resolution of 1280x1024, a horizontal width of 14.8 inches and a vertical width of 11.85 inches. A Dell Pentium 4 computer (Dell Computer Corporation, Round Rock, Texas) running Microsoft Windows XP Service Pack 2 was used to run the program.

Striped grating patterns were utilized to measure the degree of visual discomfort of the subjects. The grating patterns seen in Figures 1, 3, 5 and 7 differ in the number of cycles (pairs of white and black bars of equal widths) of the grating per degree of visual angle, thus they are each said to have a different fundamental spatial frequency. The duty cycle for these gratings was set at 50%, meaning brightness for these grating patterns was at its maximum for 50% of each cycle (i.e. for each pair of black and white bars). The brightness of these gratings, measured along a line perpendicular to the bars of the grating, varied according to a square waveform, therefore, these grating are said to have a square waveform. Figure 1 shows the 3.0 CPD grating pattern. This pattern has a fundamental spatial frequency of 3.0 CPD, 50% duty cycle and a square wave luminance profile. This type of grating had previously been demonstrated to induce discomfort in migraineurs (Wilkins et al., 1984; Marcus & Soso, 1989). Figure 3 shows
the 0.5 CPD grating pattern. This pattern has a fundamental special frequency of 0.5 CPD, 50% duty cycle and a square wave luminance profile. This low spatial frequency grating pattern had previously been shown to induce little or no pattern sensitivity in either migraineurs or control subjects (Wilkins et al., 1994). The grating patterns seen in Figures 1 and 3 are both subtended 5°. The diameter of each grating pattern is determined by the distance from which it is displayed to the subject and the angle from which it is subtended. Therefore, it is possible to increase the diameter of the grating pattern by increasing the subtended angle. Figures 5 and 7 show grating patterns that are subtended 10°. All grating patterns were viewed from a fixed distance of 50 cm.

Subjects were positioned on a chin rest in order to maintain a fixed position of 50 cm from the monitor that presented the stimuli.

**Procedures**

Testing took place in a testing room at the Psychology Department at the University of Hawaii at Manoa interictally (no headache for at least 3 days prior to the appointment). Subjects were tested one at a time. Subjects were seated in front of the computer monitor with their chin placed on a chin rest to maintain the viewing distance from the computer monitor. A testing session for each subject lasted approximately 20 minutes.

Testing was conducted in two blocks, the order of which was counterbalanced across subjects. In one block, subjects were given either a stressful mental arithmetic task (A) or a non-stressful mental arithmetic task (B) that lasted three minutes. Prior to the administration of the mental arithmetic task, subjects were asked to complete a 7-point rating scale (see Appendix I), in which they were asked to rate their current level
of stress. Subjects then were instructed to complete either math task A or B (math task A consisted of serially subtracting backwards by 17 from a beginning number of 7000 and math task B consisted of serially subtracting backwards by 1 from a beginning number of 100). Subjects were asked to work as quickly and accurately as possible. If subjects were silent for a period of 30 seconds, they were prompted by the experimenter to continue. If subjects lost their place they were asked to begin again at a different number (a number of 100 less than their last starting point if doing math task A or a number of 10 less than their last starting point if doing math task B). Upon completion of the task, subjects were again asked to rate their level of stress using the same 7-point rating scale. Subjects were then shown 10 grating patterns that randomly alternated between fundamental spatial frequencies of 3.0 CPD (Figure 1) and 0.5 CPD (Figure 3). Each grating was randomly presented five times (for a total of ten presentations) and each time was on the screen for a maximum of 15 seconds. Subjects were asked to press a key (designated as the U key) on the computer keyboard as soon as the grating pattern being shown became uncomfortable to view. If subjects pressed the U key, they would then escape from viewing the current pattern and move on to the next pattern. If they did not press the U key then the pattern would stay on the screen for a maximum of 15 seconds, after which, the next pattern would appear. The duration spent looking at each of the grating patterns and the number of escapes (presses of the U key) were recorded. At the end of the first block, subjects were shown two more gratings (shown in Figure 5 and Figure 7) separately for 10 seconds, during an interblock period. They were then asked to complete a checklist after viewing each of the grating patterns (Appendix J) to indicate the visual illusions experienced while viewing the gratings. The checklist
included categories relating to the color (red, green, yellow, blue) and shape (blurring, shimmering, flickering, bending of the lines, shadowy shapes) of the illusion. Subjects were also allowed to indicate illusions that were not on the checklist. Subjects were then asked to rate the grating patterns on a scale of 1 to 5 (1 - very unpleasant, 3 - moderately pleasant, 5 - very pleasant). Following the completion of the illusion checklist, the second test block began and subjects were again asked to rate their current level of stress using the same 7-point rating scale used prior to the presentation of the first mathematical task. Subjects were then presented with the second mathematical task (math task B if they began block one by doing math task A or math task A if they began block one by doing math task B). The math task again lasted for a duration of three minutes. Subjects presented with math task B were instructed to serially subtract by 1 from a beginning number of 100 and subjects presented with math task A were instructed to serially subtract by 17 from a beginning number of 7000. Subjects were asked to work as quickly and accurately as possible. If subjects were silent for a period of 30 seconds, they were prompted by the experimenter to continue. If subjects lost their place they were asked to begin again at a different number (a number of 10 less than their last starting point if doing math task B or a number of 100 less than their last starting point if doing math task A). Subjects were informed that they were being evaluated on the speed and accuracy of their responses. Upon completion of the task, subjects were asked to rate their level of stress using the same 7-point rating scale. Immediately after the presentation of the mental arithmetic problem, subjects were again presented with the visual discomfort task, exactly as in the first block, in which they
were again presented with 10 grating patterns that alternated between 3.0 CPD (Figure 1) and 0.5 CPD (Figure 3).

Once subjects completed testing they were informed that the mental arithmetic tasks were not an intelligence test and that responses to this task were not recorded but simply presented to induce minor psychological stress. They were also informed once more that they should contact the experimenter(s) should they experience any adverse reactions within 12 hours of testing. Following this, the experimenter then answered subjects’ questions and reimbursed them $24 for their time. Please refer to Figure 9 for a procedural flow chart for this experiment.

Results

Stress ratings obtained from math task A (counting backwards from 7000 by 17) indicate that the task was effective in inducing a stressful state in both migraineurs and controls. Univariate analysis of variance was performed on the post math ratings in both block 1 and block 2. The hard math task (A) was found to be significantly more difficult than the easy math task (B). There was a significant effect of stress in block 1 (F[1, 33] = 13.902; p = .001) and block 2 (F[1,33] = 8.372; p = .007).

Shown in Figure 10 are the mean total escapes for the MA and C subgroups in the two stress sequences (stress to no stress and no stress to stress). The performance in the two sequences was very much the same and therefore the subgroups were combined in the statistical analysis. The effect of the stressor on the number of escapes from viewing the grating patterns are shown in Figure 11 for the migraine and control groups. The mean number of escapes is plotted for each pattern for the stress condition (upper
panel) and no stress condition (lower panel). There was a higher level of escapes in the migraine group than in the control group for both the 3.0 CPD and 0.5 CPD patterns in both stress conditions. Mean values for the number of escapes when looking at the grating pattern were analyzed with a mixed-effects analysis of variance with diagnosis as the between-groups factor and with both grating pattern (0.5 CPD, 3.0 CPD) and stress (stress or no stress) as the within-groups factors. There was a significant main effect of diagnosis ($F[1, 35] = 10.54; p = .0026$). There was also a significant main effect of grating pattern ($F[1, 35] = 11.66; p = .0016$). No interaction was found between grating pattern and diagnosis ($F[1, 35] = 1.17; p = .2870$) or stress and diagnosis ($F[1, 35] < 1.00$). A three-way analysis of variance found no significant interaction among stress, grating pattern and diagnosis ($F[1, 35] < 1.00$).

The effects of the stressor on duration spent looking at the grating patterns in block 1 and block 2 are shown in Figure 12 for the migraine and control groups. The mean duration spent looking at each grating pattern is plotted by trial. Durations are generally lower in the migraine group compared to the control group. Mean values for the duration spent looking at the grating patterns were analyzed with a mixed-effects analysis of variance with diagnosis as the between-groups factor and both grating pattern (0.5 CPD, 3.0 CPD) and stress (stress and no stress) as the within-groups factors. There was a significant main effect of diagnosis ($F[1, 35] = 8.83; p = .0053$). There was a significant main effect of grating pattern ($F[1, 35] = 14.49; p = .0005$). No interaction was found between grating pattern and diagnosis ($F[1, 35] = 2.29; p = .01396$). There was found to be no significant stress effect ($F[1, 35] = 1.03; p = .3173$). A three-way analysis of variance found no significance between stress, grating pattern and diagnosis.
Since there was no effect of stress, the trial by trial curves were pooled and are shown Figure 13. Figure 14 further shows the overall mean duration for both the MA and C groups in the no stress and stress conditions.

Results of the pleasantness ratings (Appendix J) taken during the interblock are shown in Figure 15 for the MA and C groups. Mean values were analyzed with a repeated measures analysis of variance. There was no significant main effect of diagnosis (F[1,33] = 3.289; p = .079) or stress (F[1,33] = .026; p = .873). There was no interaction between diagnosis and stress (F[1, 33] < 1.00). There was a significant main effect of grating (F[1,33] = 14.527; p = .001). Although the migraine group appeared to rate the two patterns as somewhat less pleasant than the control group, no interaction was found between grating pattern and diagnosis (F[1, 33] = 1.332; p = .257). Furthermore, there was no interaction between grating pattern and stress (F[1, 33] = 3.24; p = .081). A three-way analysis of variance found no significant interaction among grating pattern, stress and diagnosis (F[1, 33] < 1.00).

During the interblock, new 10° subtended patterns were presented to all subjects. Each subject responded to the illusion checklist immediately after viewing the new patterns. The responses to the illusion checklist (Appendix J) are shown in Figure 16 plotted as percent of subjects in each group who reported seeing illusions for both the new 0.5 CPD and 3.0 CPD patterns. There was no difference between the migraine group and the control group. Furthermore, there was no effect of stress on percent seeing illusions. A Chochran-Mantel-Haenszel test, an extension of a chi-squared test, was performed to detect a relationship among grating pattern, stress and diagnosis in seeing illusions during the presentation of the gratings during the interblock. Across
different diagnoses, grating pattern and stress were not related in terms of the frequency in which illusions were experienced ($x^2 = 1.7418$, $p = 0.1869$).

The mean number of illusion descriptors used by subjects in the two groups are shown in Figure 17 for the new $10^\circ$ subtended 3.0 CPD and 0.5 CPD grating patterns in the interblock. There was a noticeable increase in the number of descriptors used by migraineurs when viewing the 3.0 CPD grating. The number of descriptors used by control subjects did not change between the 3.0 CPD and 0.5 CPD grating patterns. Mean values for the number of illusion descriptors mentioned by the MA and C group were analyzed with a mixed-effects analysis of variance. There was a main effect of diagnosis ($F[1,33] = 7.649$, $p = .009$. There was no main effect of stress ($F(1, 33) < 1.00$). There was no interaction between diagnosis and stress ($F(1, 33) < 1.00$). There was a significant main effect of grating pattern ($F[1,33] = 26.229; p < .001$) and an interaction between grating pattern and diagnosis ($F[1,33] = 9.026; p = .005$). No interaction was found between grating pattern and stress ($F(1, 33) = 2.890; p = .099$). A three-way analysis of variance found no significant interaction among grating pattern, stress and diagnosis. In none of these measures did a stress effect appear. The results are interesting because the stressor was effective.

Discussion

The primary purpose of this work was to demonstrate that combining a cognitive stressor with grating patterns known to induce visual discomfort would increase the aversiveness of viewing the grating pattern. Specifically, the introduction of a cognitive stressor was expected to accentuate the effects of visual discomfort when viewing the
3.0 CPD grating pattern. Examination of both the number of escapes when viewing the grating patterns and duration spent looking at the grating patterns revealed that stress did not increase the number of escapes performed nor did it reduce time spent looking at the grating patterns. The MA subjects did not experience a heightened level of visual discomfort with the introduction of stress as compared to when stress was not presented. It should be noted that pilot work on the stressor alone produced stress levels that were significantly higher than baseline after the introduction of the difficult math task. Furthermore in this experiment, the stress task produced a significant difference in stress ratings as compared to the non-stressful task in both MA and C subjects. Thus, the difficult math task was an effective stressor. Therefore the failure to find an effect of stress on visual discomfort cannot be due to lack of an effective stressor. This indicates that the difficult math task was indeed significantly more stressful than the easy math task and thus made for an effective stressor. Overall, migraineurs found the two grating patterns used to be significantly more aversive than control subjects, thereby, supporting the findings of Wilkins et al (1984). However, there was no evidence to support the notion that the stress task had any effect on intensifying the discomfort felt when viewing the 3.0 CPD grating pattern in migraineurs.

The finding that stress did not produce changes in visual discomfort raises questions as to why this might be so. One possibility is that stress does not affect visual discomfort in migraineurs. It is difficult to take that possibility seriously since stress has been reported as a trigger of migraine attacks in the literature by both researchers and migraine sufferers. Furthermore, in this study many subjects noted during the pre-experimental interview that stress is a major precipitant of their migraine attacks. Mental
stress is regarded as a psychological event that disrupts homeostasis (Kloet et al., 2005), therefore a more likely possibility is that the cognitive stressor used in this study, although shown to be effective in inducing a feeling of stressfulness, did not produce the level of stressfulness required to initiate a migraine in a real world setting. It might be reasonable to change the approach and use a battery of stressful tasks, thereby creating a cascade of stressful events strong enough to stimulate the necessary threshold to trigger a migraine attack. This idea corresponds with Debney’s (1984) Catastrophe Model in which various environmental factors may sum to exceed the critical threshold of brain stimulation for the onset of an attack. It is also possible that the effect of the stressor was short-lived, with the effectiveness of the stressor dissipating with the presentation of each grating pattern. In future work it may be worthwhile to assess the stress levels after each trial or each block. It is worth mentioning that subjects were told prior to testing that they would be presented with a mathematical stressor. Perhaps that resulted in a heightened baseline state of stress (because of ethical considerations as requested by the Committee on Human Studies at the University of Hawaii, it was advised that notification of the use of a stressor should be given to subjects). Another methodological suggestion would be to include more objective measures of stress such as measuring blood pressure and heart rate. It is possible that these measures may be taken, unobtrusively, before and after the stressor is administered.

The work presented here utilizing stimuli shown to induce visual discomfort in migraineurs paired with a cognitive stress task confirmed that there are differences in the way migraineurs react to viewing certain grating patterns compared to controls. The visual gratings have been shown, repeatedly, to be a highly replicable task that produces
differences between migraineurs and controls. A secondary goal of this work was to test a novel computerized method for presenting the visual stimuli and to introduce more precision in the visual discomfort measures. The results validate the new technique. Both the escape and duration measures of visual discomfort produced clean evidence that migraineurs experienced the gratings as more aversive than controls. This new procedure should contribute to the standardization and precision of future work on visual discomfort in the migraine population.

Although this work is a good starting point for research examining the effects of stress in migraineurs using visual discomfort, it is obvious that further work needs to be done in this area. Nonetheless, given the presence of stress as a likely trigger of migraine, research in this area is important and will lead to a better understanding of the association between visual triggers and stress in migraineurs. Individuals suffering from migraine make up a significant part of the world population and their disability undoubtedly has a major effect on their level of function and permeates every aspect of their lives. Thus, if we can further understand how stress is involved in the initiation of a migraine attack then it may be possible to shed new light on the pathophysiology of migraine.
References


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42.


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Schoonman, G. G., Evers, D. J., Ballieux, B. E., de Geus, E. J., de Kloet, E. R.,


Figure 1. Grating pattern of 3.0 CPD and 5° subtended.
Calculations:

5 degrees subtended
3 cycles per degree
diameter = 4.37 cm
width per bar = .1456 cm

\[ \tan \theta = \frac{y}{x} \]
\[ y = x \tan \theta \]
\[ y = (50 \text{ cm}) (\tan 5^\circ) \]
\[ y = 4.37 \text{ cm} = \text{diameter of the grating} \]

diameter of grating / degrees subtended = total width per cycle
4.37 cm / 5° = 0.874 cm

total width per cycle / bars per cycle = width per bar
0.874 cm / 6 bars per cycle = 0.1456 cm

Figure 2. Calculations for grating pattern of 3.0 CPD and 5° subtended.
Figure 3. Grating pattern of 0.5 CPD and 5° subtended.
Calculations:

0.5 cycles per degree
diameter = 4.37 cm
width per bar = .1456 cm

\( \tan \theta = \frac{y}{x} \)
\( y = x \tan \theta \)
\( y = (50 \text{ cm}) (\tan 5^\circ) \)
\( y = 4.37 \text{ cm} = \text{diameter of the grating} \)

\( \frac{\text{diameter of grating}}{\text{degrees subtended}} = \text{total width per cycle} \)
\( \frac{4.37 \text{ cm}}{5^\circ} = 0.874 \text{ cm} \)

\( \frac{\text{total width per cycle}}{\text{bars per cycle}} = \text{width per bar} \)
\( \frac{0.874 \text{ cm}}{1 \text{ bar per cycle}} = 0.874 \text{ cm} 5 \text{ degrees subtended} \)

Figure 4. Calculations for grating pattern of 0.5 CPD and 5° subtended.
Figure 5. Grating pattern of 3.0 CPD and 10° subtended.
Calculations:

10 degrees subtended
3 cycles per degree
diameter = 8.82 cm
width per bar = .147 cm

\[
\tan \theta = \frac{y}{x} \\
y = x \tan \theta \\
y = (50 \text{cm}) (\tan 10^\circ) \\
y = 8.82 \text{ cm} = \text{diameter of the grating}
\]

diameter of grating / degrees subtended = total width per cycle
8.82 cm / 10^\circ = 0.882 cm

total width per cycle / bars per cycle = width per bar

Figure 6. Calculations for grating pattern of 3.0 CPD and 10° subtended.
Figure 7. Grating pattern of 0.5 CPD and 10° subtended.
Calculations:

10 degrees subtended
0.5 cycles per degree
diameter = 8.82 cm
width per bar = .882 cm

\[ \tan \theta = \frac{y}{x} \]
\[ y = x \tan \theta \]
\[ y = (50 \text{cm}) \left( \tan 10^\circ \right) \]
\[ y = 8.82 \text{ cm} = \text{diameter of the grating} \]

\[ \frac{\text{diameter of grating}}{\text{degrees subtended}} = \text{total width per cycle} \]
\[ 8.82 \text{ cm} / 10^\circ = 0.882 \text{ cm} \]

Figure 8. Calculations for grating pattern of 0.5 CPD and 10° subtended.
Figure 9. Procedural flow chart of the steps followed for this experiment.
Figure 10. Mean total escapes from the two grating patterns for the MA and C subgroups are shown for the two stress sequences (stress then no stress and no stress then stress).
Figure 11. Mean number of escapes in the stress (upper panel) and no stress (lower panel) conditions for the two grating patterns for the MA and C groups.
Figure 12. Mean durations spent looking at each grating pattern for both the MA and C groups across trials in the two blocks.
Figure 13. Mean durations spent looking at each grating pattern for both the MA and C groups after pooling the stress conditions.
Figure 14. Mean durations spent looking at each grating pattern for both the MA and C groups in the no stress and stress conditions.
Figure 15. Mean rating given by the MA and C groups for the 0.5 CPD and 3.0 CPD grating pattern (now 10° subtended). Subjects rated each of the two patterns in terms of pleasantness using a 5-point scale (1 = very unpleasant and 5 = very pleasant).
Figure 16. Percent of subjects in the MA and C groups who reported seeing illusions while viewing the 10° subtended grating pattern in the interblock test.
Figure 17. Mean number of illusion descriptors reported during the interblock test with the 10° subtended grating pattern by both the migraine and control groups in the stress and no stress conditions.
Appendix A

Recruitment Advertisements for Migraine Subjects

MIGRAINE RESEARCH
University of Hawaii at Manoa
Department of Psychology

Do you suffer from MIGRAINE?
Do you experience AURA (visual changes or disturbances) prior to your migraine attack?
Are you between the ages of 18 and 45?

If you're interested please contact:
Coty Gonzales
University of Hawaii, Dept. of Psychology
Honolulu, Hawaii
Phone (808) 956-6465
E-mail: coty@hawaii.edu

If so, then you may be eligible to participate as a volunteer in a migraine study that is being conducted by the Psychology Department at the University of Hawaii at Manoa.

The research involves:
- Completing a screening questionnaire
- Answering some questions about your migraines
- Completing a straightforward computer-based study

Appointments will be arranged at a time convenient to you.

$24.00 compensation total for time spent in the laboratory and to cover travel expenses to and from the University of Hawaii will be paid if you are selected for the study following completion of the questionnaire.

This study has been reviewed and approved by the Committee on Human Subjects, Division of Research, University of Hawaii at Manoa.
Appendix B

Recruitment Advertisements for Non-Migraine (Control) Subjects

PARTICIPANTS NEEDED
University of Hawaii at Manoa
Department of Psychology

Do you NOT suffer from headaches?
Are you between the ages of 18 and 45?

If you're interested please contact:
Coty Gonzales
University of Hawaii, Dept. of Psychology
Honolulu, Hawaii
Phone (808) 956-6465
E-mail: coty@hawaii.edu

If so, then you may be eligible to participate as a control in a migraine study that is being conducted by the Psychology Department at the University of Hawaii at Manoa.

The research involves:
- Completing a screening questionnaire
- Answering some questions about your medical history
- Completing a straightforward computer-based study

Appointments will be arranged at a time convenient to you.

$24.00 compensation total for time spent in the laboratory and to cover travel expenses to and from the University of Hawaii will be paid if you are selected for the study following completion of the questionnaire.
Appendix C

Cover Letter Included In Recruitment Packet

Cory Gonzales, Graduate Student
University of Hawaii at Manoa
Department of Psychology, Karihi Hall 206
2430 Campus Road
Honolulu, HI 96822

About: You are invited to participate in a short experiment on migraine. The experiment will contribute to Dr. Cronin’s research program in the Department of Psychology at the University of Hawaii at Manoa and serve as a component of a thesis for a master’s degree. Participation is voluntary, and if you do choose to participate, you may withdraw at any time.

You do not qualify for the study, and should take no further action, if any of the following apply.
- you are younger than 18 or older than 45
- you have epilepsy (either now or in the past)
- you have any other neurological disorder besides migraine
- you have had a serious head injury or surgery on your brain in the past
- you have any serious eye disease or disorder (severe glaucoma or contact laceration in the past)
- you are taking daily medications for migraine, epilepsy, depression, anxiety, Parkinson’s disease, or hormone replacement therapy (please call if you are unsure about your medication)

The experiment aims to investigate the effect of psychological stress on visual discomfort in people who suffer from migraine and control participants who do not have migraine. Participation will take approximately 60 minutes. For more information regarding this project, please refer to the enclosed information sheet. The research will not bring any benefit to you personally, but it will aid researchers’ general understanding of migraine. There is a risk, which we estimate at being less than 5%, that participation may cause a migraine attack should you already suffer from migraine. If this happens, you will be advised to take your usual medication, and will be offered assistance with getting home.

If you are interested in participating, please complete both the expression of interest form and the migraine questionnaire that accompany this letter. Return these in the self-addressed stamped envelope provided.
- If you are eligible to participate, we will contact you to schedule an appointment to visit the lab. Your personal details, such as your name and address, will be kept securely and confidentially, and separate from your medical details in the migraine questionnaire and any data related from this study.
- If you are not eligible, you will be contacted and a reason will be provided to you. In addition, if you permit us to do so, 94% of the migraine questionnaire, we will keep your details on file for future studies, otherwise your responses will be destroyed.

Participants who are selected and choose to participate in the computer-based part of this study will receive $25.00 as compensation for time spent in the laboratory and to cover travel expenses to and from the University of Hawaii at Manoa.
Appendix D

Study Information Sheet

INFORMATION SHEET

The influence of a laboratory stressor on pattern sensitivity in patients with migraine.

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

What is the purpose of the study?

The purpose of this study is to attempt to understand more about differences in brain function between people who suffer from migraine and people who do not. We would like to understand how stress influences visual discomfort in both migraine and control individuals. The main aim of the research is to try to understand more about the initiation of migraine attacks.

Why have I been chosen?

You have been chosen either because you suffer from migraine and you have expressed an interest in being involved in this work, or because you are a suitable control participant who does not have migraine. In total we are hoping to study about 20 people who suffer from migraine with aura and 20 control participants.

How old do I need to be to participate?

You need to be between the ages of 18 and 45 to participate in this study.

Do I have to take part?

It is up to you to decide whether or not to take part. If you decide to return the migraine questionnaire you are still free to withdraw at any time and without giving a reason.

What will happen to me if I take part?

If you decide to take part we will find and ask you to complete the expression of interest form and migraine questionnaire that accompanied this information sheet and return it to us in the stamped addressed envelope provided. When you return this form we will arrange a time for you to attend the research laboratory at the University of Hawaii at Manoa. If you take part in the study this appointment will last about 60 minutes and will be arranged at a time convenient for you.

If you experience a migraine in the 24 hours before your testing appointment please call the number given below to arrange another appointment.

When you arrive for the appointment we will explain the study in detail and if you wish to take part we will ask you to sign a consent form. You will then be asked about your general health, and about your migraine history and symptoms, if applicable. Following this, testing will take place.

If you are a migraine patient, we advise you to bring your usual migraine medication with you to this appointment as there is a possibility (which we estimate at less than 5%) that the testing may trigger a migraine. If at any time
during the testing you experience migraine, discomfort or wish to stop please tell the researcher who will stop the experiment.

Participants who are selected will receive $24.00 as compensation for time spent in the laboratory.

What do I have to do?

If you experience a migraine in the 24 hours before your testing appointment please call the number given below to arrange another appointment.

Once the testing is completed you will be able to go home. If you normally drive, testing should not impair your ability to drive.

What is the procedure that is being tested?

As a participant, you will be asked to complete a short computer-based study in which you will be presented with two series of striped patterns. For each series, you will be asked to view the striped patterns and make judgements about how uncomfortable you feel it is to view the patterns. You will also be asked to complete a checklist to indicate any visual illusions that you may see during the viewing of the striped patterns. Before one of the series of patterns is shown, you will be presented with a non-invasive and painless mental laboratory stressor, consisting of a counting-backwards mental arithmetic task. You will then make your judgments about the discomfort/illusions in the patterns.

What are the side effects of the testing?

There is a small possibility, estimated as being less than 5%, that the testing may trigger a migraine, if you already suffer from migraines. Please bring your usual migraine medication with you to this appointment just in case.

Travel from the University to your home will be provided if necessary. For control participants, it is extremely unlikely that there will be any side-effects of testing.

What are the possible benefits of taking part?

It is unlikely that there will be any direct benefits to you from taking part in this study. However, we hope the information we get from this study may help us to understand more about how migraine attacks are initiated, which may benefit sufferers in the future.

Will my taking part in this study be kept confidential?

All information that is collected about you during the course of the research will be kept strictly confidential. Your personal details (name, date of birth, and address) will be kept separate from your medical details and data recorded from this study.

What will happen to the results of the research study?

It is expected that the results of this research will be published in a number of journals. It will not be possible to identify any individual participant in any article published.

Who is organizing and funding the research?

This study is being organized by the Department of Psychology at the University of Hawaii at Manoa and is supported by a research grant from the Hawaii Biomedical Program. This grant covers the cost of the salary of the graduate research assistant and the day-to-day costs of conducting the research.
Who has reviewed the study?

This study has been reviewed by the Committee on Human Studies (CHS) at the University of Hawaii at Manoa.

For further information:

If you wish to talk to someone about this research project or have any questions about this research program, you may contact the following:

Coty Gonzales, Graduate Student  Tel: (808) 956-6465
Department of Psychology - Gartley Hall 206  Email: coty@hawaii.edu
University of Hawaii at Manoa
2430 Campus Road
Honolulu, HI 96822

Edward P. Chronicle, Ph.D.  Tel: (808) 956-6407
Department of Psychology - Gartley Hall 202A  Fax: (808) 956-4700
University of Hawaii at Manoa
2430 Campus Road
Honolulu, HI 96822

If you wish to contact someone about your rights as a research subject, please contact the following address:

University of Hawaii Committee on Human Studies
2540 Maile Way, Room 253
University of Hawaii at Manoa
Honolulu, HI 96822
(808) 956-5007

Thank you for considering volunteering to participate in this study.
Appendix E

Expression of Interest Form

The influence of a laboratory stressor on pattern sensitivity in patients with migraine.

Participant's Name: ____________________________

Participant's Address: __________________________

Telephone Number: ____________________________
   (Home) ____________________________
   (Cell) ____________________________

I confirm I have read the cover letter and information sheet related to this project and I am interested in taking part in the study.

I understand that by signing this form, I am simply expressing an interest in the study, and this does not represent a commitment. I am free to change my mind about my involvement at any time.

I understand that when I return this form, someone from the University of Hawaii at Manoa will contact me to arrange an appointment. At this appointment, we will discuss the study in detail, and if I am willing to take part, I will be asked to sign a consent form and the testing will be carried out.

I have completed the migraine questionnaire below and I understand that all the information I have provided on this form will be kept in the strictest confidence.

I understand that not all participants will be suitable for testing. If I am not suitable for testing, the reason(s) will be explained to me by a member of the research team.

Signature of Participant: ____________________________

Date: ____________________________

Please return this form and the migraine questionnaire in the stamped addressed envelope provided.

*******************************************************************************
Appendix F

Migraine Questionnaire

If you do not have many headaches you may find some of the following questions difficult to answer. If you do have trouble answering a question please do not leave it out, but try to give it an answer - even if that answer has to be "don't know".

Migraine Questionnaire

1. Do you currently experience regular headaches?
   □ YES (please go to question 2)
   □ NO (please skip to question 3)

2. How many headaches of this kind have you experienced in your lifetime?
   □ more than 5
   □ fewer than 5

3. Are your headaches similar to one another, or do you have more than one kind of headache?
   □ all broadly similar
   □ more than one type

4. If you have more than one type of headache, please give a brief description of each type.
   Type 1
   Type 2
   Type 3
   Type 4

If you have more than one type of headache you may want to answer some of the following questions separately for each type of headache. If so, please label each answer by writing "Type 1", "Type 2" etc. beside it.
Appendix F

Migraine Questionnaire

Migraine Questionnaire

If you do not have many headaches you may find some of the following questions difficult to answer. If you do have trouble answering a question please do not leave it out, but try to give it an answer— even if that answer has to be "don't know".

1. Do you currently experience regular headaches?
   □ YES (please go to question 2)
   □ NO (please skip to question 3)

2. How many headaches of this kind have you experienced in your lifetime?
   □ more than 5
   □ fewer than 5

3. Are your headaches similar to one another, or do you have more than one kind of headache?
   □ all broadly similar
   □ more than one type

4. If you have more than one type of headache, please give a brief description of each type.
   Type 1
   Type 2
   Type 3
   Type 4

If you have more than one type of headache you may want to answer some of the following questions separately for each type of headache. If so, please label each answer by writing "Type 1", "Type 2", etc. beside it.

Subject #
(FOR OFFICE USE)
5. Roughly speaking, how often do you have a headache?
   □ all the time
   □ about once a day
   □ several times a week
   □ several times a month
   □ about once a month
   □ less than once a month
   □ less than once a year

6. How many headaches have you had in the last month?

7. Are your headaches:
   □ becoming less frequent
   □ becoming more frequent
   □ not changing in frequency

8. Do your headaches tend to start at the same time of day?
   □ yes, if yes, please say when
   □ no

9. Do you stay free of headaches for a while and then get many one after another?
   □ yes
   □ no

10. Is there any other pattern in the timing of your headaches?
    □ yes
    □ no

    If so, please give details
11. How do your headaches start?
   - [ ] suddenly
   - [ ] gradually

12. How long does the pain usually last?
    with medication ________ hours
    without medication ________ hours

13. How does the pain usually stop?
   - [ ] suddenly
   - [ ] gradually

14. What is the pain usually like?
   - **throbbing**?
     - [ ] never
     - [ ] sometimes
     - [ ] usually
     - [ ] always
     - [ ] don't know
   - **bursting**?
     - [ ] never
     - [ ] sometimes
     - [ ] usually
     - [ ] always
     - [ ] don't know
   - **sharp and knife-like**?
     - [ ] never
     - [ ] sometimes
     - [ ] usually
     - [ ] always
     - [ ] don't know
   - **dull and aching**?
     - [ ] never
     - [ ] sometimes
     - [ ] usually
     - [ ] always
     - [ ] don't know
   - **squeezing and pressing**?
     - [ ] never
     - [ ] sometimes
     - [ ] usually
     - [ ] always
     - [ ] don't know
   - **like a tight band**?
     - [ ] never
     - [ ] sometimes
     - [ ] usually
     - [ ] always
     - [ ] don't know
15. How bad are your worst headaches?
   □ noticeable but not distracting
   □ fairly distracting
   □ bad enough to take time off work or cancel a social engagement
   □ so severe you have to rest
   □ almost unbearable

16. Are your headaches made worse by physical activities such as climbing stairs?
   □ yes
   □ no

17. Where does the pain start?
   all over the head
   □ never □ sometimes □ usually □ always

   on the left side only
   □ never □ sometimes □ usually □ always

   on the right side only
   □ never □ sometimes □ usually □ always

   top of head
   □ never □ sometimes □ usually □ always

   back of head
   □ never □ sometimes □ usually □ always
down the neck
☐ never ☐ sometimes ☐ usually ☐ always

middle of forehead
☐ never ☐ sometimes ☐ usually ☐ always

side of forehead
☐ never ☐ sometimes ☐ usually ☐ always

behind the eye(s)
☐ never ☐ sometimes ☐ usually ☐ always

in the eye(s)
☐ never ☐ sometimes ☐ usually ☐ always

elsewhere (please specify)

---

18. On each diagram please shade in the areas where the pain usually starts.

[Diagrams showing shaded areas on the head]

19. If the pain spreads please describe how and where.

[Space for description]
20. Either before your headache starts or during it, do you notice any of the following change in your sight?

☐ never  ☐ sometimes  ☐ usually  ☐ always  ☐ don’t know

If you do notice a change in your sight, is it:

☐ always on the left
☐ usually on the left
☐ always on the right
☐ usually on the right
☐ sometimes left, sometimes right
☐ always on both sides
☐ usually on both sides

Please describe briefly what happens:

________________________________________________________________________

________________________________________________________________________

________________________________________________________________________

Do these changes come on gradually or suddenly?

How long do they last?

mistakes in your speech or difficulty in finding your words?

☐ never  ☐ sometimes  ☐ usually  ☐ always  ☐ don’t know

If you do notice such things, please describe briefly what happens:

________________________________________________________________________

________________________________________________________________________
numbness, tingling or some other strange feeling in any part of your body?

☐ never  ☐ sometimes  ☐ usually  ☐ always  ☐ don’t know

If you do notice a feeling of this kind, is it:

☐ always on the left
☐ usually on the left
☐ always on the right
☐ usually on the right
☐ sometimes left, sometimes right
☐ always on both sides
☐ usually on both sides

Please describe briefly what happens

__________________________________________________________________________

Do these sensations come on gradually or suddenly? _________________________

How long do they last? ____________________________________________

 weakness in any part of your body?

☐ never  ☐ sometimes  ☐ usually  ☐ always  ☐ don’t know

If you do notice weakness, is it:

☐ always on the left
☐ usually on the left
☐ always on the right
☐ usually on the right
☐ sometimes left, sometimes right
always on both sides
usual on both sides

Please describe briefly what happens


Does the weakness come on gradually or suddenly?
How long does it last?

21. If you have listed symptoms in answer to question 20, what is the time interval between these symptoms and the beginning of the headache?


22. Do you have any other warning that a headache is coming?
   yes
   no

If yes, please say what it is

23. During your headache, but not before it, do you:

   lose your appetite?
   never  sometimes  usually  always  don't know

   feel sick in the stomach?
   never  sometimes  usually  always  don't know

   vomit?
   never  sometimes  usually  always  don't know

   feel light-headed?
   never  sometimes  usually  always  don't know
feel unsteady on your feet?

☐ never  ☐ sometimes  ☐ usually  ☐ always  ☐ don't know

feel hot and sweaty?

☐ never  ☐ sometimes  ☐ usually  ☐ always  ☐ don't know

Have a stiff neck?

☐ never  ☐ sometimes  ☐ usually  ☐ always  ☐ don't know

Have a tender scalp?

☐ never  ☐ sometimes  ☐ usually  ☐ always  ☐ don't know

Hear ringing in your ears?

☐ never  ☐ sometimes  ☐ usually  ☐ always  ☐ don't know

Have a stuffed-up nose?

☐ never  ☐ sometimes  ☐ usually  ☐ always  ☐ don't know

have a runny nose?

☐ never  ☐ sometimes  ☐ usually  ☐ always  ☐ don't know

have watery eyes?

☐ never  ☐ sometimes  ☐ usually  ☐ always  ☐ don't know

find that light hurts your eyes?

☐ never  ☐ sometimes  ☐ usually  ☐ always  ☐ don't know

find loud sounds unusually unpleasant?

☐ never  ☐ sometimes  ☐ usually  ☐ always  ☐ don't know

24. Can any of the following bring on your headaches?

☐ stress or anxiety

☐ menstrual cycle
☐ hunger
☐ reading
☐ coughing
☐ sudden movement
☐ noise
☐ watching TV
☐ working at a computer screen
☐ bright light please specify
☐ certain foods please specify
☐ other things please specify

25. Please list anything that makes the pain worse (i.e. noise, bright light, sudden movement, coughing)

26. Please list anything that reduces the pain (i.e. resting, darkness, medication)

27. How many different medications do you take every day? Please include all of them and write the number here ______

If you know their names please list them here:

________________________________________________________________________

________________________________________________________________________

________________________________________________________________________

________________________________________________________________________

________________________________________________________________________

________________________________________________________________________
28. What medications do you take to stop a headache that has already started?

________________________________________________________________________
________________________________________________________________________
________________________________________________________________________

29. Have any of these medications helped your headaches?

☐ yes
☐ no

If so, which one(s)?

________________________________________________________________________
________________________________________________________________________

30. Have you had any other treatment that has helped your headaches?

☐ yes
☐ no

If yes, please give details _______________________________________________________

31. Have you recently

☐ gained weight?
☐ lost weight?
☐ or has there been no change?
32. Do you find your meals appetizing?
   □ never □ rarely □ sometimes □ often □ usually

33. Do you have difficulty relaxing?
   □ never □ rarely □ sometimes □ often □ usually

34. Does worry stop you from sleeping?
   □ never □ rarely □ sometimes □ often □ usually

35. Do you wake early and then sleep badly for the rest of the night?
   □ never □ rarely □ sometimes □ often □ usually

36. Do you feel unhappy for no particular reason?
   □ never □ rarely □ sometimes □ often □ usually

37. Have you ever seen a doctor about any of the following? Please give approximate dates.

<table>
<thead>
<tr>
<th>Illness</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>sinusitis</td>
<td></td>
</tr>
<tr>
<td>ears</td>
<td></td>
</tr>
<tr>
<td>eyes</td>
<td></td>
</tr>
<tr>
<td>head injury</td>
<td></td>
</tr>
<tr>
<td>epilepsy</td>
<td></td>
</tr>
<tr>
<td>depression</td>
<td></td>
</tr>
<tr>
<td>blood pressure</td>
<td></td>
</tr>
<tr>
<td>asthma</td>
<td></td>
</tr>
<tr>
<td>travel sickness</td>
<td></td>
</tr>
<tr>
<td>diabetes</td>
<td></td>
</tr>
<tr>
<td>allergies</td>
<td></td>
</tr>
<tr>
<td>other illness (please specify)</td>
<td></td>
</tr>
</tbody>
</table>

12
38. Please say which of your relatives have had the following (your relative will not be contacted)  

<table>
<thead>
<tr>
<th>Person's relationship to you</th>
<th>migraine</th>
<th>high blood pressure</th>
<th>depression</th>
<th>epilepsy</th>
</tr>
</thead>
</table>

39. If you smoke, how many cigarettes per day? __________

40. Are you:  
- [ ] right-handed  
- [ ] left-handed

41. To answer this question, please first study the scale of frequency given below and then go on to the second part.

<table>
<thead>
<tr>
<th>Scale</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>never</td>
</tr>
<tr>
<td>B</td>
<td>less than once a year</td>
</tr>
<tr>
<td>C</td>
<td>about once a year</td>
</tr>
<tr>
<td>D</td>
<td>more than once a year</td>
</tr>
<tr>
<td>E</td>
<td>about once a month</td>
</tr>
<tr>
<td>F</td>
<td>more than once a month, but less than once a week</td>
</tr>
<tr>
<td>G</td>
<td>about once a week</td>
</tr>
<tr>
<td>H</td>
<td>more than once a week</td>
</tr>
<tr>
<td>I</td>
<td>about once a day</td>
</tr>
<tr>
<td>J</td>
<td>more than once a day</td>
</tr>
</tbody>
</table>
Using the capital letters from the scale above, please say how often you experience each of the following symptoms other than when you are having or are about to have a headache:

irritation or soreness in the eyes ______
dryness of the eyes ______
redness of the eyes ______
temporary blurring of vision (despite glasses if worn) ______
spots or shapes in front of the eyes ______
faint colors surrounding objects ______
pain in response to light ______
narrowing of vision (one or both sides) ______

42. Please say which activities, if any, bring on the above symptoms

43. How long ago did you last visit an optometrist to have your eyes tested?

44. What is your age? ______

45. What is your sex?

☐ Male
☐ Female

46. If you are unsuitable for the current study, may we keep your details on file for future studies?

☐ Yes ☐ No

Thank you very much for taking the trouble to fill in the questionnaires.
Diagnostic Interview Notes:
Appendix G

Exclusion Letter

Coty Gonzales, Graduate Student
University of Hawaii at Manoa
Department of Psychology
Garley Hall 206
2430 Campus Road
Honolulu, HI 96822

Date

Participant Name,

Aloha! Thank you for your interest in the study *The influence of a laboratory stressor on pattern sensitivity in patients with migraine.*

We have reviewed the migraine questionnaire that you returned to us and have determined that you are not eligible to participate in the computerized portion of this study.

However, we will keep your information on file and may contact you at a later time about participating in future migraine studies.

If you have further questions regarding this matter please feel free to contact me via email at coty@hawaii.edu or by phone at 956-6465. Again, thank you for your time.

Thank You,

Coty Gonzales

If you wish to talk to someone about this research project or have any questions about this research program you may contact the following:

Coty Gonzales, Graduate Student
Department of Psychology – Garley Hall 206
University of Hawaii at Manoa
2430 Campus Road
Honolulu, HI 96822

Tel: 956-6465
Email: coty@hawaii.edu

If you wish to contact someone about your rights as a research subject, please contact the following address:

University of Hawai'i Committee on Human Studies
2540 Maile Way, Room 213
University of Hawai'i at Manoa
Honolulu, HI 96822
(808) 956-5907
Appendix H

Written Informed Consent Form

Written Informed Consent Form
The influence of a laboratory stressor on patterns of sensitivity in patients with migraine.  
Dr. Edward P. Chronicle  
Principal Investigator  
(808) 956-6407  
Co-Investigator  

This research project is being conducted as a component of a thesis for a master’s degree and will also contribute to Dr. Chronicle’s research program in the Department of Psychology at the University of Hawaii at Manoa. This research project aims to investigate factors that may contribute to the initiation of a migraine attack. You are being asked to participate because you responded to the research flyers, completed the migraine questionnaire, and were found to be eligible by the research team to participate in the study, either as a migraine patient or a control subject.

Participation in the project will consist of a diagnostic interview with the principal investigator and a graduate student. Testing involves the viewing and judging of various striped patterns that will be presented via a computer program installed on a laboratory computer. You will make these judgments under two conditions: with and without a psychological stressor. This stressor simply consists of a counting-backwards mental arithmetic task. Data from the testing will be analyzed and used to further our understanding of how attacks of migraine may be initiated. No personal identifying information will be included with the research results. Completion of the computer-based testing should take no more than 60 minutes. Approximately 40 people will participate in the study.

The investigators believe there is little risk in participating in this research project. However, if you have migraine already, there is a chance (which we estimate to be less than 5%) that the testing may trigger a migraine. You have been asked to bring your usual migraine medication with you to the appointment as a precaution. If you do experience a migraine during testing, transportation home may be arranged for you.

Participating in this research may be of no direct benefit to you. It is believed, however, the results from this project will help researchers better understand how migraine attacks may be initiated by environmental factors. Participants will receive a total of $24.00 as compensation for time spent in the laboratory, assessment, travel expenses and from the University of Hawaii. Participants will receive a total of $24.00 as compensation even if they choose to withdraw from the study.

Research data will be confidential to the extent allowed by law. Agencies with research oversight, such as the UH Committee on Human Subjects, have the authority to review research data. All research records will be stored in locked file cabinets in the principal investigator’s office for the duration of the research project. Your personal information about your medical history will be kept separate from your name and address to ensure confidentiality. All records from this study will be kept under lock and key.

Participation in this research project is completely voluntary. You are free to withdraw from participation at any time during the duration of the project with no penalty or loss of benefit to which you would otherwise be entitled. If you are injured during the course of this research procedure, you alone may be responsible for the treatment of your injuries. If you have any questions regarding this research project, please contact the researcher, Edward Chronicle, at 956-6407. If you have any questions regarding your rights as a research participant, please contact the UH Committee on Human Subjects at 956-6407.

Participant:
I have read and understand the above information, and agree to participate in this research project.

Name (printed)

Signature

Date

(Principal Investigator’s Copy)
Appendix I

Rating Scale for Math Task

<p>| | | | | | | | |</p>
<table>
<thead>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

Least Stressed | Moderately stressed | Very stressed
Appendix J

Checklist of Visual Illusions

Directions: For the striped pattern you have just viewed, please check all the illusions that you experienced.

Colors

☐ red
☐ green
☐ yellow
☐ blue

Other colors please list: ________________________________

☐ blurring
☐ shimmering
☐ flickering
☐ bending of the lines
☐ shadowy shapes

Other please list: ________________________________

Directions: Please rate the striped pattern that you just viewed based on its level of unpleasantness.

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Unpleasant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderately Pleasant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very Pleasant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>