Central and Peripheral Visual Fields in Patients with Migraine

by

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Dedication

First and foremost I would like to thank my parents, Arwa Al-Hafi and Ahmad Eshtayah for being there for me and supporting me throughout the years. I love you very much.

To my wonderful siblings Ehab, Dima, Dana and Reem: Thank you for cheering me on during rough times.
You rock!!!

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God Bless You All

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Abstract

Purpose: To determine if patients with migraine show clinically apparent visual field deficits in the peripheral visual field compared to healthy controls.

Methods: Normal observers (n=25; mean age 41 y, range 15-67 y) and patients with migraine (n=12, mean age 48 y, range 21-55 y) were examined with a fully automated kinetic perimetry program (Octopus 900, Haag-Streit, Switzerland) on two separate study visits within two weeks. The program examined 3 isopters (I4e, I2e, I1e) at stimulus velocities of 5°, 4°, and 3°/s respectively. For every isopter, 12 stimulus vectors were presented at meridians spaced 30° apart, in random order, and each isopter was measured 3 times. Patients with migraine had been diagnosed by a neuro-opthalmologist according to criteria of the International Headache Society.

Results: Differences in mean isopter radius between migraine observers and healthy controls were small (< 1.3°) and not statistically significant (P>0.05, Mann-Whitney U). No learning or practice effects were observed between study visits, and AKP showed reasonable repeatability for all three isopters.

Conclusion: Patients with migraine did not demonstrate decreased peripheral visual fields in comparison to controls. This study had sufficient power (90%) to detect a group difference in mean isopter radius of approximately 2°.

List of Abbreviations and Symbols Used

MA	Migraine with Aura
MO	Migraine without Aura
CSD	Cortical Spreading Depression
SAKP	Semi-Automated Kinetic Perimetry
MIR	Mean Isopter Radius

CHAPTER 1. Introduction

Migraine is a disabling primary headache that affects approximately 10-15% of the general population [1-3]. Migraines have triggers that may be environmental, visual, or physical in nature. To date, there is no single universally accepted theory for the etiology of all migraines [4-6]. There are two major sub-types of migraine; migraine without aura (MO), and migraine with aura (MA). MO is a moderate to severe, usually unilateral disabling headache lasting 4-72 hours that is associated with nausea and/or vomiting, photophobia (light sensitivity) and/or phonophobia (sound sensitivity). MA is a visual and/or sensory symptom experienced either during, after, or more commonly 15-20 minutes prior to a migraine headache [2].

Research thus far suggested that the visual cortex of migraine patients and controls differ, and in particular that of MA and MO [6]. Visual cortical differences include but are not limited to cortical neural excitability, cerebral blood flow changes to electrical and visual stimulation, structural changes found on magnetic resonance imaging (MRI), and clinical presentation [4, 7-11]. Of particular interest are studies that compare MA to MO patients. Such interest arises from the discovery that Cortical Spreading Depression (CSD) is a mechanism seen in patients with MA but not MO sufferers. CSD is defined as a wave of short lasting neural and glial depolarization, starting posteriorly in the visual cortex and moving anteriorly in all directions at a speed of 3-5 mm/min. It is initially accompanied by hyperperfusion (increased blood flow), and then followed by a longer period of hypoperfusion (decreased blood flow) [12, 13]. Visual cortical differences between the groups are the basis for research on visual fields in patients with migraine, and in particular MA and MO patients.

The visual field is the portion in space that is simultaneously visible to the steady fixating eye [14]. There are several different ways of measuring the field of vision: in clinical use are static automated perimetry (SAP) using the Humphrey Field Analyzer (HFA, Carl-Zeiss Meditec, Dublin, CA), and kinetic perimetry using the Goldmann perimeter (Perimeter 940, Haag-Streit AG, Switzerland). The Goldmann perimeter is no longer manufactured, and its parts can no longer be replaced. Semi-automated kinetic perimetry (SAKP) is a technique

available in the Octopus 900 perimeter, which is now increasingly replacing the manual Goldmann perimeter.

Comparison of the visual fields of patients with migraine and controls has thus far focused on the central 30° of the visual field [15-20]. Given that patients with migraine have peripheral in addition to central visual complaints, and that the neural propagation of CSD occurs in the visual cortex, which may involve the peripheral visual field, we suspect that we might uncover visual field deficits by examining the peripheral visual fields of patients with migraine using automated kinetic perimetry (AKP). Test retest variability of AKP will be determined for controls to provide the information necessary to determine the sample sizes for future studies that set out to determine differences between groups of participants, and change over time in individual participants. Furthermore, the learning effects between eyes and between sessions will be investigated.

1.1. Purpose of the Study

The primary purpose of our study is to investigate the hypothesis that migraine patients have a reduced peripheral visual field compared to controls, and to investigate how these differences, if present, are related to the frequency, duration, severity of migraines and presence of a visual aura. The secondary purpose is to investigate test retest variability and between-subject variability in controls and migraine patients using AKP.

1.2. Hypothesis

Our hypothesis is that patients with migraine have reduced peripheral visual fields compared to controls, and that the visual fields will be worse in patients with a higher severity, frequency and duration of migraine. Furthermore, we hypothesize that MA patients will have smaller peripheral visual fields than MO patients.

1.3. Importance of this research

It is important to examine and compare the visual fields of migraine patients and controls, as well as MA and MO patients because the knowledge gained about their differences may address some of the concerns of migraine patients. For instance, MA patients have concerns about permanent visual field loss with increased duration and frequency of migraines.

Furthermore, knowledge might be gained on the effect of migraines, and in particular migraine auras on the field of vision. The type of visual field loss experienced by migraineurs may provide information on the affected area of visual pathway, as well as etiology and pathophysiology of the disease. This knowledge may help in the clinical diagnosis, management and treatment of migraine headaches.

CHAPTER 2. Migraine

2.1. Classification and Diagnosis

In 1988 the headache classification committee published a unified, valid and exhaustive classification and diagnostic criteria for all headache disorders, in 2004 revised in the second edition [1, 2, 21, 22]. A uniform way to classify and diagnose headaches is helpful for clinical diagnosis and treatment, evidence-based clinical research, and for epidemiologic studies.

The classification of headache disorders is organized in a hierarchal manner; with a major type of headache followed by its subtypes. According to the most recent classification, there are 6 subtypes of primary migraines: Migraine without aura, migraine with aura, childhood periodic syndromes that are precursors of migraine, retinal migraine, complication of migraine, and probable migraine [2]. The following section will give an overview of the all types of migraines, with an emphasis on the two types of interest in the current study.

2.1.1. Migraine without Aura

The Diagnosis is based on at least five attacks of a headache lasting 4-72 hours, which has been untreated or unsuccessfully treated, and characterized by at least two of the following symptoms: unilateral location, pulsating quality, moderate or severe pain intensity, and aggravation by routine physical activity. For a complete diagnosis, it must be associated with nausea and/or vomiting, or photophobia and/or phonophobia [2].

2.1.2. Migraine with Aura

There are several subtypes of migraine with aura, as the aura may be followed by a migraine headache, and other times may be present without a headache, or the aura is followed by a headache that does not fit the diagnostic criteria of a "migraine without aura". Migraine auras may also be associated with motor weakness as found with familial and sporadic hemiplegic migraines. Rarely, there are basilar-type migraines which are associated with brainstem symptoms such as ataxia, dysarthria, and vertigo. The most common sub-type of interest in this study is the "typical aura with migraine headache".

For the diagnosis of "typical aura with migraine headache", the patient has to have at least two attacks of migraine with an aura, with fully reversible visual, sensory, or speech disturbances. Additional criteria are two episodes of two of the following symptoms: homonymous visual symptoms and/or unilateral sensory symptoms, or an aura developing gradually over ≥ 5 minutes, or each symptom lasting between 5 and 60 minutes. The final criterion is an onset of a "migraine without aura" headache either during or after the visual aura within 60 minutes [2].

2.1.3. Other Types of Migraine

There are other less common types of migraine. Childhood periodic syndromes are commonly precursors of migraine; they present with episodic vomiting with severe nausea, abdominal pain lasting 1-72 hours with normality between episodes, and episodic attacks of vertigo in an otherwise healthy child. A retinal migraine is a monocular visual disturbance (scintillations, scotoma, or blindness) that is associated with a migraine headache. In a complicated migraine; one could either experience a migraine for more than 15 days per month lasting for more than 3 months, or a debilitating migraine lasting longer than 72 hours, or a visual aura lasting more than one week with or without signs of infarction, or a seizure triggered by a migraine aura. The last of the lesser common migraines is probable migraine, which is a category that consists of unusual variations of migraines with and without aura, and of a chronic migraine [2, 21].

2.2. Epidemiology

2.2.1. Global Prevalence of Migraine

There are several published papers on the epidemiology of migraines. Earlier studies have identified various ranges of migraine prevalence and incidence, primarily related to the differing methodological approach in the diagnosis of migraine, as well as the various distributions of age, gender, and race [23, 24]. Recent migraine prevalence[1] studies that use the diagnostic criteria of the International Headache Society (IHS) found an overall global adult migraine prevalence of 10-11%, a lifetime prevalence of 14%, and an almost 3 times

[1] Prevalence is defined as the proportion of the study population that had the disease over a one year period.

higher prevalence in women (14-18%) than men (6-7%). Prevalence is highest between ages of 25-55, and begins to decline around the age of 40 [3, 22, 23].

2.2.2. Prevalence of Migraine with and without Aura

There are no recent papers on the epidemiology of MA and MO based on the 2004 updated version of the IHS criteria. The 2004 criteria vary from the 1988 criteria in the diagnosis of MA, in that they lack the description of the type of headache that precede or follow the MA. Nevertheless, based on an epidemiologic study [22], the prevalence of MA over a one year period is 4% and the lifetime prevalence is 6%. The prevalence of MO is 6%, with a lifetime prevalence of 9%. Overall, MO has a greater prevalence per year and over a lifetime. Furthermore, MO and MA are the most common subtypes of migraine [2]

Studies that reported the overall prevalence of migraine in school or community children and teenagers between the ages of 3-18 years reported a prevalence 3-11% with a mean of 7% [25].

2.2.3. Prevalence According to Socioeconomic and Geographic Distribution

Geographically, migraine is most prevalent in the North American white population, intermediate in Europe and Central/South America, and lowest in Asia and Africa. Socioeconomically, prevalence of migraine increases in those with a lower education and income. From the two possible hypotheses for this phenomenon, the one that has gained greater support is the causation hypothesis, which suggests that the increase in disease prevalence is due to environmental factors associated with low income, rather than the disease causing low income [3].

2.2.4. Incidence of Migraine

The incidence[2] of MA in women is 14.1/1000, peaking at the age of 12-13 years. The incidence of MO incidence is 18.9/1000, peaking at the age of 14-17 years. Incidence for migraine in men occurs at a lower rate of 6.6/1000 for MA and 10/1000 for MO, peaks at a younger age of 5 for MA and 10-11 for MO [26, 27]. Therefore, migraine incidence rates are

[2] Incidence is defined as the onset of a new case of disease in a population of 1000 over a one year period.

higher in women, and peak earlier in men than women, and the incidence of MA peaks earlier than MO in both men and women.

2.3. Causes and Triggers of Migraine

Migraines are complex disorders because they take many forms, have various associated symptoms, and may occur in a variety of circumstances. There are common factors that trigger or elicit migraines. Several theories attempt to explain the physiological basis of a migraine headache. The most recent are related to the vasomotor activity of arteries, and the chemistry and electric activity of the nervous system. However, to date, there is no single universally accepted theory that can explain the etiology of all migraine headaches [5, 6, 28]

Migraines may be elicited under many circumstances or factors. They may be triggered by one or more of the following: arousal, let-down, physical crashes, flickering lights, visual stimulations, specific foods, and the menstrual cycle. Examples of migraines elicited by arousal are those associated with bright lights, loud noises, smells, and drastic changes in weather. Physical crashes are those associated with extremely hot weather, after eating a big meal, or the opposite, by fasting, and passive motion. Situations of let-down are migraines that occur after a long stressful week of work, after examinations, or after childbirth. Nocturnal migraines occur when patients are in deep sleep and are woken up by a migraine headache. Flickering lights, and fluorescing lights are also triggers to migraines. Specific food types such as cheese, wine, chocolate, ham and others, which vary between individuals, were reported to elicit a migraine. The most common trigger of migraine in woman is the menstrual cycle [4, 11].

An interesting trigger of migraines is that related to visual stimulations, which are predominantly complaints of patients who suffer from MA. These patients are extremely sensitive to, and their migraines may be elicited by specific geometries, such as parallel light rays shining through window blinds, checkerboard patterns, and striped objects. In some rare cases, an induced aura may be elicited by certain images that, to them, seem transformed or diverge from the expected, which results in an aura that may present as metamorphopsia (distortion of an image) [5].

2.4. Visual Manifestations of a Migraine Aura

2.4.1. Fortification Spectra/Scintillating Scotoma

The visual aura experienced by MA patients may have various presentations. The most common positive visual aura that is often diagnostic of MA is termed fortification spectrum or scintillating scotoma. Fortification spectra develop over 5 to 20 minutes and last for less than an hour, which may or may not be preceded/followed by a migraine headache. The aura typically begins as a small bilateral central, or more commonly paracentral visual disturbance (blur, luminosity, distortion, scotoma), that expands in one hemifield to scintillating (shimmering) zigzag-like patterns. The zigzag patterns then expand and become brighter and flicker faster over time, covering the entire visual field before disappearing into the periphery. Commonly, a bean-shaped negative scotoma, an area of complete or partial blindness, is formed at the inner edges of the scintillating zigzags. The scotoma is present at the onset of the migraine aura and also expands with the zigzags [12]. The word fortification is used to describe the zigzag patterns as they resemble the wall of a fortress, and spectra denotes the spectrum of light sometimes experienced. The visual disturbances of a MA are typically bilateral and are fully reversible [6].

2.4.2. Other Positive Visual Phenomena

Positive visual phenomena are visual disturbances that are occasionally seen by migraine aura patients. Positive visual phenomena include the scintillating scotomas, and in its simplest forms are blurred vision, and heat-wave appearance; however, positive visual phenomena include phosphenes, fragmented vision and kaleidoscopic vision. Phosphenes may present as flashes of light, sparks, or be star-shaped, and could number from one to hundreds. A single phosphene is usually confined to one quadrant or half of the visual field and does not cross the midline. Fragmented vision or a cracked glass appearance describe a visual phenomenon in which the image is broken into polygonal facets and fitted together as a mosaic. If the facets are small in size, the image is grainy looking, and if scattered and large enough the image may become unrecognizable. Kaleidoscopic vision describes a visual phenomenon of complex shapes of changing colour, similar to those mirror reflecting symmetrical images seen through a kaleidoscope [5, 29].

2.4.3. Negative Visual Phenomena

Negative visual phenomena are those that cause partial or complete loss in the visual field such as homonymous hemianopia, transient monocular visual field loss, tunnel vision, and black spots [5, 30].

2.4.4. Cortical Visual Disturbances

Cortical visual disturbances are those involving higher brain centers, which entail complex perceptual symptoms that precede their migraine headache. Déjà vu, jamais vu, Lilliputian vision (micropsia), Brobdignagian (macropsia), zoom, mosaic, and cinematographic vision are all examples of cortical visual disturbances. Déjà vu is the sudden feeling of familiarity and certitude, and jamais vu is the opposite, a sudden feeling of unfamiliarity and strangeness. Micropsia is when images appear smaller and macropsia is when images appear larger. When the image enlarges gradually rather than suddenly, it is referred to as zoom vision. Mosaic vision is when the percept is broken into polygonal surfaces and rearranged in a mosaic. Cinematographic vision is when the notion of motion is lost, so that the patient sees still flickering images rapidly. Since these visual symptoms are complex, patients usually have difficulty reporting them [5, 31].

2.5. Visual Cortex of Migraine Patients verses Controls

There are several reasons to support the theory that the visual cortex of migraine patients may differ from that of controls, in particular the cortices of patients with MA. Studies that analyzed visual evoked potentials concluded that migraine patients have increased amplitudes and reduced latencies compared to controls, with MA patients having higher amplitudes compared to MO patients [7]. This increased excitability in the visual cortex of migraine patients was also demonstrated in a study that determined phosphene thresholds by means of transcranial magnetic stimulation (neural depolarization or hyperpolarization of intracranial neurons). They found that phosphenes could be induced at much lower intensities in migraine patients than controls, and with lower intensities in MA than MO patients [10]. In addition, there were cerebral blood flow velocity (CBFV) differences between migraine patients and controls [9]. CBFV of the middle cerebral and posterior cerebral arteries were found to be larger in migraine patients than controls with visual stimulation

2.6. Migraine Auras and their Connection to the Visual System

Slight variations in the descriptions and drawings of the visual aura exists between those who observe them; however, there is uniformity and constancy to some degree, suggesting a common mechanism [12]. Karl S. Lashley was the first scientist to draw and time his fortitification spectrum during a migraine attack, and concluded they were moving at a rate of 3 mm/min. He argued that MA must be caused by a propagating neural disturbance since his visual auras propagated over time [6, 29]. Three years later, in 1944 a scientist named Aristides A. P. Leão described in detail an unusual neural disruption observed while electrically stimulating the visual cortex of a rabbit in experimental epilepsy. He termed this neural phenomenon Cortical Spreading Depression (CSD) [13]. CSD is defined as a wave of short lasting neural and glial depolarization, starting posteriorly in the visual cortex and moving anteriorly in all directions at a speed of 3-5 mm/min. It is initially accompanied by hyperperfusion, and then followed by a longer period of hypoperfusion [12]. It was not until 1958 that Milner made the connection between Lashley's propagating aura paintings and Leão's description of CSD and proposed that CSD is the mechanism behind MA [32]. This notion was confirmed recently by magnetoencephalographic fields, where CSD was observed through a spontaneous migraine attack and through direct stimulation of the visual cortex of migraine patients, which was otherwise absent in controls [33].

2.7. Migraine Aura versus Migraine without Aura

Recent research supports the view that CSD is the mechanism of a MA and not of MO, and that the two migraine subtypes differ. A study that used magnetic resonance imaging (MRI) found that during an MA attack, there were regional changes in cerebral blood flow moving at a speed of 3 mm/min, similar to the finding of Lashley's [8]. On the contrary, studies that looked at the cerebral blood flow in MO patients could not find the spreading hypoperfusion that is reported in patients with MA [34]. Furthermore, MRI findings showed that 28.8% of patients with migraine had white matter lesions in the visual cortex, and out of those patients, white lesions where higher in MA (61.5%) than MO (38.4%) patients. The presence of lesions were highly correlated with the frequency of attacks [35].

Additionally, the clinical presentations of MA differs from that of MO patients; those with MO have a higher average frequency of attacks, greater association with menstruation, and

more debilitating migraine headaches than those of MA patients. As aforementioned, MO is more prevalent, and the incidence peaks later than with MA. Furthermore, it is more likely that MA and not MO patients have migraines provoked by visual stimuli [36].

2.8. Tools Used for Measuring Migraine Severity

There are several tools designed to indirectly measure the severity of migraine by assessing the functional impact of migraine; however only the migraine severity (MIGSEV) questionnaire assesses clinical severity based on the diagnostic criteria of the IHS. The IHS diagnostic criteria of migraine headaches are comprehensive take disability, physical illness and pain into consideration for a complete diagnosis. The most often used tool used to measure migraine severity is the Migraine Disability Assessment (MIDAS) questionnaire, which measures severity by assessing the burden a migraine headache poses on its sufferers. Questions asked relate to the number of days missed at work, or days in which household work is altered [37]. The MIGSEV questionnaire directly measures the clinical severity of the migraine by assessing 4 components: the intensity of pain, severity of nausea, extent of daily disability, and tolerability of patients to the migraine headache. The components are rated from most to least severe, and scoring system deems the migraine severity as low, intermediate, or high [38]. The MIGSEV questionnaire was chosen for this study because it is short, easily understood, comprehensive, and is comparable to the diagnostic criteria used for migraine subjects.

CHAPTER 3. Visual Fields

The visual field is the portion in space that is simultaneously visible to the steady fixating eye. The normal monocular visual field extends approximately 100°-110° temporally, 60° nasally, 60° superiorly, and 70°-75° inferiorly. The binocular visual field extends approximately 200° laterally and 130° vertically [14]. Perimetry is a quantitative measure of the extent of the visual field. There are several types of perimetry. This chapter provides a brief overview of static, kinetic, and semi-automated kinetic perimetry, compares these three commonly used techniques.

3.1. Static Perimetry

Static perimetry is a method of visual field examination in which the observer responds to a series of stationary light stimuli. In threshold perimetry, the sensitivity of a visual field location is determined by varying the stimulus intensity by 4 and 2 decibels (dB) in a stepwise staircase method, to determine the stimulus intensity that can be seen approximately 50% of the time. In suprathreshold testing, a bright stimulus 5 dB above the expected threshold is presented, and the observer responds when it is seen. By using threshold perimetry, the depth of the defect is determined, whereas suprathreshold perimetry is a screening tool to determine whether or not it is likely that there is a defect [39].

3.1.1. Stimulus Parameters

In static automated perimetry, the most commonly used stimulus size is the size III, which subtends an angle of 0.43°. On the Humphrey Field Analyzer (HFA, Carl-Zeiss Meditec, Dublin, CA) it is presented for 0.2 sec. The intensity of the stimulus can vary between 0 and 51 decibels (10000 to 0.08 apostilbs, ie 3183 cd/m^2 to 0.025 cd/m^2). Similar to Goldmann perimetry, the background sphere luminance is calibrated to 10 cd/m^2 [39].

3.1.2. Examination Technique

The HFA offers several programs. Most commonly used are the 30-2, 24-2, and 10-2. The 30-2 determines threshold at 76 locations separated by 6° and examines the central 30° of the visual field. The 24-2 determines threshold at 54 locations separated by 6° and examines the visual field 30° temporally and 24° nasally. The 10-2 determines threshold at 68 locations

separated by 2° and examines the central 10° of the visual field. With the examination strategy SITA, the examination duration for one eye is approximately 5-10 minutes. The examination algorithms, duration, and results depend on the speed and consistency of the patient's responses, and the severity of the visual field defect [39].

3.1.3. Interpretation of Test Results

The results of static automated perimetry are quantitative and therefore lend themselves to statistical analysis, unlike those of manual kinetic Goldmann perimetry. Raw examination results are displayed in a plot indicating the threshold of each tested location in decibels and in a grayscale for visualization; however, the examination results may be more thoroughly interpreted with total deviation (TD) and pattern deviation (PD) analysis, the glaucoma hemifield test (GHT), mean deviation (MD) and pattern standard deviation (PSD), and indices of reliability [39].

3.1.3.1. Total and Pattern Deviation Analysis

TD and PD plots indicate at each test location whether stimulus threshold is outside of normal limits by comparing it to the distribution of age-correlated normal participants. Results are displayed numerically in decibels and as a probability plot. In a TD and PD decibel plot, negative decibel values indicate lower than normal sensitivity and positive values indicate higher than normal sensitivity at that location. The analysis of a PD plot aims to remove any generalized depression: therefore, only focal visual field changes are visible on the PD plot. In a TD and PD probability plot, for each examined location, the sensitivities which are worse than 0.5%, 1%, 2% and 5% of age matched normals is indicated by symbols [39].

3.1.3.2. Global Indices

The global indices mean deviation (MD) and pattern standard deviation (PSD) are tools that may be used by researchers and clinicians to assist in the interpretation of exam results. The MD and PSD values are calculated by taking the mean decibel value of the TD and PD plots respectively. Therefore, MD and PSD values represent the average visual field deviation (MD value) and irregularity (PSD value) from age-correlated normal participants. The MD

and PSD values can then be used by researchers to classify disease severity, or by clinicians for patient follow up [39].

3.1.3.3. Indices of Reliability

Indices of reliability includes false positive (FP) and false negative (FN) errors, as well as fixation losses (FL). An FP error is a percentage measure of the rate at which the observer responded when no stimulus was shown. An FN error is the rate that an observer failed to respond to a stimulus that most likely was seen, which is 9 dB brighter than threshold and is presented at a location previously examined. The patient's fixation is monitored by the FL rate, which is determined by a response to a stimulus presented in the physiologic blind-spot. High FP, FN, and FL rates may indicate low reliability of results or in some cases it could be natural variability reflecting the severity of disease. In either case, the global indices help clinicians in the interpretation and analysis of test results [39].

3.2. Kinetic Perimetry

Kinetic perimetry is a method of measuring the visual field up to an eccentricity of 90°. In kinetic perimetry the stimulus is moved from an area of non-seeing to an area of seeing, and the observer responds as soon as it is seen. In this way, a contour is obtained and referred to as an isopter. Since retinal sensitivity increases in the center of the visual field, the stimulus should be seen anywhere within that isopter, with the exception of the physiologic blind spot [14].

3.2.1. Manual Kinetic (Goldmann) Perimetry

3.2.1.1. Stimulus Parameters

The Goldmann perimeter is calibrated to have constant sphere luminosity, possesses a large sphere diameter to allow measurement of the periphery, and numerous stimulus sizes and intensities to better quantify visual field defects. The sphere's luminance is calibrated to $10 cd/m^2$. The sizes of stimuli are expressed in roman numerals and are numbered 0 to V, smallest to largest. The sizes of the stimuli in millimeters squared, and the angle they subtend in degrees are outlined in table 3.1 [14, 40].

Table 3.1: Goldmann Stimulus Dimensions.

Stimulus Number	0	I	II	III	IV	V
Size (mm^2)*	1/16	1/4	1	4	16	64
Visual Angle (degrees)	0.05	0.11	0.22	0.43	0.86	1.72

*Values correspond to a distance of 300mm.

There are also two set of filters to reduce the luminance of the stimulus. One set of filters is organized from "1" to "4", and the second "a" to "e". Dimmer stimuli are expressed by smaller transparency numbers (table 3.2) [14, 40].

Table 3.2: The Goldmann Perimeter Filters and their Transmission.

	4	**3**	**2**	**1**
e	1.0	0.315	0.10	0.0315
d	0.8	0.25	0.08	0.025
c	0.6	0.2	0.063	0.020
b	0.5	0.16	0.05	0.016
a	0.4	0.125	0.04	0.0125

3.2.1.2. Examination Technique

The Goldmann stimulus and sphere luminance are initially calibrated manually by the perimetrist. For the observer's first Goldmann visual field test, the eye with the better acuity is examined first. For subsequent visits, the perimetrist may start with the abnormal eye. Pupil diameter is recorded in millimeters. The examiner moves the stimulus at a constant velocity of approximately 1-2° per second, starting with the most intense stimuli (I4e, I2e, followed by I1e). If a constriction of the I4e is found the stimulus size is increased. If a large gap is found between two isopters, intermediate isopters may be added [40].

Corrective lenses are used for the central 30°, to correct for a distance of 30 centimeters, and for the patient's age. The blind spot is plotted with the I2e or I1e stimulus, or with whichever stimulus intensity just outlines the outside of the blind-spot. If scotomas are found anywhere, the size, steepness and depth of the scotoma are determined [40].

3.2.1.3. Interpretation of Test Results

In Goldmann perimetry there is no formal quantification of the visual field as in SAP. Visual fields are usually interpreted qualitatively based on laterality, deepness, steepness,

shape and size of visual field defect. A visual field may display a local depression, generalized depression of the entire field, or one of the various forms of visual field defects of the visual pathway [14].

Visual fields may also be interpreted semi-quantitatively by making reference to where the average normal population's isopter boundaries lie [14, 40]. Qualitative and semi-quantitative observation in conjunction with other clinical and systemic findings provided clinicians with information on the severity of the visual field defect and the location of the lesion.

The need to quantify kinetic visual fields has been expressed in several studies in patients who experience peripheral and central visual field loss [41-43]. So far, there is no consensus on how peripheral visual fields can be quantified best.

3.2.2. Semi-Automated Kinetic Perimetry

3.2.2.1. Stimulus Parameters and Examination Technique

Semi-automated Kinetic Perimetry (SAKP) has identical stimulus parameters as Goldmann perimetry; however, unlike Goldmann perimetry, SAKP is automated to ensure a reproducible examination, in particular a constant speed of the stimulus (0-10°/s), and an automated calibration. With SAKP, the response latency of the subject can also be taken into account in determining isopters of the visual field [44].

3.2.2.2. Interpretation of Test Results

In SAKP, once the examination is complete, the software provides the examiner with the option of calculating the isopter area. This provides clinicians and researchers the means to interpreting results quantitatively in addition to qualitatively [45]. A disadvantage of quantifying visual fields based on isopter area is that results are unfamiliar and therefore difficult to interpret. Alternatively, results can be interpreted by determining the mean isopter radius (MIR), which is not an option provided by Octopus 900 software. The software does however store the "x" and "y" coordinates of responses which can be used to

calculate the MIR. MIR is more institutive and more closely resembles the way Goldmann visual fields have been interpreted for over 65 years.

3.3. Applications of Perimetry

Currently, both kinetic and static perimetry are used to measure central and peripheral visual field loss. However, static perimetry is more commonly used. Static perimetry is repeatable and useful in the management and monitoring of disease progression, such as glaucoma [39].

Neuro-ophthalmologists rely on Goldmann kinetic perimetry in the diagnosis and follow-up of neurological disease, as most post-retinal lesions affect the peripheral visual field. Static perimetry is less useful for measuring peripheral visual field loss because the full threshold option is time consuming, does not examine as far out to the periphery, and peripheral test points are not as densely spaced as central ones. Furthermore, threshold distributions of healthy controls are very wide, making it almost impossible to distinguish a normal from a non-normal visual field [39, 46].

CHAPTER 4. Literature Review

4.1. Visual Fields in Patients with Migraine

There are numerous reports of visual field loss experienced after a migraine attack. Cases were primarily bilateral homonymous hemianopias with and without macular sparing and enlarged blind-spots [47-51]. Most of the early publications were either single case studies or publications before the IHS diagnostic criterion of migraine headaches was established. The purpose of this section is to provide a literature review of the major studies that examined the visual fields of migraine patients.

4.1.1. Drummond and Anderson, 1992

The purpose of this study was to determine if the prevalence of persistent visual abnormalities in patients with MA were greater than those of patients with MO. The arc kinetic perimeter was used to examine the peripheral visual fields of 23 MA, 20 MO, and 21 controls. Results showed no statistically significant differences in the isopter areas between controls and migraine patients when measured seven days post-migraine. A significant reduction in the area was found in MA subjects 1 day post- migraine when compared to the visual field 7-10 days post- migraine. On the contrary, MO patients' visual fields were similar 1 day and 7-10 days post- migraine. The authors concluded that visual field defects of MA patients persisted at least one day post- migraine [20]. This study was limited by the use of an arc perimeter, which does not allow control over background and stimulus luminance or stimulus velocity.

4.1.2. McKendrick et al, 2000

The purpose of this study was to determine if there was a significant difference in the visual fields between migraine patients and controls, as well as between MA and MO patients. A second aim was to determine whether static or flicker perimetry showed greater sensitivity to visual field loss in migraine subjects. Third, the authors sought to characterize the visual field defects as cortical or pre-cortical in nature. The Medmont M-600 perimeter was used to examine the central 22° of 15 MA, 1 MO, and 15 controls using static and flicker perimetry. Results revealed a significant difference in pattern standard deviation (PSD)

between migraine and control subjects to temporally modulated stimuli, but not to statically presented stimuli. There was no significant difference between MA and MO, and no cortical visual field losses were identified [15]. The study's limitation was the small sample size in the MO group, and participants were not matched for age or sex.

4.1.3. McKendrick, Cioffi, and Johnson, 2002

The purpose of this study was to determine if a significant difference in visual fields exists between migraine patients and controls, as well as MA and MO using two types of static testing strategies. The HFA's 24-2 strategy was used to examine visual fields of 11 MA, 12 MO, and 20 controls using standard automated perimetry (SAP), and short-wavelength automated perimetry (SWAP), as it was thought to be sensitive to vasospastic disorders such as migraine. Differences in MD and PSD were not statistically significant between migraine patients and controls using SAP. A borderline statistically significant difference ($p=0.04$) was found between migraine patients and controls, but not between MA and MO participants, using SWAP. The authors concluded that the absence of a significant difference in MD and PSD between MA and MO, and the absence of bilateral homonymous defects, suggest that defects were independent of the visual aura and were pre-cortical in nature [16].

4.1.4. McKendrick and Badcock, 2004a

The purpose of this study was to determine differences between the visual fields of MA and MO patients, and if the severity of field loss was related to the frequency and duration of migraine attacks. The Medmont M-700 flicker test was used to examine the central 22-30° of the visual field. Acknowledging the limitations of their previous study [15], sample size was increased to 28 MA, 25 MO patients, and comparisons were made to the retest variability of 24 age and sex matched controls. Migraine patients showed lower visual sensitivity and greater incidence of visual field loss compared to the control group, and visual field loss increased with severity of migraine headache. There were no statistically significant differences between the visual fields of MA and MO patients [17].

4.1.5. McKendrick and Badcock, 2004b

The purpose of this study was to determine the time course of visual field loss after a migraine attack. The Medmont M-700 static and flicker tests were used to examine the central 22-30° of the visual field of 10 MA, 12 MO, and 22 control age and sex matched controls. Measurements were taken 1 day, and 7 days after a migraine attack. The authors reported that there were no statistically significant differences between the visual fields of MA and MO patients. Significantly decreased visual sensitivities were found in migraine patients 1 day post-migraine, which persisted 7 days post-migraine using flicker perimetry [18].

4.1.6. Harle and Evans, 2005

The purpose of this study was to compare the visual fields of patients with migraine and controls. The central 30° of the visual fields were examined using the HFA perimeter and the frequency doubling technology (FDT) perimeter. Furthermore, the authors sought to determine if visual field summary measures were correlated with the migraine history. The study involved 25 migraine patients and 25 controls. There were no statistically significant differences between the visual fields of migraine patients and controls using either perimeter. The visual field parameters were not correlated with the severity, frequency, duration or date of last migraine headache [52].

4.1.7. Summary

From reviewing past and current studies on the topic of visual fields in migraine patients, it appears that results differ depending on the stimulus used. With flicker perimetry and SWAP, a significant difference was found between migraine patients and controls. On the contrary, SAP and kinetic arc perimetry revealed no significant differences between migraine patients and controls. Studies on the time course of visual field loss after a migraine attack also showed differences. Drummond and Anderson were able to detect decreased visual field sensitivity using arc perimetry in MA patients when compared 1 and 7-10 days after migraine, which completely resolved 7 days after the attack. However, McKendrick and Badcock found decreased visual sensitivity using flicker perimetry the day after a migraine attack that was similar for MA and MO patients, and persisted for 7 days after a migraine attack.

4.2. Manual Kinetic Perimetry and SAKP

4.2.1. Ross et al, 1984

This study investigated the test-retest variability of visual field measurements in normals and patients with retinitis pigmentosa. The Goldmann perimeter was used to assess the visual fields of 21 controls and 26 patients with retinitis pigmentosa using the V4e and II4e stimulus at two separate study visits. Twenty-four stimulus vectors were tested, separated by 15°. Results were interpreted by measurements of the area enclosed by the isopter in square inches, and by measuring the isopter circumference in linear inches. Results indicated that variability was greater in patients with RP than in controls, 5.5% and 12% on average respectively. However, this study quantified results in square inches on a printout of unknown scale, and therefore the results are not comparable to other papers in this field [53].

4.2.2. Parrish et al, 1984

The purpose of this study was to determine test retest variability of visual field measurements in static and kinetic perimetry; however, only results of kinetic perimetry will be discussed here. The Perimetron Program 6 was used to assess kinetic visual fields of 11 normal controls using the I4e and I2e stimuli at a velocity of 5° and 2°-5°/sec respectively. Participants were examined with 13 vectors, 5 times with a maximum of 2 visual field examinations per day. Results were quantified by recording the distance from fixation at which participants responded to the stimulus. Results showed that mean isopter radius of the I4e and I2e isopter were 60.8° (SD=3.9) and 35.0° (SD=3.9) respectively. The authors concluded that the I4e and I2e have similarly low retest variability, and that responses to temporal stimuli are more variable than responses to nasal stimuli [46].

4.2.3. Nowomiejska et al, 2005

The purpose of this study was to compare manual Goldmann kinetic perimetry to SAKP using the Octopus 101. A total of 77 patients were examined, 36 with advanced retinal nerve fiber layer loss, 20 with visual field constriction, and 21 with hemionopia. Patients were examined using the III4e, I4e, I3e and I2e stimulus at a velocity of 3°/sec. Twelve to 24 different vectors were presented for each stimulus. Results were quantified by the area

enclosed by the isopters in degrees squared, with the exception of the II4e and I4e that were additionally quantified by mean isopter radius. Goldmann visual fields were 20% smaller on average compared to SAKP fields. The areas of the two tests overlapped by 97%, 94%, and 98% for patients with advanced retinal nerve fiber layer loss, visual field constriction, and hemianopia respectively. Comparison of the two isopters by mean isopter radius showed that the mean difference between perimetric techniques was 1.4° and 1.7° for the III4e and I4e respectively. The authors concluded that the shape and size of visual fields using manual Goldmann kinetic perimetry were comparable to that of SAKP using the Octopus 101 [45].

4.2.4. Ramirez et al, 2008

The purpose of this study was to determine if Goldmann kinetic perimetry is comparable to SAKP, and to determine the repeatability of SAKP using the Octopus 101. A total of 10 glaucoma patients were examined using both perimetric techniques, and a sub-group of 7 were examined twice using SAKP to determine repeatability. Patients were examined using the IV4e, I4e, I3e, and I2e at a velocity of 3°/sec. A total of 8 stimulus vectors were examined separated by 60°. Visual fields were compared by area of visual field on a printout in cm^2. Comparison was also made by mean isopter radius (MIR) agreement of the two adjacent vectors in each quadrant (2 nasal, 2 superior, 2 temporal, and 2 inferior). Agreement was defined as a difference of ≤ 5° in MIR. Results showed that Goldman visual fields were smaller than SAKP by 15% on average. The highest agreement in MIR was with the IV4e and decreased with decreasing stimulus intensity. There were no significant difference between study visit 1 and visit 2 using SAKP. The authors concluded that results of Goldmann perimetry were comparable to SAKP, and that SAKP was a repeatable test [54].

4.2.5. Bittner, Iftikhar, and Dagnelie, 2011

The purpose of this study was to determine test retest variability of Goldmann visual fields in patients with retinitis pigmentosa. A total of 37 patients with retinitis pigmentosa were examined using the V4e and/or II4e stimuli at approximately 5°/sec by an experienced perimetrist. A total of 24 stimulus vectors were examined separated by 15°. Each patient was examined twice in a single day, separated by 1-2 hours. Computer software was used to digitize the Goldmann visual fields to calculate the planimetric and retinal areas. Results

showed no statistically significant differences in the visual field areas between study visit 1 and visit 2. Repeatability was higher for the V4e than III4e stimuli, with a coefficient of repeatability of 32.8% and 23.7% respectively. The authors concluded that Goldmann perimetry with an experienced perimetrist yielded no significant test retest effects (learning, fatigue, stress) in patients with retinitis pigmentosa [42].

CHAPTER 5. Methods

5.1. Research Design

This was a prospective study of 37 participants, 9 diagnosed with migraine with aura (MA), 3 with migraine without aura (MO), and 25 healthy controls. For an unbiased comparison, all participants received an identical visual field examination performed by a single examiner and were given the same instructions. For diagnostic consistency, migraine participants were diagnosed by a single neuro-ophthalmologist based on the diagnostic criteria of the International Headache Society [2].

5.2. Justification of Sample Size

Formal power sample size calculations could not be performed since there are no previous studies on the precision of AKP using the Octopus 900. However, a series of articles have been published that compared the visual fields of migraine patients to controls, and MA to MO patients [15-19]. These works have used a sample size close to n=25 for each group [15-18].

5.3. Study Population

Twenty-five migraine headache-free, healthy controls were used as a reference group to determine if patients with migraine show any apparent visual field loss. The two migraine groups chosen for this study were MA and MO. They shared one aspect, the migraine headache, and differ in one aspect, the migraine aura. Hence, any differences in the visual fields between the two groups may be attributed to the presence or absence of the visual aura.

The inclusion criteria for the study sample were visual acuity equal to or better than 0.3 logMAR (6/12) on the ETDRS chart in both eyes and a refractive error within ±6 diopters sphere and ±3 diopters cylinder. The exclusion criteria are a diagnosis of any ocular disease known to affect the visual field (i.e. glaucoma).

5.4. Identification and Recruitment of Participants

All migraine patients were identified, prescreened and initially contacted by their neuro-ophthalmologist before they were followed-up by the primary investigator. Migraine patients were either identified through the data-book (a notebook containing all patients seen by the neuro-ophthalmologist and their diagnosis), or during their regular visit to the eye clinic. Migraine patients who had been identified through the data-book had their charts pre-screened to see if they fit the inclusion criteria. They were then contacted by phone and asked if they would like to participate in the study. Migraine patients identified through their regular eye clinic visit were approached at the end of their visit for consent. The primary investigator contacted patients interested in participating in the study and went over the study purpose and procedures, giving patients a copy of the consent form to review before their scheduled appointment. Controls were recruited by word of mouth and advertisement on hospital billboards.

5.5. Organization of Study Visits

All participants were expected to attend two study visits separated by at least 24 hours, but within one week from each other. However, if a patient had a migraine attack, the second visit was postponed to at least 14 days after their last migraine attack.

During the baseline study visit, informed consent, migraine and ocular history, visual acuity, spectacle power, and the visual fields of both eyes (always starting with the right eye) were determined. Additionally, images of the optic nerve and fundus were taken, intraocular pressures were measured, and patients completed a migraine severity assessment questionnaire. On the second study visit, only visual the field examinations were repeated.

To determine if a significant difference existed between the visual fields of migraine patients and controls with greater precision, it was believed that an average of at least two visual field measurements on each eye are required. However, the values may be averaged only if no large systematic differences between study visits are found. Furthermore, the data of two study visits can be used to estimate the test-retest variability.

Retest visits were scheduled between 1-14 days after the initial visit to provide patients with a significant break to overcome examination fatigue and to overcome the residual visual field loss caused by a migraine in the case of a migraine attack. A previous study has shown that residual visual field deficits were present one day after a migraine attack, and may still be present a week later [18]. In an earlier study, peripheral visual field constriction persisted 10 days after a migraine attack, and declined thereafter [55].

5.6. Baseline Visit Assessments

5.6.1. Migraine and Ocular History

During the baseline visit, all participants were asked questions pertaining to any significant ocular history, and to any known systemic condition that may cause visual field damage. Migraine patients were further asked specific questions about the age of onset, duration, and the past and current frequency of their migraine attacks. In addition, the type of migraine, date of the last migraine headache, localization of pain, the type of drugs used to treat any headaches, and any associated migraine symptoms (nausea, vomiting, photophobia) were determined. Questions in reference to previous visual field examinations were asked, such as the type of perimeter used (kinetic or static), and the number of times participants previously had had a visual field examination.

5.6.2. Migraine Severity Assessment

Migraineurs were given the MIGSEV (Migraine Severity) questionnaires to fill out (appendix A) [38]. The MIGSEV questionnaire requires that participants rate four items with reference to only their last migraine attack. The items were rated from least to most severe. The items are intensity of pain, nausea, disability in daily activity, and tolerability. The MIGSEV questionnaire is the only tool designed to exclusively measure the clinical severity of migraine attacks, and it is the only one consistent with the criteria of the International Headache Society [38].

5.6.3. Visual Acuity

Visual acuity was determined using the logMAR ETDRS chart. The chart is unique because of its logarithmic progression of letter sizes from line to line, enabling statistical analysis [56].

All participants were examined in the same room, and under the same conditions. The right eye was tested first. To score a line, at least 3 out of 5 letters must be identified correctly [57]. The results were recorded in metric form with the number of letters missed, if any, and the number of letters determined on the next line.

5.6.4. Intraocular Pressure

Intraocular pressures were determined using Goldmann applanation tonometry, which is considered the gold standard for intraocular pressure measurements [58, 59]. Goldmann applanation is based on the concept that the pressure inside a sphere is proportional to the force exerted on its surface needed to flatten a given area. Intraocular pressures of greater than 21mmHg were taken into consideration in concordance with imaging and visual field examination results to ensure a healthy eye examination and to ensure that patients were not suspected of having glaucoma. Participants that were deemed as suspects for glaucoma were eliminated from the analysis.

5.6.5. Heidelberg Retinal Tomography (HRT-II)

All participants were imaged with the HRT-II on their baseline visit. The HRT-II is a scanning laser ophthalmoscope specifically designed to acquire three-dimensional images of the optic disc. Results of the HRT-II include the size and shape of the optic disc and the area of neuroretinal rim of the optic cup. This type of imaging was used by the glaucoma specialist (L.S) to identify glaucoma suspects along with intraocular pressure measurements, visual field exam results, and other types of imaging [60].

5.6.6. Optical Coherence Tomography (OCT, Stratus)

All participants were imaged with the OCT on their baseline visit. The OCT provides cross sectional images of the retina and providing objective measurements of the thickness of the retinal nerve fiber layer. It is a reliable and useful tool in the diagnosis of macular disease and in particular helpful in the diagnosis of glaucoma [61]. The OCT was used by the glaucoma specialist to identify glaucoma suspects along with intraocular pressure measurements, visual field exam results, and other types of imaging.

5.6.7. Fundus Photography

All participants received stereoscopic fundus and disc photos. Fundus photography is considered as a gold standard imaging technique for the diagnosis of glaucoma suspects [62]. Fundus photos were used by the glaucoma specialist to identify participants with any retinal disease. Furthermore, they were used to eliminate glaucoma suspects along with intraocular pressure measurements, visual field exam results, and other types of imaging (OCT and HRT). There was special emphasis to eliminate glaucoma suspects due to the association of migraine and the development of visual field abnormalities [63-66].

5.7. Visual Field Examination

5.7.1. Automated Kinetic Perimetry

All visual field examinations were conducted by a single examiner using the Octopus 900. Automated Kinetic perimetry (AKP) is a new method of measuring the visual field up to 90° from fixation. Compared to static automated perimetry (SAP) in which the subject responds to a series of stationary stimuli of various intensities, the stimuli of AKP are kept at a constant intensity and moved from the periphery into the central visual field until the subject first presses the response button to indicate they were seen. In this respect, AKP is similar to Goldmann perimetry, a manual technique still widely used to examine peripheral vision losses in patients with strokes and other lesions of the visual pathway. Unlike Goldmann perimetry, AKP ensures a completely reproducible examination, in particular a constant speed of the stimulus. This makes AKP independent on the skills of the examiner, unlike in manual Goldmann perimetry. Its results are therefore expected to be more objective, more comparable between different subjects and different examiners, and more consistent over time.

5.7.2. Programmed Visual Field Exam

All participants were examined using three stimuli: I4e, I2e, and I1e, at a speed of 5°, 4°, and 3° per second respectively [44, 45]. The blind spot was manually plotted with the I2e stimulus at 2°/sec. Each isopter consisted of 12 stimulus vectors, and 12 response-time vectors. The stimulus vectors start approximately three standard deviations peripheral to the normal limit of the visual field for the specified isopter, and terminate at the central fixation

target. Estimates of the location of response of normals were given by the Octopus 900. The vectors were 30° apart, starting at 15° and ending at 345°. Each stimulus vector was presented 3 times, in random order starting with the I4e, I2e, and followed by the I1e stimulus.

The Octopus 900 has a disadvantage in that it produces a continuous motor noise with the presentation of stimulus. To avoid participants from responding due to anxiousness or anticipation, false positive vectors were presented in the extreme inferior-nasal periphery position where they cannot be possibly seen; they started at 225° and moved to 90° in the periphery. In summary, there were 108 stimulus vectors, and 9 false positive vectors, yielding a total of 153 automatically presented vectors. The blind spot was plotted manually since its location varies from patient to patient, making it difficult to plot in an automated way.

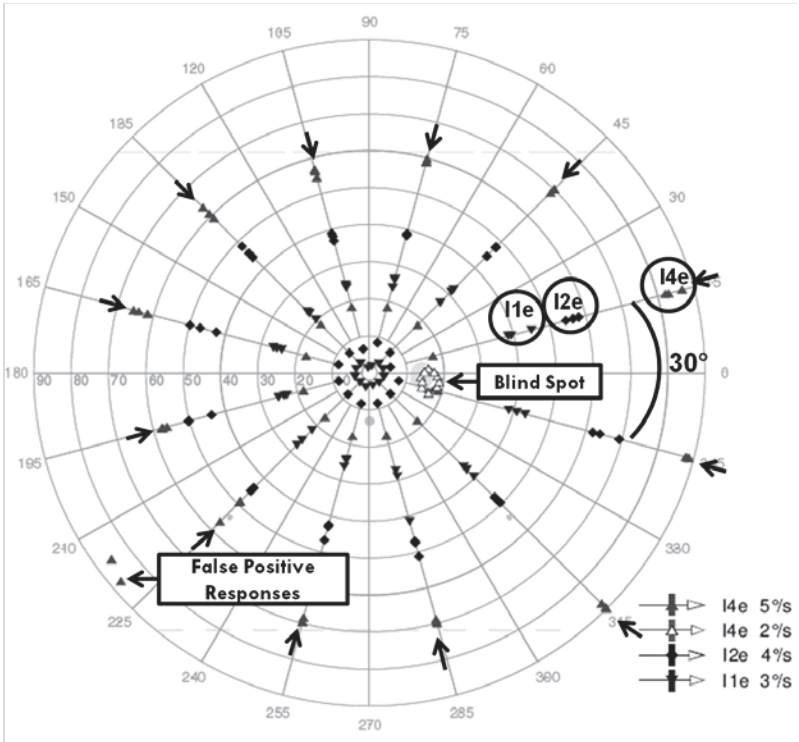


Figure 5.1: Raw visual field result of the right eye of a 27 year old control. Arrows point to the 12 stimulus vectors which are separated by 30°. Circles show the three tested stimuli (I4e, I2e, and I1e), which were examined 3times each at a velocity of 5°, 4°, and 3°/sec respectively. Responses to 2 of 9 false positive presented stimuli are shown at bottom left. The blind spot (approximately 15° nasal) was examined manually with the I4e at a velocity of 2°/sec.

5.7.3. Construction of the Program

In order to program 153 vectors quantitatively, all vectors were programmed using "xml" language [67]. Saved examinations are stored in a file named KineticAutomaticCT.xml (appendix D) where each vector in the file is defined by a code that gives the stimulus intensity, size, speed, and the stimuli's start and end point in Cartesian coordinate system. The chosen coordinates in degrees were changed to Cartesian coordinates in an excel sheet, and then transferred to be coded in the file KineticAutomaticCT.xml.

5.7.4. Examination Instructions and Procedures

After obtaining informed consent, all participants were given standardized instructions by a script (appendix B) [68]. All participants were initially familiarized with the perimeter. The script began by outlining the purpose of the visual field exam, followed by instructions on how to perform the exam, length of time it takes to do, number of breaks given, and how to pause the exam if necessary. Participants were then seated at the perimeter with their chin on the chin-rest, and forehead against forehead band. The response button was placed in the participant's preferred hand.

The visual field task instructions were standardized to the "neutral" one used in a study by Kutzko, Brito, and Wall, 2000. They found that instructions significantly altered the patient's threshold in static automated perimetry; in comparison to the neutral instructions, those given liberal instructions were more likely to respond, and those given conservative instructions were less likely to respond to static stimuli [68].

Upon completion of each isopter, participants were given a one minute break during which the room lights were turned on and the opaque occluder was removed. Between examination of the right and left eyes participants were given at least a 5 minute break to ensure that the previously occluded eye had enough time to light adapt [69]. Appropriate corrective lenses were placed only for the I1e stimulus.

CHAPTER 6. Results

6.1. Collected Data

6.1.1. Study Participants' Demographics

A total of 39 participants were examined (controls=26, migraine with aura (MA)=10, and migraine without aura (MO)=3). One MA and 1 control participants were eliminated from the analysis since they were deemed glaucoma suspects by the glaucoma specialist based on review of all images (OCT, HRT, and fundus photos). The demographic details of the participants that meet the inclusion criteria are outlined in table 6.1.

Table 6.1: Demographic Details.

		Control (n=25)	MA (n=9)	MO (n=3)
Gender (women/men), n		13/12	8/1	2/1
Age (y)	Mean (SD)	40 (14)	43 (11)	44 (10)
	Median (IQR)	40 (27)	46 (16)	39 (8.5)
Follow-up (days)	Mean (SD)	7 (6)	17 (15)	6 (2)
	Median (IQR)	6 (3)	9 (17)	7 (2)

Abbreviations: SD standard deviation, IQR interquartile range.

The planned sample size of the MA (n=25) and MO (n=25) groups were not reached because the anticipated number of primary migraine patients attending the neuro-ophthalmology clinic was lower than anticipated. The MA group was larger because most participants that attended the eye clinic had visual complaints. Due to the small sample size of our MO group, the data of MO (n=3) and MA (n=9) groups were combined under the title of "migraine" for all analyses.

There were more women than men because migraines are more common in females. The follow-up period between study visits wwas longest for the MA group since these participants to be seen at least two weeks after their last migraine attack, and several participants had to rebook their appointments due to a migraine attack between study visits.

6.1.2. Migraine History

For the migraine groups, the age of onset, duration (period in years since age of onset), and frequency (over a 3 months period) of migraine headaches for both MA and MO participants are outlined in table 6.2.

Table 6.2: Migraine History Data.

		MA	MO
Age onset (y)	Mean (SD)	15 (6)	16 (2)
	Median (IQR)	14 (9)	17 (2)
Duration (y)	Mean (SD)	29 (12)	32 (13)
	Median (IQR)	31 (15)	32 (10)
Frequency (n/3 months)	Mean (SD)	5 (4)	2 (1)
	Median (IQR)	3 (2)	2 (1)

Abbreviations: SD standard deviation, IQR interquartile range.

Most migraine participants had had at least one kinetic visual field as part of their first clinic visit, only 2 of them had regular static or kinetic visual fields once a year for 5-10 years.

Severity of last migraine headache for each participant was assessed using the MIGSEV questionnaire. Migraine participants filled out the questionnaire (appendix A). Five had low severity (3 of which were MO participants), 4 had intermediate severity, and 3 had high severity of migraines.

All control participants were healthy with no history of migraine headaches. Only one control had previously had regular static and kinetic perimetry examinations. The remainder either had no previous experience, or one static visual field as part of an eye examination.

6.1.3. Visual Acuity

All of our participants met our inclusion criterion for vision (a visual acuity better than +0.3 logMAR). The visual acuity data of our participants are outlined in table 6.3.

Table 6 3: Visual Acuity Data.

			Control	MA	MO
Visual Acuity (logMAR)	R	Mean (SD)	-0.02 (0.10)	-0.07 (0.06)	-0.13 (0.15)
		Median (IQR)	0.00 (0.10)	-0.10 (0.10)	-0.12 (0.15)
	L	Mean (SD)	-0.07 (0.11)	0.02 (0.31)	-0.05 (0.08)
		Median (IQR)	-0.10 (0.18)	-0.10 (0.18)	-0.10 (0.07)

Abbreviations: SD standard deviation, IQR interquartile range.

6.1.4. Visual Field Data

Figure 6.1 shows one example of a visual field of a 27 year old female control. The remaining of visual field results are provided in appendix C. Visual fields are displayed as normally viewed by clinicians, with the first study visit on the top row and second study visit on the bottom row.

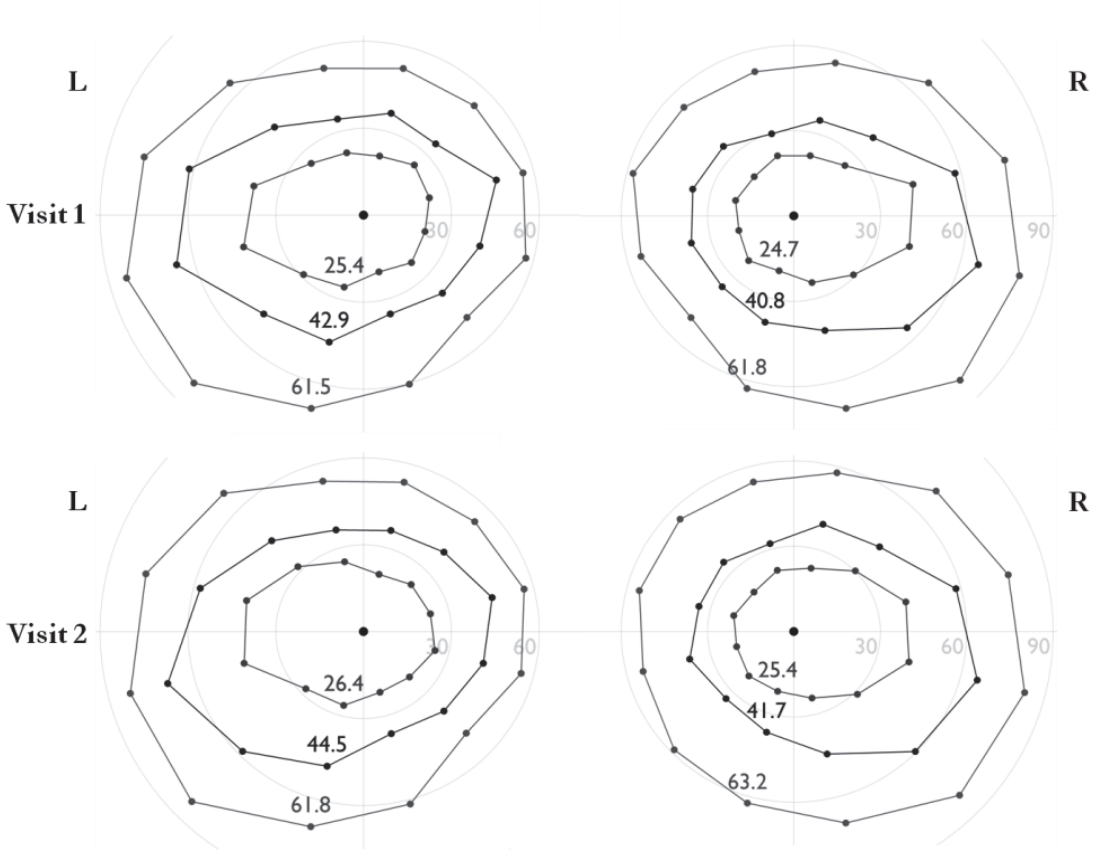


Figure 6.1: Visual field results of right and left eyes on two separate visits for a 27 year old female control. Outermost to innermost isopters are the I4e, I2e and I1e respectively. Numbers next to each isopter denote the mean isopter radius.

6.2. Analysis of Study Visit 1 and Visit 2

6.2.1. Learning Effect between Study Visit 1 and Visit 2

Tables 6.4 and 6.5 below summarize the raw data obtained from the first and second study visits of control and migraine participants. The Wilcoxon, non-parametric paired test was used to determine if the differences between the means of visit 1 and visit 2 were statistically significant. There were no statistically significant differences, with the exception of the left eye of the I4e isopter (Mean difference (SD)=-0.7 (1.4), degrees), and right eye of the I1e isopter (Mean difference (SD)=-1.0 (1.3), degrees). For both of these isopters the mean differences were negative, i.e. in the opposite direction of a learning effect. In addition, the mean differences were ≤ 1°, which was not thought to be clinically meaningful.

Table 6.4: Summary Data for Healthy Controls.

			I4e	I2e	I1e
MIR (visit 1)	R	Mean (SD)	58.1 (3.6)	38.6 (4.0)	23.1 (4.0)
		Median (IQR)	58.9 (2.0)	38.1 (5.4)	23.0 (4.5)
	L	Mean (SD)	58.6 (2.6)	39.4 (3.5)	22.7 (3.6)
		Median (IQR)	58.4 (2.8)	39.4 (3.8)	22.9 (3.4)
MIR (visit 2)	R	Mean (SD)	58.3 (2.9)	39.1 (3.6)	22.1 (3.8)
		Median (IQR)	58.2 (2.4)	39.5 (4.8)	22.3 (4.0)
	L	Mean (SD)	58.0 (3.0)	39.3 (3.7)	22.3 (2.9)
		Median (IQR)	57.6 (2.2)	39.6 (4.5)	22.3 (2.5)
Difference (visit 2- visit 1)	R	Mean (SD)	0.2 (1.9)	0.5 (2.1)	-1.0 (1.3)
		Median (IQR)	0.3 (2.1)	0.4 (2.2)	-0.7 (1.8)
	L	Mean (SD)	-0.7 (1.4)	0.0 (1.5)	-0.4 (1.8)
		Median (IQR)	-0.5 (1.5)	0.2 (1.9)	-0.7 (1.9)
P-value*	R		0.55	0.43	<0.002
	L		0.017	0.97	0.16

Abbreviation: MIR mean isopter radius, SD standard deviation, IQR interquartile range.
*Wilcoxon non-parametric paired test comparing visit 1 to visit 2.

Table 6. 5: Summary Data for Migraine Participants.

			I4e	I2e	I1e
MIR (visit 1)	R	Mean (SD)	60.2 (3.2)	39.1 (4.0)	23.3 (3.7)
		Median (IQR)	60.3 (4.4)	38.6 (5.1)	22.9 (2.7)
	L	Mean (SD)	59.1 (2.4)	37.6 (4.7)	21.4 (3.1)
		Median (IQR)	58.7 (3.3)	37.9 (3.9)	20.9 (4.5)
MIR (visit 2)	R	Mean (SD)	60.0 (3.3)	37.7 (3.4)	22.2 (2.7)
		Median (IQR)	61.0 (4.1)	38.5 (9.3)	22.3 (3.2)
	L	Mean (SD)	59.1 (2.3)	37.5 (3.1)	21.6 (3.1)
		Median (IQR)	59.2 (2.4)	38.4 (4.5)	21.6 (3.3)
Difference (visit 2- visit 1)	R	Mean (SD)	-0.2 (1.2)	-1.3 (3.4)	-1.1 (2.9)
		Median (IQR)	-0.3 (2.1)	-1.4 (4.1)	-1.1 (2.6)
	L	Mean (SD)	0.0 (1.7)	-0.1 (3.1)	0.3 (1.9)
		Median (IQR)	0.0 (2.7)	0.6 (3.1)	0.8 (2.2)
P-value*	R		0.53	0.16	0.27
	L		0.88	0.81	0.48

Abbreviation: MIR mean isopter radius, SD standard deviation, IQR interquartile range.
*Wilcoxon non-parametric paired test comparing visit 1 to visit 2.

The lack of learning effect can be visualized in a scatter plot by plotting the MIR of visit 1 on the x-axis, and the MIR of visit 2 on the y-axis (figures 6.2-6.4). A learning effect would manifest in a greater number of points above the diagonal line.

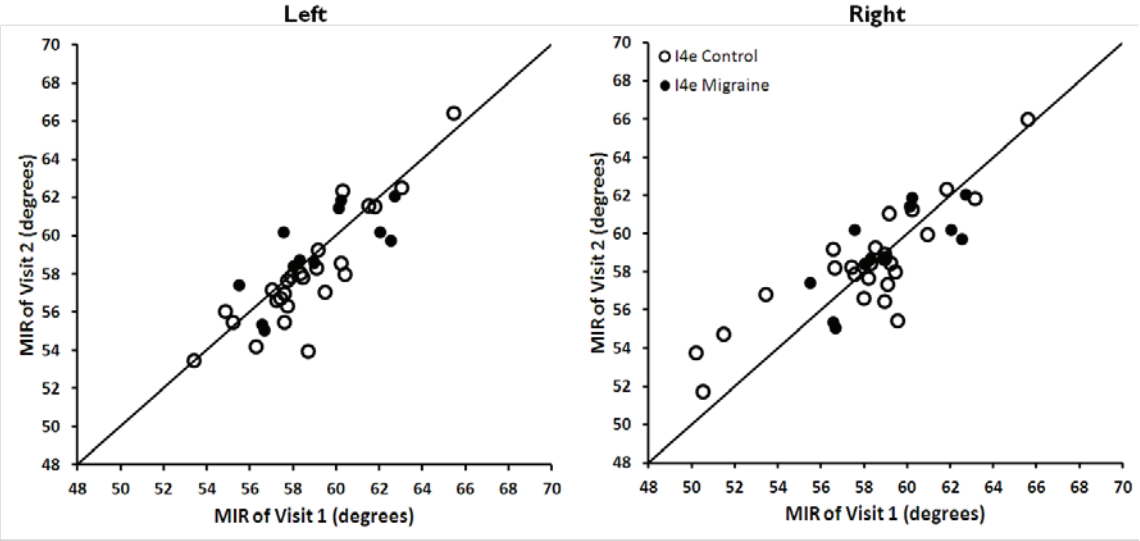


Figure 6.2: Scatter plots of the MIR of the I4e isopter. Visit 1 is on the x-axis and visit 2 is on the y-axis.

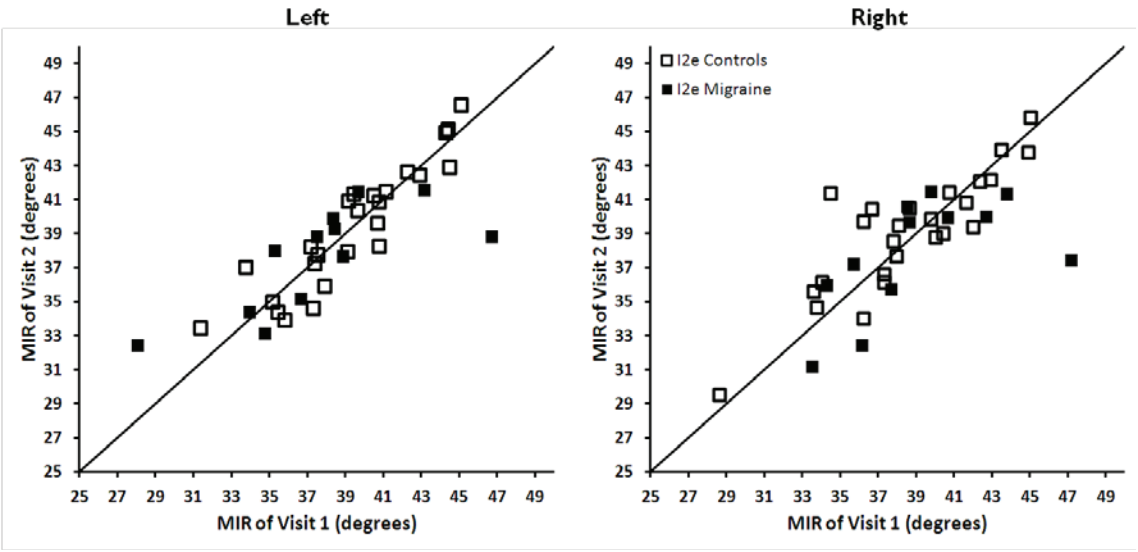


Figure 6.3: Scatter plots of the MIR of the I2e isopter. Visit 1 is on the x-axis and visit 2 is on the y-axis.

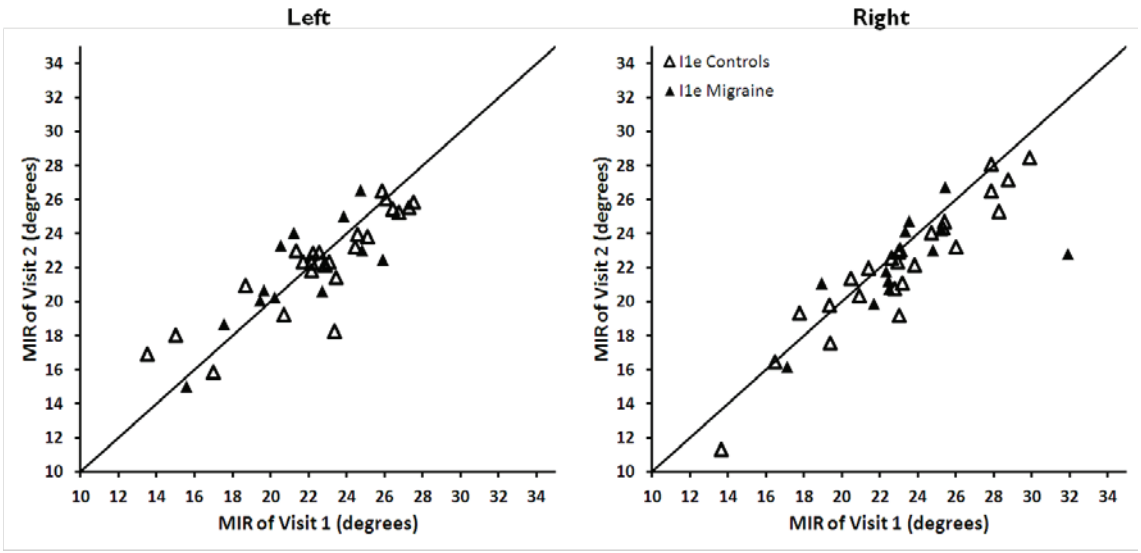


Figure 6.4: Scatter plots of the MIR of the I1e isopter. Visit 1 is on the x-axis and visit 2 is on the y-axis.

6.2.2. Test Retest Variability

To investigate the precision of the test results, the test retest variability and coefficient of repeatability were calculated for each isopter (table 6.6 and 6.7). Test retest variability is different from learning effect in that it relates to the spread of the differences between visit 1 and visit 2. For controls, test retest variability appears to be similar across all three isopters.

Table 6. 6: Test Retest Variability Data for Control Participants (n=25).

		I4e	I2e	I1e
SD of Differences	R	1.9	2.1	1.3*
	L	1.4	1.5*	1.8
Coefficient of Repeatability	R	3.6	4.2	2.6
	L	2.7	3.0	3.5

Abbreviation: SD standard deviation.

Table 6. 7: Test Retest Variability Data for Migraine Participants (n=12).

		I4e	I2e	I1e
SD of Differences	R	1.2	3.4	2.9*
	L	1.7	3.1*	1.9
Coefficient of Repeatability	R	2.3	6.6	5.6
	L	3.3	6.1	3.8

Abbreviation: SD standard deviation.

*P<0.05, F-test for larger test-retest variability in migraine patients compared to controls.

Migraine participants appeared to have greater test retest variability than controls with the I2e isopter of the left eye (p=0.003), and I1e isopter of the right eye (p=0.001). Test retest variability can be visually illustrated by a Bland-Altman plot (figure 6.5). A Bland-Altman plot shows the spread of the random differences and how this spread depends on the mean. In figure 6.5, it appears that variability is greater in the right than left eye, and the majority of the points fall within ±4.8 ° for the right and ±4.4° for the left eye.

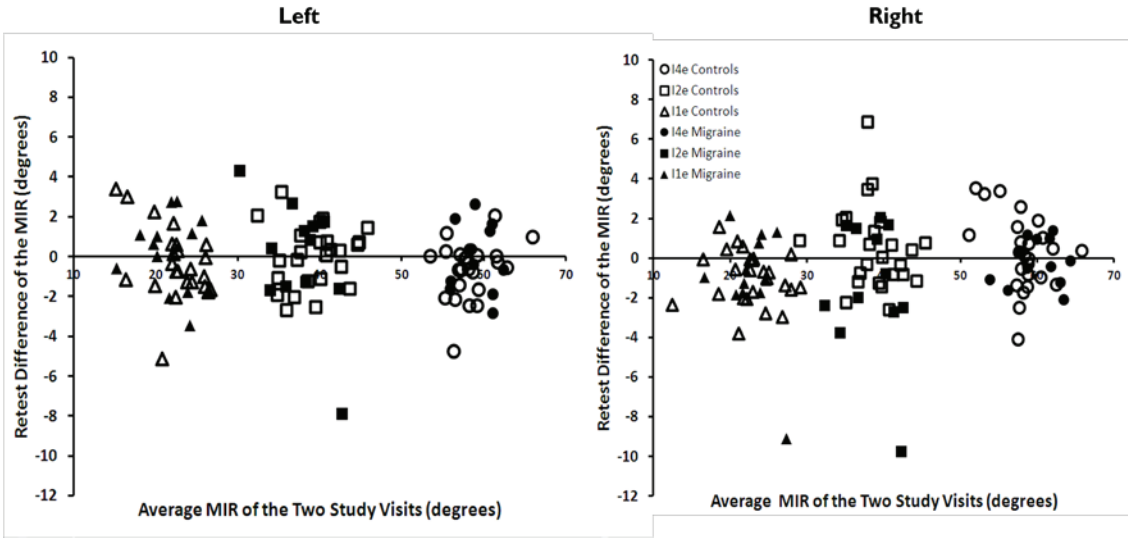


Figure 6.5: Bland-Altman Plots of average MIR on the x-axis and retest difference of MIR on the y-axis

In summary, there were no clinically important learning effects between visit 1 and visit 2. Therefore, we can justify averaging the MIR values of visit 1 and visit 2 to obtain data with greater precision to determine if there were a significant difference between the MIR of migraine patients and controls.

6.3. Comparison of Right and Left Eyes

In this section it was determined if there was a significant difference between the responses between the right and left eyes. Data from visit 1 and visit 2 were averaged (table 6.8), and the Wilcoxon, non-parametric paired statistical test was used to determine if there was a significant difference between the data of right and left eyes for each isopter.

Table 6 8: Right and Left Eyes Comparison Data for Migraine Patients and Controls.

			I4e	I2e	I1e
Control MIR	R	Mean (SD)	58.2 (3.1)	38.8 (3.6)	22.6 (3.8)
		Median (IQR)	58.2 (1.4)	38.8 (4.1)	22.6 (3.9)
	L	Mean (SD)	58.3 (2.7)	39.3 (3.5)	22.5 (3.1)
		Median (IQR)	57.9 (2.3)	40.0 (4.4)	22.5 (2.5)
Difference (left – right)		Mean	0.1	0.5	-0.1
		Median	-0.3	1.2	-0.1
P-value*			0.88	0.17	0.56
Migraine MIR	R	Mean (SD)	60.1 (3.2)	38.4 (3.3)	22.7 (2.9)
		Median (IQR)	60.8 (3.9)	39.4 (4.7)	22.9 (2.9)
	L	Mean (SD)	59.1 (2.2)	37.6 (3.6)	21.5 (3.1)
		Median (IQR)	58.8 (3.3)	38.2 (4.0)	21.8 (3.9)
Difference (left – right)		Mean	-1.0	-0.8	-1.2
		Median	-2.0	-1.2	-1.1
P-value*			0.028	0.015	0.01

Abbreviation: SD standard deviation, IQR interquartile range

*Wilcoxon non-parametric paired test comparing right and left eyes.

There were no statistically significant differences between the means of the right and left eyes for control participants, for any isopter. However, the differences between right and left eyes for the migraine participants were small (<1.2°), but statistically significant for all isopters. A difference of ≤1.2° between eyes may be statistically significant but was thought not to be clinically meaningful. Therefore, we can justify averaging the values between eyes.

This will provide data with greater precision to determine if there is a significant difference between the MIR of migraine and control participants.

6.4. Differences between Migraine and Control

In this section, the main question of our study purpose was analyzed, which was to determine if there is a statistically significant difference between the mean MIR of migraine patients and controls. Thus far, it has been shown that there were no clinically important differences between the MIR of study visit 1 and visit 2, and between right and left eyes. Therefore, the data of visit 1 and visit 2 were averaged, as well as the data of the right and left eyes, which are summarized in (table 6.9). The non-parametric independent Mann-Whitney U test was used to determine if there is a statistically significant difference between the mean MIR of migraine patients and controls.

Table 6.9: Summary Results for Migraine and Control Participants.

		I4e	I2e	I1e
Control Participants	Mean (SD)	58.3 (2.8)	39.1 (3.4)	22.6 (3.4)
	Median (IQR)	58.0 (1.5)	39.1 (4.5)	22.5 (3.3)
Migraine Participants	Mean (SD	59.6 (2.6)	38.0 (3.5)	22.1 (2.9)
	Median (IQR)	59.8 (3.4)	39.0 (4.5)	22.0 (3.6)
Absolute Difference	Mean	1.3	1.1	0.5
	Median	1.8	0.1	0.5
P-values*		0.092	0.46	0.54

Abbreviation: SD standard deviation, IQR interquartile range.
*Mann-Whitney U test.
Visits 1 and 2, and right and left eyes were averaged for the analysis.

In summary, there were no statistically significant differences in the size of visual fields of migraine patients and controls. However, this analysis did not take into account the age of participants. Therefore, a multiple regression analysis was performed.

6.5. The effect of age and migraine on MIR

In this section, the effect of age and migraine on the MIR is investigated by carrying out a multiple regression analysis. Results of the multiple regression analysis are outlined in table 6.10. The multiple regression equation takes the following form:

MIR= m * age + c * migraine + b, where "m" is the age coefficient, "c" is the migraine coefficient, "migraine" is an indicator variable that is 0 for controls and 1 for migraine patients, and "b" is the y-intercept.

Results indicate that the migraine coefficients were not statistically significant for any of the three isopters. This suggests that migraine does not affect the relationship between age and MIR. Age has a negative and significant effect on all isopters (table 6.10). This relationship can be visualized in figure 6.6. It is calculated that with each 10 years of increase in age, the MIR is reduced by 1.0°, 1.3° and 1.0° for the I4e, I2e and I1e isopters respectively.

Table 6. 10: Multiple Regression Results for two Groups of Participants at Age 40.

	I4e	I2e	I1e
Y-intercept, degrees	62.2	22.2	26.4
Age coefficient, degrees (p-value*)	-0.10 (0.003)	-0.13 (0.002)	-0.10 (0.019)
Migraine coefficient, degrees (p-value*)	1.64 (0.068)	-0.73 (0.494)	-0.17 (0.872)
MIR at age 40, migraine, degrees	59.9	38.3	22.4
MIR at age 40, control, degrees	58.3	39.0	22.6

*Multiple Regression.

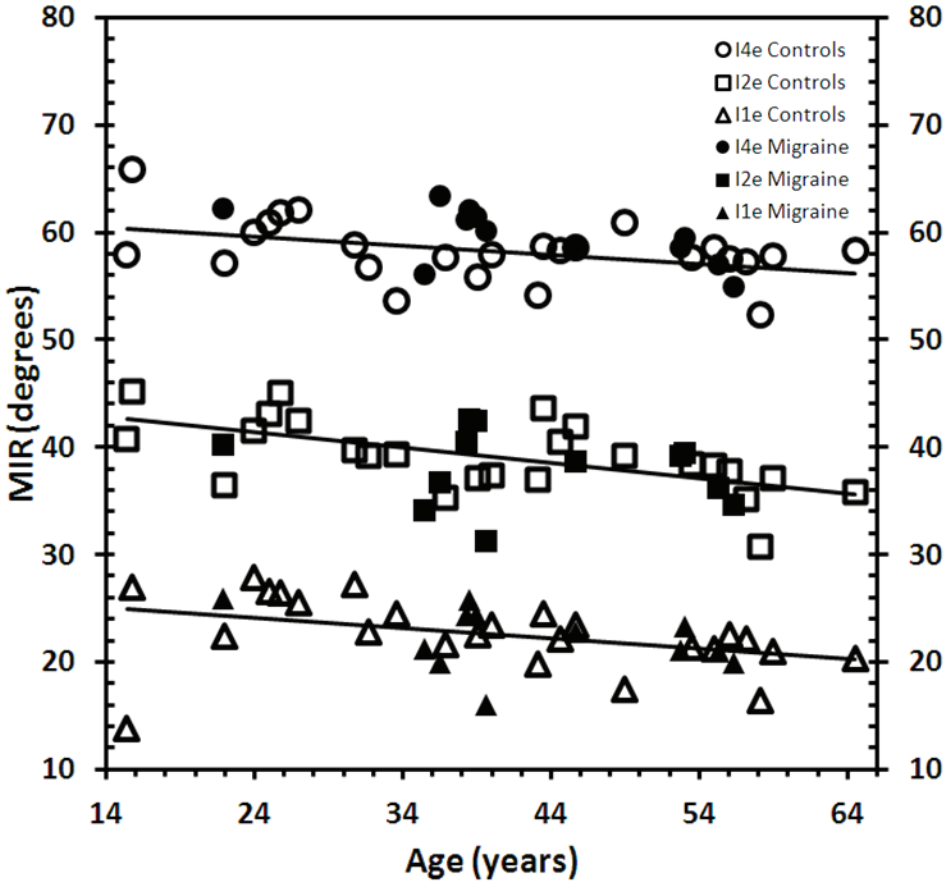


Figure 6.6: The relationship between age on the x-axis and MIR on the y-axis. The line for best fit is fitted for control participants.

6.6. Power Analysis

Our study had 12 migraine and 25 control participants. In order to calculate power, the between-subject variability of each isopter in each group was calculated. There were no statistically significant differences ($p<0.01$) in between-subject variability between the migraine and control groups for any isopter. Therefore, we derived the pooled between-subject variability and used this to calculate the power of our study. The power analysis shows that our study would have been able to detect a difference in MIR between controls and migraine patients of between 3.4° -3.9°, with 90% power (figure 6.7), at a type I error rate of 5%.

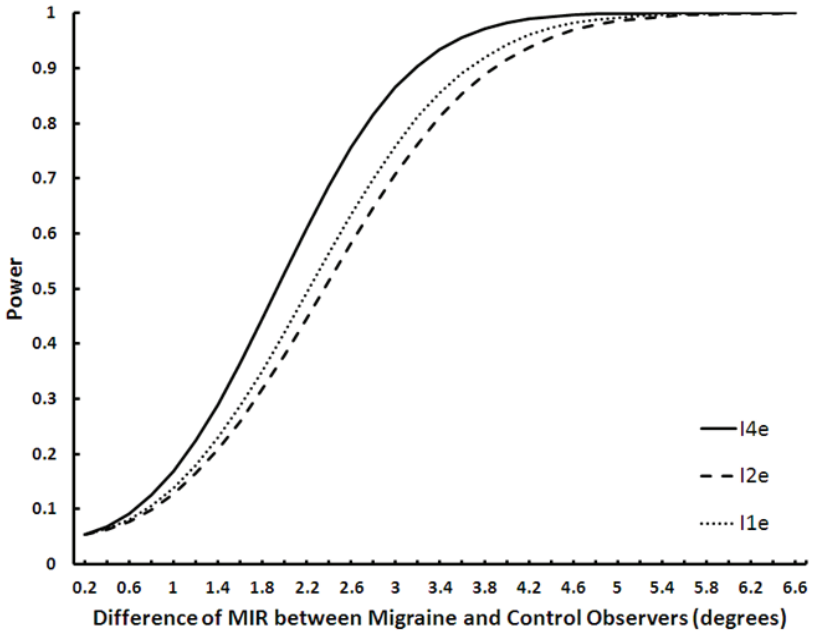


Figure 6.7: Detectable difference of MIR between migraine patients and controls on the x-axis and power is on the y-axis, for each isopter.

Furthermore, the relationship between sample size and power was explored with a true difference of 2 and 5 degrees in MIR. Figure 6.8 illustrates that larger differences are detectable between groups with a smaller sample size and greater power. For example, with a true difference of 5 degrees, only between 7-11 participants are needed to achieve 90% power. However, with a difference of 2 degrees, 35-65 participants are needed to achieve the same power.

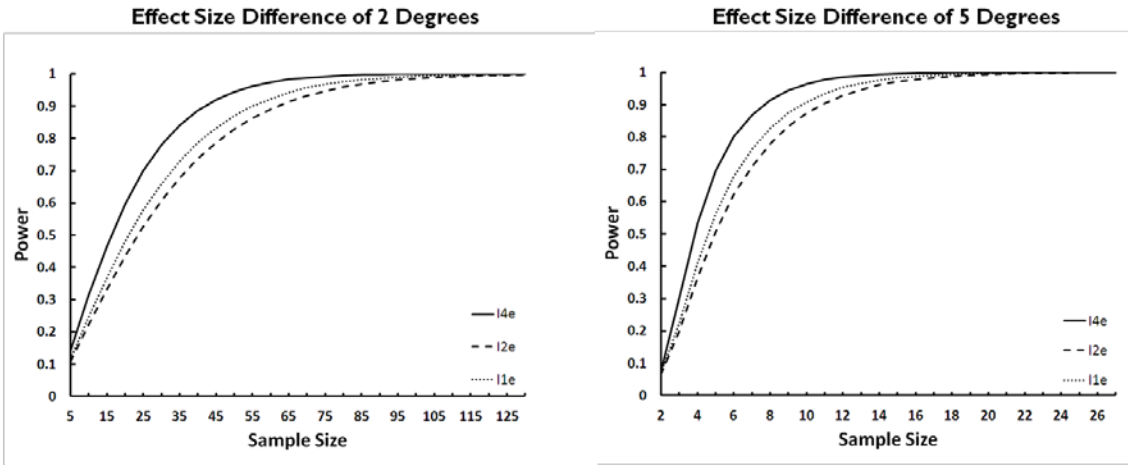


Figure 6.8: Sample size on the x-axis, and power on the y-axis with a difference of 5 (right) and 2 (left) degrees.

It is apparent that, at our sample size of n=25, a difference of 2-3 degrees in MIR would have been detectable (figure 6.9).

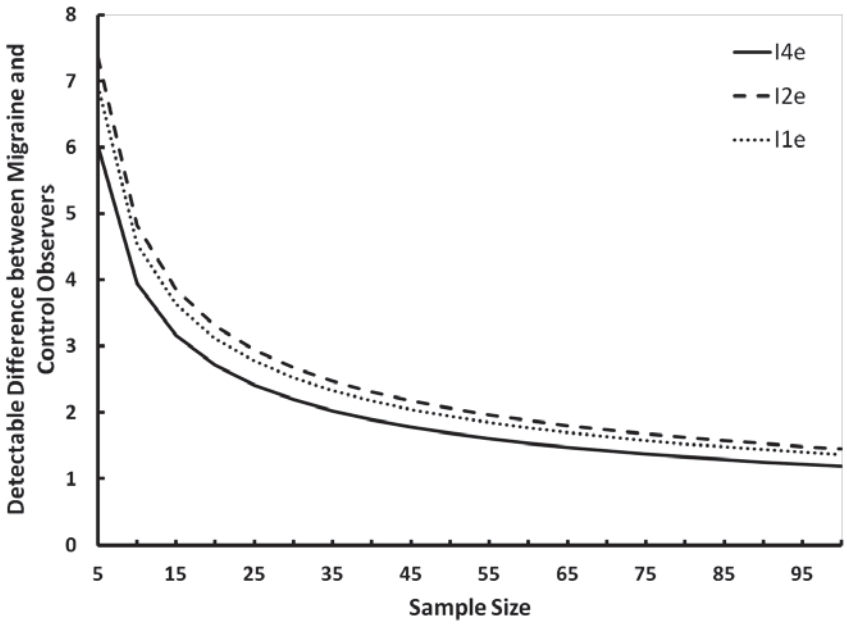


Figure 6.9: Sample size on the x-axis, and difference between migraine patients and controls on the y-axis for both right and left eyes separately.

In conclusion, our study shows acceptable test retest variability with the AKP program we have designed. We were able to demonstrate that differences of approximately 2°-3° between controls and migraine patients could have been detected with high power. However, we did not see such differences. This suggests that there is no evidence to indicate that peripheral visual fields of migraine patients are smaller than those of controls.

CHAPTER 7. Discussion and Conclusion

Several previous research groups have investigated visual field loss in patients with migraine and in particular migraine with aura (MA) patients. As previously summarized (Chapter 2.5 – 2.7), there is supporting evidence for the hypothesis that patients with migraine may have reduced visual fields in comparison to controls. Research thus far has examined the central 30° of the visual field using several different types of perimetric techniques. Results were conflicting depending on the perimetric technique used. Flicker and short wavelength automated perimetry showed that migraine patients have decreased visual sensitivity in comparison to controls. The arc kinetic perimeter showed no differences in the visual fields of migraine patients and controls. Static perimetry using the Medmont M-700, as well as the more commonly used Humphrey Field Analyzer, revealed no differences in the visual fields of patients with migraine and controls [15, 17-20].

Since patients with migraine have peripheral visual complaints and changes in the visual cortex that correspond to the peripheral visual field it was hypothesized that migraine patients may have reduced peripheral visual fields in comparison to controls. This hypothesis was investigated by examining the central and peripheral visual fields in patients with migraine and controls. We did not find any evidence for the hypothesis that migraine patients have reduced visual fields in compared to controls. We further carried out a multiple regression analysis and found that migraine does not affect the relationship between age and size of the peripheral visual field. We also determined the confidence with which we can reject the hypothesis that there are migraine-related peripheral visual field losses by conducting a power analysis. Results revealed that the current study would have detected differences in MIR between migraine patients and controls of 2° with high power. Finally, the automated kinetic perimetric examination design used with the Octopus 900 was found to be repeatable for all three isopters (I4e, I2e, and I1e).

There are several outcomes to the study that are of benefit to future research, and in addition have clinical applications. This study is the first to examine test-retest variability in controls using a program of fully automated kinetic perimetry. Between-subject variability results from 25 controls provide a foundation for power calculations for future studies using

automated kinetic perimetry. Furthermore, we derived a useful linear equation which provides the MIR of controls at any given age for each of the three Isopters (I4e, I2e, and I1e).

A clinical application of this study is to demonstrate that automated kinetic perimetry on the Octopus 900 can be a repeatable test. This is important since clinicians still rely heavily on the Goldmann perimeter, which is no longer manufactured. The Octopus 900 is the official successor of the Goldmann perimeter, and will ultimately replace it in many centers. An advantage of this instrument is that the velocity of the stimulus can be precisely controlled. Furthermore, SAKP has automated calibration and the isopter boundaries can be corrected for response time. These features reduce between-examiner variability, making the test repeatable and important in monitoring change of disease over time. Research that compared kinetic Goldmann perimetry to SAKP showed that even though the mean isopter area or radii were, on average 15%-20%smaller using Goldmann perimetry, these two tests were comparable [45, 54]. Furthermore, SAKP was shown to be a repeatable test, similar to Goldmann perimetry by an experienced perimetrist [42].

Our study provides an answer to a question that migraine sufferers find very concerning. Most migraine aura patients upon having their first attack present to the hospital emergency with concerns about either having a stroke, or some other serious visual problem. Significant healthcare resources are spent in the management of such patients involving emergency and family medicine as well as neurology and neuro-ophthalmology. Our study suggests that migraine auras of primary migraines are fully reversible and have no lasting effect on the peripheral visual field.

This study has several limitations. The groups were not matched for age and sex and the sample size of the migraine group was smaller than planned (13 vs 50). Only a small number of MO subjects could be recruited. Due to the small sample size of our MO group, we were unable to analyze the differences between MA and MO patients. Furthermore, the protocol for visual field examination stipulated that migraine patients would be examined at least two weeks after their last attack, and this criterion could have created a bias toward having participants with a lesser severity of migraines. However, according to the MIGSEV

questionnaire which is based on the international headache society criteria, frequency of migraines was not one of the factors used to assess the severity of migraines [38, 70].

We hope that our research project will provide a foundation for future studies. Peripheral visual fields are being studied for several reasons, for example pharmacovigilance with; vigabatrin, a seizure medication that has been found to cause peripheral visual field loss with prolonged use; retinopathy of prematurity a condition found in premature babies in whom the retina is underdeveloped; retinitis pigmentosa or Usher syndrome, a group of genetic eye diseases that can lead to complete blindness [42, 71-73]. All of the given examples have change over time as a common factor. The repeatability of the Octopus 900 makes it a useful tool in the assessment of change in the peripheral visual field of these patients.

Appendix A

MIGSEV questionnaire [70]

Subjects are asked to rate the following items according to the possible reply modes:

Intensity of pain
1 Mild
2 Moderate
3 Intense
4 Very intense

Nausea
1 None
2 Mild
3 Intense
4 Vomiting

Disability in daily activity
1 No
2 Mild
3 Marked
4 Confined to bed

Tolerability
1 Tolerable
2 Barely tolerable
3 Intolerable

Scoring system:

Firstly, the number of items for which the lowest possible and the highest possible rating is determined. Secondly, a ternary (low, intermediate and high) overall rating of severity is attributed using the following decision tree.

Low (Grade 1): at least one of the four items with a minimum score, and no item with a maximum score.

High (Grade 3): at least one of the four items with a maximum score, and no item with a minimum score OR at least two items with a maximum score.

Intermediate (Grade 2): all other cases.

Appendix B

Script to Visual Field Test [68]

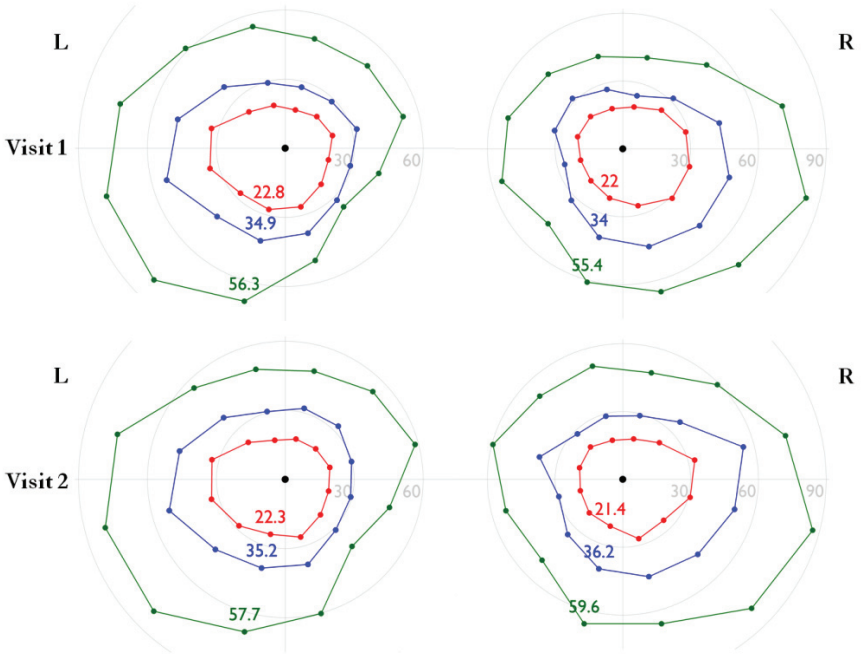
Participants are initially familiarized with the perimeter. They are shown the buzzer, central fixation point, and two mirrors in the inside. They are also informed that their fixation will be monitored on the computer screen. Then they are given the following instructions:

"For the purpose of this study, yourself, and all my other participants will receive similar instructions on how this visual field exam works. I ask you to please be patient while I give you instructions and wait until the end if you have any questions. The purpose of this visual field exam is to test your peripheral field of vision, so what that means for example, is if you are currently fixating at my nose, and I wave my hand off to the side (demonstrating by waving my hand in their periphery), are you able to see my hand or not? However, this visual field machine is different in the sense that your point of fixation will be this green dot (pointing at it), and it doesn't use such a large target like my hand, instead it uses a white spot of light of different brightness and size (showing them a demo of the I4e target). This visual field exam takes about 15 minutes per eye; I will give you 3 breaks during the exam. However, if you want me to pause the test earlier, let me know and I will pause it, please do not stop doing your test until I say "you may take a break now. Once I start the test, always look straight ahead at the central green fixation point. The white spot of light will be brought from off to the side toward the center, press the buzzer whenever you see the spot of light. You are not expected to see all of them. The best time to blink, is just as you press the button [68]. Do you have any questions?"

Participants were set up on the perimeter, chin on chin-rest, and forehead touching head-band. The buzzer is held in the hand of preference.

Appendix C

Raw Data

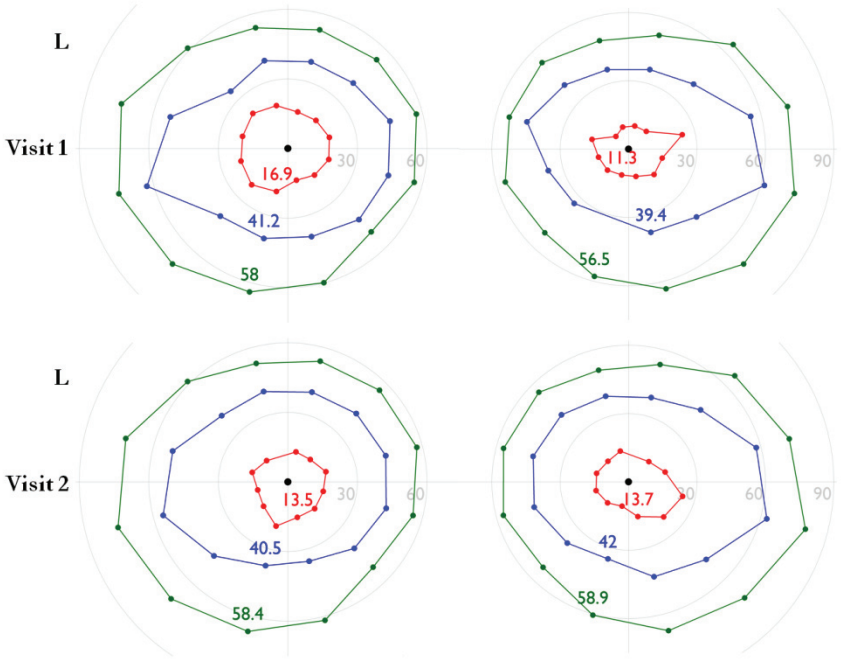


Participant # 1:

Group: Control

Age: 57

Gender: Male

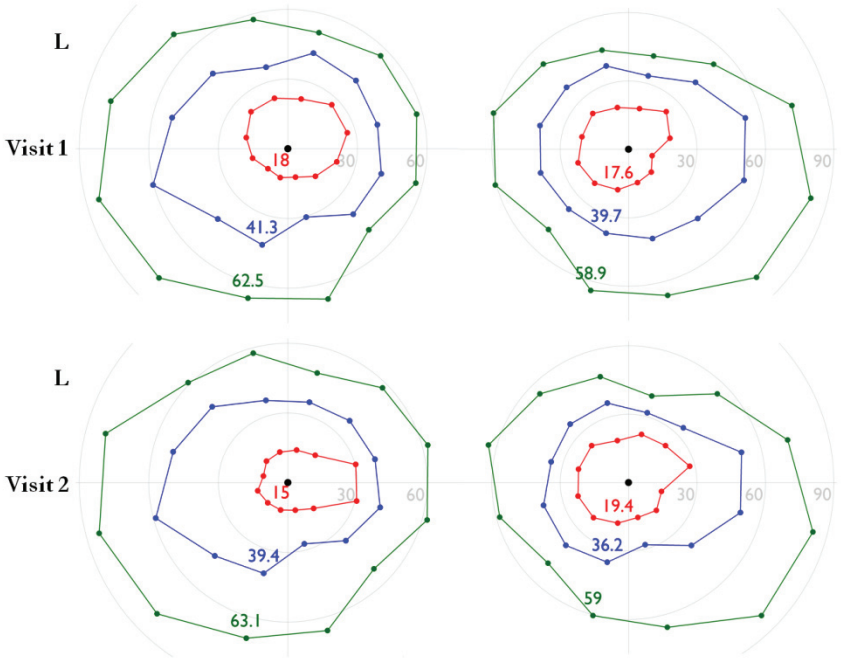


Participant # 2:

Group: Control

Age: 15

Gender: Male

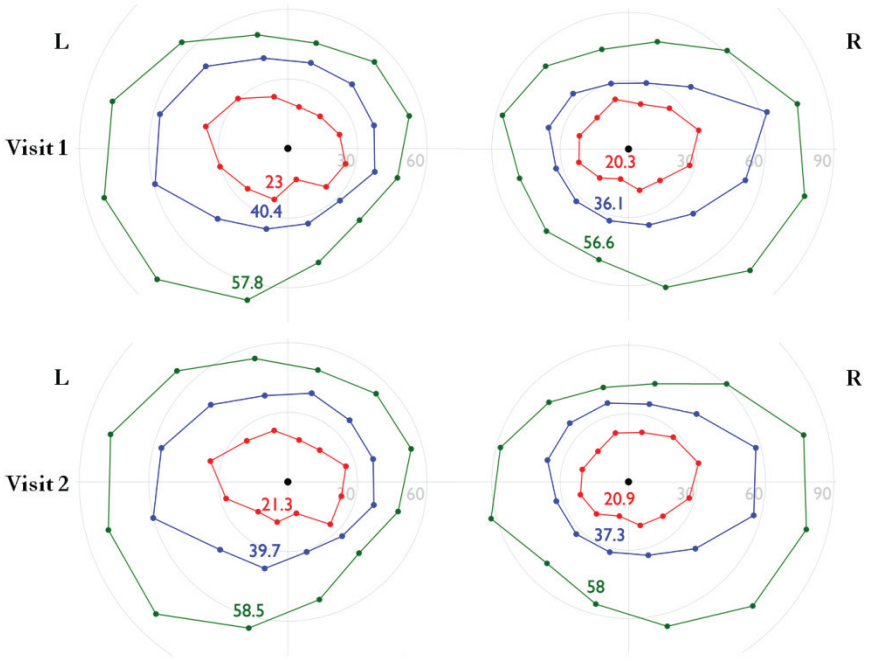


Participant # 3:

Group: Control

Age: 49

Gender: Female

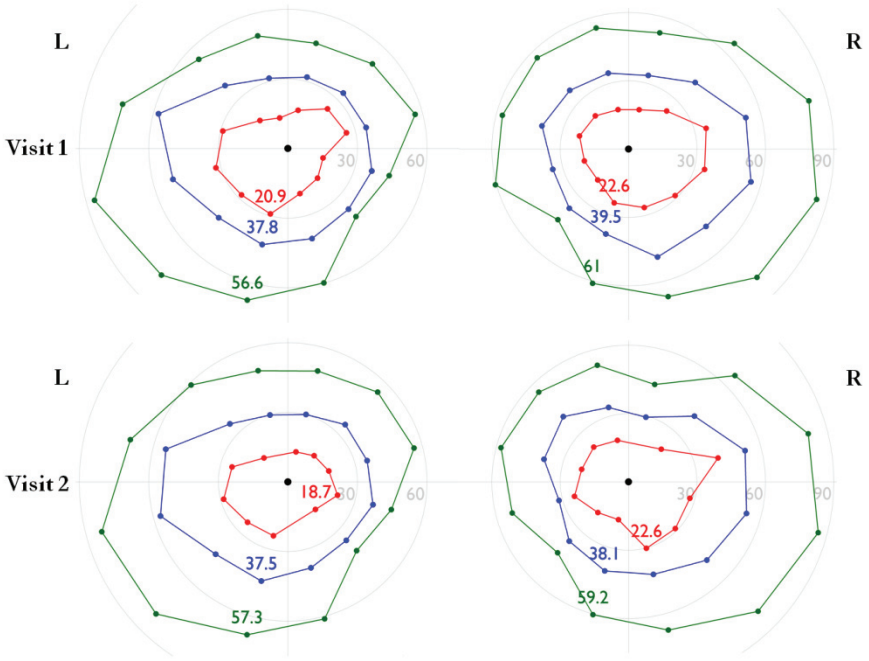


Participant # 4:

Group: Control

Age: 54

Gender: Female

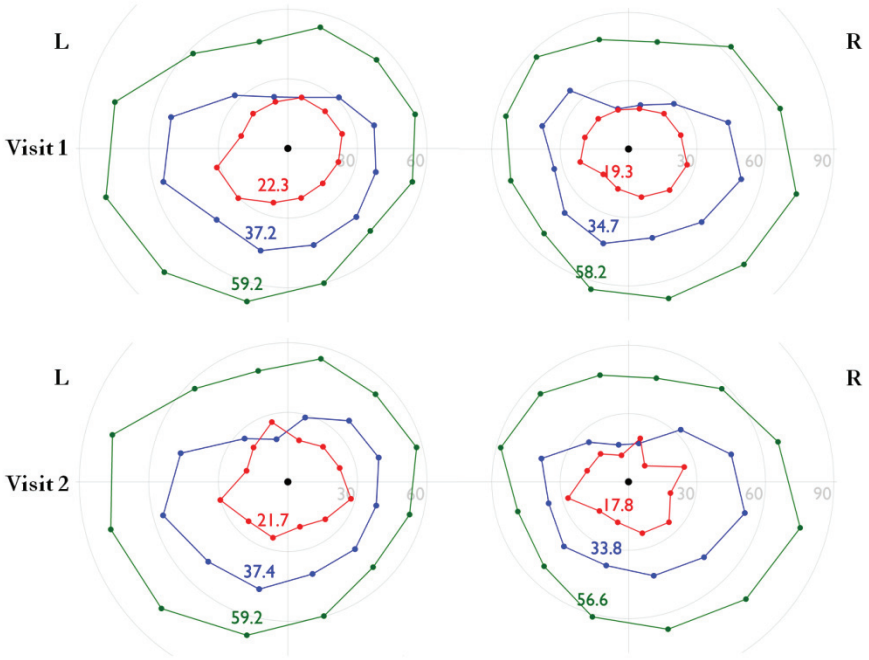
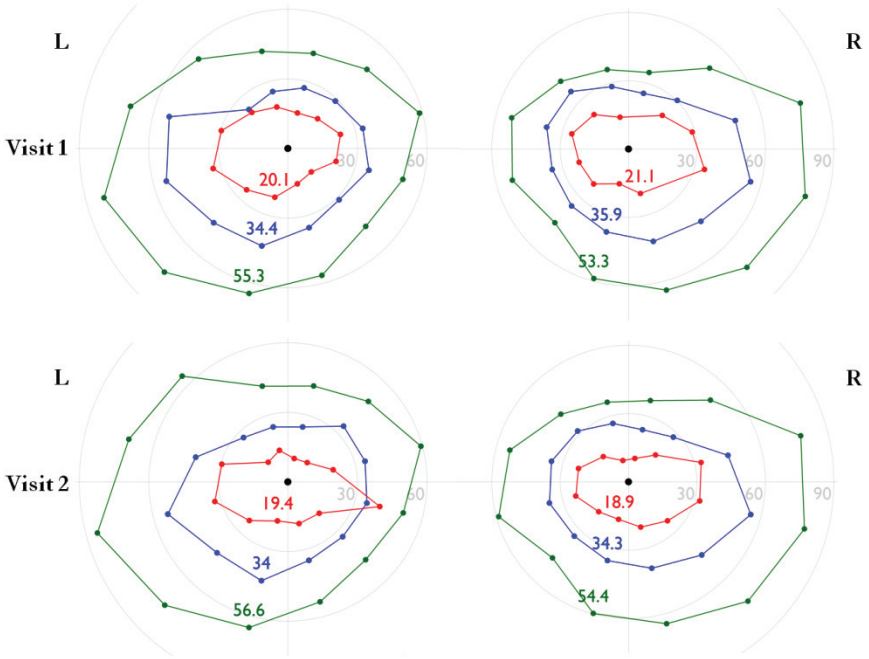


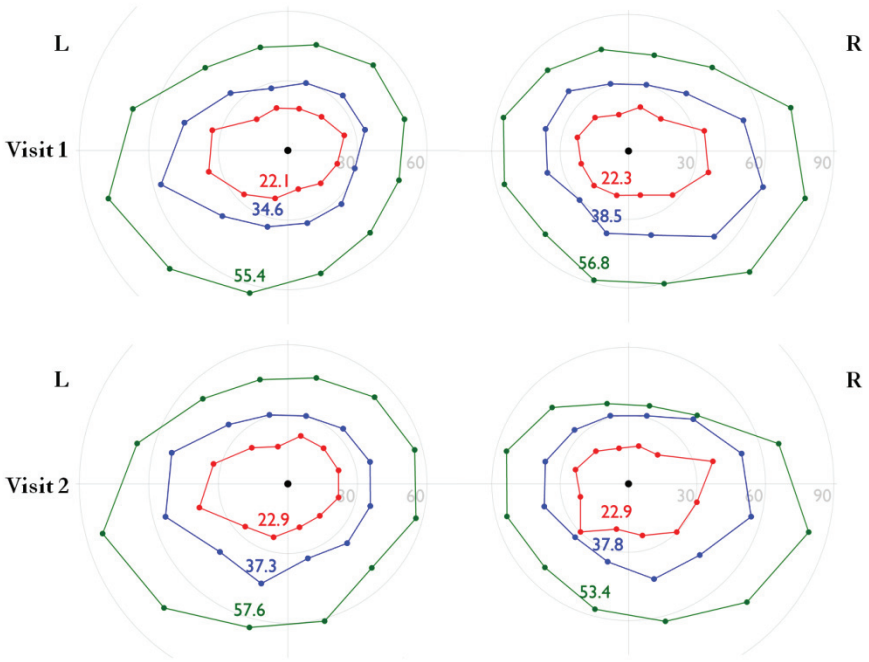
Participant #5:

Group: Control

Age: 55

Gender: Male

	Participant #6: Group: Control Age: 65 Gender: Male
	Participant #7: Group: Migraine with aura. Age: 56 Gender: Male

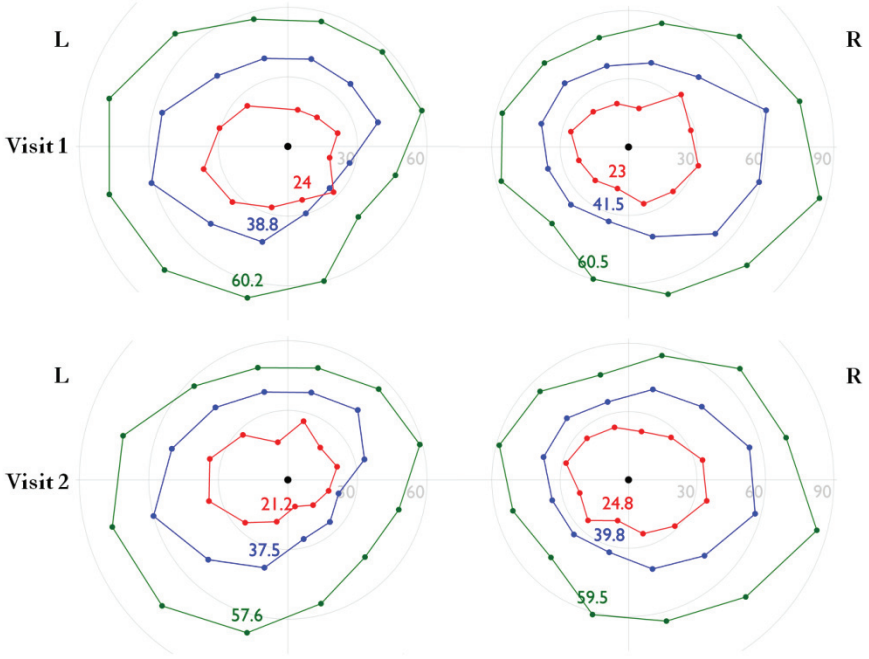


Participant #8:

Group: Control

Age: 39

Gender: Male

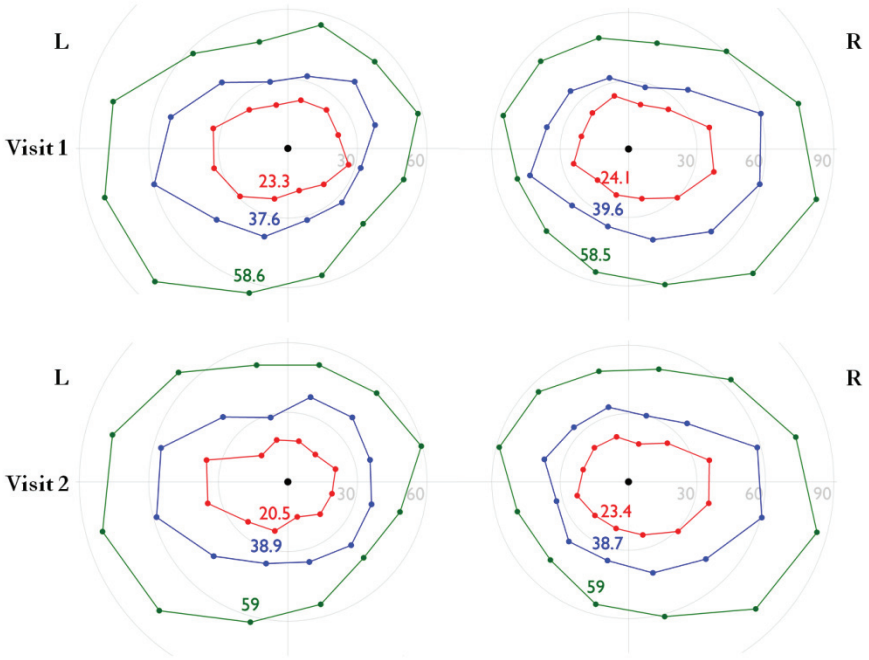


Participant #9:

Group: Migraine with aura.

Age: 53

Gender: Female

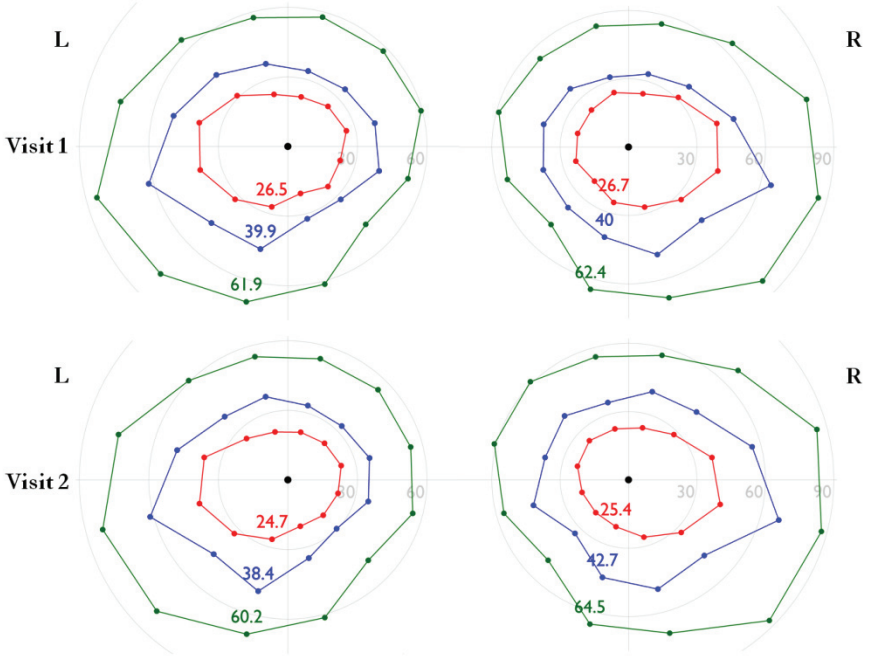


Participant #10:

Group: Migraine with aura.

Age: 46

Gender: Female

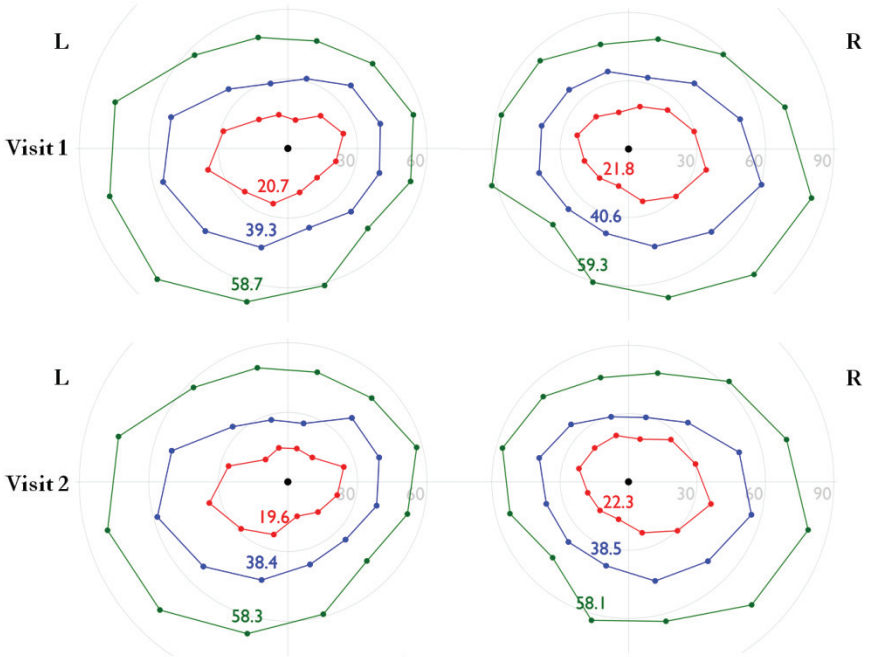


Participant #11:

Group: Migraine with aura.

Age: 22

Gender: Female

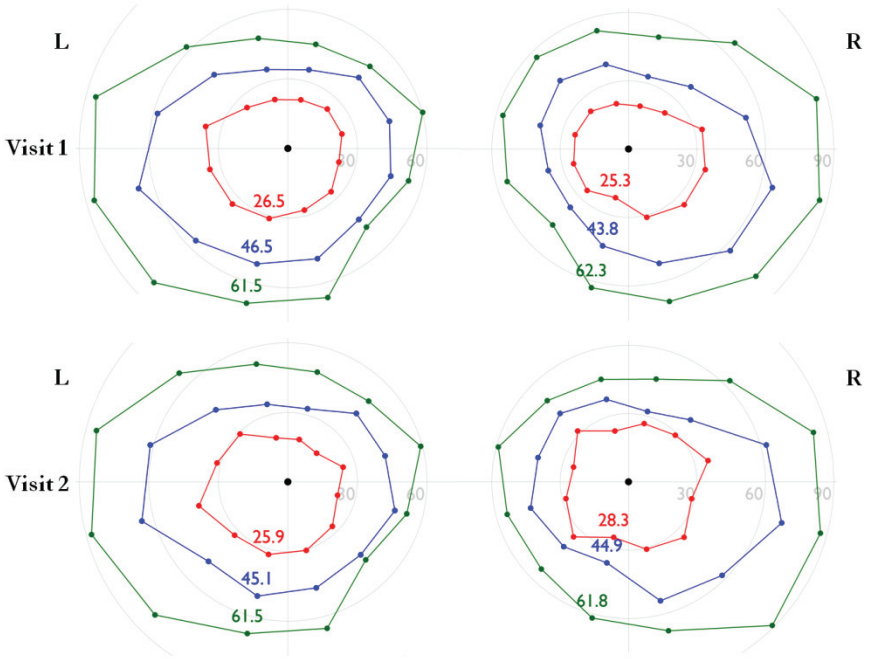


Participant #12:

Group: Migraine with aura.

Age: 53

Gender: Female

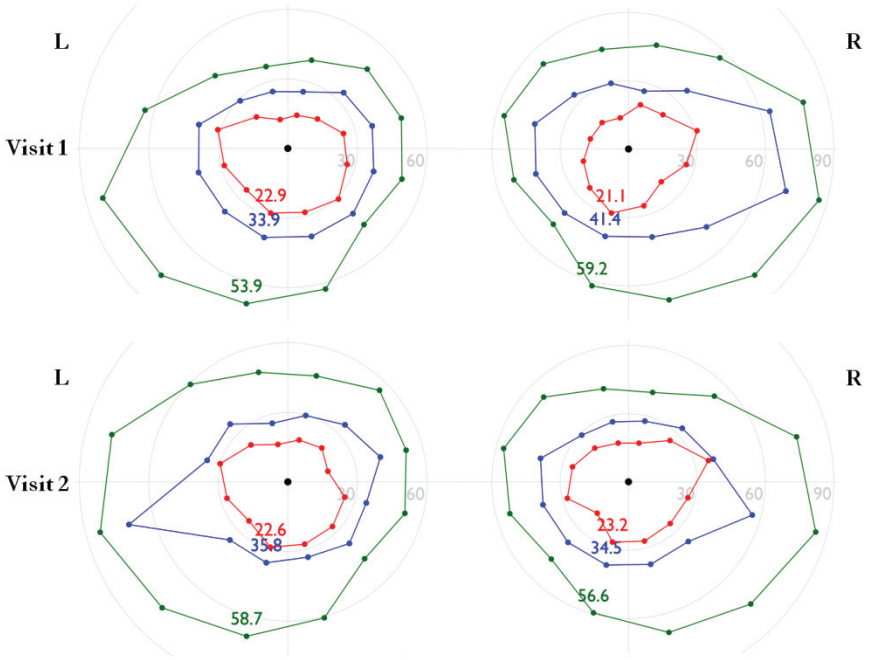
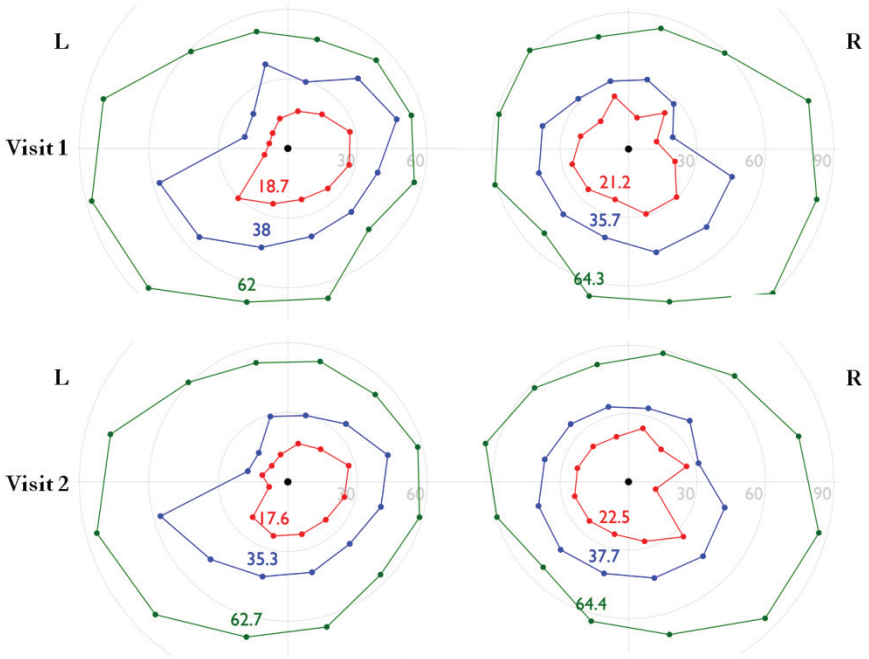


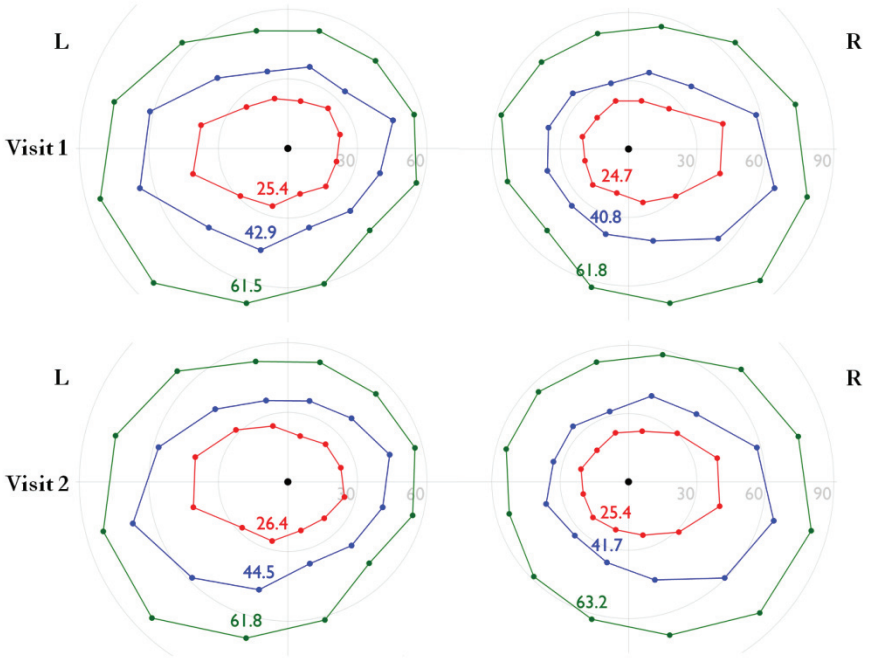
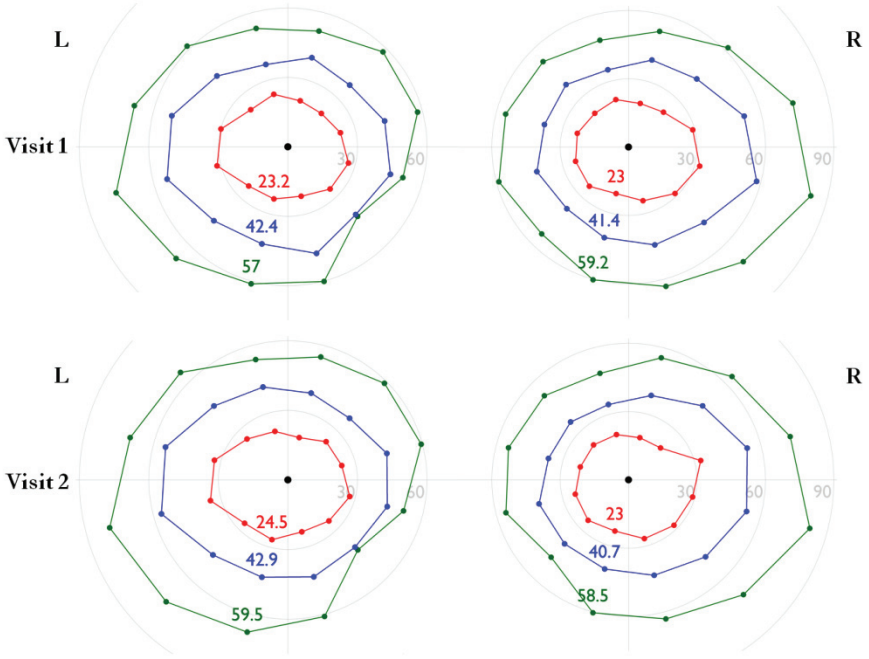
Participant #13:

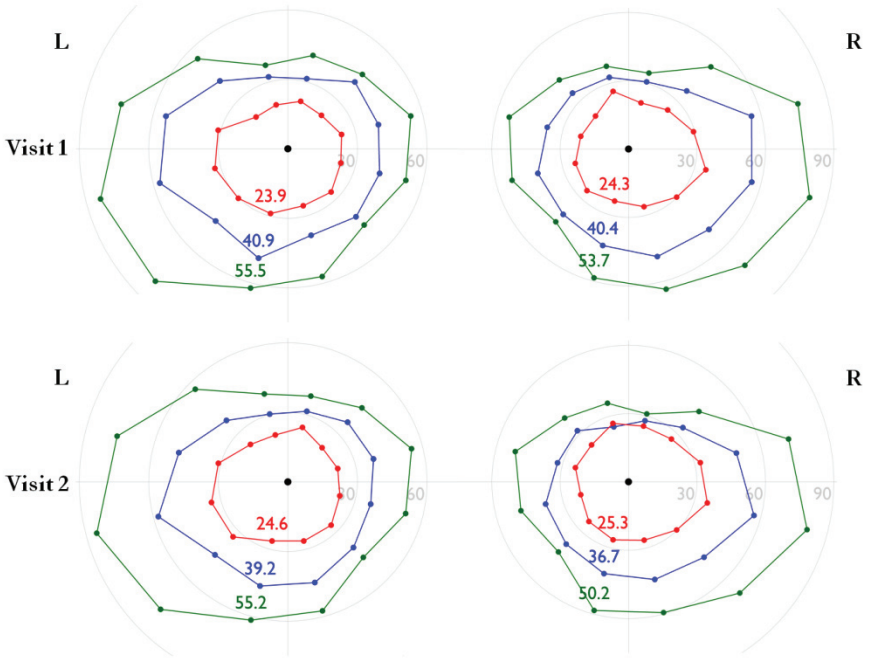
Group: Control

Age: 26

Gender: Male

	Participant #14: Group: Control Age: 22 Gender: Female
	Participant #15: Group: Migraine with aura. Age: 37 Gender: Female

	Participant #16: Group: Control Age: 27 Gender: Female
	Participant #17: Group: Control Age: 46 Gender: Female

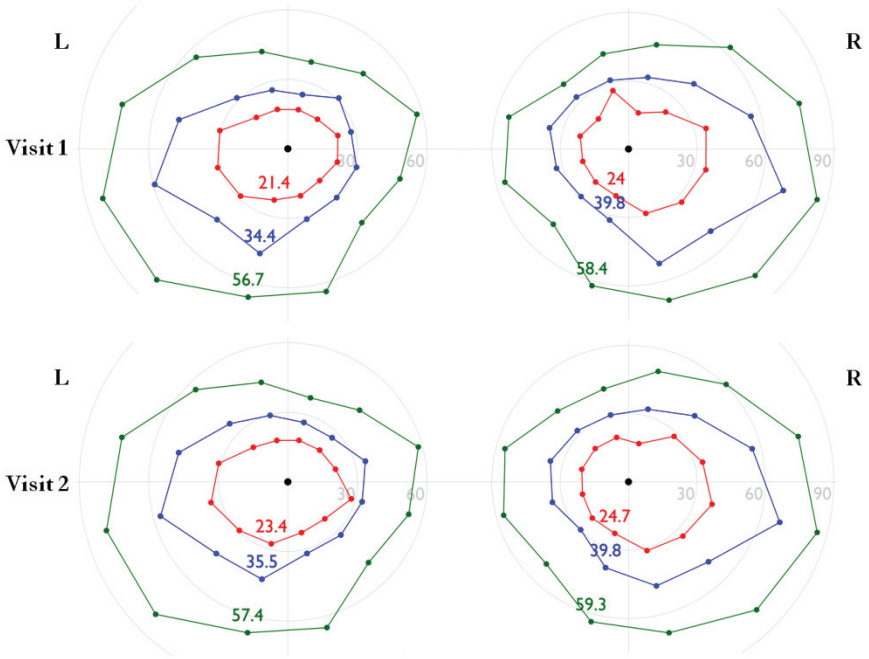


Participant # 18:

Group: Control

Age: 34

Gender: Male

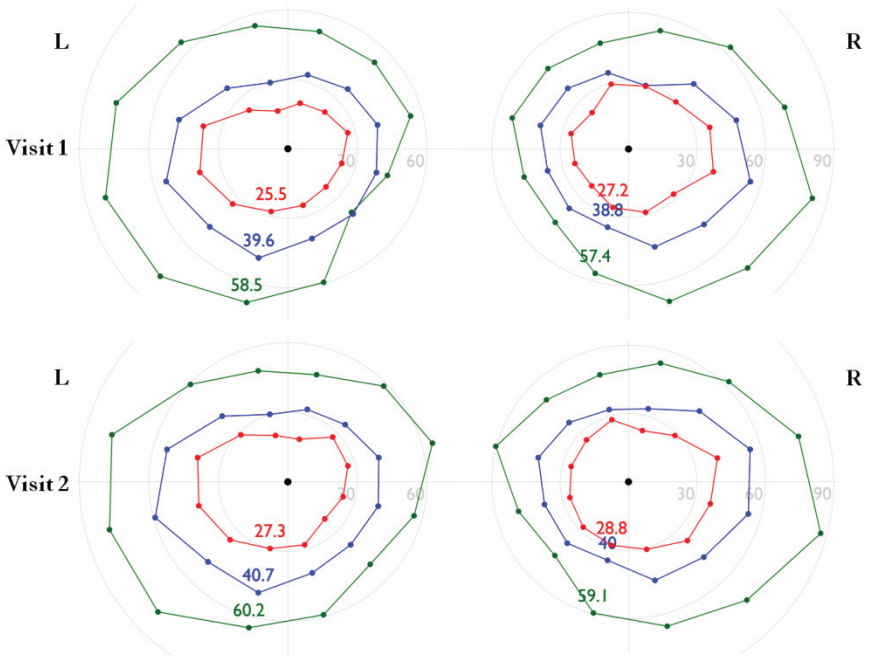
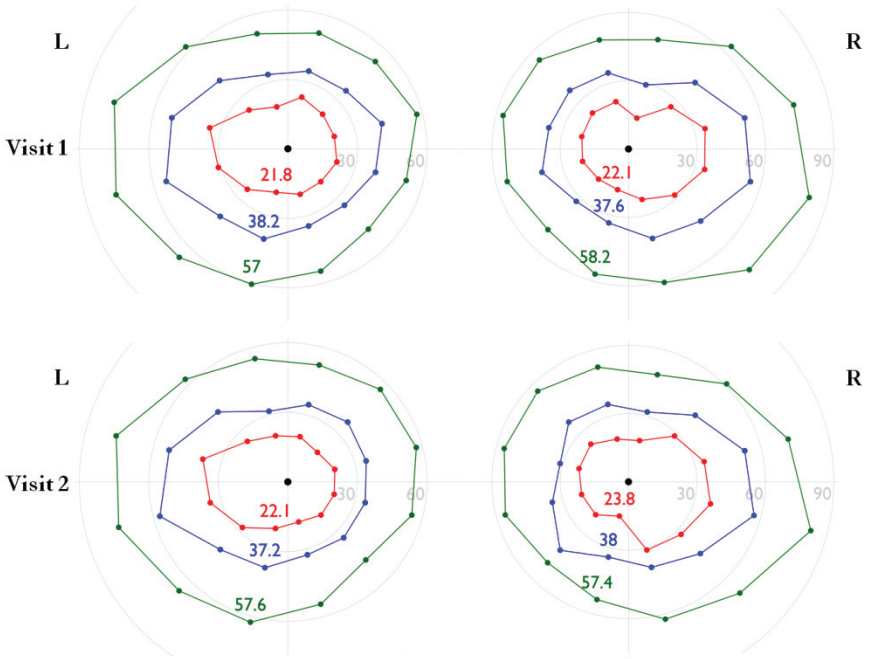


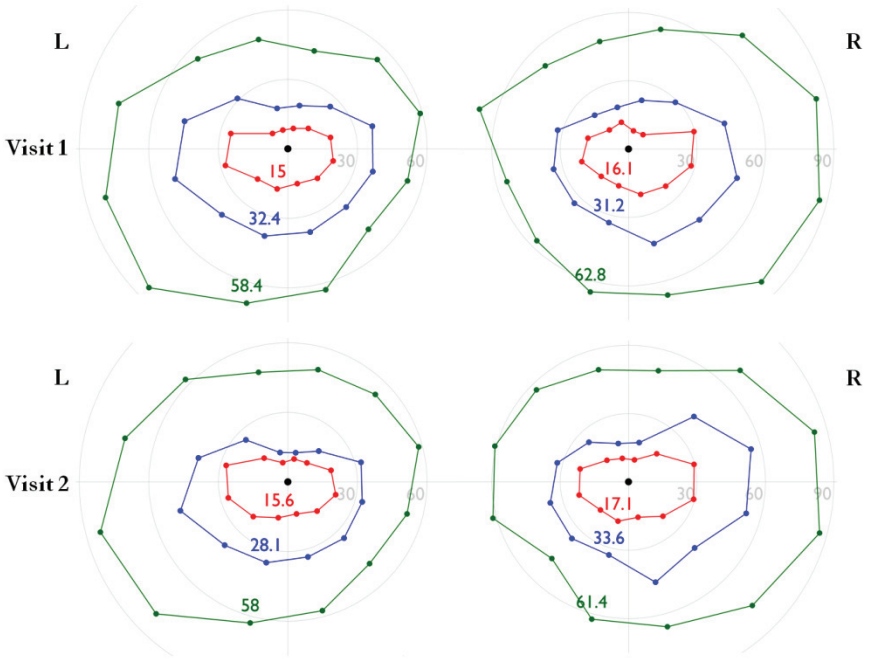
Participant #19:

Group: Control

Age: 40

Gender: Male

	Participant #20: Group: Control Age: 31 Gender: Female
	Participant #21: Group: Control Age: 56 Gender: Female

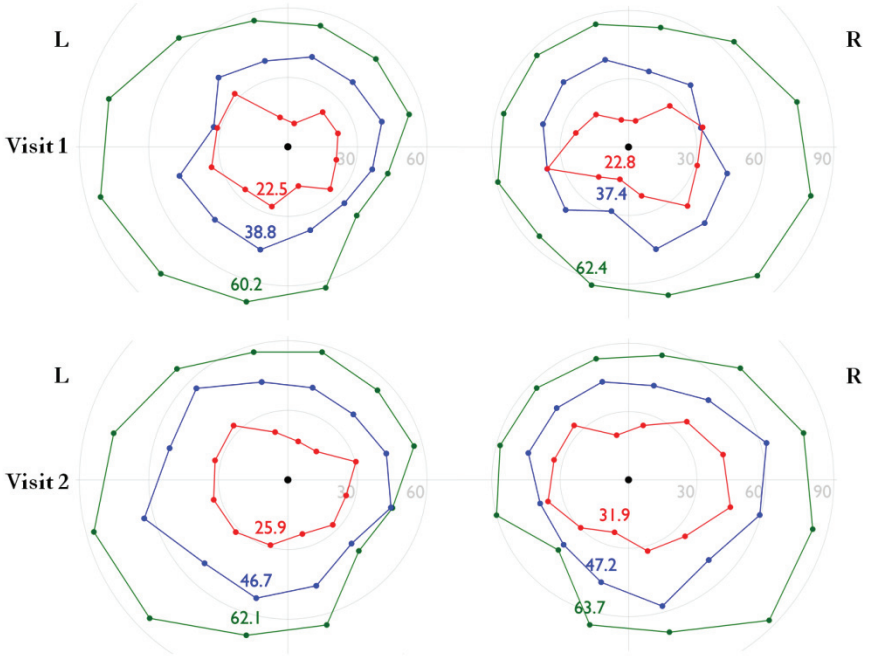


Participant #22:

Group: Migraine with aura

Age: 51

Gender: Female

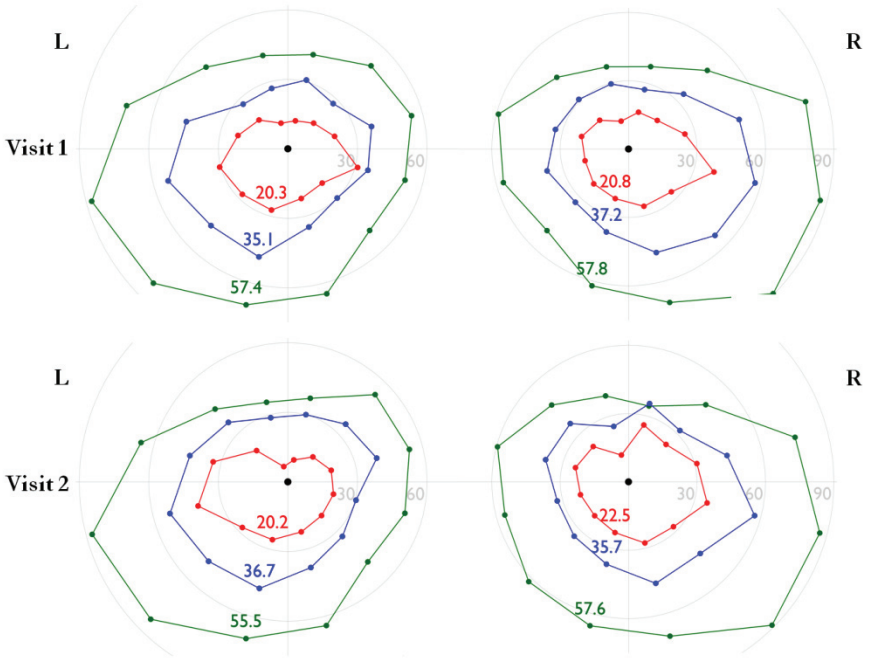


Participant #23:

Group: Migraine with aura.

Age: 38

Gender: Female

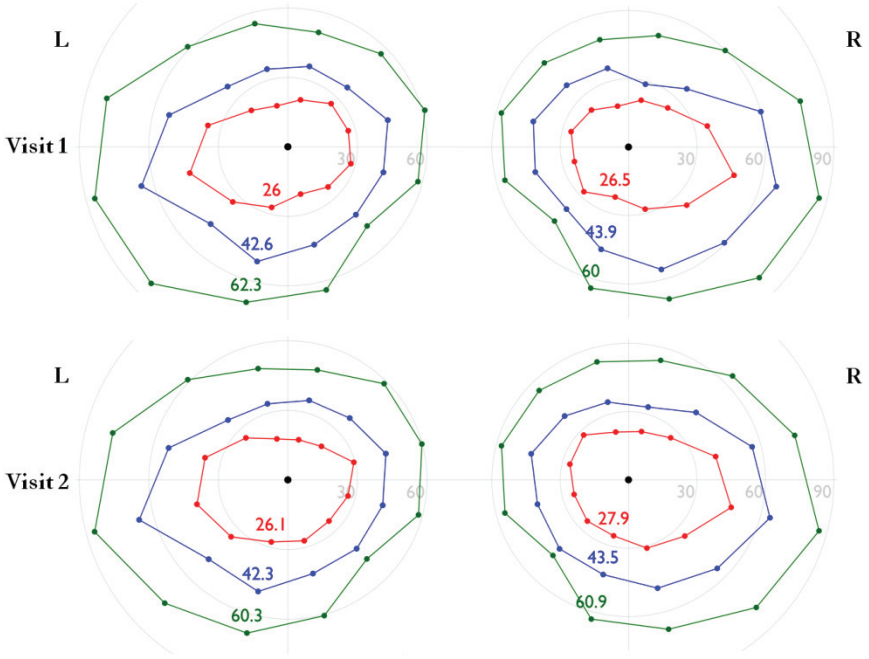


Participant #24:

Group: Migraine without aura.

Age: 55

Gender: Female

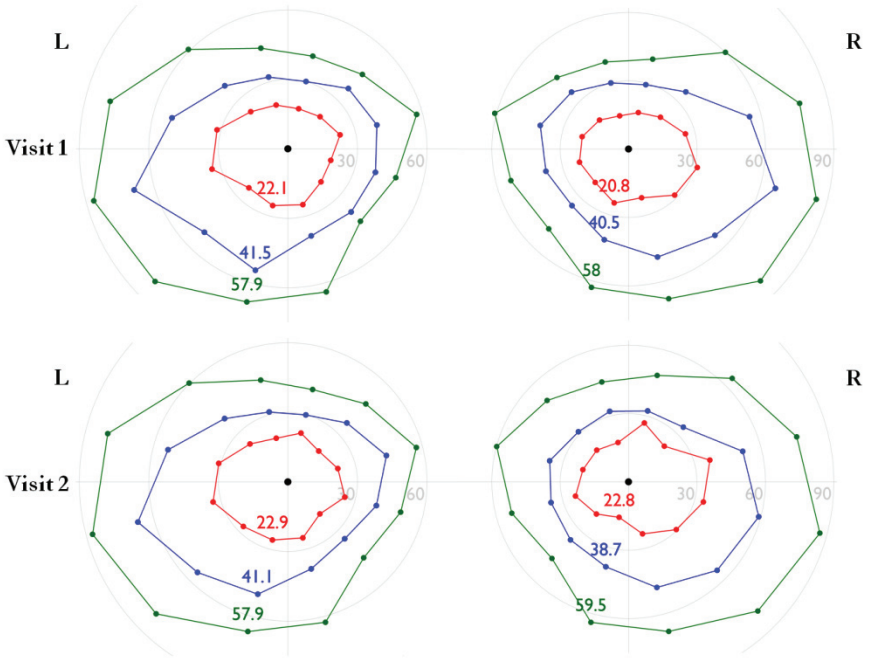
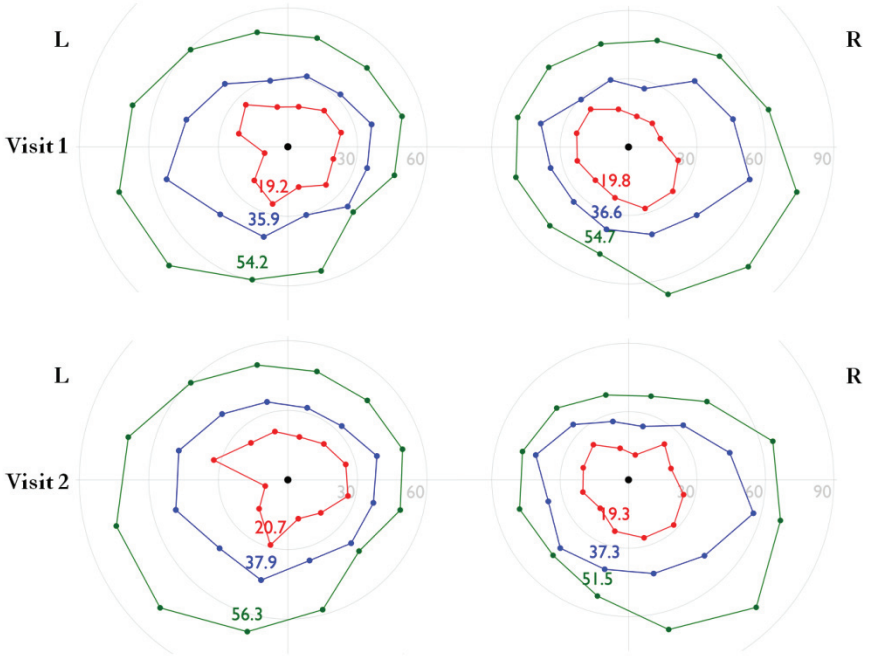


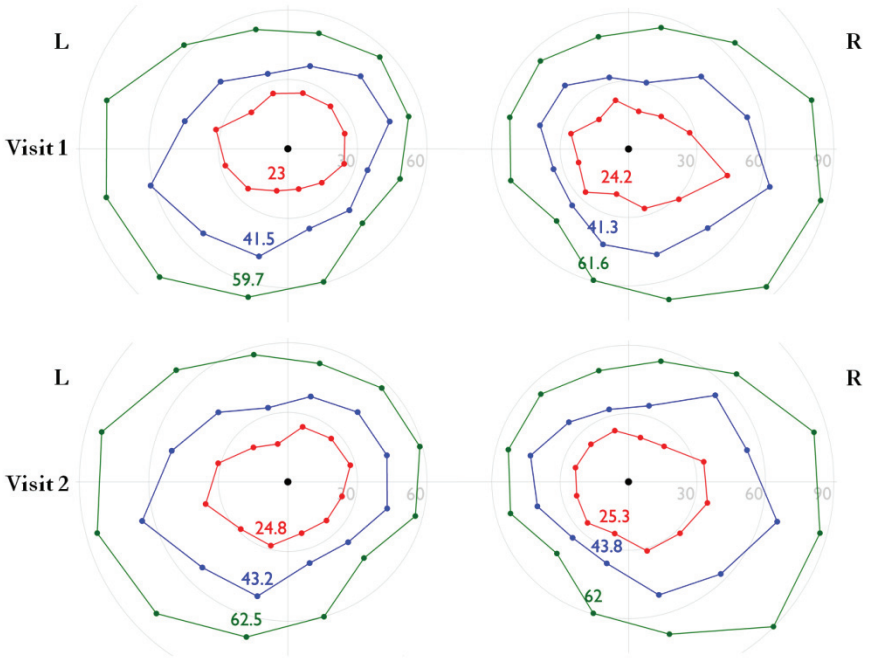
Participant # 25:

Group: Control

Age: 25

Gender: Female

	Participant #26: Group: Control Age: 45 Gender: Male
	Participant #27: Group: Control Age: 43 Gender: Male

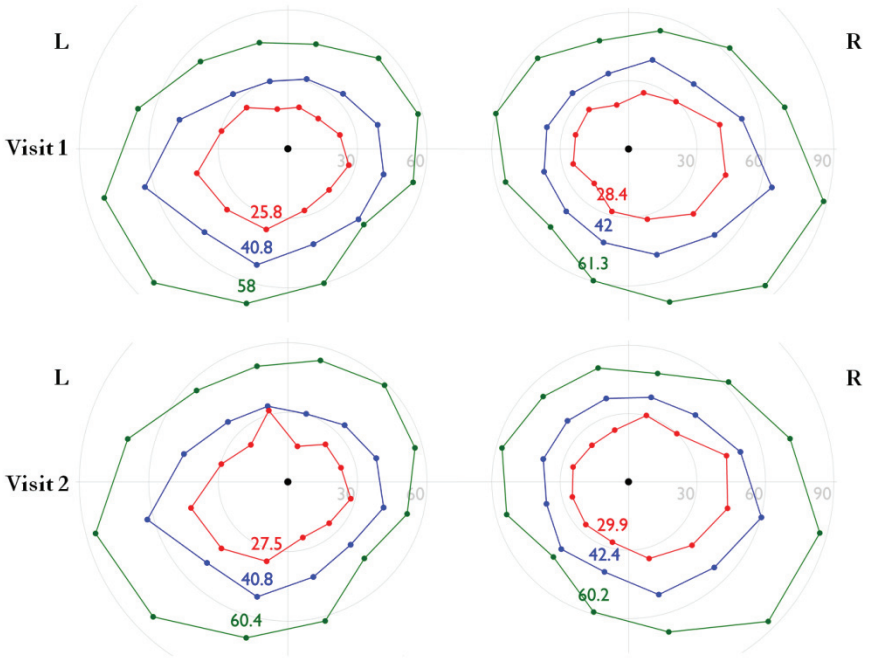


Participant #28:

Group: Migraine without aura.

Age: 39

Gender: Female

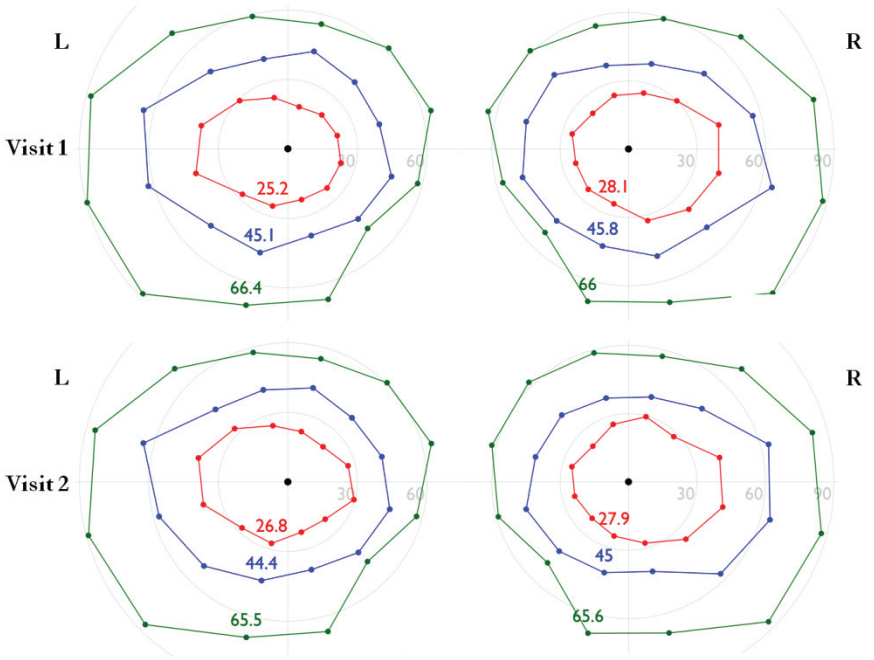


Participant #29:

Group: Control

Age: 24

Gender: Female

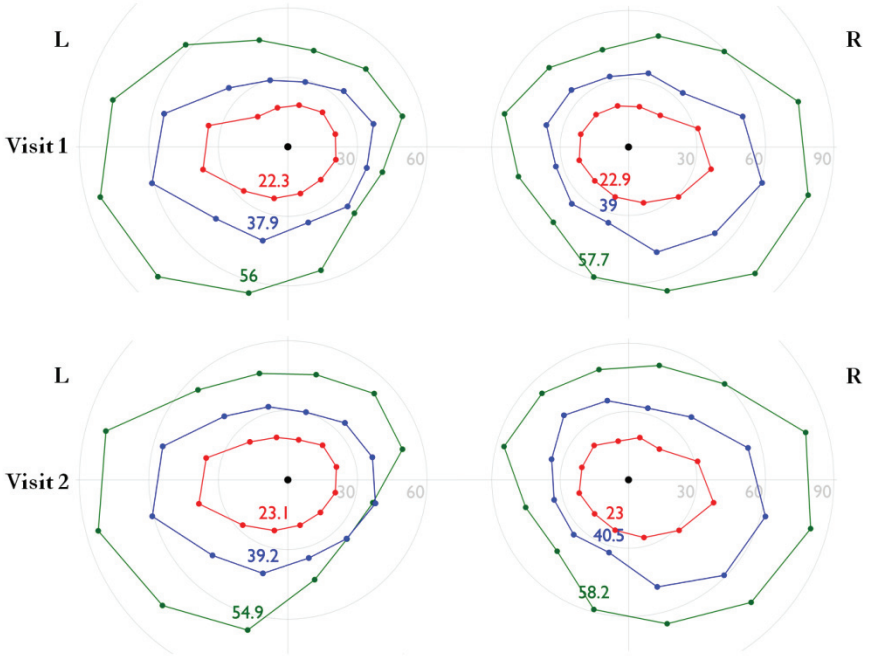


Participant # 30:

Group: Control

Age: 16

Gender: Female

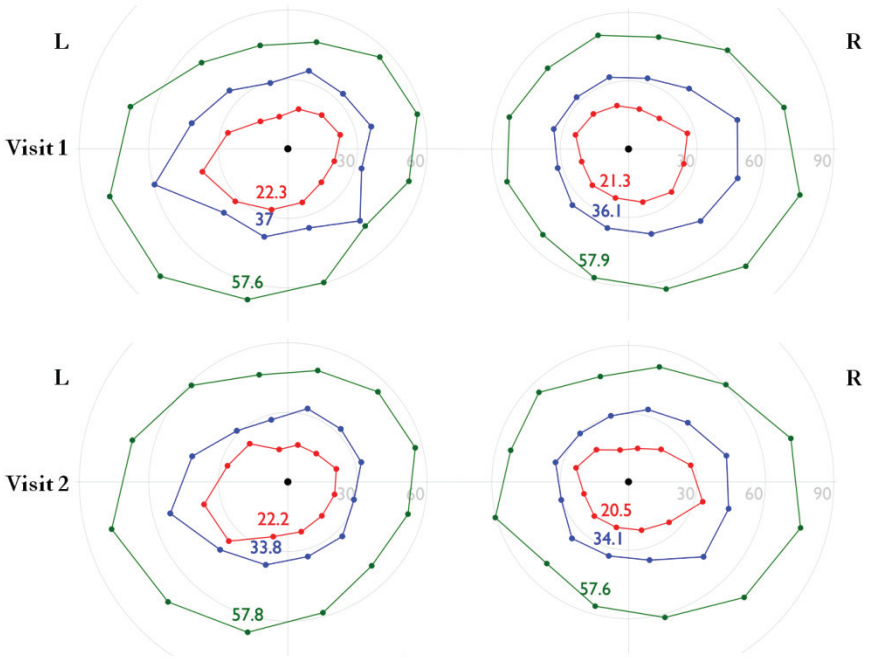


Participant #31:

Group: Control

Age: 32

Gender: Male

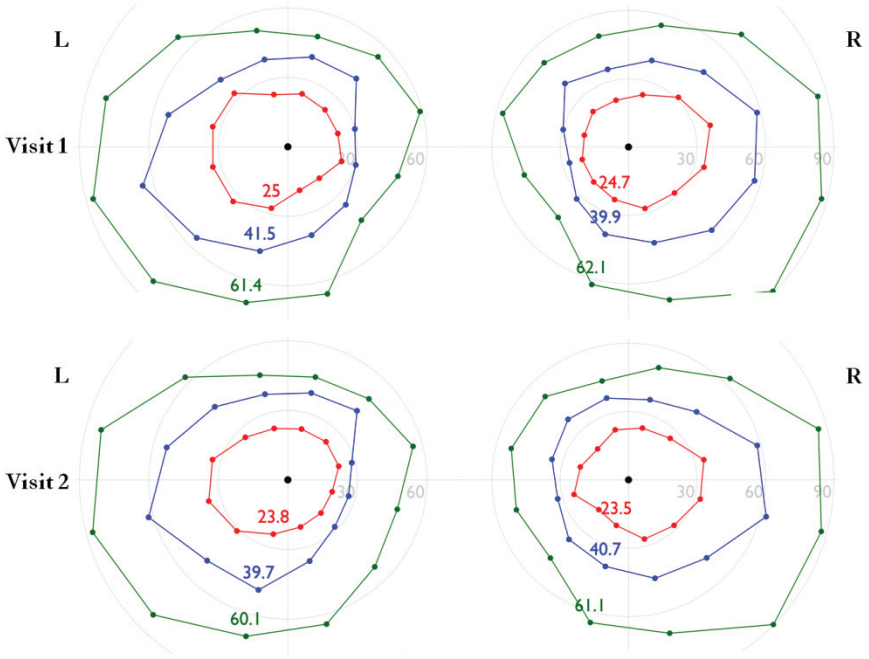


Participant #32:

Group: Control

Age: 37

Gender: Female

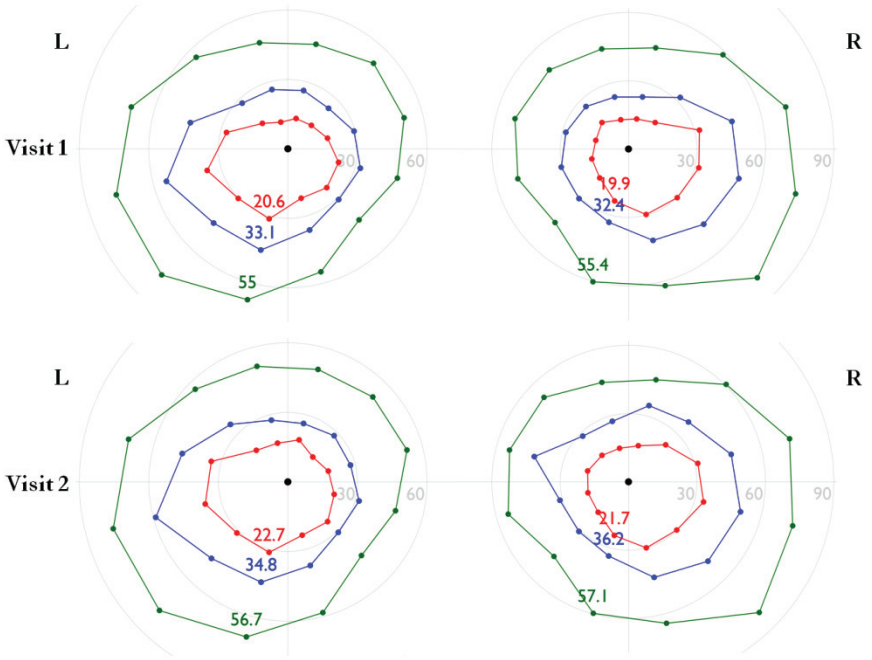


Participant #33:

Group: Migraine without aura.

Age: 38

Gender: Male

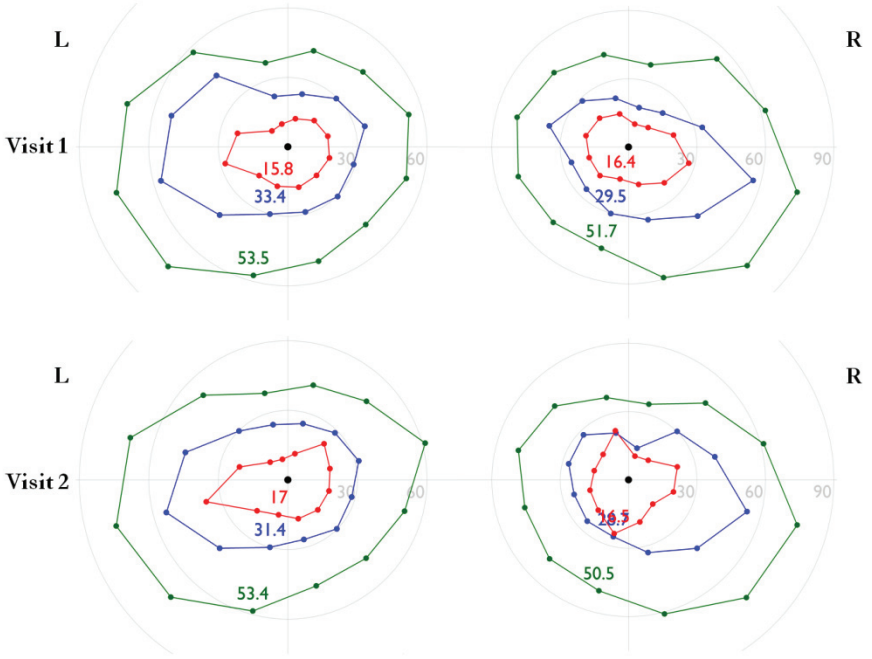


Participant #34:

Group: Migraine with aura

Age: 35

Gender: Female

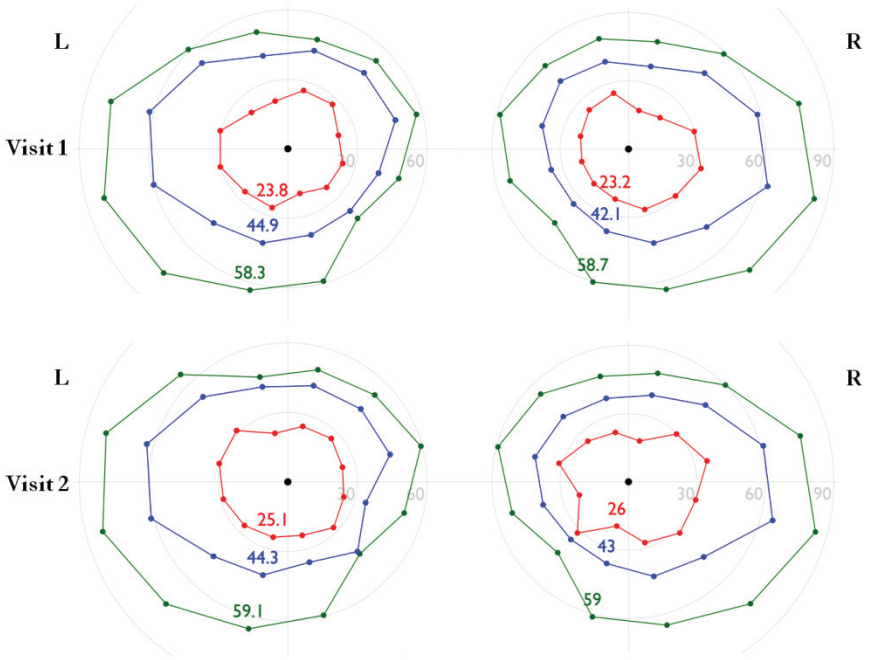
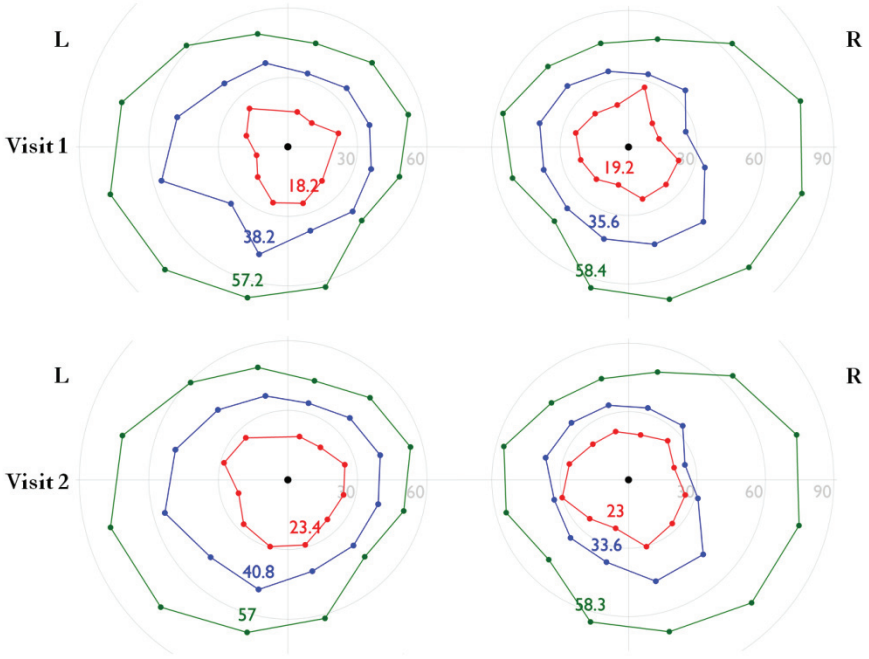


Participant #35:

Group: Control

Age: 58

Gender: Female

	Participant #36: Group: Control Age: 44 Gender: Female
	Participant #37: Group: Control Age: 59 Gender: Male

Appendix D

Designed Automated Kinetic Visual Field Exam

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<java version="1.6.0_03" class="java.beans.XMLDecoder">
 <int>10</int>
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 <int>0</int>
 <int>0</int>
 <int>0</int>
 <int>0</int>
 <int>0</int>
 <int>0</int>
 <int>0</int>
 <int>0</int>
 <int>1</int>
 <string>Hadil.E</string>
 <int>0</int>
 <int>144</int>
 <object class="projbasic.perikinetic.exdata.KineticAutomaticVector">
  <void property="intensity">
   <int>0</int>
  </void>
  <void property="size">                                        ;
   <int>1</int>
  </void>
  <void property="speed">
   <int>5</int>
  </void>
  <void property="startX">
   <double>15.5291427061512</double>
  </void>
  <void property="startY">
   <double>57.9555495773441</double>
  </void>
  <void property="stopX">
   <double>0.0</double>
  </void>
  <void property="stopY">
   <double>0.0</double>
  </void>
 </object>
…
```

```
<object class="projbasic.perikinetic.exdata.KineticAutomaticVector">
  <void property="RTVector">
   <boolean>true</boolean>
  </void>
  <void property="intensity">
   <int>15</int>
  </void>
  <void property="size">
   <int>1</int>
  </void>
  <void property="speed">
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  </void>
  <void property="startX">
   <double>-0.7764571353076</double>
  </void>
  <void property="startY">
   <double>2.8977774788672</double>
  </void>
  <void property="stopX">
   <double>0.0</double>
  </void>
  <void property="stopY">
   <double>0.0</double>
  </void>
 </object>
</java>
```

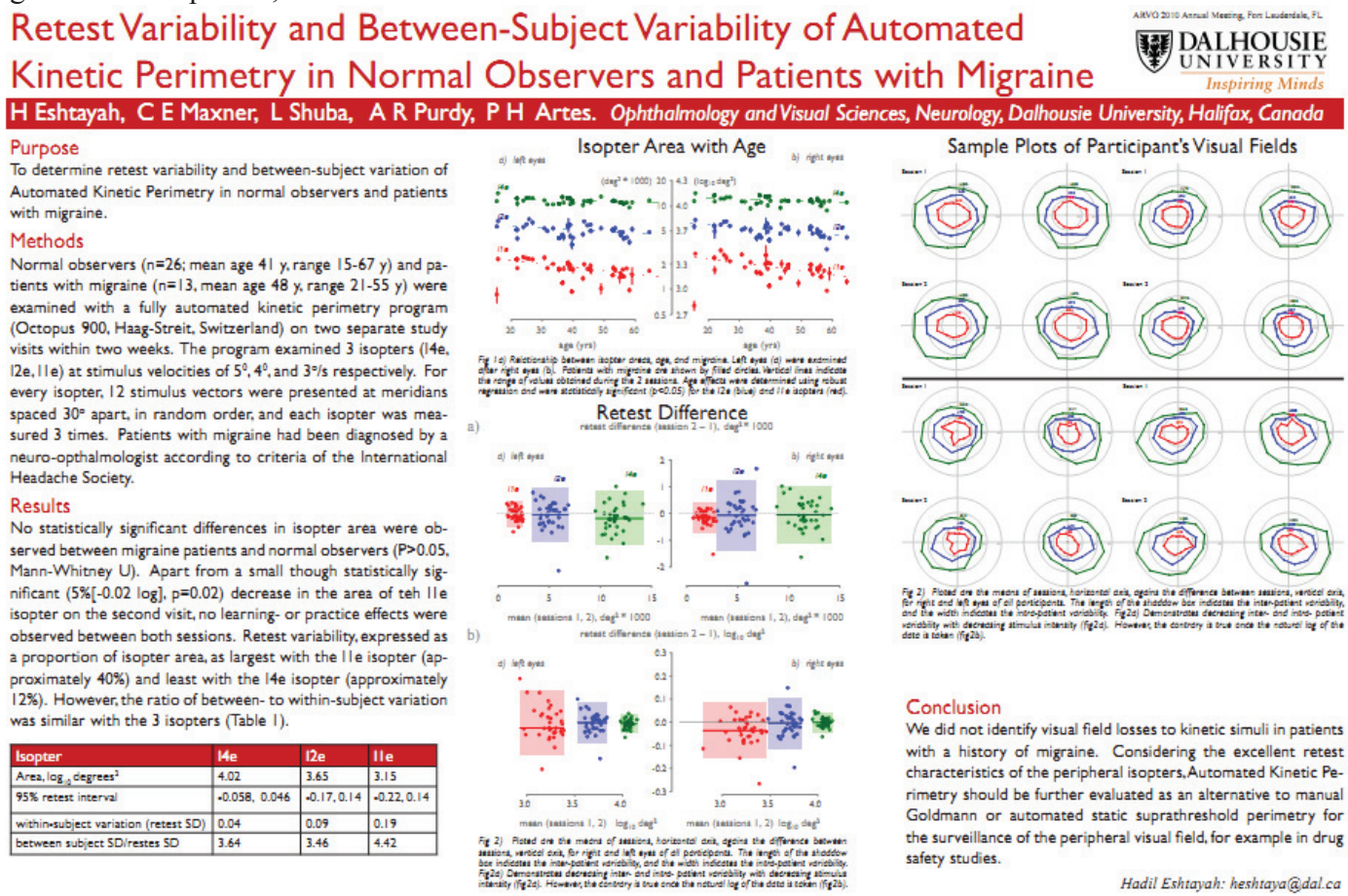
Appendix E

Poster Presentation

H. Eshtayah, C. E. Maxner, L. Shuba, A. R. Purdy, and P. H. Artes

Retest Variability and Between-Subject Variation of Automated Kinetic Perimetry in Normal Observers and Patients With Migraine

ARVO Meeting Abstracts April 11, 2010 51:2337



Retest Variability and Between-Subject Variability of Automated Kinetic Perimetry in Normal Observers and Patients with Migraine

ARVO 2010 Annual Meeting, Fort Lauderdale, FL

DALHOUSIE UNIVERSITY Inspiring Minds

H Eshtayah, C E Maxner, L Shuba, A R Purdy, P H Artes. *Ophthalmology and Visual Sciences, Neurology, Dalhousie University, Halifax, Canada*

Purpose

To determine retest variability and between-subject variation of Automated Kinetic Perimetry in normal observers and patients with migraine.

Methods

Normal observers (n=26; mean age 41 y, range 15-67 y) and patients with migraine (n=13, mean age 48 y, range 21-55 y) were examined with a fully automated kinetic perimetry program (Octopus 900, Haag-Streit, Switzerland) on two separate study visits within two weeks. The program examined 3 isopters (I4e, I2e, I1e) at stimulus velocities of 5°, 4°, and 3°/s respectively. For every isopter, 12 stimulus vectors were presented at meridians spaced 30° apart, in random order, and each isopter was measured 3 times. Patients with migraine had been diagnosed by a neuro-opthalmologist according to criteria of the International Headache Society.

Results

No statistically significant differences in isopter area were observed between migraine patients and normal observers (P>0.05, Mann-Whitney U). Apart from a small though statistically significant (5%[-0.02 log], p=0.02) decrease in the area of teh I1e isopter on the second visit, no learning- or practice effects were observed between both sessions. Retest variability, expressed as a proportion of isopter area, as largest with the I1e isopter (approximately 40%) and least with the I4e isopter (approximately 12%). However, the ratio of between- to within-subject variation was similar with the 3 isopters (Table 1).

Isopter	I4e	I2e	I1e
Area, $\log_{10}$ degrees^2	4.02	3.65	3.15
95% retest interval	-0.058, 0.046	-0.17, 0.14	-0.22, 0.14
within-subject variation (retest SD)	0.04	0.09	0.19
between subject SD/restes SD	3.64	3.46	4.42

Isopter Area with Age

Fig 1a) Relationship between isopter areas, age, and migraine. Left eyes (a) were examined after right eyes (b). Patients with migraine are shown by filled circles. Vertical lines indicate the range of values obtained during the 2 sessions. Age effects were determined using robust regression and were statistically significant (p<0.05) for the I2e (blue) and I1e isopters (red).

Retest Difference

Fig 2) Plotted are the means of sessions, horizontal axis, against the difference between sessions, vertical axis, for right and left eyes of all participants. The length of the shaddow box indicates the inter-patient variability, and the width indicates the intra-patient variability. Fig2a) Demonstrates decreasing inter- and intra- patient variability with decreasing stimulus intensity (Fig2a). However, the contrary is true once the natural log of the data is taken (Fig2b).

Sample Plots of Participant's Visual Fields

Fig 3) Plotted are the means of sessions, horizontal axis, against the difference between sessions, vertical axis, for right and left eyes of all participants. The length of the shaddow box indicates the inter-patient variability, and the width indicates the intra-patient variability. Fig2a) Demonstrates decreasing inter- and intra- patient variability with decreasing stimulus intensity (Fig2a). However, the contrary is true once the natural log of the data is taken (Fig2b).

Conclusion

We did not identify visual field losses to kinetic simuli in patients with a history of migraine. Considering the excellent retest characteristics of the peripheral isopters, Automated Kinetic Perimetry should be further evaluated as an alternative to manual Goldmann or automated static suprathreshold perimetry for the surveillance of the peripheral visual field, for example in drug safety studies.

Hadil Eshtayah: heshtaya@dal.ca

References

1. *Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Headache Classification Committee of the International Headache Society.* Cephalalgia, 1988. **8 Suppl 7**: p. 1-96.

2. Society, H.C.C.o.t.I.H., *The International Classification of Headache Disorders: 2nd edition.* Cephalalgia, 2004. **24**((Suppl. 1)): p. 9-160.

3. Bigal, M.E. and R.B. Lipton, *The epidemiology, burden, and comorbidities of migraine.* Neurol Clin, 2009. **27**(2): p. 321-34.

4. Friedman, D.I. and T. De ver Dye, *Migraine and the environment.* Headache, 2009. **49**(6): p. 941-52.

5. Friedman, D.I., *The eye and headache.* Ophthalmol Clin North Am, 2004. **17**(3): p. 357-69, vi.

6. Maxner, C.E. and J.J. Moeller, *Visual disturbances and migraine.* Curr Neurol Neurosci Rep, 2005. **5**(5): p. 376-81.

7. Sand, T., et al., *Visual evoked potential latency, amplitude and habituation in migraine: a longitudinal study.* Clin Neurophysiol, 2008. **119**(5): p. 1020-7.

8. Hadjikhani, N., et al., *Mechanisms of migraine aura revealed by functional MRI in human visual cortex.* Proc Natl Acad Sci U S A, 2001. **98**(8): p. 4687-92.

9. Nedeltchev, K., et al., *Cerebrovascular response to repetitive visual stimulation in interictal migraine with aura.* Cephalalgia, 2004. **24**(9): p. 700-6.

10. Young, W.B., et al., *Consecutive transcranial magnetic stimulation: phosphene thresholds in migraineurs and controls.* Headache, 2004. **44**(2): p. 131-5.

11. Andress-Rothrock, D., W. King, and J. Rothrock, *An analysis of migraine triggers in a clinic-based population.* Headache, 2010. **50**(8): p. 1366-70.

12. Schott, G.D., *Exploring the visual hallucinations of migraine aura: the tacit contribution of illustration.* Brain, 2007. **130**(Pt 6): p. 1690-703.

13. Leao, A.A.P., *Spreading depression of activity in the cerebral cortex.* J.Neurophysiol, 1944. **3**(28): p. 359-390.

14. Anderson, D.R., *Testing the Field of Vision*. 1982, St.Louis, Toronto, London: The C. V. Mosby Company.

15. McKendrick, A.M., et al., *Visual field losses in subjects with migraine headaches.* Invest Ophthalmol Vis Sci, 2000. **41**(5): p. 1239-47.

16. McKendrick, A.M., G.A. Cioffi, and C.A. Johnson, *Short-wavelength sensitivity deficits in patients with migraine.* Arch Ophthalmol, 2002. **120**(2): p. 154-61.

17. McKendrick, A.M. and D.R. Badcock, *An analysis of the factors associated with visual field deficits measured with flickering stimuli in-between migraine.* Cephalalgia, 2004. **24**(5): p. 389-97.

18. McKendrick, A.M. and D.R. Badcock, *Decreased visual field sensitivity measured 1 day, then 1 week, after migraine.* Invest Ophthalmol Vis Sci, 2004. **45**(4): p. 1061-70.

19. Harle, D.E. and B.J.W. Evans, *Migraine headache sufferers and visual field defects.* Cephalalgia, 2004. **24**(9): p. 775-775.

20. Drummond, P.D. and M. Anderson, *Visual field loss after attacks of migraine with aura.* Cephalalgia, 1992. **12**(6): p. 349-52.

21. Iversen, H.K., et al., *Clinical characteristics of migraine and episodic tension-type headache in relation to old and new diagnostic criteria.* Headache, 1990. **30**(8): p. 514-9.

22. Rasmussen, B.K., *Epidemiology of headache.* Cephalalgia, 1995. **15**(1): p. 45-68.

23. Stovner, L., et al., *The global burden of headache: a documentation of headache prevalence and disability worldwide.* Cephalalgia, 2007. **27**(3): p. 193-210.

24. Stewart, W.F., et al., *Population variation in migraine prevalence: a meta-analysis.* J Clin Epidemiol, 1995. **48**(2): p. 269-80.

25. Lipton, R.B. and M.E. Bigal, *The epidemiology of migraine.* Am J Med, 2005. **118 Suppl 1**: p. 3S-10S.

26. Breslau, N., et al., *Joint 1994 Wolff Award Presentation. Migraine and major depression: a longitudinal study.* Headache, 1994. **34**(7): p. 387-93.

27. Stewart, W.F., et al., *Age- and sex-specific incidence rates of migraine with and without visual aura.* Am J Epidemiol, 1991. **134**(10): p. 1111-20.

28. Hargreaves, R.J., *Pharmacology and potential mechanisms of action of rizatriptan.* Cephalalgia, 2000. **20 Suppl 1**: p. 2-9.

29. Hupp, S.L., L.B. Kline, and J.J. Corbett, *Visual disturbances of migraine.* Surv Ophthalmol, 1989. **33**(4): p. 221-36.

30. Evans, R.W. and B.M. Grosberg, *Retinal migraine: migraine associated with monocular visual symptoms.* Headache, 2008. **48**(1): p. 142-5.

31. Vincent, M.B. and N. Hadjikhani, *Migraine aura and related phenomena: beyond scotomata and scintillations.* Cephalalgia, 2007. **27**(12): p. 1368-77.

32. Milner, P.M., *Note on a possible correspondence between the scotomas of migraine and spreading depression of Leao.* Electroencephalogr Clin Neurophysiol, 1958. **10**(4): p. 705.

33. Bowyer, S.M., et al., *Magnetoencephalographic fields from patients with spontaneous and induced migraine aura.* Ann Neurol, 2001. **50**(5): p. 582-7.

34. Olesen, J., et al., *The common migraine attack may not be initiated by cerebral ischaemia.* Lancet, 1981. **2**(8244): p. 438-40.

35. Gozke, E., et al., *Cranial magnetic resonance imaging findings in patients with migraine.* Headache, 2004. **44**(2): p. 166-9.

36. Russell, M.B., et al., *Migraine without aura and migraine with aura are distinct clinical entities: a study of four hundred and eighty-four male and female migraineurs from the general population.* Cephalalgia, 1996. **16**(4): p. 239-45.

37. Stewart, W.F., et al., *Development and testing of the Migraine Disability Assessment (MIDAS) Questionnaire to assess headache-related disability.* Neurology, 2001. **56**(6 Suppl 1): p. S20-8.

38. El Hasnaoui, A., et al., *Assessing the severity of migraine: development of the MIGSEV scale.* Headache, 2003. **43**(6): p. 628-35.

39. Anders H, V.M.P., ed. *Essential Perimetry: The field analyzer primer.* Third Edition ed., ed. M.J. Haley. 2002, Carl Zeiss Meditec AG: Dublin, California. 4-147.

40. Haag-Streit, A., *Goldmann perimeter 940: Instructions for use.*, in *Ophthalmological Instruments*, Haag-Streit AG: Liebefeld, Switzerland.

41. Iannaccone, A., et al., *Kinetics of visual field loss in Usher syndrome Type II.* Invest Ophthalmol Vis Sci, 2004. **45**(3): p. 784-92.

42. Bittner, A.K., M.H. Iftikhar, and G. Dagnelie, *Test-retest, within-visit variability of Goldmann visual fields in retinitis pigmentosa.* Invest Ophthalmol Vis Sci, 2011. **52**(11): p. 8042-6.

43. Sergott, R.C., et al., *Vigabatrin-induced peripheral visual field defects in patients with refractory partial epilepsy.* Epilepsy Res, 2010. **92**(2-3): p. 170-6.

44. Vonthein, R., et al., *The Normal Age-Corrected and Reaction Time-Corrected Isopter Derived by Semi-automated Kinetic Perimetry.* Ophthalmology, 2007. **114**(6): p. 1065-1072.e2.

45. Nowomiejska, K., et al., *Comparison between semiautomated kinetic perimetry and conventional Goldmann manual kinetic perimetry in advanced visual field loss.* Ophthalmology, 2005. **112**(8): p. 1343-54.

46. Parrish, R.K., 2nd, J. Schiffman, and D.R. Anderson, *Static and kinetic visual field testing. Reproducibility in normal volunteers.* Arch Ophthalmol, 1984. **102**(10): p. 1497-502.

47. Hollenhorst, R.W., *Ocular manifestations of migraine: report of 4 cases of hemianopsia.* Proc Staff Meet Mayo Clin, 1953. **28**(24): p. 686-93.

48. Lewis, R.A., et al., *Visual field loss in migraine.* Ophthalmology, 1989. **96**(3): p. 321-6.

49. Ebner, R., *Visual-Field Examination during Transient Migrainous Visual-Loss.* Journal of Clinical Neuro-Ophthalmology, 1991. **11**(2): p. 114-117.

50. Connor, R.C.R., *Complicated Migraine - a Study of Permanent Neurological and Visual Defects Caused by Migraine.* Lancet, 1962. **2**(7265): p. 1072-&.

51. Wakakura, M. and Y. Ichibe, *Permanent homonymous hemianopias following migraine.* J Clin Neuroophthalmol, 1992. **12**(3): p. 198-202.

52. Harle, D.E. and B.J. Evans, *Frequency doubling technology perimetry and standard automated perimetry in migraine.* Ophthalmic Physiol Opt, 2005. **25**(3): p. 233-9.

53. Ross, D.F., et al., *Variability of visual field measurements in normal subjects and patients with retinitis pigmentosa.* Arch Ophthalmol, 1984. **102**(7): p. 1004-10.

54. Ramirez, A.M., et al., *A comparison of semiautomated versus manual Goldmann kinetic perimetry in patients with visually significant glaucoma.* J Glaucoma, 2008. **17**(2): p. 111-7.

55. Sullivan-Mee, M. and B. Bowman, *Migraine-related visual-field loss with prolonged recovery.* J Am Optom Assoc, 1997. **68**(6): p. 377-88.

56. Ferris, F.L., 3rd, et al., *New visual acuity charts for clinical research.* Am J Ophthalmol, 1982. **94**(1): p. 91-6.

57. Arden, G.B., *[The standard of measurement of visual acuity]*. J Fr Ophtalmol, 1988. **11**(11): p. 779-92.

58. Troost, R., et al., *Clinical comparison of two intraocular pressure measurement methods: SmartLens dynamic observing tonography versus Goldmann.* Graefes Arch Clin Exp Ophthalmol, 2001. **239**(12): p. 889-92.

59. Iester, M., et al., *New Tonopen XL: comparison with the Goldmann tonometer.* Eye (Lond), 2001. **15**(Pt 1): p. 52-8.

60. Kourkoutas, D., et al., *Comparison of glaucoma progression evaluated with Heidelberg retina tomograph II versus optic nerve head stereophotographs.* Can J Ophthalmol, 2007. **42**(1): p. 82-8.

61. Gondal, T.M., et al., *Accuracy of the retinal nerve fiber layer measurements by stratus optical coherence tomography for perimetric glaucoma.* J Coll Physicians Surg Pak, 2011. **21**(12): p. 749-52.

62. Saito, H., et al., *Correlation of disc morphology quantified on stereophotographs to results by Heidelberg Retina Tomograph II, GDx variable corneal compensation, and visual field tests.* Ophthalmology, 2010. **117**(2): p. 282-9.

63. Comoglu, S., et al., *Glaucomatous visual field defects in patients with migraine.* J Neurol, 2003. **250**(2): p. 201-6.

64. Cursiefen, C., et al., *Migraine and tension headache in high-pressure and normal-pressure glaucoma.* Am J Ophthalmol, 2000. **129**(1): p. 102-4.

65. Drance, S., D.R. Anderson, and M. Schulzer, *Risk factors for progression of visual field abnormalities in normal-tension glaucoma.* Am J Ophthalmol, 2001. **131**(6): p. 699-708.

66. Corbett, J.J., et al., *The neurologic evaluation of patients with low-tension glaucoma.* Invest Ophthalmol Vis Sci, 1985. **26**(8): p. 1101-4.

67. Walsh, N., *A Technical Introduction to XML.* World Wide Web Journal, 1998: p. 1-2.

68. Kutzko, K.E., C.F. Brito, and M. Wall, *Effect of instructions on conventional automated perimetry.* Invest Ophthalmol Vis Sci, 2000. **41**(7): p. 2006-13.

69. Anderson, A.J. and C.A. Johnson, *Effect of dichoptic adaptation on frequency-doubling perimetry.* Optom Vis Sci, 2002. **79**(2): p. 88-92.

70. El Hasnaoui, A., et al., *Assessment of migraine severity using the MIGSEV scale: relationship to migraine features and quality of life.* Cephalalgia, 2004. **24**(4): p. 262-70.

71. Sergott, R.C. and C.A. Westall, *Primer on visual field testing, electroretinography, and other visual assessments for patients treated with vigabatrin.* Acta Neurol Scand Suppl, 2011(192): p. 48-56.

72. Quinn, G.E., et al., *Visual field extent at 6 years of age in children who had high-risk prethreshold retinopathy of prematurity.* Arch Ophthalmol, 2011. **129**(2): p. 127-32.

73. Fishman, G.A., et al., *Natural course of visual field loss in patients with Type 2 Usher syndrome.* Retina, 2007. **27**(5): p. 601-8.