NOTE TO USERS

Assessment of Magno-, Parvo-, and Koniocellular Visual Streams in Migraine

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Abstract

Although visual abnormalities have been noted in migraine, no studies have specifically sought to assess all three visual processing streams. We are the first to psychophysically assess visual functionality of the magnocellular (MC), parvocellular (PC), and koniocellular (KC) parallel streams at different hierarchical visual pathway loci across groups of individuals with migraine with aura (MA; $n = 13$), migraine without aura (MWO; $n = 14$), and controls ($n = 15$). Participants completed four tasks: (1) visual field analysis using short-wavelength automated perimetry (SWAP), (2) chromatic discrimination along cone-excitation axes using the Cambridge Colour Test, (3) chromatic contrast sensitivity across isoluminant bichromatic spatial Gabor gratings, and (4) luminance contrast sensitivity across heteroluminant spatial Gabor gratings. Our results suggest that deficits are selective to short-wavelength-sensitive cones and the associated KC visual stream. Furthermore, functional inconsistencies and consistencies between our SWAP and chromatic discrimination measures and SWAP and chromatic sensitivity measures, respectively, provide evidence for a retinal locus of dysfunction in MA that is compensated for at downstream locations within the KC visual stream.

Introduction

Migraine is thought to be the most common chronic pain condition, with an estimated lifetime prevalence as high as 33 percent in women and 13 percent in men (Launer, Terwindt, & Ferrari, 1999). In the U.S. alone, it is estimated that over 1 billion dollars are spent on direct costs associated with migraine diagnosis and treatment, and indirect cost (e.g., loss of employment productivity) exceed 18 billion dollars annually (Hu, Markson, Lipton, Stewart, & Berger, 1999). Unfortunately, the burden of migraine headaches is not limited to financial matters. Migraine headaches have a devastating impact on the individuals it afflicts, often leading to reduced quality of life in domains such as physical, mental, and social functioning (Terwindt, Ferrari, Tijhuis, Groenen, Picavet, & Launer, 2000).

Due to the overwhelming burden of migraine on individuals and on society, recent efforts have been made to improve the diagnosis and treatment of this condition. Unfortunately, these efforts have been slow to progress due primarily to the fact that the underlying pathophysiology of the condition is not yet fully understood. Currently, abnormalities within the trigeminovascular system, and its associated subcortical structures, are thought to underlie the condition (for reviews see Moskowitz, 1990; Rapoport & Edmeads, 2000; Sandrini, Cecchini, Hristova, Sances, & Nappi, 2001). However, there remains a great deal of uncertainty regarding what triggers activation of the trigeminovascular system and the associated headache. Recently, it has been proposed that a "migraine generator", most likely located in the brainstem, may be responsible for depolarizing the trigeminal ganglion leading to the activation of nociceptors within the ophthalmic division of the trigeminal nerve (Weller, May, Limmroth, Juptner, Kaube, Schayck, et al., 1995). The reason for the initial activation of the trigeminal ganglion, or

activation of the "migraine generator", remains unclear, however, it is likely that environmental trigger factors initiate the cascade of events that eventually leads to migraine headaches (Cao, Welch, Aurora, & Vikingstad, 1999). Whether the two main types of migraine: migraine with aura (MA) and migraine without aura (MWO) share a common pathophysiological basis also remains uncertain.

Abnormalities such as visual triggers, visual hallucinations (aura), and photophobia are commonly associated with migraine, and therefore the visual system has received significant attention by migraine researchers. The majority of research seems to suggest that abnormalities in visual functioning may not be homogenous across the entire visual system, but instead, deficits may be specific to one or more of the three main parallel processing visual streams: the magnocellular (MC) stream, the parvocellular (PC) stream, and the koniocellular (KC) stream. Pre-cortical transmission and processing of visual information from retinal cells to the visual cortex occurs mainly through these three anatomically distinct, yet interrelated, streams. MC and PC streams have been investigated for some time. Research on the KC system, however, has only recently received significant attention. Each of these streams serves to transmit and process different attributes of visual information. For example, the MC stream is involved in luminance contrast processing and is effectively color-blind (e.g., Pokorny & Smith 1997). Signals carried through the MC stream are initiated through summating information from long-wavelength-sensitive (LWS) and middle-wavelength-sensitive (MWS) cones and are thought to transmit this information to the parasol retinal ganglion cells (Ogden, 1984). MC cells have band-pass spatiotemporal characteristics, and are especially sensitive to high-temporal frequencies. In contrast, the PC stream is thought to be involved in color opponency, particularly related to red/green chromaticities. Input

into the PC stream is based on the differencing of LWS and MWS cones (Derrington, Krauskopf, & Lennie, 1984), and is likely transmitted mainly from the photoreceptors to midget ganglion cells, and to a lesser degree through parasol ganglion cells (Dacey & Peterson, 1992). Psychophysical tests have provided data which suggest that cells associated with this stream have low-pass spatiotemporal characteristics to chromatic stimuli, but a band-pass spatiotemporal characteristics to achromatic stimuli (Pokorny & Smith, 1997). From the photoreceptors, signals for both the MC and PC streams are transmitted via midget and parasol ganglion cells to their respective layers within the lateral geniculate nucleus and eventually to V1.

In migraine research, deficits have been noted primarily in the MC stream. However, some studies have suggested that more discrete deficits may be present in the PC visual stream. Several studies have examined visual field loss that is specific to these pathways in migraine. The most common method to date has been through the use of temporally modulated perimetry (TMP) and standard automated perimetry. TMP attempts to identify areas of visual field loss by asking participants to indicate when they perceive a flickering stimuli, with the temporal frequency of the stimuli varying from 9 to 18 cycles/sec or Hertz (Hz) positioned at different spatial locations throughout the visual field. Flicker thresholds are then determined for the various field locations. TMP perimetry is designed to assess MC related visual field loss. In contrast, standard automated perimetry (SAP) is designed to assess both MC and PC stream functions, in which participants are asked to indicate when they perceive a steady point of light at various visual field positions. Visual field loss using TMP and SAP have both revealed deficits in migraine patients. For example, McKendrick and Badcock (2004a) attempted to identify the influence of duration of migraine history, frequency of attacks, and

migraine type (i.e., MA or MWO) on flicker perimetry performance. They found that visual field loss was similar across both migraine sub-types. However, length of migraine history and frequency of attacks over the past 12 months was associated with a lower sensitivity to flickering stimuli. An additional study by the same authors suggested that decreased visual field sensitivity is more pronounced immediately following a migraine attack as compared to a week following an attack (McKendrick & Badcock, 2004b). The extent of visual deficits may be related to temporal properties of the stimuli, (McKendrick, Vingrys, Badcock, & Heywood, 2000) where higher temporal frequencies tend to produce greater performance deficits in MA patients, suggesting more prominent MC abnormalities in the migraine subtype with symptomatic visual phenomena.

Additional evidence for MC deficits stem from studies that have combined perimetric and psychophysical assessment of the specific visual streams. McKendrick and Badcock (2003) attempted to isolate the contrast processing of the MC and PC streams. Initially, participants were pre-selected based on visual field deficits identified through TMP. In a steady-pedestal condition, which assessed PC functionality, four squares were presented continuously on a surround. The surround in this condition was stable with a luminance level of 30 cd/m^2. During each trial, one of the squares was luminance-incremented for 30 ms. Participants were then asked to indicate which of the four squares incremented in luminance (i.e., "brighter"). In the pulsed-pedestal condition, which assessed MC functionality, a small fixation marker was presented continuously within the surround. However, the four squares were presented for only a 30 ms interval, during which one of the squares was incremented relative to the background. Again, only one square had an incremental difference and the participants' task was to indicate which square was incremented. In both these detailed descriptions, one can see the importance

of modifying the spatiochromatic and/or spatiotemporal properties of a stimulus so that it can selectively probe the operations of each of the visual processing streams. McKendrick and Badcock (2003) tested both foveal and mid-peripheral contrast thresholds. Foveal testing targeted specific regions that were identified to be abnormal according to TMP. Contrast discrimination deficits were identified in perifoveal areas (i.e., 12.5° from fixation) visual field for both MC- and PC-selective stimuli; however, controls and migraine groups performed similarly on foveal tests. This study was unique in that it identified both MC and PC deficits in perifoveal positions.

The third (KC) visual stream has only recently been elucidated in vision research. This stream would appear to be mainly involved in color opponency as it specifically relates to blue-yellow chromaticities, although it is also probably involved in luminance and motion perception (e.g., Calkins, 2001). Signals for KC system originate mainly from short-wavelength-sensitive (SWS) cones. Unlike the LWS and MWS cones, SWS cones are less common and comprise of only 5-10 percent of the total cone retinal mosaic. Through their associated bipolar cells, SWS cones are responsible for the S-ON component of the S-ON/(M+L)-OFF portion of color opponency. The (M+L)-OFF process occurs when the signals from LWS and MWS-cones converge at the ganglion cell level and offset the input from the SWS cones. Retrograde tracing and intracellular recordings techniques reveal that the S-ON/(M+L)-OFF signal input into the LGN originates from the small bistratified retinal ganglion cells (Dacey & Lee, 1994; Martin, White, Goodchild, Wilder, & Sefton, 1997). For chromatic information, these small bistratified retinal ganglion cells receive information directly from SWS cone bipolar cells, as well as input from MWS and LWS cones, and then project through KC middle layers of LGN to distinct blob areas within V1 (Calkins, 2001; Martin et al., 1997).

In migraine research, the search for abnormalities specific to the newly rediscovered KC stream has started to reveal some exciting findings. Researchers are now beginning to identify significant deficits related to SWS cone operations and their associated KC streams. Advances in color vision research in migraine have been greatly extended by the timely invention of short-wavelength automated perimetry (SWAP). SWAP, or "blue-on-yellow" perimetry, is a visual field test designed to assess early visual field loss in several conditions including glaucoma, retinitis pigmentosa, and diabetes. As implied by the name, SWAP makes use of a short-wavelength target (i.e., 440 nm) to assess visual field loss. The use of a bright 100 cd/m^2 "yellow" background saturates the rods as well as the LWS and MWS cones. Therefore, this test primarily activates only the SWS-cones and their associated small bistratified ganglion cells (Sample, 2000). In terms of psychophysical research, SWAP provides a valuable measure of SWS cone operations, and consequently the KC stream functionality.

McKendrick, Cioffi, and Johnson (2002) were among the first to compare short-wavelength sensitivity measurements in migraine patients and controls using SWAP and the Stiles 2-colour increment procedure to assess Stiles π_1 (i.e., SWS-cone sensitivity) and Stiles π_4 (i.e., MWS-cone sensitivity) mechanisms. Results from the SWAP showed that 50 percent of migraine patients had short-wavelength sensitivity loss during periods between migraine attacks. Two subjects, who participated in the Stiles 2-color increment procedure showed a gain reduction change in threshold-vs.-intensity (tvi) curves for MWS- (i.e., low-luminance "yellow" with a "blue" target) and SWS-selective (i.e., high-luminance "yellow" background with a "blue" target) stimuli. Greater sensitivity loss was identified with SWS-selective stimuli as compared to MWS-selective stimuli as assessed by the tvi curves measured 6 days and 3 weeks following a migraine. However,

the small sample used questions the generalizability of this effect. It is also important to note that deficits in migraine patients, according to SWAP, were often localized to one eye. This would suggest that the SWS deficits noted by the authors are prestriatal, as opposed to cortical (V1) in which case deficits would have been expected in both eyes (McKendrick et al., 2002).

Yenice, Temel, Incili, and Tuncer (2006) used SWAP and confirmed SWS visual field loss in migraine patients. In this study, the SWAP results were examined in terms of their relevance to the Migraine Disability Assessment Questionnaire (MIDAS). The MIDAS assesses the number of days of school or work missed because of migraine, as well as inability to conduct household work, and family social or leisure activities. Furthermore, the MIDAS collects information on the frequency and intensity of headaches in the last year. Results showed that 53.3 percent of migraine patients had SWAP visual field sensitivity loss. Significant positive correlations were found between sensitivity losses as assessed by SWAP and migraine frequency, as well as the overall MIDAS scores. Furthermore, in most cases, visual field deficits were ipsilateral to the side of experienced headache pain.

A recent study has also sought to identify abnormalities in visual fields of female migraine patients using SWAP (Yucel, Akar, Dora, Akar, Taskin, & Ozer, 2005). In addition, this study examined hormonal levels at various phases of the menstrual cycle. Results indicated that SWAP mean sensitivity was significantly lower in both migraine and control groups during the luteal phase as compared to the follicular phase of the menstrual cycle. However, migraineurs showed even greater menstrual cycle-dependent sensitivity loss as compared to controls. This would suggest a greater influence of reproductive cycle effects in the migraine group. Although this study failed to identify

any large difference between migraine and controls, it does provide evidence for hormonal influences on visual field tests, which is suggested to be an important variable to examine in future SWAP studies (Yucel et al., 2005).

Confirmatory evidence for selective deficits in the SWS-cone functionality in migraine patients has been established by Shepherd (2005, 2006a, 2006b). Shepherd (2005) used a paradigm whereby migraine patients and controls underwent three color sensitivity tests. The first clinical test was the Farnsworth-Munsell 100 Hue-test used to assess color discrimination and blindness. The task involves arranging a series of colored discs so that they form a sequence between two reference disks. This test determines deficits in color discrimination based on SWS-, MWS- and LWS-cone operations. The second test assessed chromatic sensitivity by measuring thresholds using a four-alternative forced choice paradigm. Subjects were asked to detect a single square that was of a slightly different chromaticity from three other squares. Chromaticities were chosen along the cardinal receptor-based color directions (Krauskopf, Williams, & Heeley, 1982). The luminance and chromaticity of the backgrounds were changed to ensure that trials would assess specific modulation along either SWS-, or MWS- and LWS-cone thresholds. The third test was a color scaling experiment where five circles were presented on a "gray" surround. Two of the presented circles were of a uniform chromaticity and participants were asked to set the hue of the other three circles so that the change of color between the circles was uniform. Results from these experiments all indicated that deficits in color sensitivity were restricted to chromaticities associated with SWS-cone operations (i.e.,"blue" and "yellow"). The first two experiments identified that migraine patients had an impaired ability to discriminate "blue" and "yellow" colors as compared to controls. Results from the third test showed that migraine patients were

more likely to choose less saturated "blue" and "yellow" colors as compared to controls. A significant positive correlation was identified within migraine patients, whereby individuals who set less saturated yellow settings in the third test also tended to make errors during trials that presented a forced-choice decision of color differences presented on a yellow background in the second test. This correlation suggests deficits are restricted to SWS streams. Collectively, the results from the three sensitivity measures suggest that migraine patients have elevated increment detection thresholds, impaired discrimination, and altered suprathreshold color scaling in response to SWS-cone-related chromaticities. Shepherd suggested that since strong positive correlations did not occur for all three tests, it is likely that the observed differences in SWS-cone streams occurs prior to the merging of the color opponent pathways.

In order to help identify the locus of SWS dysregulation, Shepherd (2006a) attempted to identify the extent to which color vision was impaired at various stages of chromatic processing. Specifically, attentive and pre-attentive processes involved in visual search were examined. Visual stimuli that selectively activated LWS, MWS, and SWS-cones were used in each of the two experiments. The first experiment presented a series of disks each of which were of a chromaticity that maximally activated a specific cone type, one of which varied significantly in chromaticity from the others. The background was "mid grey" with a luminance value of 11 cd/m^2. Participants were required to indicate which disk differed in chromaticity from the others as quickly as possible. This task attempted to measure pre-attentive mechanisms, as the target was generally easy to pick out, or "pop out", with little attentive demands. The second experiment was similar to the first in that a series of colored disks were presented to the participant; however, the chromaticities of the distracters varied only slightly in

chromaticity, making the task more difficult. This task would involve attentional mechanisms, as the task required attention to identify the less salient target. Results from this study did not find any overall difference between migraine patients and controls in regards to "red" and "green" targets associated with MWS and LWS cones. However, significant differences were found as migraine patients were asked to identify "yellow" and "purple" targets in the pre-attentive task but not in the attentive task. The author interprets the difficulty in target discrimination of short-wavelength chromaticities in this task to be indicative of pre-attentive deficits in color processing (i.e., sensory as opposed to top-down cognitive difficulties). If this were not the case, then deficits on both tasks would have been evident.

To date, three studies have examined the relationship between chromatic and spatial properties of vision in migraine patients. The first was conducted by Chronicle and Wilkins (1991) who asked migraine patients to select a hue and manipulate the saturation of a light source to the most and least comfortable while reading text or viewing high contrast Gabors. Although the colors varied for each individual, they were most likely to choose a red light as the least comfortable color. Chronicle, Wilkins, and Coleston (1995) extended this finding by examining target detection of grating patterns under illuminants that were "red", "blue", or "neutral grey" in appearance. The target in this study was an uppercase "E" that was projected onto a screen at various orientations. The background consisted of a circular grating patch with a spatial frequency of 3.1 cycles/degree (cpd). The background was chosen to disrupt target detection and induce visual illusions, purportedly due to a failure of inhibition in response to the highly excitable grating pattern. Thus, if inhibitory deficits exist in migraine then this effect would be expected to be more obvious as compared to controls. In this study, participants

were asked to detect the letter and its orientation on the background. Chromaticity randomly varied with each trial presentation. Detection thresholds were higher in migraine with aura as compared to migraine without aura or controls. For both migraine groups, "red" and "neutral" illuminated target displays resulted in a greater increase in threshold compared to the detection thresholds obtained under a "blue" illuminant, the authors interpret these findings to be indicative of GABAergic inhibitory dysfunction in migraine. The third spatial-chromatic study by Yenice et al. (2007) examined both SWAP performance and a test of spatial-contrast function in migraine patients. The spatial contrast task consisted of the Functional Acuity Contrast Test (FACT). The FACT consists of presenting 45 sine-wave gratings with frequencies of 1.5, 3, 6, 12 and 18 cpd. Significant correlations were found between SWAP performances and contrast sensitivity scores at all spatial frequencies. Based on the SWAP findings the authors suggested there are MC abnormalities apparently ignoring previous research that has suggested that SWAP primarily assesses KC stream function (Sample, 2000). Despite these conflicting conclusions, the Yenice et al. (2007) contrast sensitivity findings suggest dysregulation may occur in both MC and PC streams, as deficits were noted for all the spatial frequencies used.

An attempt to further elucidate the potential locus of SWS-cones abnormalities in migraine was carried out by Tibber and Shepherd (2006). This study made use of the transient tritanopia (TT) technique combined with measures of pattern sensitivity. TT relies on the fact that there tends to be a reduction of short-wavelength sensitivity following excitation of LWS and MWS-cones through the use of a bright "yellow" adapting display, similar to that used in SWAP. TT has been identified as a post-receptoral process in humans and primates that likely occurs at the horizontal cell level of

the retina. Following adaptation, participants were presented with a ring of small circles on a neutral grey background, one segment of the ring contained circles of a different chomaticity than the remaining segments. Both decrement (i.e., "yellow" targets) and increment (i.e., "blue-purple" targets) thresholds for SWS-cone stimuli were determined in this manner. TT was induced in both migraine and controls as demonstrated by increased increment thresholds in both groups with the incremental sensitivity loss being significantly greater in the migraine group. Furthermore, the magnitude of sensitivity loss was positively correlated with reports of pattern sensitivity and susceptibility to visually triggered migraines. This study identified abnormalities in retinal circuits that most likely mediate SWS pathway deficits in that the lack of sensitivity can be inferred to occur in a post-receptoral location, possibly due to abnormal GABAergic or glutamatergic activity within the horizontal cells of the outer retina (Tibber & Shepherd, 2006)

Collectively, both parametric and psychophysical assessments indicate selective deficits that are prominent in both MC and KC visual streams. However, the locus of these deficits remains unknown. A great deal of research, however, suggests that cortical structures of migraine patients are hyperexcitable as evidenced by studies using various methodologies including: electroencephalogram (e.g., Afra, Ambrosini, Genicot, Albert, & Schoenen, 2000; Afra, Cecchini, De Pasqua, Albert, & Schoenen, 1998; Evers, Bauer, Suhr, Husstedt, & Grotemeyer, 1997; Wang, Timsit-Berthier, & Schoenen, 1996), transcranial magnetic stimulation (Aurora, Barrodale, Chronicle, & Mulleners, 2005; Aurora, Cao, Bowyer, & Welch, 1999; Gerwig, Niehaus, Kastrup, Stude, & Diener, 2005; Mulleners, Chronicle, Palmer, Joehler, & Vredeveld, 2001), and advanced psychophysical measures (Marcus & Soso, 1989; McColl & Wilkinson, 2000; Shepherd, 2001). These studies support the concept of hyperexcitability, especially within the visual

cortex, that may be due to diminished cortical inhibition (Palmer, Chronicle, Rolan, & Mulleners, 2000).

The lack of inhibition observed in cortical structures may be related to the onset of migraine headaches. Recently, it has been proposed that a phenomena known as cortical spreading depression (CSD) may act as the triggering mechanism for migraines. The phenomena of CSD is described as a wave of intense neuronal and glial activation that spreads from a point of origin within the central nervous system at rate of 4 mm a minute throughout cortical tissue. The wave of excitation is further characterized by dramatic increases in cortical steady potential, temporary increases in extracellular ions, and transient increases in cortical flow preceded by sustained decrease in blood flow (Bolay, Reuter, Dunn, Huang, Boas, & Moskowitz, 2002; Lauritzen, 1994). Following the wave of neural excitation, a period of inhibition occurs in the areas that were previously activated. In migraine research, CSD is most commonly studied as being initiated within the visual cortex due to its link to visual auras. However, it is likely that CSD can occur across all cortical structures and this may extend to the eye itself (Bolay et al., 2002; James et al., 1999; Martins-Ferreira & Ribeiro, 1995; Somjem, 2001; but see Hadjikhani et al., 2001). Recent evidence suggests that CSD can directly activate the trigeminovascular system and may thus trigger the headache associated with migraine (e.g., Ayata, Jin, Kudo, Dalkara, & Moskowitz, 2006; Bolay, Reuter, Dunn, Huang, Boas, & Moskowitz, 2002).

To date, CSD has been observed in migraine patients with aura, which occurs prior to the onset of the headache. Early studies suggested abnormalities in cortical cerebral blood flow in migraine patients, especially in those that experience aura (Lauritzen, Skyhoj Olsen, Lassen, & Paulson, 1983; Lauritzen & Olesen, 1984; Olesen,

Lauritzen, Tfelt-Hansen, Henriksen, & Larsen 1982; Skyhoj Olsen, Friberg, & Lassen 1987). Although these early studies have been heavily criticized for the inherent problems associated with imaging techniques (e.g., Olsen, 1995), studies using improved imaging techniques have provided convincing evidence that a CSD-like phenomenon does occur in MA patients. For example, Olsen et al. (1990) used an improved approach inducing migraines through angiography and identified that aura symptoms are experienced after a decrease of blood flow, particularly in posterior regions of the contralateral hemisphere from where the pain was experienced. More recent studies have made use of single photon emission computed tomography (SPECT) and have identified features that resemble CSD in MA (e.g., Olesen et al., 1990; Soriani et al., 1997). Alternative techniques such as positron-emission tomography (Andersson, Muhr, Lilja, Valind & Lundbergm 1997; Woods, Iacoboni, & Mazziotta, 1994), magnetoencephalography (Barkley, Tepley, Simkins, Moran, & Welch, 1990; Tepley & Wikesinghe, 1996), and MRI techniques (e.g., Hadjikhani et al., 2001; Sanchez del Rio et al., 1999) have all provided similar support for the role of CSD in MA. Unfortunately, CSD that is initiated in the visual cortex does not explain activation of the trigeminovascular system in MWO, as studies have failed to identify this phenomenon within this population. Alternatively, it has been proposed that CSD may be initiated in other cortical areas, such as sensory or motor areas, which would explain non-visual aura and MWO headaches. Furthermore, it is possible that phenomena similar to, yet not as easily detected as CSD, may occur in MWO (Bolay et al., 2002; Buzzi & Moskowitz, 2005).

Although there is ample evidence suggesting cortical dysfunction in migraine, it remains uncertain whether this is the cause of the observed visual stream deficits that

have been previously described. In terms of perimetric testing, most studies suggest precortical involvement due to the fact that bilateral homogenous deficits are not generally observed. Ischemia and vasospasmic nerve damage within the visual system, similar to those observed in glaucoma, have been suggested to be a source of damage to photoreceptors in migraine (Yenice, Temel, Incili, & Tuncer, 2006; Wang, Mitchell, & Smith, 1997). As noted above, perimetric studies support a pre-striatal deficit locus, and some additional evidence has been found in psychophysical paradigms (e.g.,Tibber & Shepherd, 2006). However, which process is initially responsible for visual degeneration in migraine remains elusive. It is possible that repeated CSD could cause post-receptoral damage or alter neuronal function at the cortical level. Currently, with the breadth of supporting evidence for CSD and the generally hyperexcitable of visual cortical functioning in migraine patients, it seems reasonable to assume cortical involvement in migraine-related visual deficits.

The present study sought to answer several questions that have remained elusive in visual research in migraine. First, although several studies have examined one or two of the visual streams, no study has sought to specifically assess all three streams simultaneously. This is surprising given that these three visual streams are distinct; yet merge at several points throughout the visual system. An abnormality in one visual stream does not necessarily exclude influences on other streams. Furthermore, the identification and comparison of abnormalities within each visual stream will provide a more comprehensive analysis of visual deficits and their pathway specificity. In addition, we made use of four separate experiments that target different hierarchical loci of visual processing in order to help determine the origin of the visual deficits.

If photoreceptoral damage, or visual cortex abnormalities, is caused by CSD in the visual cortex, then several predictions can be made. First, it would be expected that individuals with MA should show increased abnormalities in photoreceptor functionality as compared to MWO. Second, there should be a linear relationship with regards to aura frequency and visual deficits. In other words, individuals who have more frequent attacks should have more prominent deficits across our measures. Alternatively, if photoreceptoral abnormalities are due to vasospasm or ischemia that is independent of CSD within the visual cortex, then these deficits should be equal between both MA and MWO individuals. Based on previous research, we would expect these deficits to be more evident on measures that assess MC and KC stream operations.

In order to test these hypotheses, we measured four different sensitivity metrics: SWS-cone photoreceptor sensitivity using the SWAP, chromatic discriminability using the Cambridge color test, chromatic contrast sensitivity using bichromatic isoluminant Gabors, and achromatic contrast sensitivity using heteroluminant Gabors. Additional demographic data were collected with regards to frequency (i.e., how often headaches occur), duration (i.e., how long the patient has had headaches), and level of disability associated with headaches.

Method

Participants

All participants were recruited through introductory psychology subject pools and through posted and electronic advertisements. Prior to completing the study, all participants were fully informed regarding the nature and procedures of the study and provided written informed consent. All procedures were reviewed and approved by the Research Ethics Board at Lakehead University.

Our study included a total of 15 control participants (10 women and 5 men) with no history of migraine or frequent headaches. Our clinical groups consisted of 13 individuals with MA (11 women and 2 men) and 14 participants with MWO (10 women and 4 men). Participants were approximately age matched with the average age for controls, MA, and MWO being: $M = 21.3 \pm 2.87$ (*SD*), $M = 22.15 \pm 6.58$ (*SD*), and $M = 21.86 \pm 3.48$ (*SD*), respectively. All migraine participants were required to meet criteria for MA or MWO as defined by the International Classification of Headache Disorders (International Headache Society, 2004). Participants provided written consent to allow the researchers to contact the diagnosing physician/neurologist to confirm the diagnosis. All MA participants were required to have visual symptoms as part of their auras in order to draw inferences regarding visual processing that is specific to this group.

All participants underwent visual acuity screening using the Frieberg Visual Acuity Test (FrACT; Bach, 1996). Only participants with a FrACT near visual acuity score greater than 0.04log MAR were included in the study. Color vision deficits were preliminarily assessed using Ishihara pseudoisochromatic plates (1993, 24–plate edition) to ensure participants were not dichromats. All participants were free from any acute or chronic eye disorders and had no history of glaucoma, hyper/hypotension, diabetes, or epilepsy. Individuals taking daily medication were excluded from the study. In addition, participants that were taking prophylactic anti-migraine medication were excluded from the study, as were participants that had a migraine attack within a 48 hour period prior to testing or had taken acute anti-migraine medication within this period.

We made use of the Migraine Disability Assessment questionnaire (Appendix A; MIDAS, 2001) and an additional questionnaire to assess information related to headache duration, frequency of attacks, average duration of headache attack, and time elapsed

since the last attack (see Appendix A; Headache Questionnaire). Some variability was noted on these variables. The MIDAS provides a score of disability based on the number of days over the past three months during which a migraine headache has caused significant distress in social, occupational, and household activities. In our sample, participants in the MA category had an average score of $M = 25.54 \pm 41.41$ (*SD*) and the MWO group $M = 16.07 \pm 13.28$ (*SD*), although the groups did not differ significantly on this variable $t(25) = .813$, $p = .424$. These scores indicate that the majority of participants were in the moderate to severe range of disability. The MIDAS also provides information regarding the level of pain experienced during an average headache, this scale ranges between 0 (no pain at all) to 10 (pain as bad as it can be). The average rating on this pain scale was $M = 6.61 \pm 1.89$ (*SD*) in the MA group and $M = 6.14 \pm 2.03$ (*SD*) for the MWO group.

Average lifetime duration of migraine headaches was $M = 10.5 \pm 7.58$ (*SD*) years for MA compared to $M = 9.6 \pm 6.3$ (*SD*) years for the MWO group. The average number of headaches experienced per month were $M = 2.75 \pm 2.6$ (*SD*) in the MA group and $M = 4 \pm 3.46$ (*SD*) in the MWO group. In terms of the average duration of individual headache episodes, the MA group reported an average length of headache of $M = 5.45 \pm 6.4$ (*SD*) hours while the MWO group reported an average duration of headache of $M = 9.16 \pm 13.3$ (*SD*) hours. The average time since the last headache was $M = 22.75 \pm 18.82$ (*SD*) days in the MA group and $M = 9.9 \pm 9.45$ (*SD*) days for the MWO group. Given the variability of these variables between groups, we conducted a series of t-tests that failed to identify any statistically significant differences across groups. However, we did analyze the relationship of these variables with our main dependent variables across our various experiments.

Recent evidence suggests that hormonal shifts may have an influence on visual processes, this may be especially true for chromatic visual processing. In order to control for the influence of menstrual cycle we asked all female participants to complete a questionnaire (Appendix A; Menstrual Cycle Questionnaire) regarding their use of birth control and provide information that could be used as an estimate of menstrual phase. We used the backward count method to identify which phase of their cycle (i.e., menstrual, periovulatory, or luteal) participants were in on the day of testing. Our results indicate that there was not a significant difference of menstrual phase across groups, χ^2 (4, N = 28) = 1.101, p = .894. Similarly, no significant differences were noted in the number of individuals taking birth control medication across groups, χ^2 (2, N = 30) = .087, p = .958.

Experiment 1: Short-Wavelength Automated Periphery (SWAP)

Following the screening procedures, participants underwent SWAP measurements. In the present study, an AP200BY Automated Perimeter (Opto-Global, Adelaide, South Australia) was used to assess short-wavelength sensitivity across the visual field in a randomly selected eye. The apparatus required participants to position themselves on a chin-rest and view a stimulus bowl that covers 100° of their visual field. The background of the bowl was illuminated with a bright (100 cd/m^2) 530-nm "yellow" light, thus adapting and controlling for rods and MWS- and LWS-cone inputs. Participants dark adapted for 5 minutes and then focused on a 640-nm "red" fixation point for a period of 3 minutes to ensure proper retinal light adaptation. Following adaptation, participants were given a joystick and asked to indicate when they perceived the target stimuli. The target stimulus consisted of a Goldmann Size V 440-nm "blue" circular point (1.72°) that was presented along 162 points across the visual field. Results from this experiment provided a map of the participant's sensitivity to the target stimuli

across the visual field. The apparatus tracked pupil position using an infrared camera image to ensure proper foveal fixation and target image positioning at designated retinal positions.

The SWAP software (AP200BY Software, Opto-Global, Adelaide, South Australia) provides several valuable data points that were used as dependent variables. Generally, the software compares values of the participant to a normative sample that has been previously collected. However, because migraine prevalence is estimated to be between 33 percent in women and 13 percent in men (Launer et al., 1999) the normative database would not necessarily provide a valid comparison. Therefore, we made use of measures that were based on this normative sample but also examined direct comparisons of values between groups.

The standard values provided by the software included: average defect (AD), pattern defect (PD), overall average (AVG), and Zero Level (ZL). The BY (blue-on-yellow) Threshold Strategy included in the perimeter software, was used to ascertain these levels. This procedure measures retinal SWS-cone sensitivity and provides decibel (dB) outputs. AD can be considered a measure of global field depression, or elevation, and is within the range of -9 and +9 dB. PD provides a measure of local changes (i.e., comparisons of various regions within the visual field) that show a lack of sensitivity, the range is between 0 and 9 dB. Individuals with a smooth field with few deficits should have a PD close to 0 dB, whereas individuals with a high amount of variability within their entire visual field would have higher values. The PD measure is therefore not sensitive to global field depression, which would be more accurately assessed by AVG. AVG is a simple measure of overall performance on all points tested, each point not perceived by the participant is assigned a negative value (-1 dB) and this is subtracted

from all points observed. Finally, the ZL provides a measure that is the most common dB value (i.e., mode of all assigned values) recorded in the field tested.

Although the values provided by the perimeter are of interest, AD and PD values are based on norm comparisons. As such, the presence or absence of individuals with migraine in the normative database is unknown. Therefore, we completed direct comparisons between ZL and AVG values, which are not based on the normative sample, between our migraine groups and controls. Furthermore, we examined the actual sensitivity of 32 points across four major quadrants: vertical superior, vertical inferior, horizontal temporal, and horizontal nasal. We further divided these quadrants into two additional locations based on eccentricity: central (between 6° and 15° eccentricity for vertical quadrants, and between 3° and 15° eccentricity for horizontal quadrants) and peripheral (between 22° and 50° eccentricity for both vertical and horizontal quadrants), for a total of eight retinal locations (See Appendix B; SWAP Zones). The average (within-group) sensitivity value for each point within each quadrant was used as a measure of sensitivity for this area. We were also interested in examining group differences in central areas that were not orientation specific; therefore we examined average values from central rings within 1°, 3°, and 6° retinal eccentricities.

In order to ensure the validity of the results, it was necessary to measure false positive errors (i.e., participants pressing the button when no stimuli is present) and false negative errors (i.e., no response when retested on an area that has been previously tested positive). Participants with an excess of 20 percent false positive or false negative errors were removed from the analyses.

Experiment 2: Cambridge Colour Test

The Cambridge Colour Test [Cambridge Research Systems (CRS), Rochester, UK] is based on the work of Regan, Reffin, and Mollon (1993) and is used to infer chromatic discrimination sensitivity along cardinal protan, tritan, and deutan axes (trivector test). Furthermore, the test produces chromatic discrimination ellipses and has been used to assess KC and PC abnormalities in Parkinson's disease (Silva, Faria, Regateiro, Forjaz, Januario, Freire, & Castelo-Branco, 2005) and Multiple sclerosis (Regan, Freudenthaler, Kolle, Mollon, & Paulus, 1998). Extensive norms for this test have been collected and it has been shown to have high level of reliability and validity (Ventura, Silveira, Rodrigues, de Souza, Gualtieri, Bonci et al., 2003).

The stimuli was presented on a 22-inch Mitsubishi Diamond Pro 2070 monitor powered by a CRS ViSaGe stimulus generator with 14 bit resolution per color channel at a 200 Hz frame rate. The stimulus computer consists of a Dell Precision Workstation with a Pentium 4 processor running at 3.6 GHz. Calibration and gamma-correction of the software and monitor was conducted with a Minolta colorimeter and calibration software provided with the ViSaGe system. The calibration was verified using a spectroradiometer (RadOMA GS-1253; Gamma Scientific, San Diego, California).

The method used in this experiment is similar to that used by Silva et al. (2005) in their assessment of magno-, parvo- and koniocellular pathways in Parkinson's disease. The experiments presents participants with a Landolt-like C-shaped ring (gap size = 1°, outer diameter: 7.6°, inner diameter: 3.81°) at a viewing distance of approximately 309 cm. Participants were asked to indicate the location of the gap in the C, which could occur at one of four possible positions (up, down, left, right). Random variations of luminance and spatial noise characteristics force the participant to use only color cues to

identify the gap in the C (Regan, Reffin, & Mollon, 1993). In this task, only the chromaticity of the C is adjusted, chromaticities based on CIE 1976 (u' v') color space allow the isolation of cone or colour-opponent processes. The Trivector version of the test was used to ascertain chromatic performance along the classical protan, deutan, and tritan axes. Examples of stimuli specific to each axis are provided in appendix C. The trivector test provides psychophysical discrimination thresholds based on assessing three interweaved random independent staircases.

In addition, discrimination ellipses (i.e., confusion areas) were assessed along eight symmetrical color vectors centered on the following three different locations CIE 1976 space: 0.1977, 0.4689; 0.1925, 0.5092; 0.2044, 0.4160. The software produces three discrimination ellipses centered on each of these points. Eight vectors for each of the three discrimination ellipses represented excursions from the center point across vectors spaced 45° from each other. Chromaticities were varied using an interleaved independent random staircase procedure, for each of the three staircases. Each correct answer decreased the target chromaticity to one closer to the background; whereas an error caused an increase in target chromaticity relative to the background. The test was completed following 11 reversals on each of the staircases. These ellipses were defined in terms of confusion vector length, ellipse length, axis ratio, and angle. Vector length can be considered a measure of the magnitude of chromatic deficits, whereas the axis ratio indicates the specificity of the damage deficits, and the angle can be used to assess the chromatic pathway most affected.

These quantitative measures were used to ascertain relative functionality of "red-green" (i.e., PC) and "blue-yellow" (i.e., KC) streams. Whereas Experiment 3 below assesses cortical contrast sensitivity for PC and KC streams, the Cambridge color test

assesses both chromatic discrimination thresholds (jnds) for stimuli that are specific for cone types and provides ellipses which identify stream-specific deficits.

Experiment 3: Chromatic Spatial Contrast

In order to assess the chromatic properties associated with PC and KC visual streams we measured chromatic spatial contrast sensitivity. The experiment assessed spatial chromatic contrast sensitivity to bichromatic isoluminant stimuli of varying spatial frequencies. Specifically, the stimuli consisted of chromatic sinusoidal gratings that selectively isolated LWS-, MWS- and SWS-cone contrast mechanisms. Chromatic contrast sensitivity measures such as this have been previously used to selectively identify PC and KC stream functionality in a variety of conditions including: Leber hereditary optic neuropathy, Parkinson's disease, macular degeneration, age-related visual loss, and mercury toxicity (Delahunt, Hardy Okajima, & Werner, 2005; Hardy, Delahunt, Okajima, & Werner, 2005; Rodrigues et al., 2007; Ventura et al., 2005).

The spatiotemporal stimuli were presented on a gamma corrected Viewsonic G225 21-inch CRT monitor with a resolution of 1024x768 pixels at 150 Hz. The display was be driven by a NVIDIA GeForce 6600 LE graphics card on a Dell Dimension DXP051 PC with a 3.2 GHz processor.

Similar to the methods used by Ventura et al. (2005) we used stimuli with chromatic properties based on S-(L+M) and L-M geniculate cone vectors (De Valois, De Valois, Switkes, & Mahon,1997). The chromaticities of our stimuli varied between "blue-and-yellow" (i.e., S-(L+M) varying) and "red-and-green" (i.e., L-M varying). In this paradigm, the "blue-and-yellow" (B/Y) varying stimuli can be used to infer chromatic properties of the KC stream. Similarly, the "red-and-green" (R/G) varying stimuli can infer chromatic properties of the PC stream.

Isoluminant bichromatic vertical sinusoidal gratings were presented at spatial frequencies of 0.5, 1.5, and 4 cpd. We used both steady-state and temporal 4-Hz counterphase modulation presentations for each spatial frequency. The chromatic properties of our stimuli in 1931 CIE space were red: .3828, .2846; green: .2639, .3772; blue: .2739, .2263; yellow: .4280, .4976. The stimuli varied in spatiochromaticity across individual linear vectors between the above CIE specified endpoints (See appendix C, Chromatic Properties of B/Y and R/G Stimuli) and were centered on an approximation of D6500 (.3255, .3216, for R/G gratings; .3132, .3158, for B/Y gratings). The average luminance levels were 35.73 cd/m2 for the R/G gratings and 34.95 cd/m2 for B/Y gratings. Examples of the stimuli used are presented in Appendix C. The visual properties of all stimuli were verified using a spectroradiometer (RadOMA GS-1253; Gamma Scientific, San Diego, California).

The stimuli were presented binocularly with the participant seated 75 cm from the display. Testing began after a seven-minute dark adaptation followed by a three minute light-adaptation to the background. Participants were pseudo-randomly assigned to complete either the B/Y or R/G presentations first. Contrast thresholds were assessed using a 2AFC, 2-interleaved staircase procedure. Each grating was circular and had a visual angular diameter of 5°. We used logarithmic step sizes of 0.1 which required one correct response for an increase in step size and one incorrect response for a decrease in step size. Each staircase terminated after four (for practice trials) or six (for experimental trials) reversals. Each stimulus was presented within a one second window, after which participants were asked to indicate with a response pad which side of a "white" (CIE 1931 chromaticity of x = .305 y = 0.3275, and luminance value of 18 cd/m^2) crosshair the Gabor appeared on (left or right side). Participants were asked to complete two threshold

discriminations for each spatial frequency in both conditions, the geometric mean of which defined chromatic spatial contrast threshold. The inverse of this threshold defined CS performance for both KC and PC stream operations.

Experiment 4: Achromatic Luminance Contrast Sensitivity

In order to assess achromatic luminance contrast sensitivity we made use of a luminance-based contrast sensitivity measure. Stimuli were presented on a high-resolution Nanao 9080i colour monitor driven by a 32 bit microprocessor (Texas Instruments Volante 34020 GSP) specialized for graphics operations. The luminance range of each of the 256 levels of the R, G, and B phosphors were expanded using a resistance gray-scale expander box into 32,768 monochrome levels. In order to compare results of this experiment with the chromatic contrast isoluminant experiment, we used the same spatial (.05, 1.5, and 4 c/deg) and temporal (0 Hz and 4 Hz) frequencies. Prior to experimental testing, participants dark adapted for seven minutes, followed by three minutes of light adapt to the spatial averaged "gray", 13.57 cd/m^2 background. Luminance values for the gratings were 20.2 cd/m^2 for the peak and 10.35 cd/m^2 for the trough. The luminance properties of all stimuli were verified using a Spectroradiometer (RadOMA GS-1253; Gamma Scientific, San Diego, California). The psychophysical procedure was the same as Experiment 2. This experiment was designed to measure achromatic thresholds with an emphasis on MC isolation. The lower spatial-higher temporal frequency stimuli optimally activate MC streams.

In all, Experiment 1 provides functional information about retinal sensitivity, Experiment 2 provides information about receptoral and postreceptoral operations necessary to achieve chromatic jnds and Experiment 3 & 4 provide information about postreceptoral, cortical processing necessary for considering orientation-specific

spatiotemporal contrast gratings, both in the chromatic domain (for maximal PC- and KC-responsivity) and achromatic domains (for maximal PC- and MC-responsivity).

Statistical Analysis

Prior to conducting statistical analysis, all data were screened for statistical outliers and violations of normality. If distributions were significantly skewed or non-Gaussian (Kolmogrov-Smirnov tests, $p < 0.05$) the appropriate non-parametric statistic (i.e.,Mann-Whitney U tests or Kruskal-Wallis H test) was used. Analyses of parametric data was conducted using MANOVAs and independent group t-tests. We also included descriptive correlations, either Spearman rank correlation coefficients or Pearson's correlation tests, to identify relationships between migraine group characteristics and our dependent variables.

Results

Experiment 1: Short-Wavelength Automated Perimetry

SWAP values provided by the perimeter software were analyzed with MANOVAs with migraine type (MA, MWO, and Controls) while covarying for age. Two separate MANOVAs were used to analyze the variables provided by the SWAP software. The first MANOVA assessed the group differences on variables that were based on the normative database (i.e., AD & PD). Results of this analysis were not significant, F (2, 36) = .483; p >.05. Histograms of the AD and PD findings are shown in Figure 1. The second MANOVA was used to assess group differences on sensitivity measures that were not based on a normative sample (i.e., AVG, and Zero Level). This analysis showed a significant effect for group, F (4, 68) = 4.55; p< .05. These findings are depicted in Figure 2. Planned comparisons revealed significant differences between MA (M = 21.85 ± 2.67) and controls (M = 24 ± 2.06) and between MA and MWO (M =

24.37, ± 2.53) on the AV measure. Similar results were identified for the Zero Level measure, which indicated significantly lower scores for the MA group (M = 26.75, ± 1.81) as compared to controls (M = 28.33, ± 2.28), and slightly lower than MWO (M = 27.18, ± 2.14).

As previously mentioned, we analyzed specific SWAP points across the retina we divided these points into a total of eight quadrants. The sensitivity measure for each quadrant for each clinical group are reported in Figure 3. We analyzed this data using a 3 (group) x 8 (quadrant) MANOVA with age as a covariate. The results of this analysis were significant, $F(8,30) = 3.524, p < .01$. Planned comparisons were conducted between groups across all quadrants. Significant differences between groups are graphically depicted in Figures 3 and 4. Results indicate significant differences between MA and controls in the following retinal locations: vertical superior central, vertical inferior peripheral, horizontal nasal central, horizontal temporal peripheral, and horizontal temporal central. Contrasts between the MWO and control group revealed a significant difference only in the horizontal nasal central location. The only significant difference between MA and MWO was in the horizontal temporal region. All contrasts were significant at $p < 0.05$.

Based on these results, we examined correlations between headache variables (number of headaches per month, length of average headache, days passed since last headache, lifetime duration of migraine, and pain rating of headaches) and SWAP values. Amongst these relationships, significant correlations were found only between lifetime duration of migraine and ZL in the MA group, Spearman's $\rho(12) = -.729, p < 0.01$. Partial correlations were used to assess if lifetime duration of migraine was associated with SWAP values while controlling for age. Results indicated a strong negative

correlations for both ZL and AV values in the MA group: $\rho\,(12) = -.743, p < .05$; and $\rho\,(7) = -.840$, $p < .01$, for ZL and AV, respectively. No significant differences were identified based on menstrual phase as related to any of the SWAP indices.

Experiment 2: Cambridge Color Test

In order to ascertain chromatic discrimination thresholds, we used two test approaches included in the Cambridge Color Test. The first approach, the Trivector Test, examines chromatic discrimination across the major protan, deutan and tritan confusion lines. These results are presented in Figure 5, which depicts the excursion from the neutral white across protan, deutan, and tritan axes. We used a MANOVA to test for these differences. Our results did not show any significant differences across groups on any of the three discrimination axes, $F\,(3, 33) = 2.11, p =$ ns. However, individual analysis suggests that differences between MA and controls approached significance on the tritan line, $t\,(23) = 1.846, p = .078$. We also created MacAdam discrimination ellipses based on eight vectors initiated within CIE u' v' colour space. Results for the three ellipse measures are presented in Figures 6, 7, and 8. Ellipse data were analyzed with Kruskall-Wallis H tests which showed no significant group differences ($p > .05$).

We also examined correlations between headache variables and menstrual cycle, none of which were significant. However, a strong negative correlation was identified between results on the tritan line and the ZL SWAP measure in MA, Spearman's $\rho\,(7) = -.782, p<.01$.

Experiment 3: Chromatic Spatial Contrast Sensitivity

Chromatic CS results are presented in Figure 9 and 10 for B/Y spatial (0 Hz) and spatiotemporal (4 Hz) stimuli, and Figure 11 and 12 for R/G spatial (0 Hz) and spatiotemporal (4 Hz) stimuli, respectively. As the data were significantly non-Gaussian,

differences between groups were identified through Kruskall-Wallis H tests. A significant difference between groups was identified for the steadily presented 4 cpd B/Y gratings, χ^2 (2, N = 32) = 6.455, p< .05. No significant differences were identified for R/G gratings at any spatial frequency in either the steady, or temporally modulated presentations. No significant correlations were identified between headache variables and CS measures at any spatial frequency. However, statistically significant correlations were identified between the average of all of the SWAP quadrants and CS measures to non-temporally modulated B/Y gratings at 4 cpd in the MA group ρ (10) = .45, p = .013.

Experiment 4: Achromatic Contrast Sensitivity

Similar to the chromatic data, group differences were ascertained through Kruskall-Wallis H tests. Results for steady and temporally modulated stimuli are presented in Figures 9 and 10, respectively. No significant differences were identified for gratings at any spatial frequency in either the steady, or temporally modulated, presentations. No significant correlations were identified between CS measures and headache variables.

Discussion

In order to assess the properties of the three visual streams in migraine, we made use of both perimetric and psychophysical measurements. Results from our SWAP measurements suggest an SWS-cone subsensitivity in MA individuals. Only subtle subsenstivities were observed with MWO, and these generally did not reach statistical significance. We identified significantly reduced sensitivity across the visual field as determined by the AV and ZL measurements in the MA group. Furthermore, our results indicate that various regions within the retina appear to be less sensitive than others, as identified in our SWAP quadrant comparisons We also identified, using perimetric rings,

a significant reduction in sensitivity in central 3° and 6°, but not within 1° regiona. Although there tended to be similar reduction in many of these regions in the MWO group, these did not approach statistical significance with the exception of the horizontal nasal quadrant. These results suggest that subsensitivities in SWS-cone are obvious in MA, but are more discrete in MWO.

Results from our SWAP analyses are largely in agreement with previous SWAP studies that have identified SWS-cone deficits in periods between migraine headaches (e.g., McKendrick & Badcock, 2004; McKendrick et al., 2007;Yenice et al., 2006; Yenice et al., 2007). However, unlike these studies, we found far more obvious deficits in MA as compared to MWO. Whereas previous studies have made use of norm-based comparisons, we found these results to be insignificant, most likely due to comparisons with a compromised normalized population. Furthermore, we were interested in providing more specific analyses of the quadrants described, thus providing additional information regarding retinal regions affected. Collectively, our SWAP results suggest a more widespread deficiency than has been previously reported that exists not only within peri-foveal areas (e.g., McKendrick et al., 2002), but also within central regions of the retina, and this is true mainly for MA.

Results from the Cambridge Color Test provided some interesting results, although the mean differences across groups failed to reach statistical significance. Discriminability along the tritan axis for MA versus controls approached significance. However, the direction of this difference was opposite of what was expected, with the MA group showing improved discrimination as compared to controls (i.e., smaller differences in chromaticity between the Landolt 'C' and background were required for discrimination with the MA as compared to control group). At first glance, this appears to

contradict our SWAP findings (i.e., SWS-cone desensitizations in MA), which intuitively might produce increases in the amount of excursion along the tritan line. This apparent contradiction, however, may be due to differences in functional hierarchy where perimetric results are defined as quantal and trichromatic, but chromatic discrimination is characterized by post-receptoral color opponent channels derived by the sums and differences of the receptor outputs. This means that performance based on stimuli modulated along cardinal axes may be separable (i.e., we can probe and isolate the two primary opponent mechanisms) but are still intercorrelated, possibly by means of a mutually inclusive gain operation (Gunther & Dobkins, 2003). Further evidence for this proposition stems from the fact that sensitivity on protan and deutan lines were superior in MA, although not sufficiently different to be statistically significant. With the understanding of functional hierarchy, it is possible to reconcile a sub-sensitive SWS-cone retinal system with a supra-sensitive discrimination capability in MA patients, the latter of which may be governed by compensating gain operations from the opponent LWS- and MWS-cones contributions that make up the KC stream. This sort of compensatory interaction would occur at a post-receptoral location, likely at the level of the ganglion cell or LGN (e.g., De Valois, Cottaris, Elfar, Mahon, & Wilson, 2000; Lee, Valberg, Tigwell, & Tryti, 1987; Lennie & Movshon, 2005; Solomon & Lennie, 2005).

Alternatively, unlike SWAP, the Cambridge Color Test relies on converging properties of a large amount of cones across various regions of the retina. Therefore, although SWAP sensitivity was reduced across some areas of the retina, other areas showed normal sensitivity levels. Therefore, discrimination based on the summation of subsensitive and normally sensitive receptive fields could potentially increase

discrimination capabilities in the MA group. Again, this would rely on summating properties that occur at a level downstream of the photoreceptor.

In order to further examine higher level chromatic processing, we examined chromatic contrast sensitivity selective to the PC (R/G) and KC (B/Y) streams in Experiment 3, using isolumuminant Gabors that selectively assessed stream operations at the cortical level. The chromatic CS measures showed no apparent differences with stimuli that preferentially activated the PC stream. No significant differences were found between groups for any of the spatial frequencies tested, whether temporally modulated at 4 Hz or not.

The B/Y chromatic contrast stimuli that probed KC stream operations, however, did show a significant difference among groups with non-temporally modulated stimuli at 4.0 cpd. This finding suggests that contrast sensitivity remains comparable across groups at peak spatial frequencies, possibly due to gain compensation originating from LWS- and MWS- input into the KC stream; however, once the spatial frequency begins to approach the upper spatial limits of the KC stream (at 4.0 cpd), this proposed compensation may not be sufficient, thus leading to significantly lower contrast sensitivity levels.

In Experiment 4, we sought to assess achromatic contrast processing across groups using spatiotemporal Gabors that optimally activate PC or MC streams. Results of this experiment failed to identify any significant differences across groups. Visual stream deficits associated with PC operations would have been observed with non-temporally modulated Gabors at higher spatial frequencies, whereas MC deficits should have been apparent in the temporally modulated Gabors at lower spatial frequencies. In either case, such differences were not identified.

Our results regarding the lack of deficits in the PC and MC streams differ from some studies which have found equivalent deficits in contrast processing across PC and MC streams (e.g., McKendrick & Badcock, 2003). Our results also challenge past perimetric findings which identified more prominent deficits in MC as compared to PC streams (e.g., McKendrick et al., 2003). This divergence may be due to various factors. First, it is possible that those studies that identified MC deficits may have been picking up on KC stream deficit artifacts particularly if the ventral, along with the dorsal, KC streams are influenced by migraine. The ventral KC stream does play a role in luminance and temporal aspects of vision (Calkins, 2001); although again, because all temporally modulated stimuli produced no significant group effects in our study, this proposition is not fully supported. Second, the majority of studies that have identified MC effects have made use of TMP, a perimetric measure of MC-related operations that does not necessarily involve the higher-end light contrast operations that have been activated in Experiments 3 and 4 in our study. Third, our sample of migraine sufferers had a lower mean age than those of most other studies, and our participants had been suffering from headaches for a period of time that was lower than those in most other studies. As such, it is possible that the deficits associated with the MC, and to a lesser extent the PC, stream occur as a result of senescence, lifetime duration of the migraine condition, and/or attack frequency.

In order to further examine the influence of these last variables, we examined correlations between self-report headache characteristics and our experimental results. With the exception of lifetime duration of migraine, none of these variables were significantly related to our neurometric measures. However, there were strong negative correlations between lifetime durations and ZL SWAP measurements in the MA group.

Partial correlations between SWAP measures and the influence of lifetime duration of migraine while controlling for age revealed significant negative correlations for both the ZL and the AVG measurements. These results suggest that more prominent reductions in SWS-cone sensitivity exist in individuals who have had migraines for a longer period of time.

Recently, the nature of SWS-cone abnormalities have been linked to glaucoma-like damage due to ocular vascular dysregulation within the eye, which would initially affect the disease-vulnerable SWS-cone system (e.g., McKendrick & Badcock, 2004; McKendrick et al., 2007; Yenice et al., 2006; 2007). Cortical blood flow is certainly diminished during migraine attacks (e.g., Olesen et al., 1990; Soriani et al., 1997) and vascular dysregulation has been shown to extend to peripheral locations such as the fingers of migraine patients (Hegualijai, Meienberg, Dubler, & Gasser, 1997). Therefore it is possible that ischemic, hypoxic, or vasospasmic damage may occur within the eye due to this dysregulation. This proposition has recently been challenged, however, by Harle and Evans (2006) who proposed SWS-cone mechanism deficits due to neural dysfunction operating on the less populated SWS-cones rather than physical, glaucoma-like damage to photoreceptors.The nature and functional impact of SWS-cone deficits remains to be further explored, and we cannot rule out a cortical contribution to sub-sensitivity contrasts; however, our results are also consistent with a pre-striatal locus of dysfunction as has been suggested by others (e.g., McKendrick & Badcock, 2004a; Tibber & Shepherd, 2006; Yenice et al., 2007). We identified SWS-cone subsensitivites in our SWAP measurements. The subsensitivities did not extend to the higher-ordered chromatic discrimination task, but in fact revealed an almost, albeit non significant, supra-discriminability for the MA group. From an even higher-ordered cortical

perspective, migraineurs showed lowered contrast sensitivity but only with sustained, high spatial frequency B/Y Gabors—a stimulus condition that lies within the upper extreme end of the KC pathway operating range. Had our measured performance deficits been exclusively cortical in origin, we would have expected more robust findings including reduced discrimination capabilities and more obvious contrast sensitivity deficits at all spatial frequencies in the B/Y condition. Although previous studies have examined contrast properties in SWS-cone specific chromaticities (e.g., Shepherd 2005, 2006a, 2006b), we are the first to integrate a paradigm that makes use of bichromatic isoluminant stimuli to preferentially assess PC and KC stream properties. Based on our findings we suggest that at the level of LGN (or higher), SWS-cone subsensitivites are compensated for by postreceptoral (L+M) inputs. However, our results indicate that this compensation may only be sufficient for spatial frequencies that are near optimal levels for the KC stream. Once the frequencies approached KC spatial limits, we noted a significant separation between MA and controls.

Our failure to find similar findings between the steady and temporally modulated stimuli are likely due to either the temporal frequency limitations of the SWS-cone system (e.g., Liu & Wandell, 2005) or to differential dysregulation between the dorsal, middle and ventral KC stream divisions. This is consistent with the decreased, yet not significant, thresholds in the temporally modulated B/Y condition. Ventral LGN layers of the KC stream are thought to be involved in motion aspects of vision and functions within the superior colliculus, including reflexive control of eye moments. Middle layers are thought to be involved in color opponency through projections to V1 blobs, whereas dorsal layers are thought to be involved in low-acuity visual information (Calkins, 2001;

Hendry & Reid, 2000). Therefore, it is possible that our results reflect abnormalities that are specific to only the "middle" layer output as opposed to ventral layers.

In summary, our results from the SWAP analysis are in general agreement with previous studies that have identified subsensitivities in SWS-cone functionality. However, whereas other studies have identified these deficits in specific hemifields, our analysis suggests that such deficits exist across various regions of the retina, including both central and peripheral locations. Furthermore, we identified a strong negative correlation between SWAP variables and duration, suggesting that the longer an individual has experienced migraines, the more prominent SWS-cone deficits appear to be. This observation was only true in the MA group. Participants with MWO tended to have similar, though slightly lower, SWAP values as compared to controls. The finding that MA group had more prominent SWS-cone deficits than the MWO group, suggests that although the two disorders share similar features, there is a unique property of MA which causes additional stress to the visual system, thus leading to more prominent deficits. Researchers have suggested that the broad cortical dysfunction, CSD, is one of the key pathophysiological differences between the two disorders. It therefore remains reasonable to assume that this may be why some of our experimental tasks tended to differentiate MA from MWO performances. Having said this, however, our results also, from a hierarchical neural perspective, would seem to suggest that retinal SWS-cone deficiencies precede cortical abnormalities with the latter compensating for the former dysregulation.

The current study extends previous literature regarding visual deficits in migraine by establishing that visual deficits in migraine can be largely limited to SWS-cone operations, and may extend to higher end visual stream processes involving the KC

system. Although we did find some effects at the specific stimulus frequencies, a more robust deficit may be evident with those who have had longer experiences with the disorder. Future studies can help elucidate the exact locus of these possible KC deficits. For example, using an isoluminant B/Y chromatic Gabor presented at various orientations, may provide important insights as to the cortical-based lateral inhibitory processes associated with KC dysregulation. Certainly this argument was made with respect to heteroluminant contrast measures carried out by Wilkinson and Crotogino (2000) who found no clear achromatic inhibitory differences.

The integration of perimetric and higher-end psychophysical measures represents an improved method for identifying the locus of migraine-related visual deficits. Future studies should seek to continue to combine these methods, as well as integrate physiological or brain imaging techniques in order to further our understanding of not only possible spatially-defined locus of migraine disorders, but also the associated temporal neural events. This can be accomplished by combining effective psychophysical probing tasks with event-synchronized EEG measurements. Finally, there is a definite need for longitudinal neuro- and psychometric analysis across migraine symptom expression to further assess the progression of CSD with putative hierarchical visual disruptions or deficits. Such studies would help identify whether deficits exist prior to the onset of migraine headaches, or whether they are the result of migraines themselves with a dependency on the duration and/or frequency of the disorder.

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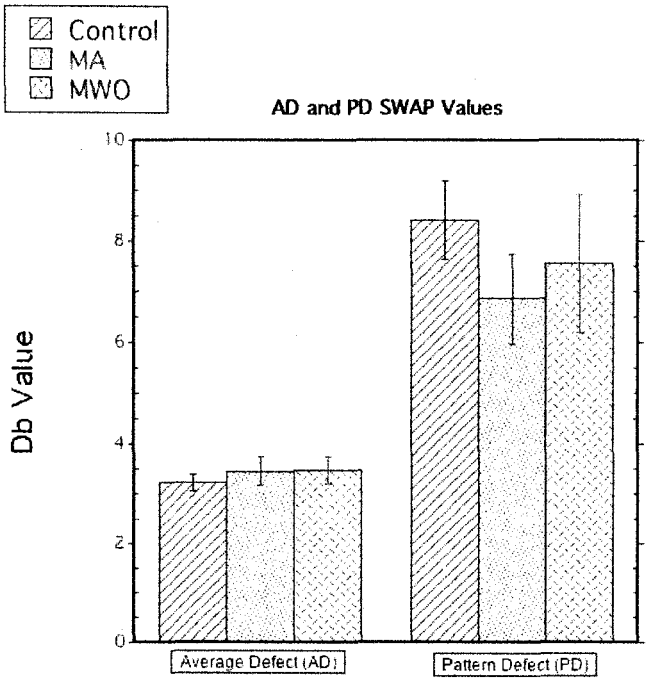


Figure 1. SWAP Values for average defect (AD) and pattern defect (PD) across groups. No significant differences were identified between groups. Error bars = ± SEM.

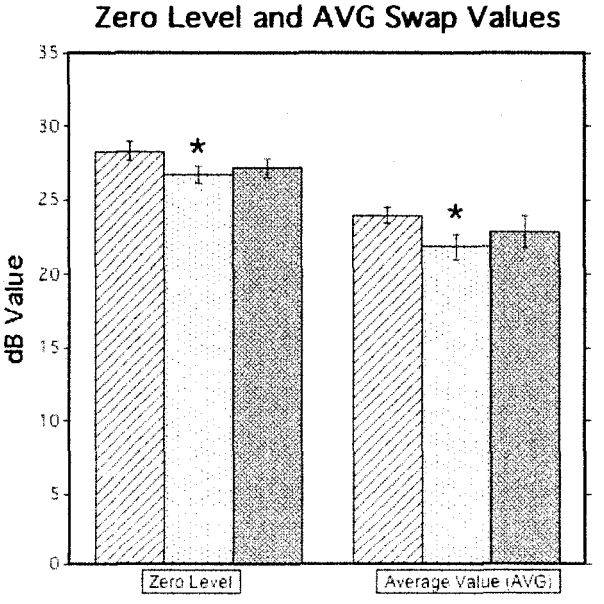


*Figure 2. SWAP Values for Zero Level(ZL) and Average (AVG) across groups. *: $p < 0.05$. Error bars = ± SEM.*

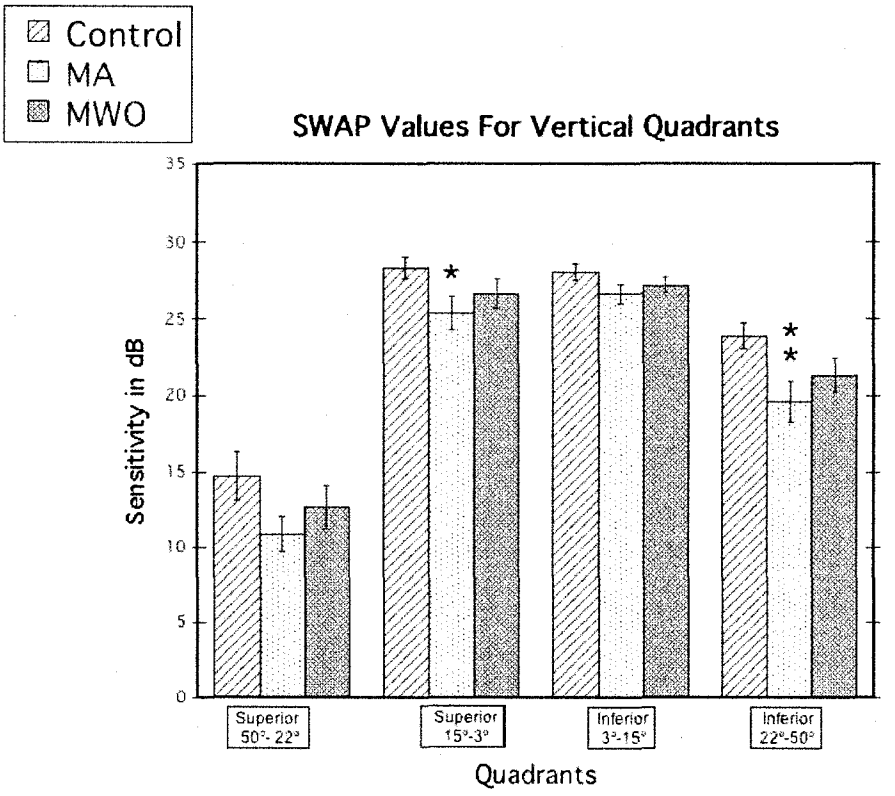


*Figure 3. SWAP sensitivity values for vertical quadrants. *: p< 0.05; **:p< 0.01. Error bars = ± SEM.*

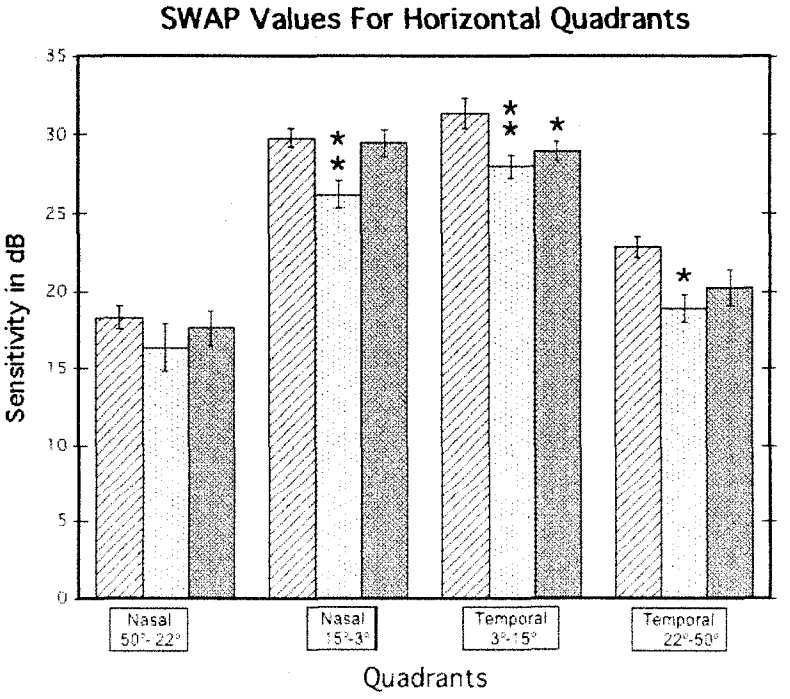


*Figure 4. SWAP sensitivity values for horizontal quadrants. *: p< 0.05; **:p< 0.01. Error bars = ± SEM.*

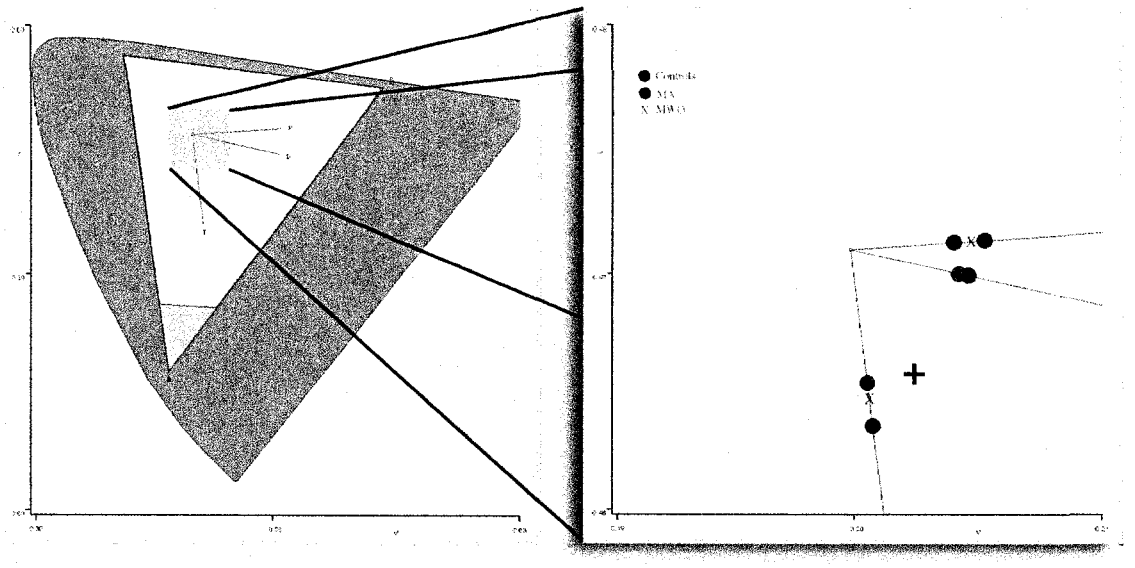


Figure 5. Trivector results from the Cambridge color test. The circles and 'x' represent excursions from the neutral point across protan (P), deutan (D), and tritan (T) lines. Excursions along any line indicate the magnitude of difference required between the 'C' and background necessary for correct discrimination. +: p = .078 (two-tailed).

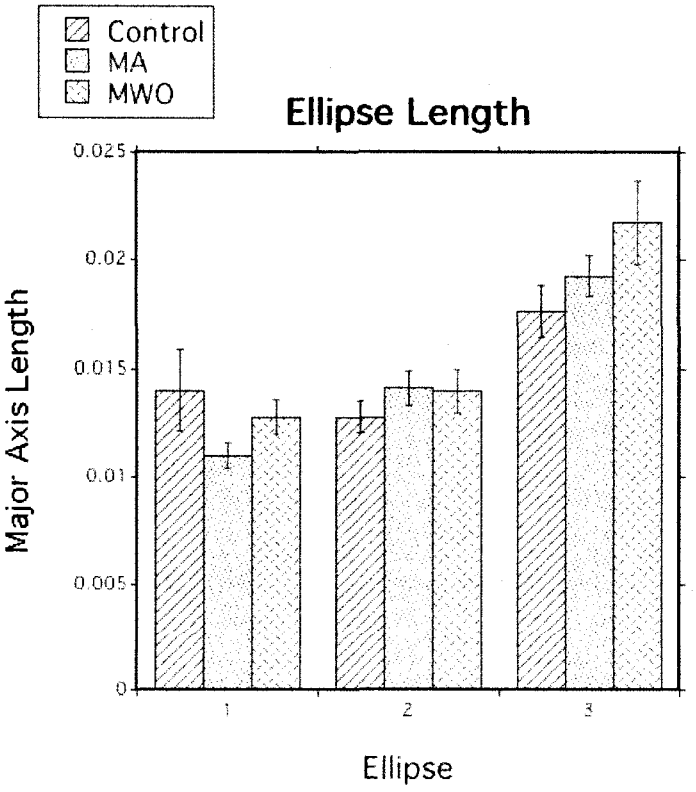


Figure 6. Ellipse major axis length from the three separate ellipses. Results were non-significant for group comparisons. Error bars = ± SEM.

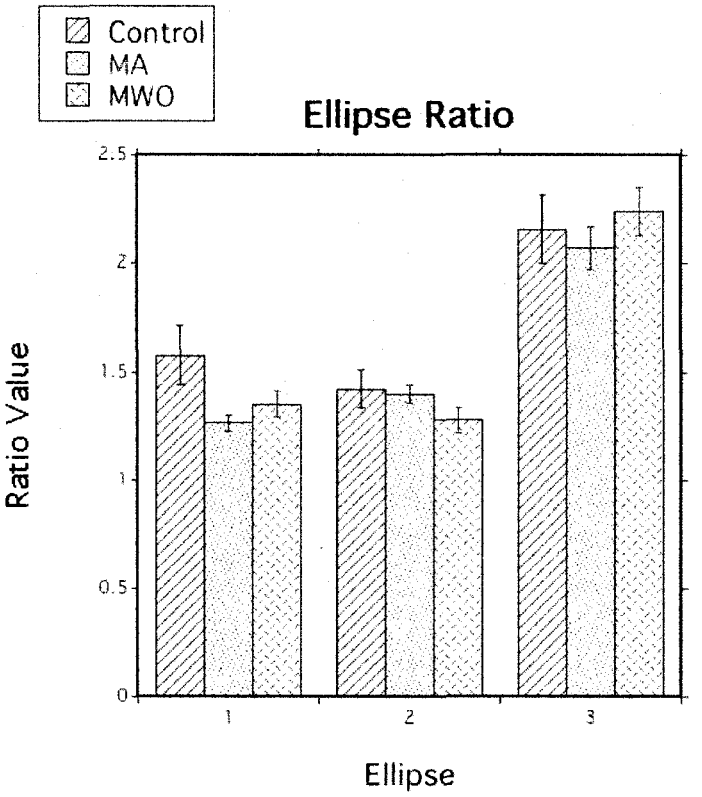


Figure 7. Ellipse ratio from the three separate ellipses. Results were non-significant for group comparisons. Error bars = ± SEM.

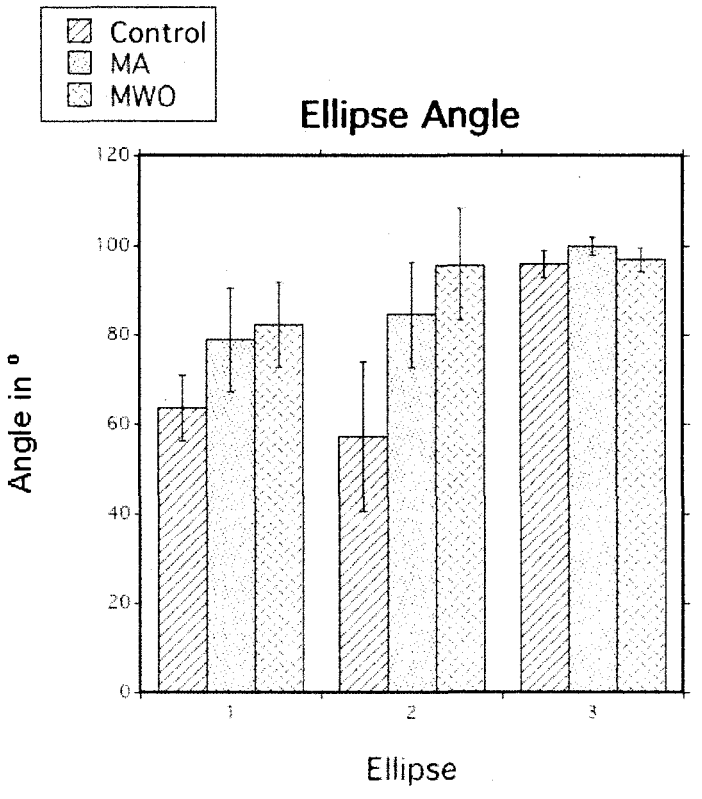


Figure 8. Ellipse angle from the three separate ellipses. Results were non-significant for group comparisons. Error bars = ± SEM.

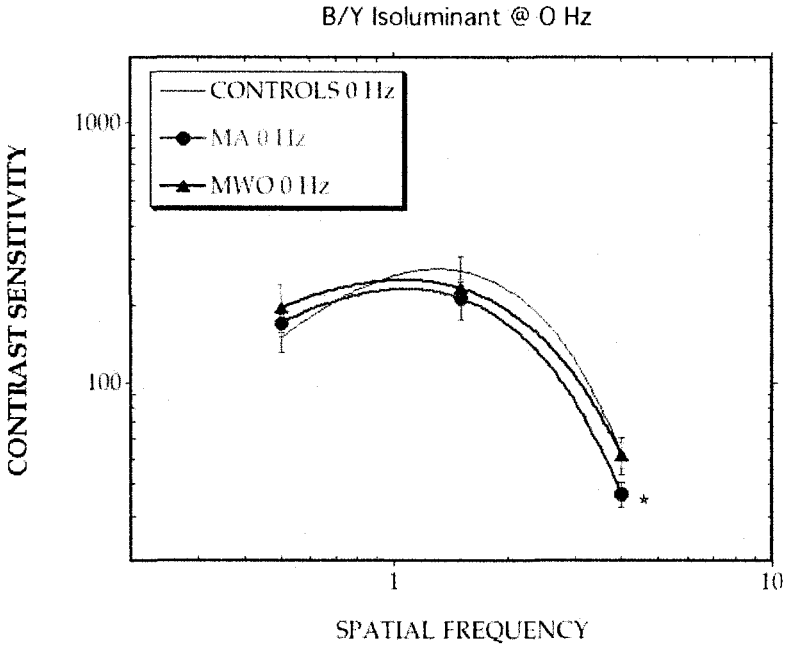


*Figure 9. Chromatic contrast sensitivity for stimuli steadily presented "blue-yellow" stimuli. Points indicate average chromatic contrast sensitivity for each group. Axes are plotted using a log-log scale, and a double exponential fit was used to better delineate data trends. *: $p < 0.05$. Error bars = ± SEM.*

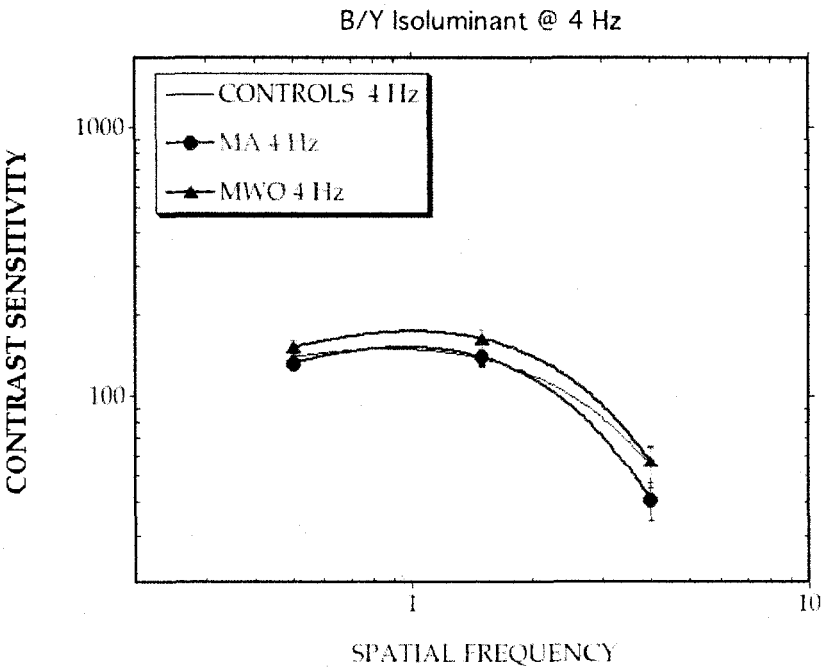


Figure 10. Chromatic contrast sensitivity for temporally modulated "blue-yellow" stimuli. Details are the same as in Figure 9. No significant differences were found between groups. Error bars = ± SEM.

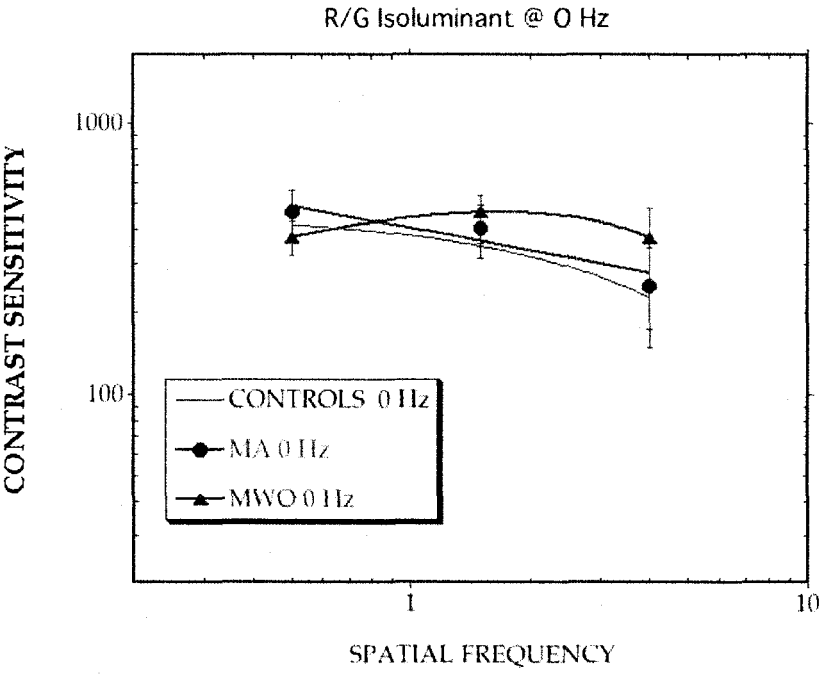


Figure 11. Chromatic contrast sensitivity for stimuli steadily presented "red-green" stimuli. Details are the same as in Figure 9. No significant differences were found between groups. Error bars = ± SEM.

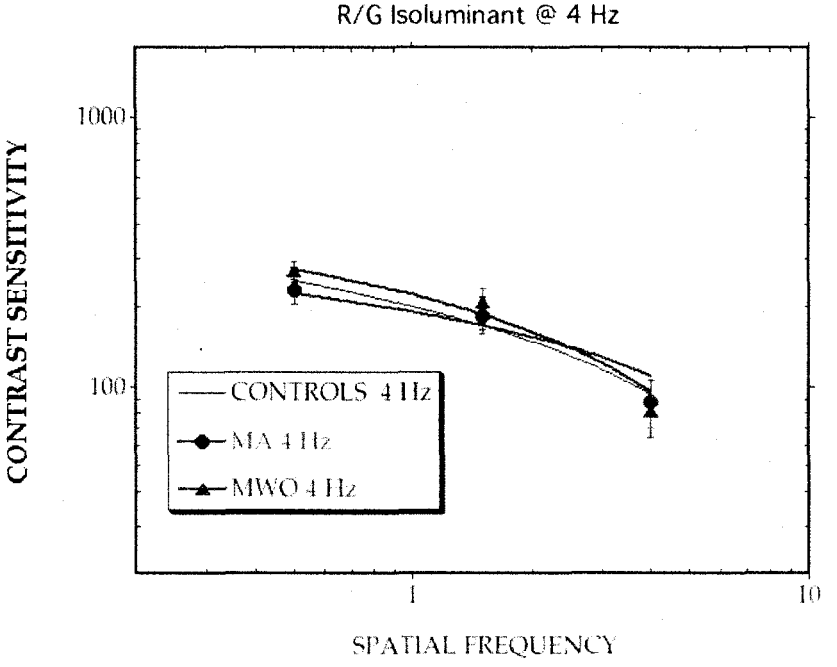


Figure 12. Chromatic contrast sensitivity for temporally modulated "red-green" stimuli. Details are the same as in Figure 9. No significant differences were found between groups. Error bars = ± SEM.

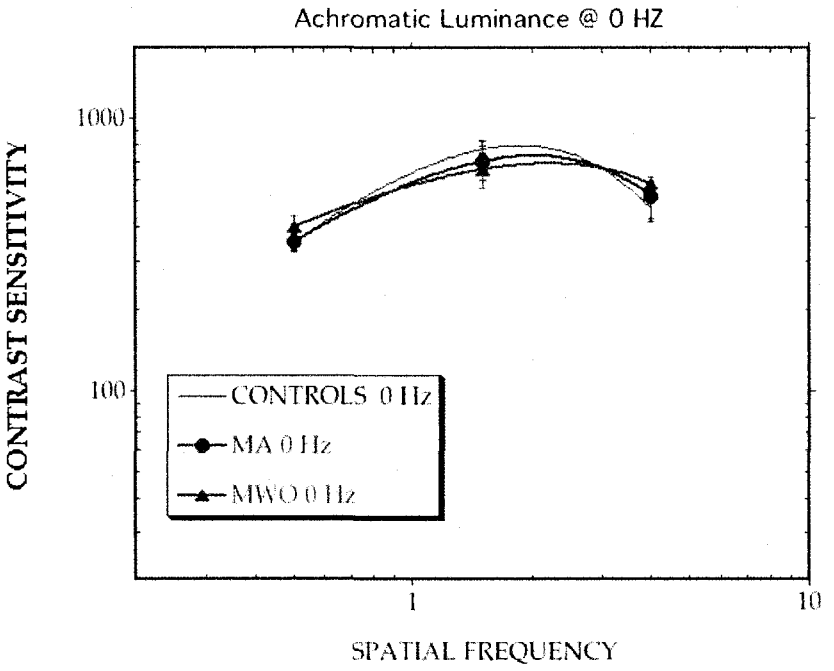


Figure 13. Contrast sensitivity for steadily presented achromatic stimuli. Points indicate average achromatic contrast sensitivity for each group. Axes are plotted using a log-log scale, and a double exponential fit was used to better delineate data trends. Error bars = ± SEM.

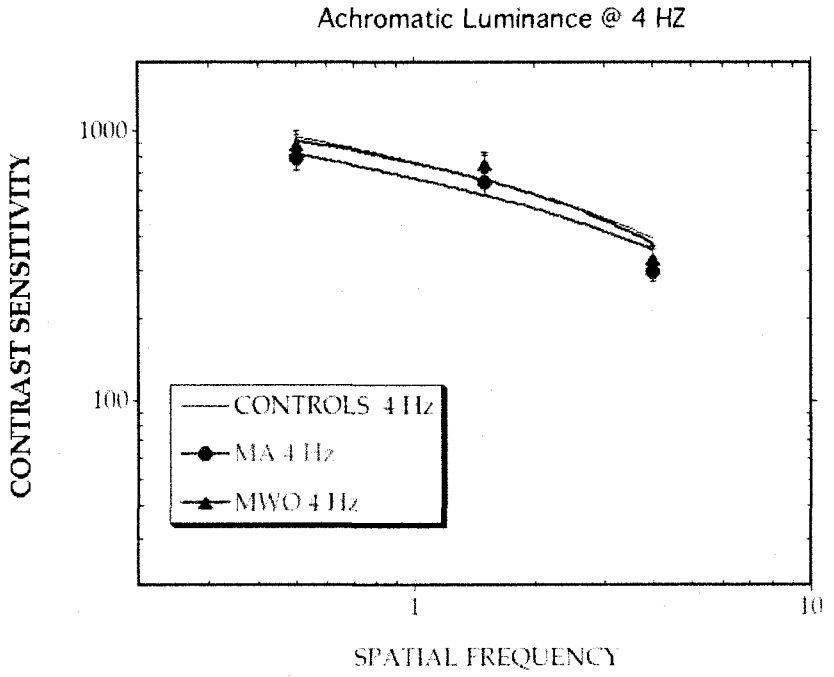


Figure 14. Contrast sensitivity for temporally modulated achromatic stimuli. Details are the same as in Figure 13. Error bars = ± SEM.

Appendix A

MIDAS

The Migraine Disability Assessment Test

The MIDAS (Migraine Disability Assessment) questionnaire was put together to help you measure the impact your headaches have on your life. The information on this questionnaire is also helpful for your primary care provider to determine the level of pain and disability caused by your headaches and to find the best treatment for you.

INSTRUCTIONS Please answer the following questions about ALL of the headaches you have had over the last 3 months. Select your answer in the box next to each question. Select zero if you did not have the activity in the last 3 months.

_____ 1. On how many days in the last 3 months did you miss work or school because of your headaches?

_____ 2. How many days in the last 3 months was your productivity at work or school reduced by half or more because of your headaches? (Do not include days you counted in question 1 where you missed work or school.)

_____ 3. On how many days in the last 3 months did you not do household work (such as housework, home repairs and maintenance, shopping, caring for children and relatives) because of your headaches?

_____ 4. How many days in the last 3 months was your productivity in household work reduced by half of more because of your headaches? (Do not include days you counted in question 3 where you did not do household work.)

_____ 5. On how many days in the last 3 months did you miss family, social or leisure activities because of your headaches?

_____ Total (Questions 1-5)

_____ A. On how many days in the last 3 months did you have a headache? (If a headache lasted more than 1 day, count each day.)

_____ B. On a scale of 0 - 10, on average how painful were these headaches? (where 0 = no pain at all, and 10 = pain as bad as it can be.)

Scoring: *After you have filled out this questionnaire, add the total number of days from questions 1-5 (ignore A and B)*

MIDAS Grade	Definition	MIDAS Score
I	Little or no disability	0-5
II	Mild disability	6-10
III	Moderate disability	11-20
IV	Severe disability	21+

Please give the completed form to your clinician.

This survey was developed by Richard B. Lipton, MD, Professor of Neurology, Albert Einstein College of Medicine, New York, NY, and Walter F. Stewart, MPH, PhD, Associate Professor of Epidemiology, Johns Hopkins University, Baltimore, MD.

Headache Questionnaire

Subject #: _____

1. At what age did you first begin to experience migraine headaches?

___ years old

2. Approximately how many migraines do you have each month?

___

3. How long does the headache part of your migraine last on average?

___ Hours ____ Minutes

4. When was the last time you experienced a migraine attack?

____ Months ____ Days

5. Do any of your family members suffer from migraines?

Yes / No

If Yes, which relatives (e.g.,parent, sibling, grandparent, etc.):

_____

_____

_____

6. Are you aware of any factors that can your trigger migraine attacks?

Yes / No

If Yes, what are they:

_____

_____

_____

Menstrual Cycle Questionnaire

1. Are you currently using any form of hormonal contraceptive (e.g., "the pill", "the patch", Depo Provera, oral contraceptives, etc.)?

   YES NO

   If yes, what hormonal contraceptive are you taking? _

   _____

2. Have you ever taken any form of hormonal contraceptive? YES NO

   If you have **previously taken a hormonal contraceptive** but are not taking them right now, how many years and months has it been **since you last took oral contraceptives**?

   _____years and_____months

3. What is the average length of your menstrual cycle right now (i.e., How many days are there from the first day of one period to the first day of your next period most people range between 25 and 35)?
   _____ days

4. Which statement best describes your menstrual cycle **right now**? (Check the box with an "X" beside the appropriate response.)

   [ ] I never have my period.
   [ ] Some months I get my period and some months I don't.
   [ ] I usually get my period every month, but it is irregular and I cannot predict when it will start.
   [ ] I usually get my period within two or three days of when I expect it.
   [ ] My period is like clockwork and the same number of days elapse between periods each month.

5. Are you currently breast-feeding or lactating (please circle)?

   YES NO

6. Using the calendars below, please **circle** the **first** day of your **last** menstrual period. If you are not completely sure, please estimate the day that you believe you started menstruating on. Also, please put an **X** over the day that you believe your **next** period will start.

February 2008

M	T	W	T	F	S	S
				1	2	3
4	5	6	7	8	9	10
11	12	13	14	15	16	17
18	19	20	21	22	23	24
25	26	27	28	29		

March 2008

M	T	W	T	F	S	S
					1	2
3	4	5	6	7	8	9
10	11	12	13	14	15	16
17	18	19	20	21	22	23
24	25	26	27	28	29	30
31						

April 2008

M	T	W	T	F	S	S
	1	2	3	4	5	6
7	8	9	10	11	12	13
14	15	16	17	18	19	20
21	22	23	24	25	26	27
28	29	30				

7. How confident are you that the above circled day was the first day of your last period?
(Circle the best response)

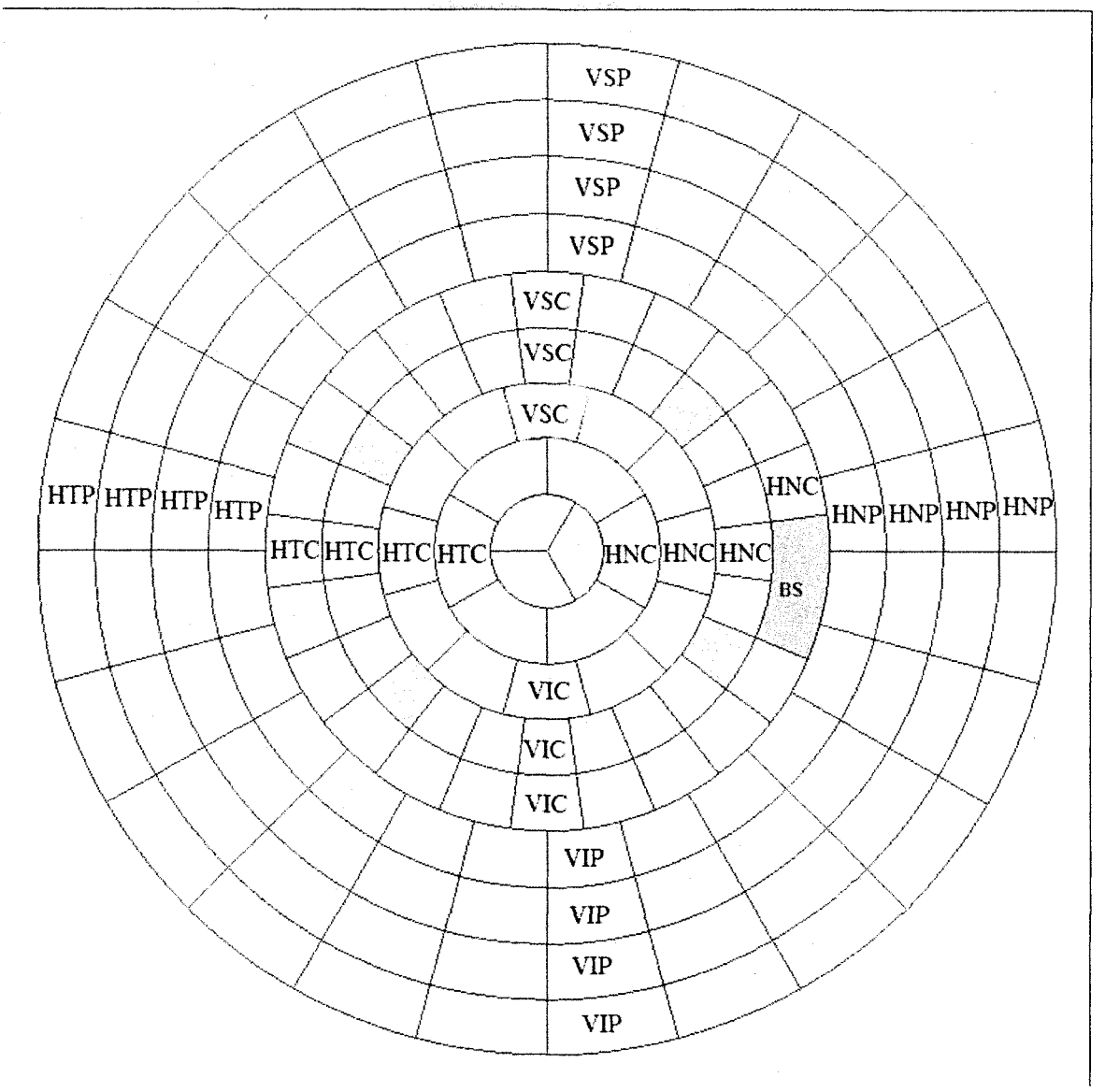
0%		25%		50%		75%		100%
0	1	2	3	4	5	6	7	8

8. How confident are you that the above day with an X is the day that you will next get your period? (Circle the best response)

0%		25%		50%		75%		100%
0	1	2	3	4	5	6	7	8

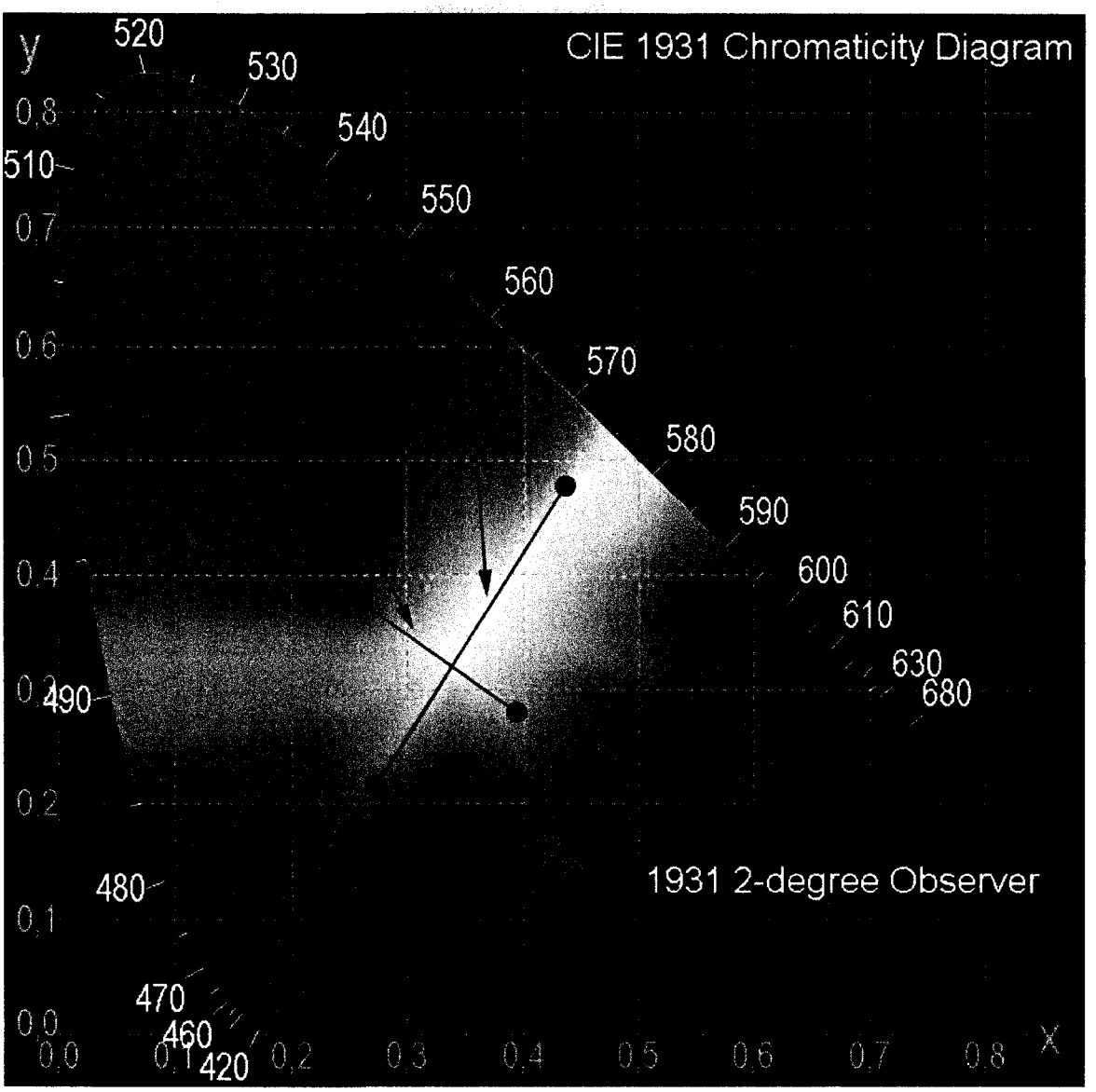
9. Are you currently menstruating/bleeding? YES NO

Appendix B

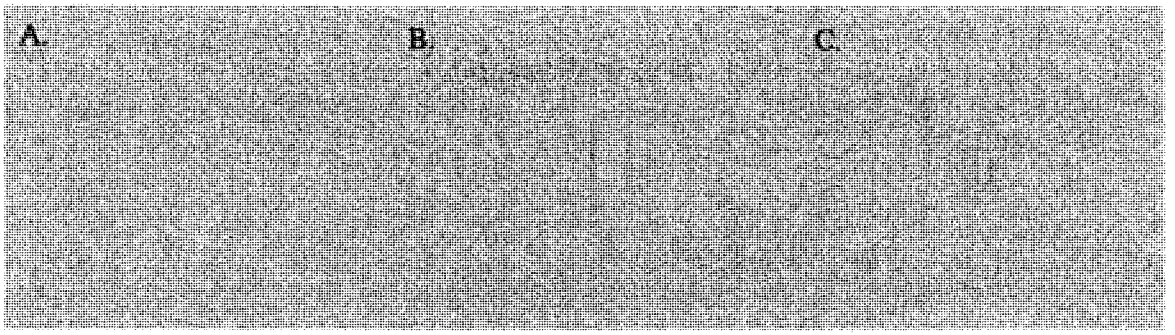


SWAP quadrants for the left eye. VSP: Vertical Superior Peripheral; VSC: Vertical Superior Central; VIC: Vertical Inferior Central; VIP: Vertical Inferior Peripheral; HTP: Horizontal Temporal Peripheral; HTC: Horizontal Temporal Central; HNC: Horizontal Nasal Central; HNP: Horizontal Nasal Peripheral.

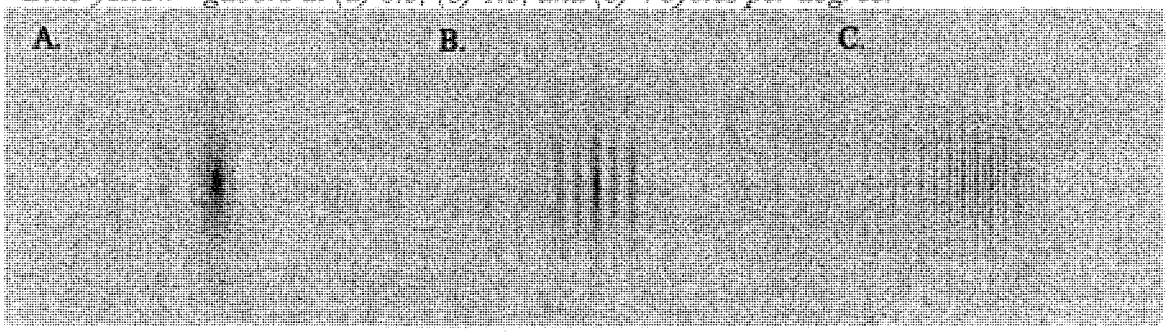
Appendix C



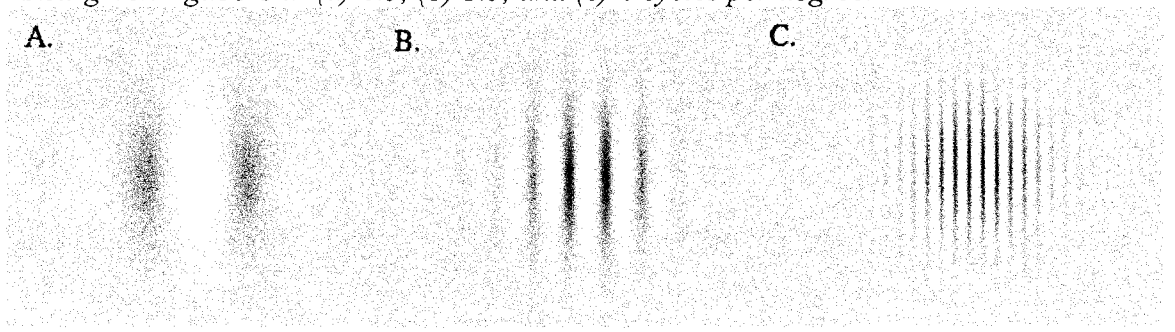
Chromatic Properties of B/Y and R/G Stimuli. Chromatic contrast modulation was defined along the two axes that connect the B/Y and R/G peak-to-trough endpoints.



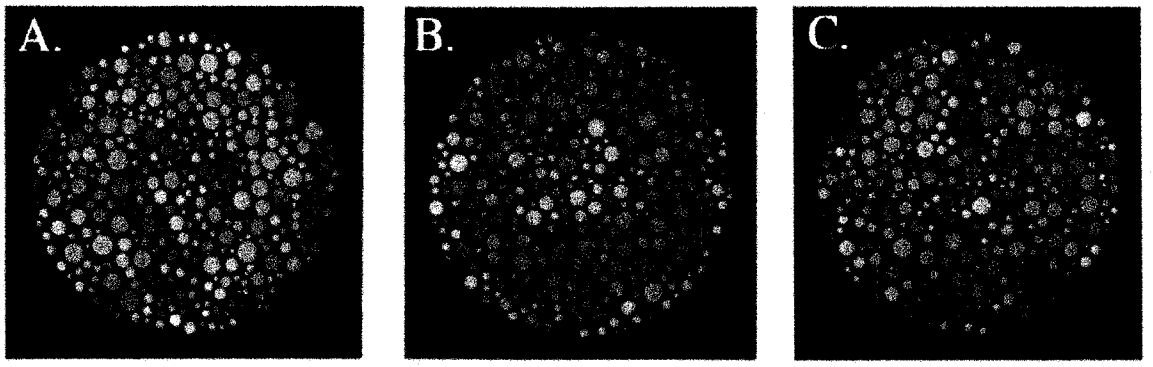
"Blue-yellow" gabors at (a) 0.5, (b) 1.5, and (c) 4 cycles per degree.



"Red-green" gabors at (a) 0.5, (b) 1.5, and (c) 4 cycles per degree.



Achromatic gabors at (a) 0.5, (b) 1.5, and (c) 4 cycles per degree.



Cambridge Color Test Stimuli along (a) Tritan, (b) Deutan, and (c) Protan lines.