CHARACTERISTICS OF THE PREFERRED RETINAL LOCI IN PEOPLE WITH BILATERAL CENTRAL SCOTOMAS

A thesis presented to the graduate faculty at the New England College of Optometry in fulfillment of the requirements for the degree of Master of Science

Joella Martire

August 7th, 2020

©Joella Martire

All rights reserved

The author hereby grants New England College of Optometry permission to reproduce and to distribute publicly paper and electronic copies of the thesis document in whole or in part.

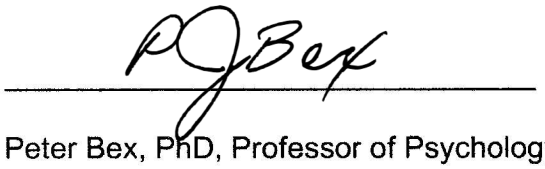
PRL CHARACTERTISTICS IN PEOPLE WITH BILATERAL CENTRAL SCOTOMAS

Joella Martire

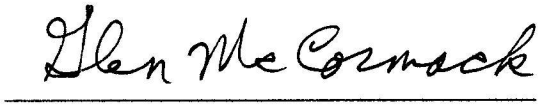
This manuscript has been read and accepted by the Thesis Committee in satisfaction of the thesis requirement for the degree of Master of Science



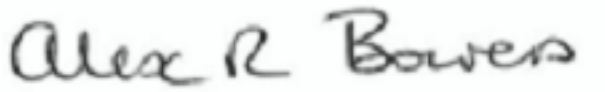
Nicole Ross, OD, MSc, FAAO; Associate Professor of Optometry, New England College of Optometry. Graduate Faculty Advisor.



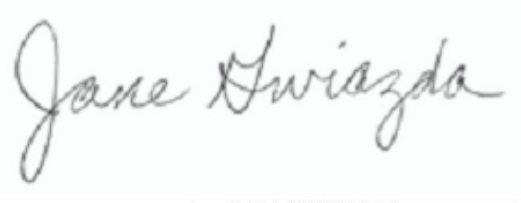
Peter Bex, PhD, Professor of Psychology, Northeastern University. Adjunct Faculty Co-Advisor.



Dr. Glen McCormack, OD, PhD, Professor of Optometry, The New England College of Optometry. Thesis Committee Member.



Dr. Alex Bowers, PhD (external member), Associate Scientist, Schepens Eye Research Institute, Associate Professor, Harvard Medical School. Thesis Committee Member.



Jane Gwiazda, PhD, Director of Graduate Studies. New England College of Optometry

Abstract

CHARACTERISTICS OF THE PREFERRED RETINAL LOCI IN PEOPLE WITH BILATERAL CENTRAL SCOTOMAS

Joella Martire

New England College of Optometry, 2020

Purpose

The majority of patients presenting for low vision rehabilitation services are affected by macular pathologies where foveal function is lost in both eyes. Without intact foveae, patients often adopt new pseudo-foveae, the preferred retinal loci (PRL). Much research has explored the properties and visual performance of the PRL in monocular viewing, however little is known about visual performance under binocular viewing conditions with bilateral, asymmetric central scotomas. The PRL, in the current study, is defined in terms of fixation stability, better known as the bivariate contour ellipse area (BCEA). The BCEA defines the area of retina, in degrees squared, that surrounds the PRL and delineates its functional limits associated with fixation by encompassing 68% of eye-fixation locations over the given duration and task. Here, we conduct an observational study in both normally sighted individuals with simulated central scotomas in addition to participants with bilateral central scotomas due to macular disease to explore the visual performance of the PRL under both monocular and binocular viewing.

Methods

We evaluated the visual performance of the PRL in monocular and binocular viewing conditions at 9 different gaze positions; this task elicited both the location with the best fixation stability (smallest BCEA) and worst fixation stability (largest BCEA) for each participant. PRL location and performance was assessed using an Eyelink 1000+ infrared eye tracker. We defined the PRL as the location as the area of peripheral retina used when the fovea is unable to be used. In the current study, quantitative evaluation of the PRL was measured based on the bivariate contour ellipse area (BCEA); the BCEA defines the area of retina, in degrees squared, that surrounds the PRL and delineates its functional limits associated with fixation by encompassing 68% of eye-fixation locations over the given duration and task. Visual performance was assessed using a contrast sensitivity function task (quickCSF) as well as a word identification task (Word / Non-Word). For CSF, observers identified band-pass filtered letters, and a quick algorithm controlled their spatial frequency and contrast. Outcome measures included high-frequency CSF threshold (CSF acuity) and area under the logCSF curve (AULCSF). For the Word / Non-Word task, participants identified whether and 5-letter word or non-word was presented at a given letter size and on-screen duration. For PRL location and scotoma size, the MAIA microperimeter was used to evaluate a central 10-2 visual field. A total of 34 participants were recruited for the current study: 24 normally sighted individuals with

simulated central scotomas as well as 10 individuals with bilateral central vision loss due to macular disease.

Results

In normally sighted individuals with simulated central scotomas, under monocular viewing conditions, contrast sensitivity decreased with increasing scotoma size, with declining CSF acuity ($p<0.01$) and decreasing AULCSF ($p<0.01$). For word identification, under monocular conditions, there was no effect of scotoma size on reading acuity but a significant effect for minimum word duration ($p<0.01$). Under binocular viewing conditions there was no significant effect of scotoma size on visual performance for any of the tasks. CSF acuity was significantly better when scotomas were asymmetric than symmetric ($p=.01$) across all sizes. There was no statistically significant difference between the monocular BCEA, and therefore in the fixation stability, between both the best and worst monocular BCEA locations ($p = .2484$) in performing the CSF and Word / Non-Word tasks. There was no statistically significant difference between the binocular BCEA, and therefore in the fixation stability, between both the best and worst binocular BCEA test locations ($p = .7789$)

In participants with bilateral central vision loss secondary to macular disease, BCEA area trended to be smaller in monocular viewing conditions ($p=0.075$). No significant differences were found in gaze position on BCEA, CSF acuity, or AULCSF. There was a statistically significantly negative association between the declining fixation stability, or larger BCEA area, and the mean area under the curve (AULCSF) ($p = .01$). There was also a trending negative association between the best fixation stability, or smaller BCEA area, and the mean area under the curve (AULCSF) ($p = .08$). There was a statistically significantly negative association between the worse fixation stability, or larger BCEA, and the resulting CSF acuity (in cpd) ($p = .03$). There was also a statistically significantly negative association between the best fixation stability, or smaller BCEA, and the resulting CSF acuity (in cpd) ($p = .01$).

Discussion

With simulated independent binocular gaze-contingent scotomas, visual performance at the PRL differs under monocular versus binocular viewing conditions. Performance depends on whether the scotomas are symmetric or asymmetric and the method used to assess visual function. In participants with bilateral central vision loss due to macular disease, visual performance at the PRL demonstrates the importance of fixation stability while performing visually demanding tasks. The current results suggest that under binocular conditions fixation stability is an important factor for visual function invariant of gaze posture. The clinical implications of the current study suggest that it is the control of eye movements, i.e. fixation stability, that may be important to elicit the best possible outcomes on visual tasks and various activities of daily living

Acknowledgements

First, and most of all, I would like to thank Dr. Nicole Ross for the continuous support of my MSc research; your motivation, encouragement and guidance throughout this process has driven the completion of this project and the writing of my thesis. You are an incredible human being and clinician who is greatly dedicated to your patients, research and practice. I could not have imagined having a better thesis advisor, professor and mentor extraordinaire through Optometry school and for my MSc study.

I would also like to thank my adjunct co-advisor, Dr. Peter Bex; I am grateful for your assistance, insightful input and suggestions throughout my project. The design and execution of this project would not have been possible without your input and support.

The completion of this MSc thesis would not have been possible without the help of Tiffany Arango. I am forever indebted to you for all the time, assistance, advice and generosity you have shown me over the last three years. I could not have imagined completing this project with anyone else by my side.

Last, but not least, I want to thank my friends and family for the continuous support of this stressful yet rewarding undertaking. I could not have completed this project without your continuous support and encouragement. To my parents: you've instilled in me the importance of knowledge and education. Thank you for the opportunities I have had and the sacrifices you have made.

Table of Contents

Chapter 1: General Introduction……..……1

The PRL, Measured and Defined……..……..4

Aims and Research Questions..……...8

Outcome Measures……..……11

Chapter 2: Phase 1 – Normally Sighted Observers with Simulated Gaze-Contingent Scotomas……...14

Methods…..……15

Results…..…….25

Discussion…….……34

Chapter 3: Phase 2 – Individuals with Bilateral Central Scotomas……..……36

Methods…….……37

Results……..……40

Discussion…….……48

Chapter 4: General Conclusion……..……52

References……..……..59

Appendices……..……..66

Appendix 1: Word Non-Word in Patients……..……66

List of Figures and Tables

Figure 1. Measures of BCEA using MAIA mircroperimetry……..…….12

Figure 2. Illustration of the optic nerve head and PRL locating task…..……..16

Figure 3. Demonstration of the symmetric and asymmetric bilateral simulated scotomas…….…..18

Figure 3a. A demonstration of the participant set-up during Phase 1 testing…….……19

Figure 4. Simulation of the 9-point grid used for the various target positions and gaze eccentricities tested……..……..20

Figure 5. Sample trial for contrast detection……..……..23

Figure 6. Sample trial for Word / Non-Word task……..……..24

Figure 7. Monocular CSF Outcomes…….……...27

Figure 8. Monocular Word/Non-Word Minimum Duration Outcomes…..……28

Figure 9. Monocular Fixation Stability Outcomes…….……..30

Figure 10. Binocular CSF Outcomes, Symmetric versus Asymmetric Scotomas……..…….31

Figure 11. Binocular Fixation Stability Outcomes……..…….33

Figure 12. Fixation Stability; Better Seeing Eye versus Binocular…..……42

Figure 13. Binocular Trial by Trial Fixation Stability Outcomes…….……...44

Figure 14. Word / Non-Word in Patients……..…68

Table 1. Binocular subject data……..……46

Table 2. Monocular subject data……..……..47

Chapter 1 General Introduction:

Macular disease is the leading cause of visual impairment, or low vision, in developed countries (Congdon, O'Colmain et al. 2004), accounting for the majority of patients presenting to private outpatient low vision rehabilitation (LVR) clinics (Goldstein, Massof et al. 2012). Specifically, macular disease impacts 6% of people over 50 and at least 30% of those over 75 (Ferris III 1983); its incidence and prevalence are increasing quickly due to the increasing age and lifespan of the population (Evans and Wormald 1996). As such, visual impairment due to macular disease, is a growing public health concern.

Based on the evaluation of 2010 United States census data, over 3 million Americans are estimated to have low vision (BCVA < 20/40) in 2017, with an annual incidence of 500,000 (Chan, Friedman et al. 2018). Low-vision rehabilitation (LVR) has been shown to be effective in reducing visual functional difficulties and improving a person's quality of life (Massof et al., 2005a, 2005b). Low vision services seek to enhance the remaining vision through training, rehabilitation and visual assistive equipment, which enable a person to accomplish necessary tasks and activities despite their reduced vision.

In macular disease, visual impairment is secondary to a loss of foveae function, and the development of central scotomas (i.e. blind spots). The fovea centralis is highly specialized for spatial resolution. A disproportionate amount of neural processing, relative to its size, is devoted to this 1.5^{o} or 5mm diameter area of retina at the center of the macula. The map of the retina on the surface of the primary visual cortex is highly anisotropic. In the retinotopic map for V1, the area of the brain responsible for visual

processing, linear dimensions of the cortex per degree of retinal eccentricity is about 32 mm/degree in the central 0.15^{o} of fovea and falls approximately inversely proportionate to the square root of eccentricity to roughly 4 mm/degree at 5° from the center of the fovea (Schira, CW et al. 2009). Nearly 50% of the optic nerve fibers originate in the fovea and the central 10 degrees of visual field, representing the fovea and parafovea, project to consume 50-60% of the visual cortex (McFadzean, Brosnahan et al. 1994). Correspondingly, visual resolution decreases from less than 1 arcmin (20/20) at the center of the fovea to about 4 arcmin (20/80) at 5° eccentricity (Randall, Brown et al. 1966).

Smooth pursuit and saccadic eye movements respectively serve to lock the fovea onto a moving object or to rapidly relocate the fovea to an object of interest in the environment. When confronted with a new object or novel environment we make a series of saccades to scan the environment and to inspect features within objects using the fovea(Norton and Stark 1971). Thus, peripheral vision with its coarse resolution previews the scene and tells us where objects of interest are located and the sequence of saccades that redirect the high resolution fovea to the various objects, and areas of interest within those objects, enabling us to identify features and build a perceptual model of the environment. Thus, loss of foveal function secondary to macular disease, although typically insignificant in size relative to the total area of the visual field, can profoundly affect the patient's ability to function in daily life.

Central vision loss impacts both ones' quality of life and the ability to perform activities of daily living such as reading (Legge, Rubin et al. 1985), face recognition (Peli, Lee et al. 1994), watching television (Wolffsohn and Cochrane 1999), driving and

mobility (Lovie-Kitchin, Mainstone et al. 1990), and is associated with elevated levels of depression (Brody 2011) and increased falls (Zheng 2012). In addition to these difficulties in tasks of daily living, macular disease and the consequent central vision loss shows strong correlations with other conditions associated with aging. Older individuals with macular disease experience double the incidence of difficulties in daily living and social activities, double the incidence of falls, triple the mortality rate, and quadruple the incidence of fractures (Statistics Canada, 2011).

In central vision loss cases, a person is forced to use low-resolution peripheral retina and may adopt one or more preferred retinal loci (PRL). The PRL is a more peripheral retinal area that has not been impacted by the macular condition, which has much lower resolution than the fovea. The PRL acts as the new “pseudo-fovea” and becomes the new area of retina that is used for fixation and “best-resolution” vision when required to look at a central target. This process can happen naturally and also fairly quickly (Skavenski, Acocella et al. 1994, Crossland, Culham et al. 2005). Generally, it is believed that the new pseudo-fovea, or PRL, is adopted in one specific retinal location and used to perform a multitude of tasks, becoming analogous to the one central fovea normally sighted individuals use to perform activities of daily living. More recently, it has been shown that individuals with central vision loss can possibly adopt more than one PRL, such that any given PRL can be used to perform any particular task such as reading or watching television, particularly when visual targets are in secondary positions of gaze (or any gaze direction that is not straight ahead) (Schuchard 2005) (Von Noorden and Mackensen 1962, Timberlake, Mainster et al. 1986). Interestingly, patients with bilateral central scotomas, when using an area of peripheral retina for

fixation tasks, place the target within a fixation area of about 1.2 to 1.7 degrees from the border of the macular lesion, adopting a PRL in an area analogous to the area occupied by the high resolution foveola (Schuchard 2005). It has also been observed that in cases of bilateral central vision loss, binocular PRLs are not symmetric in the retinas, as defined by monocular PRL measurements; that is, the binocular PRLs can be on non-corresponding points, both in distance and direction from the scotoma, of the retina, given the asymmetric presentation of the disease (Schuchard 2005). This also correlates to the observation that age-related macular degeneration, in particular, is an asymmetric disease process. Additionally, it has been observed that in binocular central vision loss, the overall resulting scotoma (as it impacts binocular vision) is smaller than each eyes' individual scotoma size for the majority of patients (Ross, Goldstein et al. 2013). Though we do understand many of the characteristics of the PRL, we understand little about how a PRL is selected, as it is not often the area of best remaining visual acuity (Chung 2013), nor is its location optimal for reading or other visually mediated tasks.

The PRL, Measured and Defined

The gold standard for determining the extent of central vision loss a person has experienced in any given condition, in addition to determining the location of the PRL they have established, is using micro-perimetry. Using a scanning laser ophthalmoscope, microperimetry maps the retinal sensitivity, and scotoma area, onto a live-captured fundus photo. Most current microperimeters also use eye-tracking abilities during testing to correct for eye movements; this allows for more accurate testing of

each retinal point. In the case of central vison loss, microperimeters can demonstrate the association between whatever remaining retina a person may have with their remaining visual function (Van de Velde 1997) – something that optical coherence tomography (OCT) and Humphreys Visual Field Analyzer (HVF) cannot do. Microperimetry, in particular, can be used in central vision loss such that we can use the outcomes to locate their remaining areas of highest visual sensitivity and more efficiently use them. Microperimeters also allow for measurement of retinal sensitivity, fixation stability and mapping the location of the PRL when there is no central fixation, as is the case in central vision loss. Though microperimetry can determine remaining visual function based on the PRL and retinal sensitivity, these outcomes are measured monocularly.

There are multiple properties that define the PRL; most common is the bivariate contour ellipse area (BCEA) which serves as a metric of fixation stability surrounding the PRL. Location refers to a physical location of retina used as the “alternative fovea” to perform a given task or activity of daily living – many individuals adopt multiple PRL locations in order to perform certain tasks with better accuracy and functionality. The bivariate contour ellipse area (BCEA) defines an area of retina that surrounds and delineates the functional limits associated with fixation (Crossland, Engel et al. 2011). To assess fixation stability, we look at the bivariate contour ellipse area (BCEA), which encompasses 68% of the gaze points (Crossland, Dunbar et al. 2009). Generally speaking, a smaller BCEA indicates more stable fixation, as seen with the normal fovea, and a larger BCEA indicates less stable fixation, as commonly seen in those with central vision loss. Fixation stability is known to be poor for those with central vision

loss, such that there are more micro fixations and eye movements seen to hold fixation when using any other retinal area rather than the anatomical fovea (Girish 2014). Additionally, those who experience vision loss at an earlier age, such as those with Stargardt's disease or congenital toxoplasmosis, exhibit better fixation stability compared to those who adopt eccentric viewing at a later age (i.e. age-related macular degeneration) (White and Bedell 1990).

A recent study by Chung and Bernard found that there was no correlation between the acuity of a given point of peripheral retina and establishment of the PRL; this indicates that patients do not necessarily select a PRL at the "next best" retinal location in terms of possible acuity (Chung and Bernard 2013). As such, we can conclude that there is more than one possible location in the peripheral retina that may serve as the PRL based on other factors than acuity alone. Multiple theories arise surrounding the reason for a given retinal point becoming the PRL. Is it the oculomotor system choosing a point that is consistently closest to the target such that the entire system minimizes eye movement amplitudes to provide better accuracy (Pidcoe and EWetzel 2006)? Or is it task-dependent such that the area chosen allows for better completion of a given task – for example, in reading, using a PRL that is to the left of the scotoma in retinal space (allowing views of the right visual field) could allow for better reading outcomes by not occluding the upcoming words (Duret 1999)?

Eccentric viewing training, a common vision rehabilitation method, aims to train a patient to adopt a new trained, or preferred, retinal locus (Seiple and Szlyk 2004, Watson, Schuchard et al. 2006) (Nilsson, Frennesson et al. 2003) that may be more

functionally beneficial to the patient, and eventually develop into an established PRL, allowing them to better use their remaining peripheral vision.

Rehabilitation specialists work to teach subjects to use a trained retinal locus, TRL, and this rehabilitation training can lead to improvements in eye movement control as well as faster and easier reading (Stelmack 1991). While normally-sighted people read up to 250 words per minute (wpm) (Zeifle 1998), people with central vision loss read much more slowly, as low as 20-50 wpm, which is considered to limit their reading comprehension (Trauzettel-Klosinski, Dieling et al. 2003). Several lines of evidence stress the importance of eye movement control for visual function: central vision loss is associated with a decreased size of forward saccades, an increased number of regressions (Crossland, Dunbar et al. 2009), and elevated fixation instability (Schuchard 2005); these oculomotor issues are correlated with deficits in the performance of a wide range of tasks including reading (McMahon, Hansen et al. 1993) and face recognition abilities (Seiple, Rosen et al. 2013). Additionally, rehabilitation data show that eye movement training may help people to read more effectively (Seiple, Szlyk et al. 2005). By learning to use their peripheral vision and establishing a new TRL within that periphery, individuals with macular disease improve performance in various tasks of daily living that involve movement or facial recognition (Seiple et al., 2015; Johnson, 2015). However, there is no consensus to date on what the goals, methods or outcomes of such training should be (Stelmack, Massof et al. 2004).

As such, we aim to uncover the underlying mechanisms of these visual tasks when central vision is compromised. Assessment of the relationship between the mentioned

outcome measures related to eccentric viewing will aid us in establishing a better understanding of the PRL.

Previous literature has examined PRL characteristics and oculomotor rehabilitation under monocular viewing, yet we experience our world binocularly, rendering clinical implications difficult. The proposed study aims to address these issues by exploring the properties of the PRL under both monocular viewing conditions and binocular viewing conditions.

Aims and Research Questions:

This study evaluated two groups: normally sighted individuals with simulated bilateral central scotomas, and individuals with established bilateral central vision loss such as age-related macular degeneration. The first group, the normally sighted individuals, normally sighted or corrected to normal, with simulated bilateral central gaze contingent pink noise mask scotomas, were recruited in order to validate and refine the methods used in the current study prior to using them for the second group, i.e. individuals with established bilateral central vision loss.

Firstly, we aim to examine PRL characteristics in various gaze positions; assessment of PRL positions and characteristics (PRL size/BCEA, PRL location) in normally sighted participants with simulated central scotomas as well as in participants with bilateral central scotomas due to macular disease to provide quantitative, evidence-based metrics for these outcome assessments. Secondly, assessment of the relationship between fixation stability, retinal location of the PRL and visual performance will be performed in normally sighted participants with simulated central scotomas as

well as in participants with bilateral central scotomas due to macular disease. Thirdly, the comparison between outcomes when assessed under monocular viewing conditions, with the better acuity eye at distance, versus binocular viewing conditions will be evaluated in both normally sighted participants with simulated central scotomas as well as in participants with bilateral central scotomas due to macular disease.

The following research questions will be addressed:

1) *What is the relationship between scotoma size and visual performance?* We will compare different scotoma sizes and combinations in normally sighted individuals with simulated central scotomas in various functional outcomes; we will evaluate both monocular and binocular outcomes with these simulated scotomas. Contrast sensitivity, best detectable acuity, and word identification (the duration required in order to discriminate whether string of 5 letters is a word or non-word) will be evaluated in relation to these various scotoma sizes and combinations.

    We hypothesize that increasing scotoma size will negatively impact visual performance; smaller scotoma size conditions will demonstrate better visual function than larger scotoma size conditions.

2) *What is the relationship between monocular (better eye) versus binocular viewing on visual outcomes, the PRL location and PRL BCEA (fixation stability)?* We will measure the BCEA area, while patients are completing vision function measurements. We will compare functional outcomes including contrast sensitivity, and best detectable acuity under both monocular and binocular

viewing conditions. We will determine whether these functional outcomes differ at different gaze positions that elicit both the best and worst fixation stability. Additionally, we will determine whether a given PRL position will elicit better fixation stability and functional outcomes. These assessments will be conducted in both normally sighted individuals with simulated central scotomas as well as in participants and patients with bilateral central vision loss.

We hypothesize that visual performance will differ between binocular viewing and monocular viewing conditions. We hypothesize that binocular viewing conditions will demonstrate improved visual performance and PRL characteristics when compared to those same visual outcomes under a monocular viewing condition.

3) *What is the relationship between fixation stability and visual performance?* We will compare whether the gaze positions that elicit the “worst” and “best” fixation stability (highest and lowest BCEA, respectively) impacts the functional outcomes including contrast sensitivity and the minimum detectable acuity; these comparisons will be done in both normally sighted individuals with simulated scotomas, as well as in participants and patients with bilateral central vision loss.

We hypothesize that better fixation stability, and therefore a smaller BCEA, will correlate to better visual function. We hypothesize that this will be noted in both testing groups: normally sighted individuals with simulated scotomas and in patients with bilateral central vision loss.

Outcome Measures:

Several aspects of the PRL can be measured or assessed to examine the outcomes of the PRL in functional settings, or when being used to perform activities of daily living. Specifically, the relationship between PRL location and fixation stability, as well as PRL eccentricity relative to the target. One way to evaluate the stability of a PRL is through a quantitative measure called the bivariate contour ellipse area (BCEA). The BCEA is an ellipse-shaped area that encompasses 68% of the eye-fixations' location over a given set of time/duration of a task in addition to the 95% confidence interval for all fixation points during the task as measured by the Eyelink 1000 eye tracker as well as the MAIA (Macular Integrity Assessment) microperimeter (Figure 1); the 68% represents the mean fixation location plus and minus one standard deviation of fixation locations. In the proposed study, we aim to use the BCEA to assess fixation stability (Crossland, Dunbar et al. 2009). A smaller BCEA indicates a more stable area of fixation and a larger BCEA indicates a less stable area of fixation. In the proposed study, we aim to evaluate how fixation stability, measured by the BCEA, correlates with PRL location and performance of visual tasks such as reading, word and letter identification.

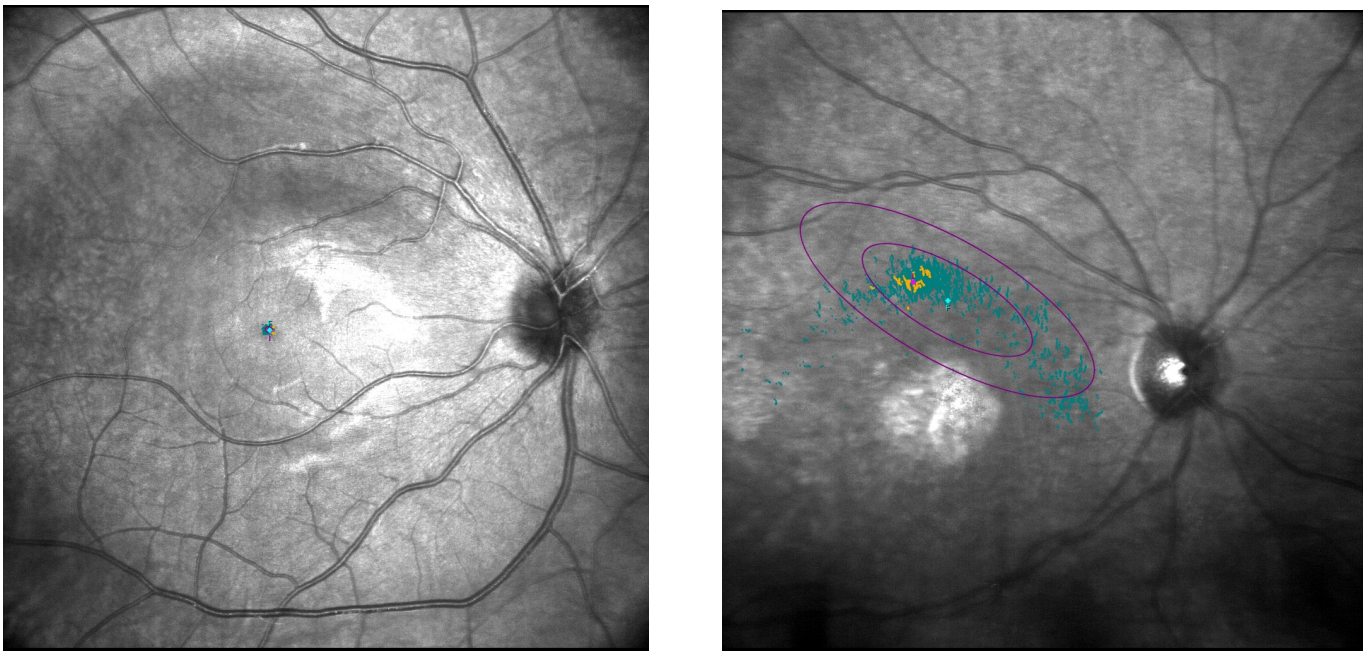


Figure 1. Measures of BCEA using MAIA microperimetry. The BCEA is an ellipse-shaped area that encompasses 68% of the eye-fixation locations over a given set of time/duration of a task in addition to the 95% confidence interval for all fixation points during the task as measured by the Eyelink 1000 eye tracker as well as the MAIA (Macular Integrity Assessment) microperimeter; the 68% represents the mean fixation location plus and minus one standard deviation of fixation locations (see equation below). In the proposed study, we aim to use the BCEA to assess fixation stability (Crossland, Dunbar et al. 2009). Fixation stability for normally sighted adults ranges from 0.5 +/- 0.7, and in patients with bilateral central vision loss from 12.7 +/- 15.2 (Wallis, Taylor et al. 2014). A smaller BCEA indicates a more stable area of fixation and a larger BCEA indicates a less stable area of fixation. In this example, the image on the left shows a normally sighted participants' MAIA retinal image and fixation area concentration in the fovea. The image on the right shows the fixation pattern of one of the participants in Phase 2 of the study, who has central vision loss, and their fixation stability pattern encompassed by the purple ellipses.

$$BCEA = 2k\pi_{H}\sigma_{v}(1-\rho^{2})^{1/2}$$

The following outcome measures of the current study will be collected for both monocular and binocular testing conditions; both monocular outcomes and binocular outcomes will be evaluated as well as compared between one another. The primary outcome measures of the current study include the bivariate contour ellipse area (BCEA) as well as visual performance measures including acuity and contrast sensitivity. These outcome measures will be evaluated under both monocular viewing

conditions and binocular viewing conditions, in addition to in different positions of gaze. Further understanding PRL characteristics by evaluating both fixation stability and reading performance relative to PRL location, or changes in PRL location, will be assessed.

Lastly, outcome measures will be compared when assessed monocularly versus binocularly. This study may allow the prediction of whether a characteristic of PRLs such as fixation stability is a measurable outcome of improved visual abilities and improved performance in various tasks of daily living such as reading in individuals with central vision loss due to macular disease. Furthermore, this study will inform clinical decisions concerning appropriate oculomotor rehabilitation strategies to improve visual function, given the outcomes of the current study.

Chapter 2 - Phase 1 – Normally Sighted Observers with Simulated Gaze-Contingent Scotomas

Introduction:

In this first study, normally sighted individuals with simulated bilateral central scotomas were recruited to explore visual function and fixation stability with gaze-contingent scotomas. The purpose of this first study was to validate and refine the methods used in this current study prior to using them for the second phase, i.e. individuals with established bilateral central vision loss. Multiple studies have addressed the use of gaze-contingent simulated scotomas to represent central vision loss in conditions such as age-related macular degeneration (McIlreavy, Fiser et al. 2013). By compromising central vision, as is the case with age-related macular degeneration and other macular diseases, participants are forced to use retina other than their central macula to perform visual tasks. Eccentric viewing is a term that describes the use of an alternative area of the retina other than the central macula and/or fovea for visual function. It is known that macular diseases, and central vision loss of any kind, causes significant difficulties in the lives of patients given that their “normal” central vision has now been compromised and thus cannot be used; this forces patients to adapt an eccentric viewing strategy for visual performance. In normally sighted individuals using simulated central scotomas, they too are forced to use an eccentric viewing strategy (Aguilar 2011); this can mimic the difficulties noted by patients with macular compromise and central vision loss. These simulated scotomas allow for the precise measurement of where participants place their “former” fovea or simulated scotoma relative to the viewed target and fixation. Of importance, is how the eyes compensate

for central vision loss by using an eccentric retinal location outside of this no-longer-available-to-use fovea as a new pseudo-fovea to accomplish most of their central vision activities such as reading (Cummings, Whittaker et al. 1985). This eccentric retinal location, or new pseudo-fovea is what is referred to as the preferred retinal locus (PRL) (Cummings, Whittaker et al. 1985). Using these bilateral simulated central scotomas can provide insight into how those with central vision loss use their remaining vision and retinal space to work around this deficit to accomplish tasks such as reading, letter or word detection, and facial recognition; this allows for the testing of hypotheses in a controlled environment prior to performing the same tasks in patient populations (Liu 2016). The current study focuses on the adoption of the PRL, its retinal location, and its characteristics in performing various tasks such as reading, letter recognition, and contrast sensitivity.

Methods:

This was a prospective, observational research study. Participants were asked to use one or both their eyes on the following task to establish both their optic nerve head (ONH) location, and subsequently, their eccentric viewing position (Arango 2019). Participants viewed a 5-degree radial grating moving in concentric/centripetal motion and were asked to maintain that radial grating in fixation. NVIDIA 3D shutter glasses, updated at the screen monitor refresh rate (120 Hz), presented a dichoptic disc to localize the optic nerve head in each eye. A 1-degree diameter disc flickering at 60 Hz that was presented to each eye separately, and manually moved by the examiner with a computer mouse to one side or the other, while the patient maintained fixation on the

central 4-degree grating, until the patient reported the disc disappeared in the location of the optic nerve head of each eye (i.e. when the disc was in their physiological blind spot) (Figure 2). This allowed for the tracking of the optic nerve head throughout each task, and then, once correlated with the MAIA microperimetry findings for each patient, also allowed for the tracking and observation of the PRL location in each eye for each participant.

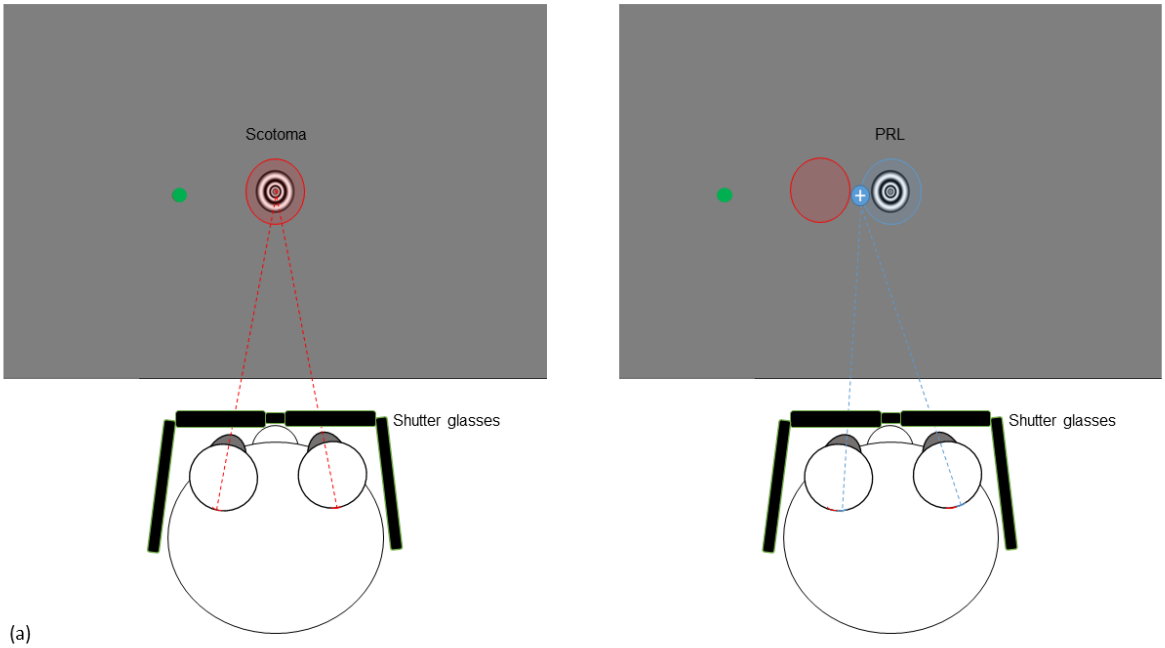


Figure 2: Illustration of the optic nerve head and PRL locating task. Observers fixated on a contracting radial grating while a colored disk, illustrated in green, is manually moved until the patient reports that it disappears into the ONH (or physiological blind spot) of each eye. Participants with central vision loss cannot look directly at the radial grating because it will be occluded by their central scotoma, illustrated here as red circle. Instead they used their already established PRL to perform the task, illustrated here as blue circle in the image on the right. The blue dot and cross element indicate the location of the eyes' position allowing for eccentric viewing and use of the PRL to adequately observe the contracting radial grating. In normally sighted observers, the same task was performed without any presence of a scotoma such that the anatomical fovea was used to fixate on the contracting grating, allowing for mapping of the ONH.

The position of the participants' eyes was recorded with a desktop Eyelink 1000 eye tracker (see http://www.sr-research.com/mount_desktop.html). The Eyelink 1000 allows for monocular and binocular eye tracking using infrared light (890 or 940 nm) to track each pupil. Normally sighted participants used shutter glasses that independently presented simulated to each eye, both under bilateral or unilateral testing conditions, allowing the simulation of asymmetric and bilateral scotomas (Figure 3 and 3a). These gaze contingent scotomas simulate vision loss regardless of gaze direction or eye position, simulating artificial central visual field loss on a fixed retinal locus by using an eye tracker and shutter glasses. The subject's task throughout the current protocol, while keeping their head placed on a chinrest, stable and at a fixed distance from the testing screen, was to move their eyes to keep the target, a fixation dot, located at various eccentricities of the screen clear and visible without covering it/hiding it with the simulated central scotomas they were experiencing in their central vision (Figure 4).

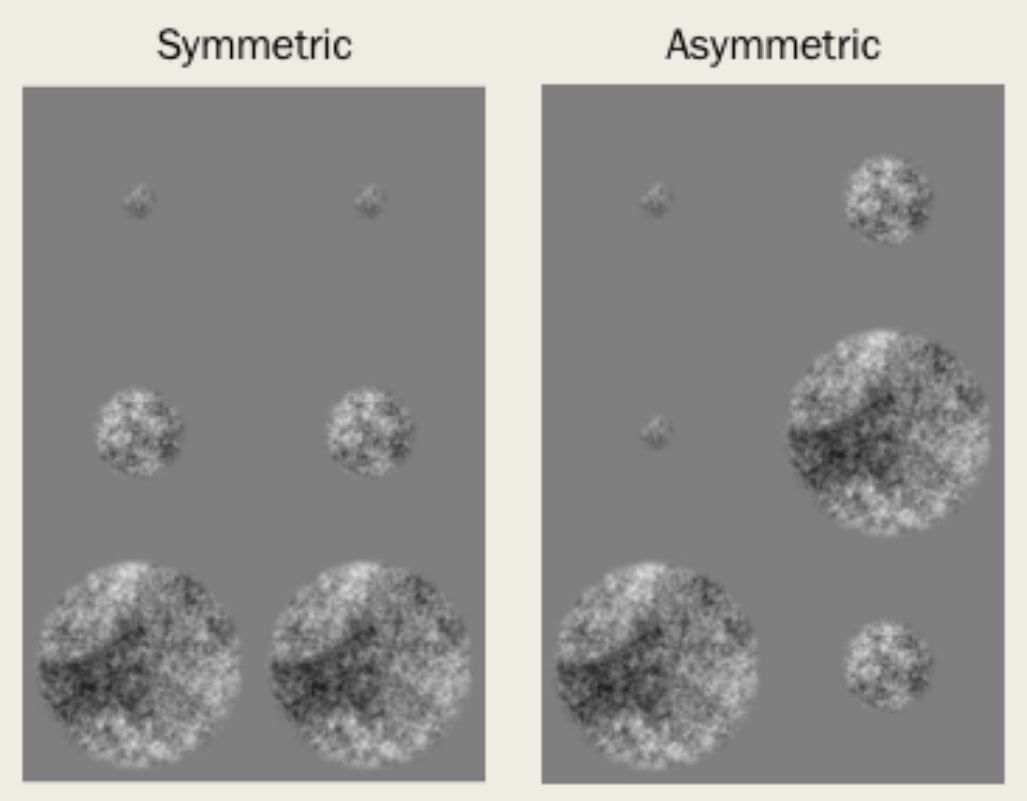


Figure 3. Demonstration of the symmetric and asymmetric bilateral simulated scotomas. On the symmetric panel, the upper and smallest scotomas are 0.5 deg, those below it are 1.0 deg, and the lower and largest ones are 2.0 deg each. These simulated scotomas can also be seen in mis-matched pairings for the asymmetric testing conditions. Each normally sighted participant in the binocular viewing condition was assigned and completed the following tasks with one of these conditions. Scotomas were independently simulated using active shutter glasses in concordance with an Eyelink 1000 eye tracker to assure that the simulated scotomas remained centered on the fovea throughout the task.

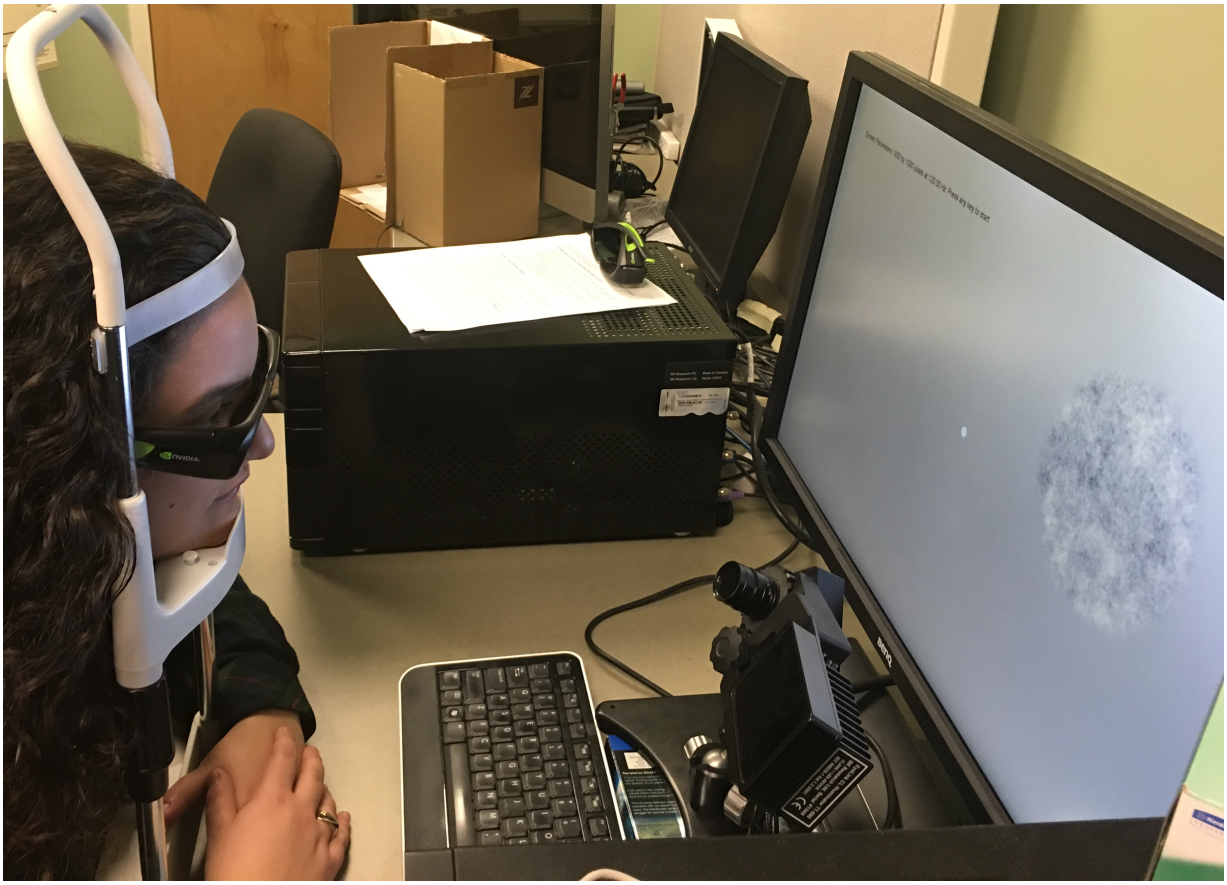


Figure 3a. A demonstration of the participant set-up during Phase 1 testing. The participant maintains their head position in the chinrest, wearing the shutter-glasses that produce the gaze-contingent simulated central scotomas. This is accomplished using the Eyelink eye tracker below the computer monitor set up at a 60 cm testing distance to track eye movements and maintain the scotomas in their central positions throughout testing.

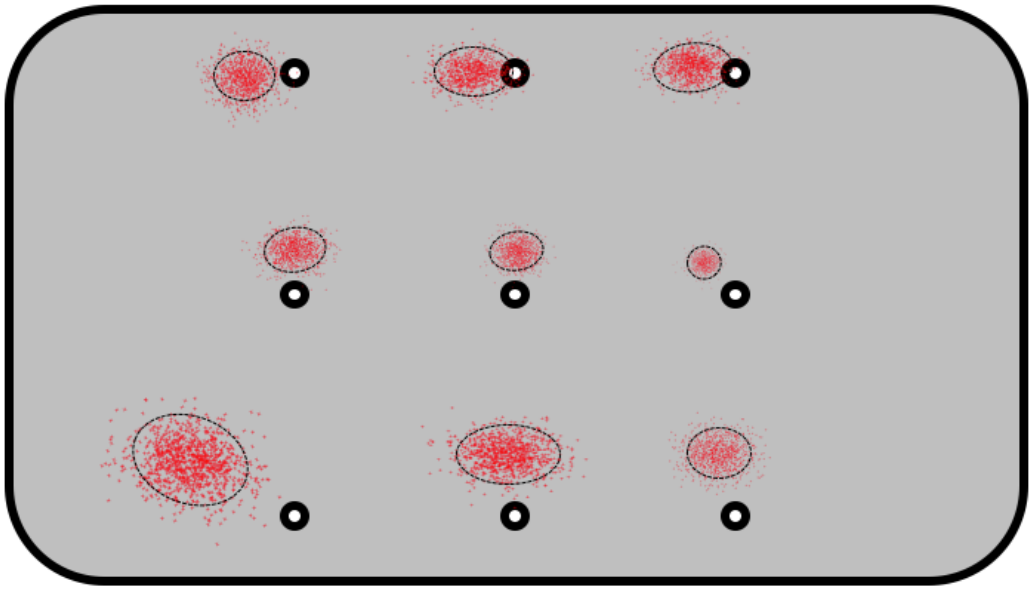


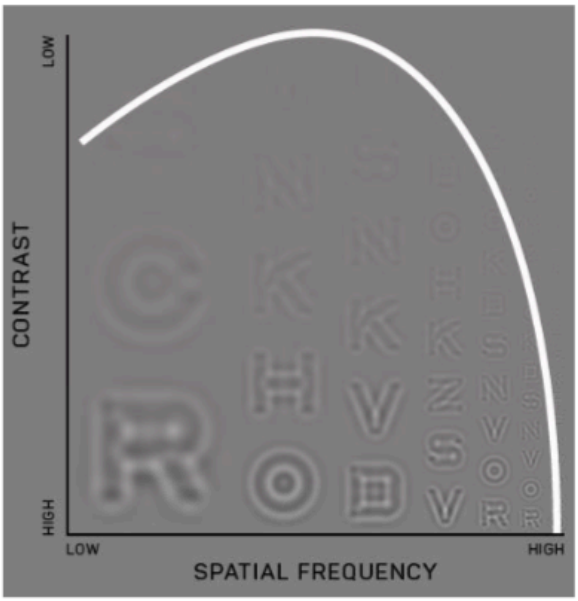
Figure 4. Simulation of the 9-point grid used for the various target positions and gaze eccentricities tested. Each participant would begin fixating on one point, while asked to maintain fixation with "clearest" vision, thus not allowing the central scotomas to interfere with viewing of the target. As the task continued, a different target position would appear on screen, forcing the participants to make a saccade; after the saccade, once again, the participant would need to keep the target visible, while not allowing the central scotomas interfere with viewing the target. Red points indicate the direction of gaze during 6 seconds of fixation, and the black ellipses represent the bivariate contour ellipse area (BCEA) for each gaze direction: the BCEA represents 68% of the gaze points as determined by the eye tracker, for a simulated participant at each position of the 9-point grid.

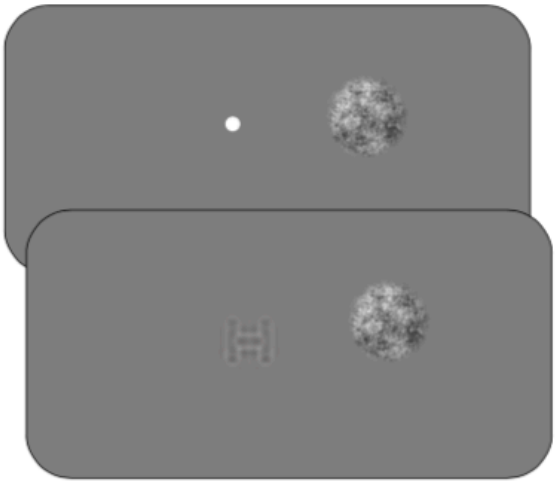
In both monocular and binocular testing situations, the target position on the screen was changed to each of nine locations of the test screen (16 degrees vertical and horizontal, separated in 8 degree steps, 8 x 8), to assess how the observer was able a) to fixate on a stationary target at different screen locations without their central vision loss obstructing their view of the target and b) make saccadic eye movements to an abruptly displaced target at the various eccentricities of the screen (Figure 4). Participants used a peripheral, non-foveal, location, as required by the simulated central scotomas, to perform a letter identification (contrast) task as well as a word recognition task at screen eccentricities that elicited both the best and worst fixation stability as

determined by the BCEA from the primary fixation task; we assessed the relationship between fixation stability, retinal location of the PRL and visual function under both monocular and binocular viewing conditions.

In this first phase of the study, the twelve participants were undergraduate Psychology students attending Northeastern University (Mean age 20, range 19-23). Participants wore and used active shutter glasses to control images presented to the left and right eyes and gaze-contingent masks on a 120Hz display to simulate binocular central scotomas that remained gaze-contingent with use of the Eyelink 1000 eye tracker. Under monocular testing conditions, the contralateral eye was covered with an eye patch and the eye tracker alone was used to present a single gaze-contingent scotoma to that eye. Participants were emmetropic or corrected with contact lenses to be included in the current study. Those with spectacle correction were excluded from the study due to the needed use of active shutter glasses in concordance with the Eyelink 1000 eye tracker; the eye-tracker was unable to perform when needing to pass through two or more sets of lenses or spectacle optics. Participants used the same method used to establish the location of their optic nerve head and PRL, as demonstrated in Figure 1 and Figure 2. They were then instructed to look towards a target; the goal was to maintain visibility of the target using their simulated PRL and not their fovea due to loss of their central visual field caused by the simulated scotomas. The target moved to three different eccentricities on the screen (4 degrees, 8 degrees, and 16 degrees from the center) creating a symmetrical 9-point grid of assessment points (Figure 4). The target stimulus moved to each of the mentioned eccentricities in a randomized order to eliminate practice effects.

Secondly, the visual function at binocular and monocular PRLs was assessed; we tested both letter detection (a measure of acuity and contrast sensitivity) and word recognition in both the best and worst positions of gaze; these locations were determined by nine different positions of gaze (Figure 4) where both the largest and smallest BCEA determine the areas of best fixation stability (smallest BCEA) and worst fixation stability (largest BCEA). We chose these two different testing locations to determine whether these functional outcomes were dependent on the stability of fixation when using a PRL. For acuity and contrast sensitivity, the quickCSF method (Lesmes, Lu et al. 2010) was used such that participants were required to report the identity of a band-pass filtered target letter – a staircase adjusted the size and contrast of the next letter based on the participants' responses (Lesmes, Lu et al. 2010)(Figure 5). This contrast detection task using the quickCSF algorithm controls the contrast and font size to maximize the expected information gain in each trial and updates the current parameters of the CSF (Lesmes, Lu et al. 2010). As a measurement of reading ability and word recognition, the word non-word task was used: this task uses five-letter pentagrams syntactically matched in English words or non-words (Medler DA 2005.). Each word was presented on a screen for a given time duration and in a given font size that was continuously updated based on the participants' responses (Figure 6). Participants were asked to determine whether presented formulations of letters are words or non-words at various font sizes and screen locations (Arango, Yu et al. 2020). Participants' PRL position and gaze position (as measured by the gaze-contingent method above) were recorded throughout the contrast sensitivity and word non-word tasks.





Sample trial for contrast detection.

Figure 5. Sample trial for contrast detection. Left: outcome measures for acuity and contrast sensitivity; the contrast sensitivity function (CSF) is illustrated by the white line and defines the boundary between targets that can be identified and those that cannot. The area under the CSF curve was used to estimate contrast sensitivity and the x-intercept of the curve was used to estimate acuity (the highest spatial frequency letter that can be identified at maximum contrast) and the peak of the curve was used to estimate peak contrast sensitivity. **Right:** sample trial for contrast detection – participants would be asked to keep the target clear and visible (the white target in this case), then a letter of given size and contrast would appear, and the participant would need to identify the letter displayed. Based on participants' responses, the letter size and contrast of the letter would vary to establish the curve (on the left).

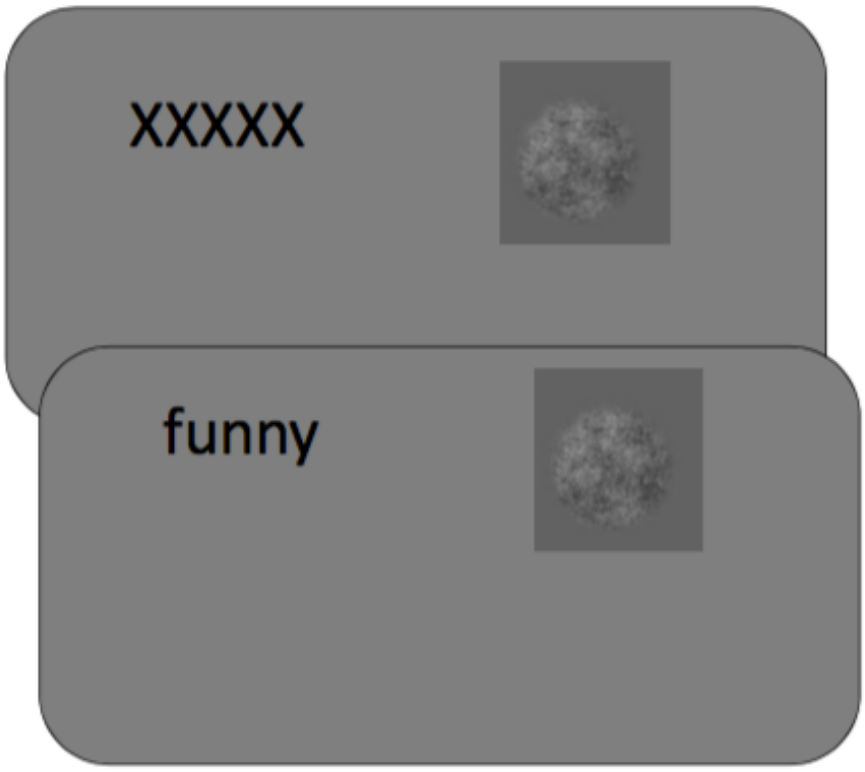


Figure 6. Sample trial for Word / Non-Word task. Participants are cued with a string of 5 X's to cue the size and location of the upcoming 5-letterword or nonword. Participants are asked to keep the target string of X's clear and visible, then the word will appear for a given duration of time and the participants are asked to determine whether what was presented was a word or not. A staircase adjusted the font size and duration of the word on each trial based on participants' responses on previous trials.

Data Analysis:

Throughout each trial, and across both study phases, we recorded eye position data at 1000Hz per eye. These data provided a quantitative measurement of fixation stability. Additionally, the distance between the center of the gaze-contingent simulated scotoma and the center of the target circle provided a quantitative estimate of the accuracy and precision of oculomotor control. ANOVA was used to evaluate the difference between means amongst the various testing groups. Under the binocular testing conditions, the various scotoma sizes and combinations, both symmetric and asymmetric,

were compared to the various testing outcome measures (including area under the curve, contrast sensitivity, acuity and reading outcomes such as minimum word duration). Under the monocular testing conditions, the various scotoma sizes were compared to each of the outcome measures of visual function (including area under the curve, contrast sensitivity, acuity and reading outcomes such as minimum word duration).

Results:

Participants

There was a total of 12 participants that enrolled for Phase 1 of this study. Each participant completed data collection for both the monocular viewing condition and the binocular viewing condition. All participants were normally sighted undergraduate Psychology students attending Northeastern University. The average age of the participants was 19, ranging from 18-23. All participants had a visual acuity of 20/20 at distance without correction or in contact lenses. The exclusion criteria omitted participants wearing spectacle correction; this was due to the inability of the eye tracker to appropriately track the anatomical fovea through both the shutter glasses and the participants' spectacle correction.

Monocular CSF Outcomes

All 12 enrolled participants for the monocular testing conditions completed data collection for this pilot study. There was a statistically significant difference in contrast sensitivity between the smallest scotoma condition (0.5 deg) and the largest scotoma condition (2.0 deg), as hypothesized; as the simulated scotoma size increased from 0.5

deg to 2.0 deg, contrast sensitivity was statistically significantly lower, the area under the curve was statistically significantly lower, and the resulting acuity was statistically significantly worse ($p < .01$). These outcomes were for both the best and worst fixation stability testing locations from the nine-point fixation grid task, i.e. the locations with the smallest and largest BCEA. Figure 7 below, illustrates data from a representative participant.

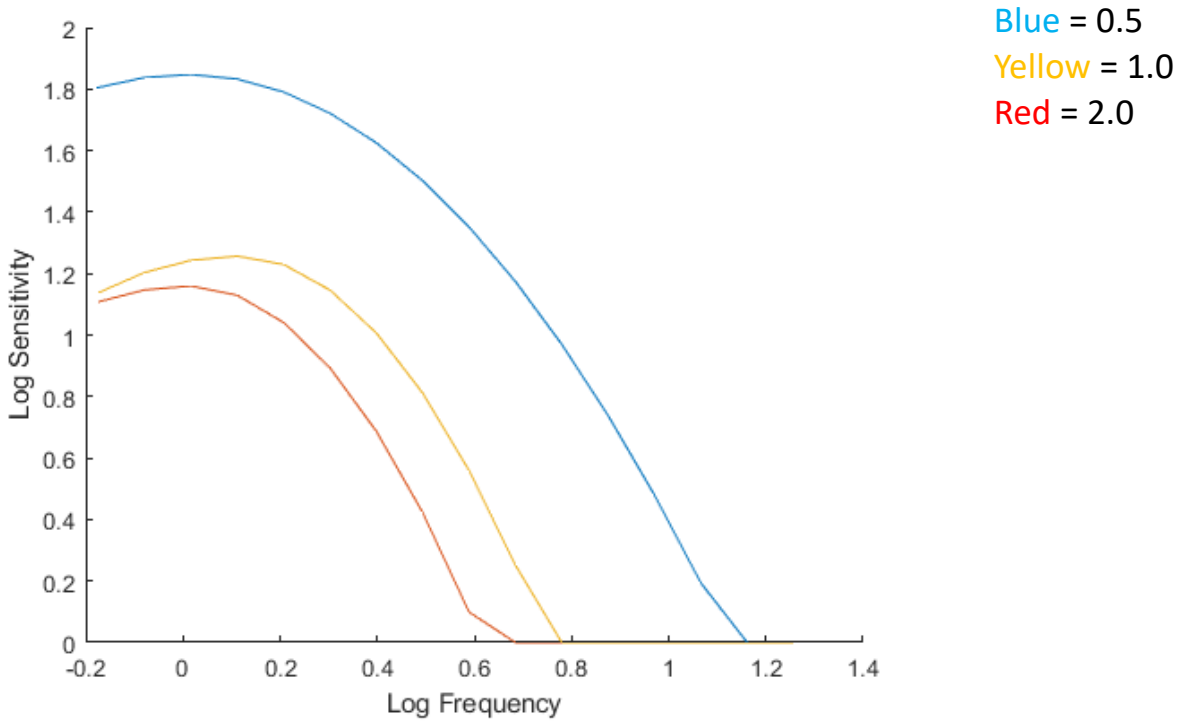


Figure 7. Monocular CSF Outcomes: Data of a candidate subject; group means for the same scotoma conditions were similar to those illustrated here. Comparison of the various tested scotoma sizes, ranging from 0.5, 1.0 and 2.0 degree radius pink noise gaze contingent scotomas. The blue curve, corresponding to the smallest scotoma condition, is associated with the largest area under the curve, the best acuity (largest x-intercept), and the best contrast sensitivity (highest y-intercept). Contrarily, the red curve, corresponding to the largest scotoma condition (2.0 deg) is associate with the smallest area under the curve, the worst acuity (lowest x-intercept), and the worst contrast sensitivity. The yellow curve, corresponding to the 1.0 deg scotoma found value intermediate to those found for the largest and smallest scotoma conditions.

Monocular Word / Non-Word Outcomes

As a subsequent task to that mentioned above, all 12 participants in the monocular viewing condition participated in the Word/Non-Word task. There was a statistically significant difference between the smallest and largest scotoma conditions (i.e. the 0.5-degree scotoma and the 2.0-degree scotoma) and the minimum word duration in the Word/Non-Word task ($p < .01$) (Figure 8). Minimum duration represents the shortest possible amount of time a participant needed to subsequently select a

correct response in the given task. As hypothesized, as scotoma size increased, the smallest minimum word duration was statistically significantly longer to elicit a correct response.

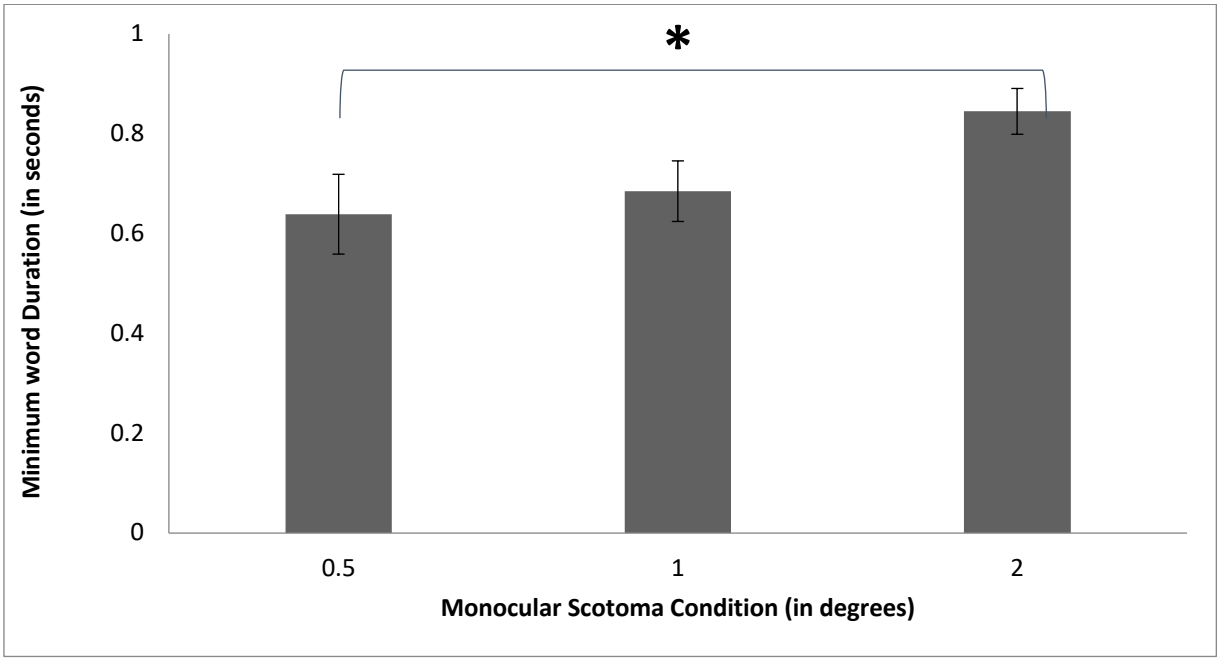


Figure 8. Monocular Word/Non-Word Minimum Duration Outcomes. Group mean word identification duration, comparing the outcomes of the minimum word duration to make a correct answer selection for the various scotoma conditions. As scotoma size increased, there was a statistically significant increase in the minimum duration of the word to appear to elicit a correct decision ($p < .01$).

There were no statistically significant differences found between scotoma size and threshold acuity during this same Word/Non-Word task ($p = .667$).

Monocular Fixation Stability Outcomes

Data of fixation stability, and thus measures of the bivariate contour ellipse area (BCEA), was collected during the performance of the various monocular tasks on all 12 enrolled participants. Participants completed a fixation task by fixating at different

eccentricities on a nine-point grid (Figure 4) using gaze-contingent monocular simulated central scotomas of various sizes (0.5, 1.0 and 2.0°). Both the location with the smallest BCEA, and the location with the largest BCEA, from the fixation task were subsequently used to complete both the monocular CSF and Word / Non-Word task. There was no statistically significant difference between the monocular BCEA, and therefore in the fixation stability, between both the best and worst monocular BCEA locations ($p = .2484$) (Figure 9). This means that the monocular fixation stability while performing various visual tasks was not location dependent: it did not differ whether the task was being performed at the location associated with the smallest BCEA, or best fixation stability, or the locations with the largest BCEA, or worst fixation stability, in the nine-point grid monocular fixation task.

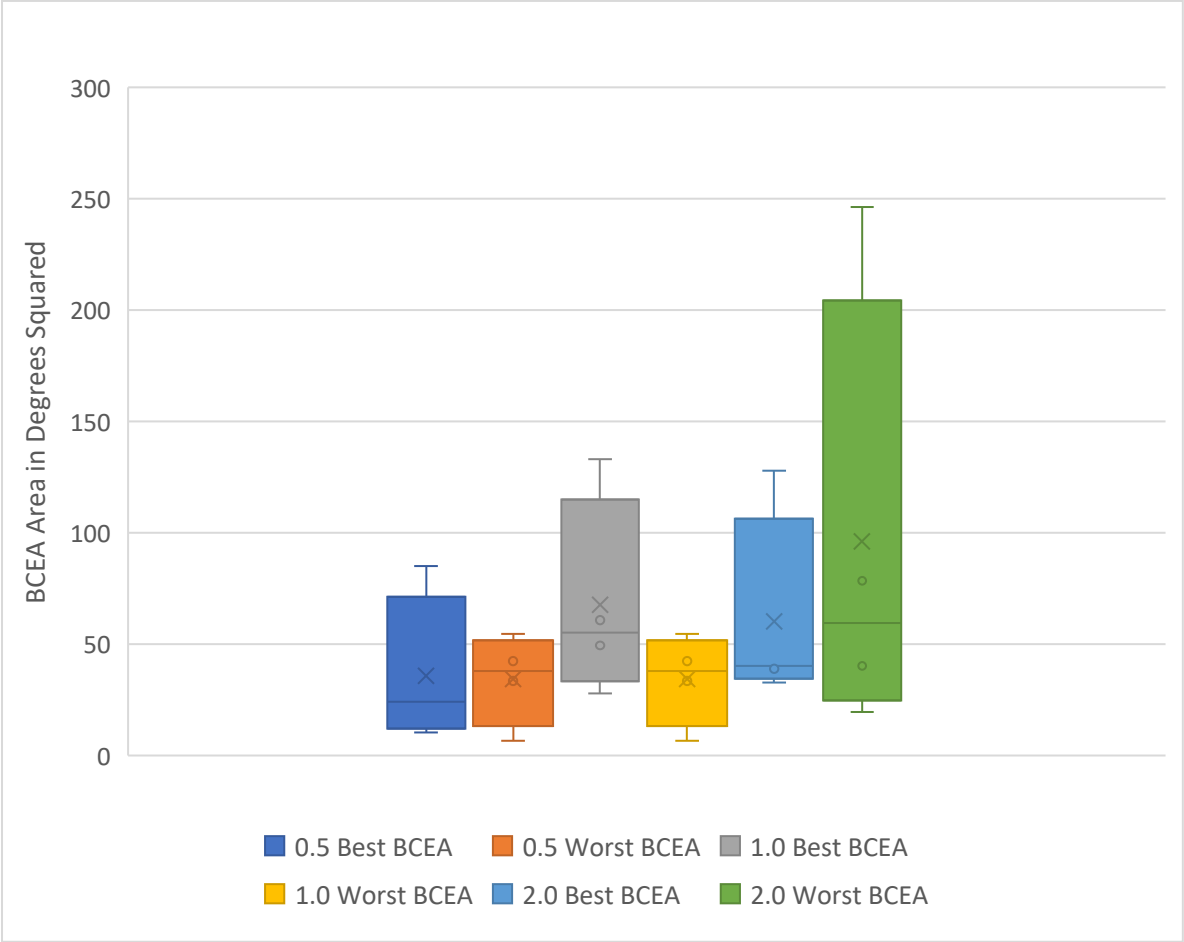


Figure 9. Monocular Fixation Stability Outcomes. The location with the smallest BCEA, the best fixation stability, and the location with the largest BCEA, the worst fixation stability, were subsequently used to complete both the monocular CSF and Word / Non-Word tasks. There was no statistically significant difference between the monocular BCEA, and therefore in the fixation stability, between both the best and worst monocular BCEA locations ($p = .2484$) in performing the CSF and Word / Non-Word tasks.

Binocular CSF Outcomes

All 12 enrolled participants for the binocular testing conditions completed data collection for this portion of Phase 1 of the study; these participants were the same 12 participants who took part in the monocular portion of this study. When comparing the symmetric binocular viewing conditions versus the asymmetric binocular viewing

conditions, there was a statistically significant difference between the resulting acuity measures (designated by the high-frequency cut-off of the established contrast sensitivity function) (p = .01) (Figure 10). That is, under symmetric scotoma viewing conditions, the resulting acuity was lower, or worse, than the acuity determined under the asymmetric scotoma viewing conditions.

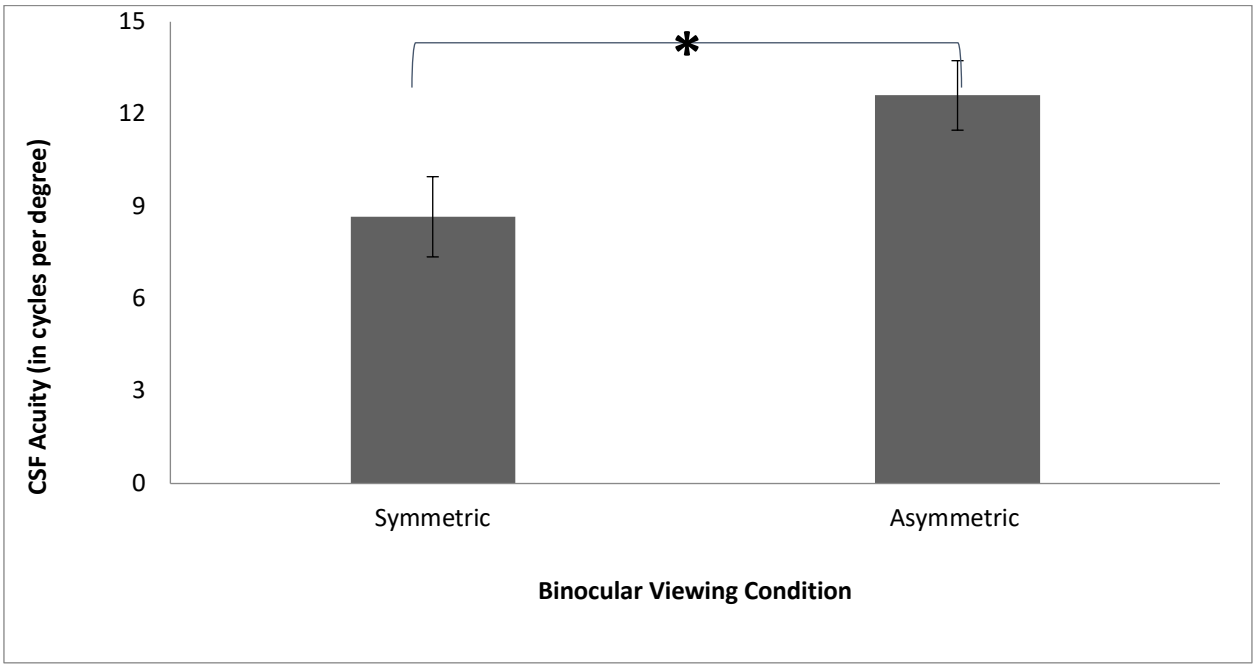


Figure 10. Binocular CSF Outcomes, Symmetric versus Asymmetric Scotomas. Under symmetric viewing conditions the resulting acuity was statistically significantly lower, or worse, than the resulting acuity when viewing with asymmetric scotomas (p = .01).

Binocular Fixation Stability Outcomes

Similar to the monocular outcomes, data of fixation stability, and thus measures of the bivariate contour ellipse area (BCEA), was collected during the performance of the various binocular viewing tasks on all 12 enrolled participants. Participants completed a fixation task by fixating at different eccentricities on a nine-point grid

(Figure 4) under various binocular gaze-contingent simulated scotoma conditions, both symmetric and asymmetric. Both the location with the smallest BCEA, the best fixation stability, and the location with the largest BCEA, the worst fixation stability, were subsequently used to complete both the binocular CSF and Word / Non-Word task. There was no statistically significant difference between the binocular BCEA, and therefore in the fixation stability, between both the best and worst binocular BCEA test locations ($p = .7789$) (Figure 11). This means that the binocular fixation stability while performing various visual tasks did not differ whether the task was being performed at the location associated with the smallest BCEA, or best fixation stability, or the location with the largest BCEA, or worst fixation stability, in the nine-point grid binocular fixation task.

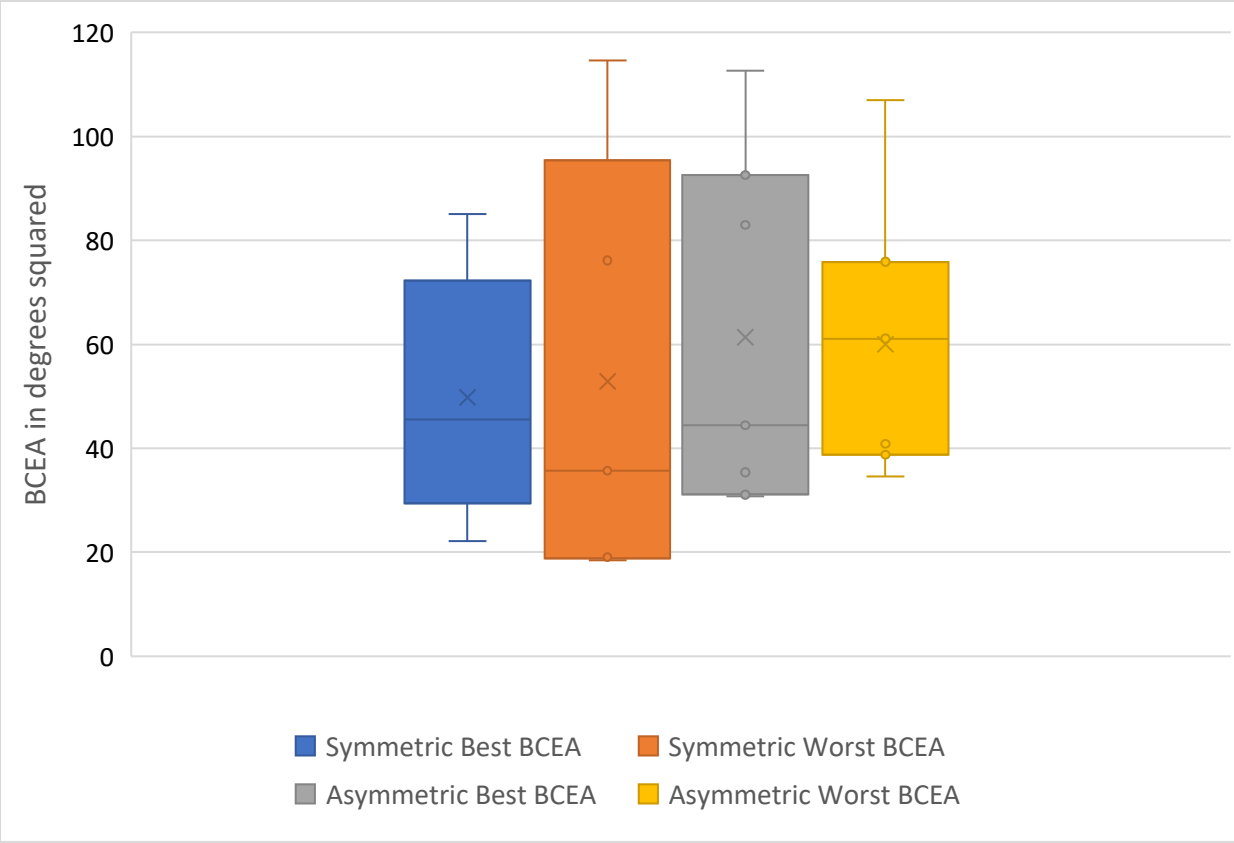


Figure 11. Binocular Fixation Stability Outcomes. There was no statistically significant difference between the binocular BCEA, and therefore in the fixation stability, between both the best and worst binocular BCEA test locations (p = .7789) (Figure 11). This means that the binocular fixation stability while performing various visual tasks did not differ whether the task was being performed at the location associated with the smallest BCEA, or the location with the largest BCEA, in the nine-point grid binocular fixation task.

Other Binocular Viewing Outcomes

When looking at the other outcome measures associated with the CSF task, there was no significant effect of binocular scotoma viewing condition, both symmetric and asymmetric, on resulting contrast sensitivity, and area under the curve (p .073). In terms of the Word/Non-Word task, under both symmetric and asymmetric binocular viewing conditions, there was no significant effect of scotoma sizes and pairings on both outcomes (minimum word duration and acuity) (p = .103, p = .375).

Discussion:

Using simulated gaze-contingent scotomas, visual performance at the PRL differs under monocular viewing conditions versus binocular viewing conditions. Under binocular viewing conditions, the current outcomes were much different than those under monocular viewing conditions – indicating that performance outcomes such as contrast sensitivity, reading acuity, and minimum word duration were not impacted by the sizes of the scotomas when both eyes were involved in the task, much to the contrary of the monocular viewing outcomes. This relates to the observation that age-related macular degeneration, in particular, is an asymmetric disease process; it may be that asymmetric but bilateral central scotomas impact visual function differently than either eye performing alone. It has been observed that in binocular central vision loss, the overall resulting scotoma (as it impacts binocular vision) is smaller than each eyes' individual scotoma size for the majority of patients (Ross, Goldstein et al. 2013). One study by Dr. Karabanou and colleagues noted different findings such that binocular performance did not differ from the monocular performance with the better seeing eye (Kabanarou and Rubin 2006). This prompts the idea for further investigation into binocular versus monocular visual performance, comparing different visual tasks such as continuous reading or facial recognition.

Additionally, it appears that fixation stability, and the subsequent size of the BCEA area, both under monocular viewing conditions and binocular viewing conditions, does not impact the functional outcomes of the CSF and Word / Non-Word task. It may be that a fixation task such as the nine-point grid used in the current study, and the BCEA determined by this task, does not translate into the fixation stability demand of a

functional task such as letter detection and word discrimination. It raises the idea that fixation stability, when performing a simple fixation task versus an active participation task differ both in their impact on visual outcomes and translation into performance of daily activities. Perhaps simple fixation tasks, and the fixation stability needed to perform such activities, differs in significance to the fixation stability required to perform more complex activities of daily living such as letter identification or continuous reading.

The current outcomes can translate into changing how we help those with central vision loss as well as how we evaluate their visual performance given the peripheral vision they have left. Outside of clinical and research settings, individuals will navigate their world binocularly. By observing their visual performance binocularly, we see that scotoma size does not impact their visual function in the ways that monocular performance has previously reported.

The majority of individuals who present for low vision exam appointments and evaluations complain of mainly issues with reading – the current study shows that reading ability is not impacted by scotoma size, progression, symmetry or asymmetry when assessed under binocular viewing conditions, the condition in which we read, in normally-sighted individuals with bilateral simulated gaze-contingent central scotomas.

Chapter 3 – Phase 2 – Individuals with Bilateral Central Scotomas

Introduction

This group of ten participants was recruited from the Janet LaBreck Low Vision Rehabilitation Center at the New England College of Optometry Center for Eye Care. Each participant was a patient with previously established bilateral central vision loss of various cause including age-related macular degeneration, degenerative myopia and Stargardt's disease. Central vision loss impacts both ones' quality of life and the ability to perform activities of daily living such as reading (Legge, Rubin et al. 1985), face recognition (Peli, Lee et al. 1994), watching television (Wolffsohn and Cochrane 1999), driving and mobility (Lovie-Kitchin, Mainstone et al. 1990), and is associated with elevated levels of depression (Brody 2011). During this study, amongst all participants, the foveae of the two eyes are not functional; this forces one to adopt a preferred retinal locus (PRL). The PRL is a more peripheral retinal area that has not been impacted by the macular condition, which has much lower resolution than the fovea. The PRL acts as the new "pseudo-fovea" and becomes the new area of retina that is used for fixation and "high-resolution" vision when required to look at a target.

Performing research studies on patients with these bilateral central scotomas can provide insight into how those with central vision loss use their remaining vision and retinal space to work around this central visual deficit to accomplish tasks such as reading, letter or word detection, and facial recognition. The current study focuses on the adoption of the PRL, its retinal location, and its characteristics in performing various tasks such as reading, letter recognition, and contrast sensitivity.

Methods:

This was a prospective observational study. Participants were tested under both monocular and binocular viewing conditions. In a manner much like the previous pilot study described in Chapter 2, participants were asked to use one or both their eyes on the following task to establish both their optic nerve head (ONH) location, and subsequently, their PRL location (Arango 2019). Participants viewed a 5-degree radial grating moving in concentric/centripetal motion and were asked to maintain that radial grating in fixation. NVIDIA 3D shutter glasses, updated at the screen monitor refresh rate (120 Hz), presented a dichoptic disc to localize the optic nerve head in each eye. There was a 2-degree diameter disc that flickered at 60 Hz that was presented to each eye separately, and manually moved by the examiner with a computer mouse to one side or the other, while the patient maintained fixation on the central 5-degree grating, until the patient reported the disc disappeared in the location of the optic nerve head of each eye (i.e. when the disc was in their physiological blind spot) (Chapter 2, Figure 2). This allowed for the tracking of the optic nerve head throughout each task, and then, once correlated with the MAIA microperimetry findings for each patient, also allowed for the tracking and observation of the PRL location in each eye for each participant.

The position of the participants' eyes was recorded with a desktop Eyelink 1000 eye tracker (see http://www.sr-research.com/mount_desktop.html). The Eyelink 1000 allows for monocular and binocular eye tracking using infrared light (890 or 940 nm) to track each pupil. In addition, microperimetry (MAIA or MP-1) was performed to determine the location of the PRL; the data from the microperimetry was correlated with the findings from the optic nerve head mapping task to determine the PRLs distance from the

physiological fovea (Chapter 2, Figure 1). Microperimetry measures the threshold sensitivity of the retina; this allows the clinician to determine ones central retinal function (Molina-Martín 2017). In the current study, we use the MAIA microperimeter to determine the retinal location, sensitivity, and function of the PRL. The subject's task throughout the current protocol was to move their eyes to keep the target, a fixation dot, located at various eccentricities of the screen clear and visible without covering it with the central scotomas they experience in their central vision (Chapter 2, Figure 4). In this testing situation, the target position on the screen was changed to various eccentricities of the test screen, to assess how the observer was able a) to fixate on a stationary target at different screen locations without their central vision loss obstructing their view of the target and b) make saccadic eye movements to an abruptly displaced target at the various eccentricities of the screen (Chapter 2, Figure 4). Participants used a peripheral, non-foveal, location, as required by their bilateral central scotomas, to perform a letter identification task; we assessed the relationship between fixation stability, retinal location of the PRL and contrast sensitivity under binocular viewing conditions.

In this second study, participants were patients at the Janet LaBreck Low Vision Rehabilitation Center at the New England College of Optometry Center for Eye Care. Given that all participants in this phase have bilateral central scotomas, no shutter glasses to simulate central scotomas were used, therefore spectacle correction was permitted for use during this phase of the study. Participants used the same method used to establish the location of their optic nerve and PRL, as demonstrated in Chapter 2, Figure 2. Once that was completed, the next task was to look towards a target; the

goal was to maintain visibility of the target using their monocular and/or binocular PRL and not their fovea due to loss of their central visual field caused by the central scotomas. The target moved to three different eccentricities on the screen (4 degrees, 8 degrees, and 16 degrees from the center) creating a symmetrical 9-point grid of assessment points (Chapter 2, Figure 4). The target stimulus moved to each of the mentioned eccentricities in a randomized order to eliminate practice effects.

Secondly, the characteristics of PRLs were assessed; we tested letter detection (a measure of acuity and contrast sensitivity) in both the best and worst positions of gaze; these locations were determined by 9 positions of gaze (Chapter 2, Figure 4) where both the largest and smallest BCEA determine the areas of best fixation stability (smallest BCEA) and worst fixation stability (largest BCEA). We used these two different testing locations to determine whether these functional outcomes were dependent on the stability of fixation when using a PRL. For acuity and contrast sensitivity, the quickCSF method (Lesmes, Lu et al. 2010) was used such that participants were required to report the identity of a band-pas filtered target letter – a staircase adjusted the size and contrast of the next letter based on the participants' responses (Lesmes, Lu et al. 2010)(Chapter 2, Figure 5). This contrast detection task using the quickCSF algorithm controls the contrast and font size to maximize the expected information gain in each trial and updates the current parameters of the CSF (Lesmes, Lu et al. 2010). Participants' PRL position and gaze position (as measured by the gaze-contingent method above) was recorded throughout the contrast sensitivity task.

Contrary to the previous pilot study, the data collected from the word non-word task, the measurement of reading ability and word recognition, was not used in the

analyses for the study in participants with established bilateral central vision loss. The task was performed on five of the six reported participants. Through our data analysis, we determined that we could not draw any statistical inferences or conclusions via the data collected. Participants with bilateral macular disease, when compared to normally sighted individuals with simulated central vision loss, were unable to adequately perform the task. See Appendix 1, which demonstrates the d prime, or sensitivity index, which separates appropriate performance of the task from inappropriate performance of the task.

Data Analysis:

Throughout each trial, and across both proposed studies, we recorded eye position data at 1000Hz per eye. These data provided a quantitative measurement of fixation stability. An ANOVA was used to evaluate the difference between means amongst the various testing groups. Under the binocular testing conditions, the various scotoma sizes and combinations that participants presented with, and as mapped by MAIA microperimetry, were compared to the various testing outcome measures (including area under the curve, contrast sensitivity, and acuity).

Results

Participants

There were 10 participants that enrolled for Phase 2 of this study. Each participant was recruited from the Janet LaBreck Low Vision Rehabilitation Center at the New England College of Optometry Center for Eye Care; 5 participants completed data

collection for the monocular component of this study and 6 participants completed data collection for the binocular component of this study and were included in the data analyses.The average age of the participants was 64 years old, ranging from 19-91. All participants had bilateral central vision loss due to macular disease, both inherited and age-related. Participants were excluded if they had a best corrected distance and/or near visual acuity (with and/or without correction) worse than 20/300 due to limitations of the testing screen size. Participants also completed a MiniMental State Examination cognitive assessment; any participants with scores less than 24 were excluded from this study. Lastly, any participants with less than 40 degrees of visual field, in other words, peripheral visual field loss, were also excluded from the current study.

Fixation Stability Outcomes: Monocular and Binocular

There were 10 participants in Phase 2 of the study; 5 participants completed data collection for the monocular component of this study and 6 participants completed data collection for the binocular component of this study and were included in the data analyses.

There was no statistically significant effect of fixation position on the bivariate contour ellipse area (BCEA) outcome. In other words, there was no particular point on the tested nine-point grid that elicits the smallest or largest BCEA area consistently. This held true for both monocular and binocular testing conditions. There was a trend observed of better fixation stability noted when using the better-seeing eye (monocular) compared to when using both eyes together ($p = .075$) (Figure 12).

There was no statistically significant effect of fixation stability (BCEA) and performance outcomes on the other measured visual outcomes including the area under the curve, contrast sensitivity, and high-frequency cutoff (best detectable acuity).

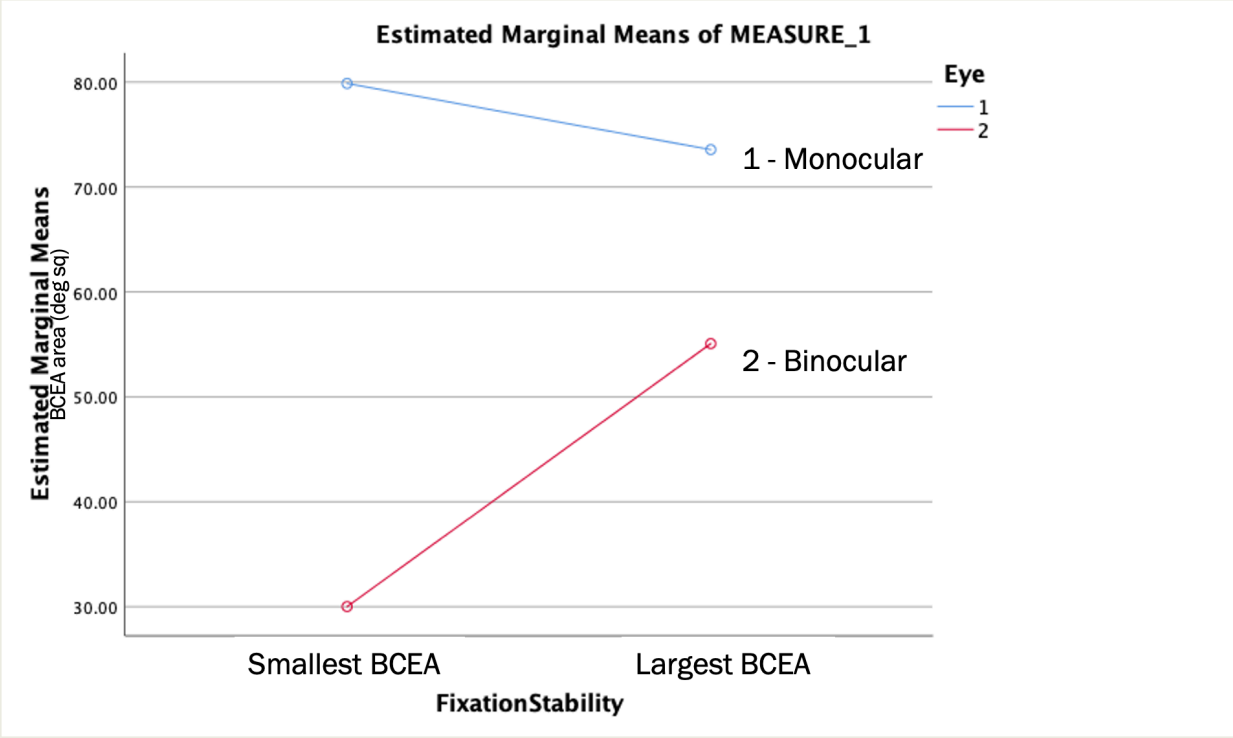


Figure 12. Fixation Stability; Better Seeing Eye versus Binocular. There was a trend observed of better overall fixation stability (both at the location of the smallest BCEA and the location of the largest BCEA from the nine-point grid fixation task) noted when using the better-seeing eye (Eye: 1) compared to when using both eyes together (Eye: 2) ($p = .075$).

Binocular Fixation Stability Outcomes: Trial by Trial Variation

The same 6 participants who partook in the tasks and analyses above were included in the current data analyses. The binocular data collected in performing the CSF task was including in the current analyses.

The CSF task included the completion of 50 individual trials that varied in time, contrast and letter size; each trial subsequently produced a single estimate of fixation stability. Each subject produced an average estimate of fixation stability over the 50 trials associated with the CSF task both in the position associated with the best fixation stability, smallest BCEA, and the position associated with the worst fixation stability, largest BCEA as determined by the nine-point grid fixation task. In the current analyses, instead of comparing mean BCEA for the CSF task, each individual trial was compared by participant and overall as a group. By using the eye tracker to monitor fixation stability only during each trial presentation and duration, we eliminated the noise or eye movement and fixation data that may have impacted the data in between trials when there was no target to fixate on or task to perform.

There was a statistically significantly negative association between the worse fixation stability, or larger BCEA area, and the mean area under the curve (AULCSF) ($p = .01$) (Figure 13). There was also a trending negative association between the best fixation stability, or smaller BCEA area, and the mean area under the curve (AULCSF) ($p = .08$) (Figure 13).

There was a statistically significantly negative association between the worse fixation stability, or larger BCEA, and the resulting CSF acuity (in cpd) ($p = .03$) (Figure 13). There was also a statistically significantly negative association between the best fixation stability, or smaller BCEA, and the resulting CSF acuity (in cpd) ($p = .01$) (Figure 13).

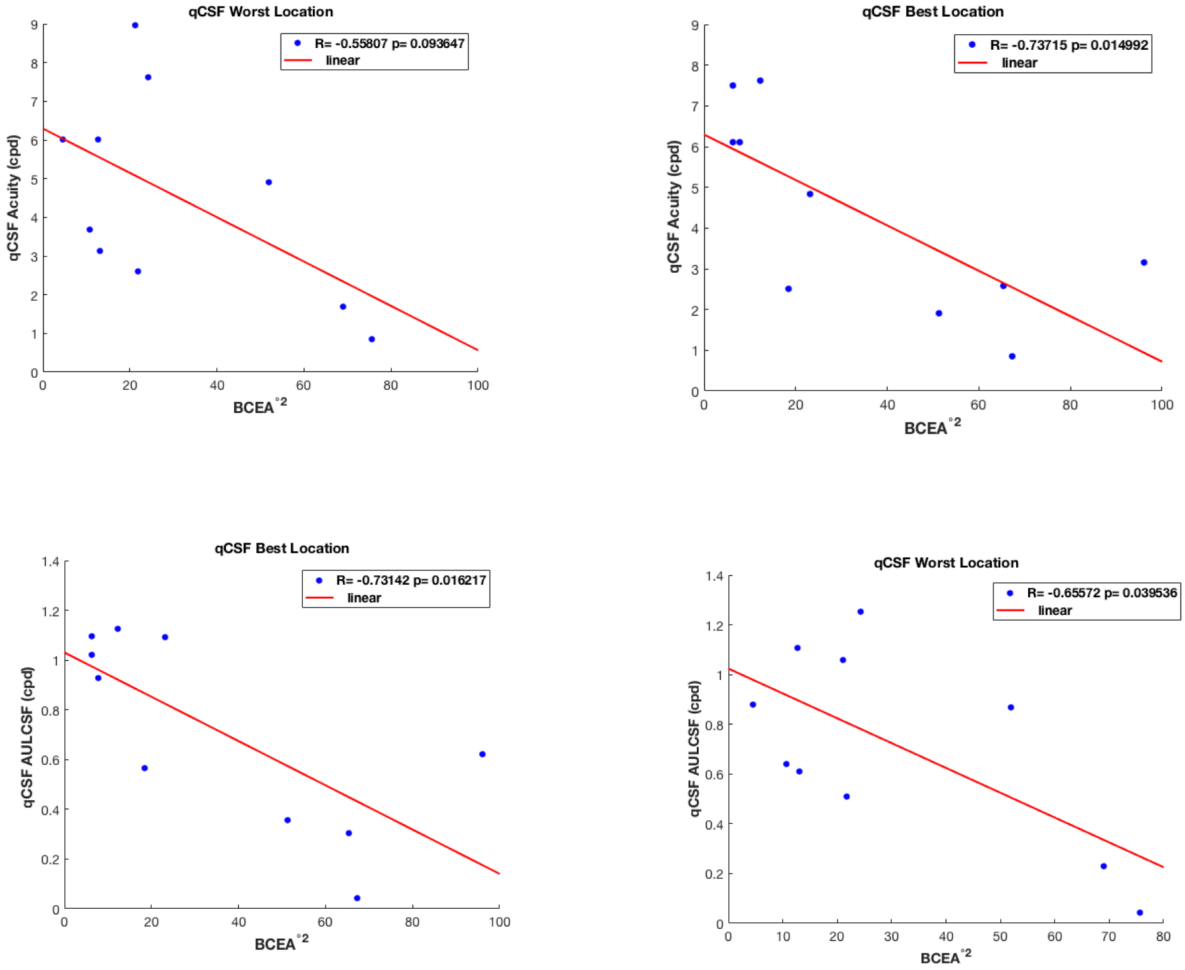


Figure 13. Binocular Trial by Trial Fixation Stability Outcomes. Fixation stability was negatively associated with both CSF outcomes (acuity in cpd and area under the curve (AULCSF)) for both binocular testing locations [location of best fixation stability (smallest BCEA) and location of worst fixation stability (largest BCEA)].

Contrast Sensitivity Function (CSF) Outcomes: Monocular and Binocular

The same 6 participants of a total possible enrolled 10 completed data collection for the monocular and binocular testing conditions for the CSF task of Phase 2 of the study. There was no statistically significant effect of viewing (whether monocular or binocular) on all CSF outcomes (i.e. area under the curve, contrast sensitivity, and high-frequency cutoff (best detectable acuity)). That is to say that the CSF outcomes did not

differ whether participants performed the task with the better seeing eye alone versus with both eyes.

Of note, a trend was noted such that the high-frequency cutoff (i.e. the best detectable acuity) was better when tested monocularly with the better seeing eye alone versus when tested binocularly ($p = .062$).

Binocular MAIA and CSF Outcomes: Correlations

Of the total 10 participants recruited for this phase of the study, 6 completed the data collection for the binocular component of the current study. Table 1 displays the CSF outcomes (acuity in cycles per degree (cpd), acuity in logMAR, area under the curve) in addition to the patients entering Snellen/ETDRS logMAR acuity and the MAIA microperimeter outcomes.

The visual field (VF) score is based on the MAIA microperimetry. Each data point in every participants' monocular MAIA was compared to its corresponding point in the other eye for that same participant; any dB value at these corresponding points greater than or equal to 10 dB was considered a "seen" point. The 10-dB cutoff point for a seen versus unseen retinal point was chosen given that a 10-dB target equates to a very bright light stimulus such that dB levels below it are associated with severe visual field deficits and profound sensitivity loss. The MAIA tested a total of 37 points; thus, the VF score equates the total number of binocularly seen corresponding points.

Subject ID	VF score	logMAR acuity (ETDRS)	CSF (AUL)	CSF acuity (cpd)	CSF acuity (logMAR)
1	28	0.6	1.039	7.537	1.00
2	1	1.0	0.266	2.131	1.15
3	35	0.5	0.589	2.829	1.05
4	37	0.5	0.566	3.074	1.00
5	37	0.5	0.986	5.429	0.85
6	7	1.1	1.101	6.763	0.70

Table 1. Binocular subject outcomes.

Among all six participants, the VF score and logMAR acuity (based on the ETDRS or Snellen chart at 6 meters) were significantly negatively correlated ($r = -.970$, $p = .001$). That is, the better performance on the VF score, or a higher number of binocularly seen points, correlated with a lower logMAR acuity (i.e. a better visual acuity). The CSF outcomes including the area under the curve and acuity (in both cycles per degree and its logMAR equivalent) were all highly correlated with one another: CSF area under the curve was positively correlated with CSF acuity in cycles per degree ($r = .945$, $p = .004$), CSF area under the curve was negatively correlated with CSF acuity in logMAR notation ($r = -.934$, $p = .006$), and lastly, CSF acuity in cycles per degree was highly negatively correlated with its equivalent finding converted to logMAR acuity ($r = -.992$, $p < .01$).

Of note, there was no significant correlation between logMAR acuity from Snellen/ETDRS and the comparable logMAR acuity determined by the CSF task (r = - .051, p = .923).

Monocular MAIA and CSF Outcomes: Correlations

Of the total 10 participants recruited for this phase of the study, 5 completed the monocular component of the current study for one or both of their eyes. Table 2 displays the CSF outcomes (acuity in cycles per degree (cpd), acuity in logMAR, area under the curve) in addition to the patients entering Snellen/ETDRS logMAR acuity, MAIA microperimeter outcomes, and PRL eccentricity as determined by the MAIA.

The visual field (VF) score is based on the MAIA microperimetry. Each data point in every participants' monocular MAIA with a dB value greater than or equal to 10 dB (a cutoff point such that dB levels below it is associated with severe visual field deficits) was considered a "seen" point. The MAIA tested a total of 37 points; thus, the VF score equates the total number of monocularly seen points.

Subject ID	**VF Score**	**logMAR acuity (ETDRS)**	**CSF (AUL)**	**CSF acuity (cpd)**	**CSF acuity (logMAR)**	**PRL eccentricity**
1-OD	1	1.00	0.451	3.498	0.95	5.695
1-OS	0	1.30	0.295	3.191	0.98	9.941
2-OD	8	0.60	0.452	2.808	1.05	5.994
2-OS	32	0.50	0.472	3.116	0.99	5.783
3-OD	33	0.50	0.559	3.881	0.89	4.429

3-OS	28	0.60	0.558	3.191	0.98	4.989
4-OS	24	0.60	0.657	3.191	0.98	N/A
5-OS	0	0.47	0.917	4.358	0.82	5.646

Table 2. Monocular subject outcomes.

Among all five participants, the VF score and logMAR acuity (based on the ETDRS or Snellen chart at 6 meters) were not significantly correlated ($r = -.659$, $p = .107$). The CSF outcomes including the area under the curve and acuity (in both cycles per degree and its logMAR equivalent) were all highly correlated with one another: CSF area under the curve was positively correlated with CSF acuity in cycles per degree ($r = .715$, $p = .046$), CSF area under the curve was negatively correlated with CSF acuity in logMAR notation ($r = -.721$, $p = .044$), and lastly, CSF acuity in cycles per degree was highly negatively correlated with its equivalent finding converted to logMAR acuity ($r = -.996$, $p < .01$). Monocular PRL eccentricity, as determined by MAIA microperimetry, was moderately positively correlated with monocular logMAR acuity (ETDRS/Snellen) ($r = .664$, $p = .104$); that is, a higher PRL eccentricity is associated with a higher logMAR acuity (i.e. a worse visual acuity).

Similar to that of the binocular analyses, there was no significant correlation between logMAR acuity from Snellen/ETDRS and the comparable logMAR acuity determined by the CSF task ($r = -.098$, $p = .817$).

Discussion

In participants with bilateral central vision loss due to macular disease, visual performance at the PRL does not differ under monocular viewing conditions versus

binocular viewing conditions. Though few conditions demonstrated slightly improved outcomes when performed monocularly with the better seeing eye versus when performed binocularly, both better fixation stability and high-frequency cutoff (best detectable acuity), these outcomes were not statistically significant.

That said, amongst both the binocular and monocular analyses, the lack of correlation between “same” measurements of distance visual acuity in logMAR from the ETDRS chart and visual acuity in logMAR from the CSF task may be explained by the different testing environments eliciting different responses. The ETDRS acuity measurement took place at a 2-meter testing distance, whereas in the setting of the CSF task, the resulting acuity is measured at 60 cm while wearing appropriate correction for that testing distance. At the 2-meter testing distance, participants may more readily use eccentric viewing to achieve this resulting acuity with significant impact of a large central scotoma on their distance vision – at a 60 cm testing distance, eccentric viewing may become more challenging as a central scotoma may provide a more significant negative impact on acuity by occupying more of the near visual area used. It is likely that the test distance and vergence angles of the subjects performing the CSF task at near could affect visual acuity and performance when compared to the acuity measured at distance while not performing a similar CSF-type task.

This raises the question of the impact of contrast sensitivity on the current outcomes. It is known that visual acuity does not determine contrast sensitivity, particularly at low and medium spatial frequencies which are what most everyday objects are composed of (Pardhan 1991). When the two eyes have equal individual contrast sensitivities, then the resulting binocular contrast sensitivity is greater, or better,

than each eyes' contrast sensitivity (Pardhan 1991). However, when the two eyes do not have the same individual contrast sensitivities, particularly when this contrast sensitivity loss is asymmetric between the two eyes, the resulting binocular contrast sensitivity is not greater than each eyes' contrast sensitivity alone, but instead, decreases to level worse than that of the monocular contrast sensitivity (Pardhan 1991). This same study has shown that at higher spatial frequencies, this effect of binocular contrast sensitivity being worse than the monocular contrast sensitivity is found (Pardhan 1991). This may confirm the findings of the current study suggesting that the monocular high-frequency cutoff (best detectable acuity), noted at the highest spatial frequency detectable by the participant, is slightly better under monocular viewing conditions rather than when viewed binocularly. Additionally, this same study found a high correlation between the binocular contrast sensitivity of their participants and their perceived visual disability (Pardhan 1991). This may also apply to the current study, given that the participants have bilateral central vision loss, and consequently, moderate to severe contrast sensitivity loss which impacts their performance of many activities of daily living not solely due to the loss of their central vision or decrease in visual acuity.

The current findings suggest that it is possibly the location of the preferred retinal locus (PRL) that contributes to the functional outcomes observed in those with bilateral central vision loss due to macular disease. It is generally assumed that the monocular PRL location is the same location of the PRL during binocular viewing (Tarita-Nistor, Eizenman et al. 2015). This same study found that there is no obvious shift in the PRL when switching from monocular viewing to binocular viewing conditions, confirming that the monocular PRL location and binocular PRLs fall on corresponding points (Tarita-

Nistor, Eizenman et al. 2015). Additionally, a study by Hassan and colleagues that assessed the location of the PRL before and after eccentric viewing training found that, though fixation stability did not change over time, the location of the PRL used to perform any given task did change from its original position (Hassan, Ross et al. 2019). This is particularly important when we look at the observed outcome measures of the current study and the lack of statistical significance under binocular viewing conditions prior to evaluating the BCEA on a trial by trial basis; this suggests that when performing tasks with both eyes open, overall or when assessed as a mean of performance throughout the whole task, the stability of fixation (BCEA), whether larger/less stable or smaller/more stable, does not contribute to the performance of the task. On the other hand, the trial-by-trial variation findings of the current study suggest that it is not the overall BCEA for the entire duration of the task that contributes to the performance of the task, but rather the BCEA (or fixation stability) at the time of each individual trial that significantly impacts performance outcomes. The current finding suggests that it is not about the location, eccentricity, or gaze direction that a task is being performed at, but rather the stability in that exact moment while they're doing that task that significantly impacts performance.

The clinical implications of the current findings suggest that binocularly, as one tends to view and navigate their environment, fixation stability does determine how one would perform on a multitude of tasks of daily living. It is the fixation stability in precise moments of performing said activities, regardless of gaze direction, that determines how one would perform on a multitude of tasks of daily living, something that differs from monocular findings.

Chapter 4 – General Conclusions

Central vision loss remains the leading cause of visual impairment, or low vision, in developed countries (Congdon, O'Colmain et al. 2004). Specifically, macular disease impacts 6% of people over 50 and at least 30% of those over 75 (Ferris III 1983); its incidence and prevalence are increasing quickly due to the increasing age and lifespan of the population (Evans and Wormald 1996). Central vision loss impacts both ones' quality of life and the ability to perform activities of daily living such as reading (Legge, Rubin et al. 1985), face recognition (Peli, Lee et al. 1994), watching television (Wolffsohn and Cochrane 1999), driving and mobility (Lovie-Kitchin, Mainstone et al. 1990), and is associated with elevated levels of depression (Brody 2011) and increased falls (Zheng 2012).

In central vision loss cases, as is the case in macular disease, a person is forced to use low-resolution peripheral retina and may adopt one or more preferred retinal loci (PRL). Generally, it is believed that the new pseudo-fovea, or PRL, is adopted in one specific retinal location and used to perform a multitude of tasks, becoming analogous to the one central fovea normally sighted individuals use to perform activities of daily living.

It has also been observed that in cases of bilateral central vision loss, binocular PRLs are not symmetric in the retinas. That is, the binocular PRLs can be on non-corresponding points, both in distance and direction from the scotoma, of the retina (Schuchard 2005). Tarita-Nistor and colleagues found differing results such that there is no obvious shift in the PRL when switching from monocular viewing to binocular viewing conditions, showing that the monocular PRL location and binocular PRLs do fall on

corresponding points (Tarita-Nistor, Eizenman et al. 2015). The available information in the literature on the PRL location at this time still varies, leading for a need for more exploration of these findings. Though we do understand many of the characteristics of the PRL, we understand little about how a PRL is selected and where on the retina it is located, as it is not often the area of best remaining visual acuity (Chung 2013), nor is its location optimal for reading or other visually mediated tasks as one would expect it to be.

The current study demonstrated differing findings between monocular visual performance of the PRL and binocular visual performance of the PRL. Interestingly, the findings noted in normally sighted individuals with simulated central vision loss did not translate into the same visual outcomes and visual performance in participants with bilateral central vision loss due to macular disease. It appears that in cases of simulated central vision loss, the visual outcomes are much as previous literature has suggested: the larger scotoma conditions, both monocular and binocular, demonstrated worse visual outcomes. That being said, these findings were not noted in participants with bilateral central vision loss due to macular disease. In the latter group, monocular and binocular visual outcomes did not differ significantly from one another; instead, it was the BCEA, or the measure of fixation stability under both monocular and binocular viewing conditions, that significantly impacted visual performance throughout the current study.

Previous literature has examined PRL characteristics and oculomotor rehabilitation under monocular viewing, yet we experience our world binocularly, rendering clinical implications difficult. The current study aimed to address these issues by exploring the

properties of the PRL under both monocular viewing conditions and binocular viewing conditions.

More specifically, we examined PRL characteristics in various gaze positions; we assessed PRL positions and characteristics (PRL size, PRL location, fixation stability/BCEA) in normally sighted participants with simulated central scotomas as well as in participants with bilateral central scotomas due to macular disease. Secondly, we assessed the relationship between fixation stability, retinal location of the PRL and visual performance in normally sighted participants with simulated central scotomas as well as in participants with bilateral central scotomas due to macular disease. Thirdly, the comparison between outcomes when assessed under monocular viewing conditions versus binocular viewing conditions was evaluated in both normally sighted participants with simulated central scotomas as well as in participants with bilateral central scotomas due to macular disease.

It has been observed that in binocular central vision loss, the overall resulting scotoma (as it impacts binocular vision) is smaller than each eyes' individual scotoma size for the majority of patients (Ross, Goldstein et al. 2013). The current study obtained results that may contribute to the latter studies' findings. Amongst the first group of participants, normally sighted individuals with simulated gaze-contingent central scotomas, monocular outcomes demonstrated statistically significantly worse performance as scotomas size increased. That is, the larger the monocular simulated scotoma, the worse their performance on contrast sensitivity and word identification measures. When those same tasks were performed binocularly, these same participants did not demonstrate any trend towards worse outcomes regardless of the

various combinations of simulated scotomas, from both small to both large and any combination in between. In our second group, in participants with established bilateral central vision loss due to macular disease, these same findings were not observed. Though the best detectable acuity was slightly better when viewed monocularly versus binocularly, there was no significant effect of scotoma size on the performance of the contrast sensitivity task and its outcomes. The current findings, particularly in those with bilateral central vision loss due to macular disease, demonstrate that performance outcomes may vary greatly when performed binocularly compared to how we expected them to perform based on the associated monocular results.

Most studies in the current literature evaluate the performance of such tasks under monocular conditions and generalize the findings to apply under binocular viewing as well. That is, it is suggested that the performance of binocular tasks is worse under binocular viewing when both central scotomas are large. The current study suggests otherwise: binocular performance of various outcome measures is not dependent on scotoma size, or amount of central vision loss, as it is under monocular conditions. It has been observed that in binocular central vision loss, the overall resulting scotoma (as it impacts binocular vision) is smaller than each eyes' individual scotoma size for the majority of patients (Ross, Goldstein et al. 2013). It may be important to perform future studies of bilateral central vision loss due to macular disease under binocular viewing conditions to further evaluate the current outcomes.

Of the many properties that define the PRL, the most common involved the bivariate contour ellipse area (BCEA). The bivariate contour ellipse area (BCEA) defines an area of retina that surrounds the PRL and delineates its functional limits associated

with fixation (Crossland, Engel et al. 2011). To assess fixation stability, we look at the bivariate contour ellipse area (BCEA), which encompasses 68% of the data points (Crossland, Dunbar et al. 2009). Generally speaking, a smaller BCEA indicates more stable fixation, as seen with the normal fovea, and a larger BCEA indicates less stable fixation, as commonly seen in those with central vision loss. Fixation stability is known to be poor for those with central vision loss, such that there are more micro fixations and eye movements seen to hold fixation when using any other retinal area rather than the anatomical fovea (Girish 2014). The current study evaluated fixation stability under both monocular and binocular viewing conditions and evaluated the visual performance at eccentricities associated with better fixation stability, i.e. small BCEA, and worse fixation stability, i.e. larger BCEA.

In both study groups, both normally sighted individuals with simulated central scotomas and individuals with bilateral central vision loss due to macular disease, under monocular conditions there was no statistically significant effect of fixation stability on the performance of visual tasks. In other words, better fixation stability, and therefore a smaller BCEA, was not associated with better performance of the current visual tasks when assessed with only one eye open. In the second study group, participants with bilateral central vision loss due to macular disease, it is shown that binocular fixation stability, when evaluated for each individual trial duration, significantly impacts visual functional outcomes. It is the binocular fixation stability, rather than the gaze direction, that impacts performance of the current visual tasks.

In the current study, the locations on the nine-point grid that elicited the smallest BCEA and largest BCEA were used as the locations where the subsequent visual tasks,

the quickCSF and Word Non-Word tasks, would be performed. One theory of the current data suggests that fixation stability differs in a fixation task and a task that is more visually demanding. In other words, it may be that the locations selected as the "best" fixation stability and "worst" fixation stability from the fixation task were not actually the locations of the "best" or "worst" fixation stability during the performance of the subsequent visual tasks. This is supported by the trial variation outcomes which demonstrated that, regardless of gaze direction as determined by this nine-point grid fixation task, fixation stability did significantly impact binocular functional visual outcomes. The clinical implications of the current findings suggest that binocularly, as one tends to view and navigate their environment, fixation stability does determine how one would perform on a multitude of tasks of daily living instead of gaze direction or PRL location. It may be that the location of the PRL does not determine the success in performing activities of daily living, and therefore, training improved fixation stability, instead of a PRL location, can be more successful in those with central vision loss.

Several lines of evidence stress the importance of eye movement control for visual function: central vision loss is associated with a decreased size of forward saccades, an increased number of regressions (Crossland, Dunbar et al. 2009), and elevated fixation instability (Schuchard 2005); these oculomotor issues are correlated with deficits in the performance of a wide range of tasks including reading (McMahon, Hansen et al. 1993) and face recognition abilities (Seiple, Rosen et al. 2013). Additionally, rehabilitation data show that eye movement training may help people to read more effectively (Seiple, Szlyk et al. 2005). The findings of the current study support these findings, such that smaller or larger BCEA, i.e. better or worse fixation

stability, significantly impact the performance of these visually demanding tasks apart from gaze direction.

In conclusion, the results from this study set the stage for many future studies to evaluate the impact of eccentric viewing and the PRL due to bilateral central vision loss caused by macular disease. It is evident that the current findings when evaluated binocularly vary greatly from those evaluated monocularly. No matter the severity of the central vision loss, it impacts both ones' quality of life and the ability to perform activities of daily living such as reading (Legge, Rubin et al. 1985), face recognition (Peli, Lee et al. 1994), watching television (Wolffsohn and Cochrane 1999), driving and mobility (Lovie-Kitchin, Mainstone et al. 1990), and is associated with elevated levels of depression (Brody 2011) and increased falls (Zheng 2012). In addition to these difficulties in tasks of daily living, macular disease and the consequent central vision loss shows strong correlations with other conditions associated with aging. The clinical implications of the current study suggest that it is the control of eye movements, i.e. fixation stability, that is important in eccentric viewing training rather than the training of the appropriate PRL location that may elicit the best possible outcomes on visual tasks and various activities of daily living.

References:

Aguilar, C. C., E. (2011). "Gaze-contingent simulation of retinopathy: Some potential pitfalls and remedies. ." Vision Research **51**(9): 997-1012.

Arango, T. (2019). "Binocular PRL Characteristics in Central Vision Loss. (Unpublished doctoral dissertation)." Northeastern University. **Boston, MA, USA.** .

Arango, T., D. Yu, Z. L. Lu and P. J. Bex (2020). "Effects of Task on Reading Performance Estimates." Frontiers in Psychology **11**.

Brody, B. L. (2011). "Depression, visual acuity, comorbidity and disability associated with age related macular degeneration " Ophthalmology **108**: 1893-1900.

Chan, T., D. S. Friedman, C. Bradley and R. Massof (2018). "Estimates of incidence and prevalence of visual impairment, low vision, and blindness in the united states." JAMA Ophthalmology **136**(1): 12-19.

Chung, S. T. and J. Bernard (2013). Does the location of the PRL correspond to the retinal location with the best acuity? Association for Research in Vision Science and Ophthalmology. Seattle.

Chung, S. T. L. (2013). "The Glenn A. Fry Award Lecture 2012: Plasticity of the visual system following central vision loss." Optometry And Vision Science: Official Publication Of The American Academy Of Optometry **90**(6): 520-529.

Congdon, N., B. O'Colmain and C. C. Kalver (2004). "Causes and prevalence of visual impairment amoung adults in the United States." Archives of Ophthalmology **122**(4): 477-485.

Crossland, M. D., L. E. Culham, S. A. Kabanarou and G. S. Rubin (2005). "Preferred retinal locus development in patients with macular disease." Ophthalmology **112**(9): 1579-1585.

Crossland, M. D., H. M. Dunbar and G. S. Rubin (2009). "Fixation stability measurement using the MP1 microperimeter." Retina **29**(5): 651-656.

Crossland, M. D., S. A. Engel and G. E. Legge (2011). "THE PREFERRED RETINAL LOCUS IN MACULAR DISEASE: Toward A Consensus Definition." Retina **Epub ahead of print**: 1-6.

Cummings, R., S. Whittaker, G. R. Watson and J. Budd (1985). "Scanning characters and reading with a central scotoma." American Journal of Optometry and Physiological Optics **62**: 833-843.

Duret, F. I., M. Safran, AB (1999). "Combined use of several preferred retinal loci in patients with macular disorders when reading single words." Vision Research **39**(16).

Evans, W. and R. Wormald (1996). "Is the incidence or registrable age-related macular degeneration increasing." British Journal of Ophthalmology **80**: 9-14.

Ferris III, F. L. (1983). "Senile macular degeneration: review of epidemiologic features." Am. J. Epidemiol. **118**: 131-151.

Girish, K. C., Susana T. L. (2014). "Characteristics of Fixational Eye Movements in People With Macular Disease." Invest. Ophthalmol. Vis. Sci. **55(8)**: 5125-5133.

Goldstein, J. E., R. W. Massof, J. T. Deremeik, S. Braudway, M. L. Jackson, B. Kehler, S. Primo and J. Sunness (2012). "Baseline traits of low vision patients served by private outpatient clinical centers in the United States." Archives of Ophthalmology **130**(8): 1028-1037.

Hassan, S., N. C. Ross, R. Massof and J. A. Stelmack (2019). "Changes in the Properties of the Preferred Retinal Locus with Eccentric Viewing Training " Optom Vis Sci **96**(2): 79-86.

Kabanarou, S. A. and G. S. Rubin (2006). "Reading with central scotomas: is there a binocular gain?" Optometry and Vision Science **83**(11): 789-796.

Legge, G. E., G. S. Rubin, D. G. Pelli and M. M. Schleske (1985). "Psychophysics of reading II. Low vision." Vision Research **25**(2): 253-266.

Lesmes, L. A., Z. L. Lu, J. Baek and T. D. Albright (2010). "Bayesian adaptive estimation of the contrast sensitivity function: the quick CSF method." J Vis **10**(3): 17 11-21.

Liu, R. K. M. (2016). "Integrating oculomotor and perceptual training to induce a pseudofovea: A model system for studying central vision loss. ." Journal of Vision Impairment and Blindness **16**(6): 10.

Lovie-Kitchin, J., J. Mainstone, J. Robinson and B. Brown (1990). "What areas of the visual field are important for mobility in low vision patients?" Clinical Vision Sciences **5**: 249-263.

McFadzean, R., D. Brosnahan, D. Hadley and E. Mutlukan (1994). "Representation of the visual field in the occipital striate cortex." British Journal of Ophthalmology **78**: 185-190.

McIlreavy, L., J. Fiser and P. J. Bex (2013). "Impact of Simulated Central Scotomas on Visual Search in Natural Scenes." Optom Vis Sci **89(9)**: 1385-1394.

McMahon, T. T., M. Hansen, J. A. Stelmack, P. Oliver and M. A. Viana (1993). "Saccadic eye movements as a measure of the effect of low vision rehabilitation on reading rate." Optometry and Vision Science **70**: 506-510.

Medler DA, B. J. (2005.). "MCWord: An On-Line Orthographic Database of the English Language.", from http://www.neuro.mcw.edu/mcword/. .

Molina-Martín, A., Piñero, D. P. & Perez-Cambrodí, R. J. (2017). "Normal values for Microperimetry with the MAIA Microperimeter: Sensitivity and fixation analysis in healthy adults and children. ." European Journal of Ophthalmology **27**(5): 607-613.

Nilsson, U., C. Frennesson and S. Nilsson (2003). "Patients with AMD and a large absolute central scotoma can be trained successfully to use eccentric viewing training, as demonstrated in a scanning laser ophthalmoscope." Vision Research **43**: 1777-1787.

Norton, D. and L. Stark (1971). "Scanpaths in saccadic eye movements while viewing and recognizing patterns." Vision Research **11**(9): 929-942.

Pardhan, S. a. G., J. (1991). "The Importance of Measuring Bincoulat Contrast Sensitivity in Unilateral Cataract " Eye **5**: 31-35.

Peli, E., E. Lee, C. L. Trempe and S. M. Buzney (1994). "Image-Enhancement for the visually-impaired - the effects of enhancement on face recognition." Journal of the Optical Society of America **11**: 1929-1939.

Pidcoe, P. E. and P. A. EWetzel (2006). "Oculomotor tracking strategy in normal subjects with and without simulated scotoma." Investigative Ophthalmology & Visual Science **47**(1): 169-178.

Randall, H., D. Brown and L. Sloan (1966). "Peripheral visual acuity." Archives of Ophthalmology **75**: 500-504.

Ross, N., J. Goldstein and R. Massof (2013). "Association of Self-reported Task Difficulty with Binocular Central Scotoma Locations." Investigative Ophthalmology & Visual Science **54**(15): 2188-2188.

Schira, M., T. CW, M. Brakespear and B. Spechar (2009). "The foveal confluence in human visual cortex." Journal of Neuroscience **29**: 9050-9058.

Schuchard, R. A. (2005). "Preferred retinal loci and macular scotoma characteristics in patients with age-related macular degneration." Canadian Journal of Ophthalmology **40**(3): 303-312.

Seiple, W., R. B. Rosen and P. M. Garcia (2013). "Abnormal fixation in individuals with age-related macular degeneration when viewing an image of a face." Optometry and Vis. Science **90**: 45-56.

Seiple, W., J. P. Szlyk, T. McMahon, J. Pulido and G. A. Fishman (2005). "Eye-movement training for reading in patients with age-related macular degeneration." Investigative Ophthalmology & Visual Science **46**(8): 2886-2896.

Seiple, W. H. and J. P. Szlyk (2004). "Eye Movement Training for Reading in Patients with Age-Related Macular Degeneration." Invest. Ophthalmol. Vis. Sci. **45**(5): 5443-.

Skavenski, A., C. Acocella, S. Heinen and A. Witkofsky (1994). Patterns of eye movement adaptation to foveal lesions in adult primates. Contemporary Ocular Motor and Vestibular Reseach: A Tribute to David A. Robinson; International Meeting Eibsee, 1993. A. F. Fuchs. Stuttgart; New York, Thieme Med. Publishers**:** 134-141.

Stelmack, J. A. (1991). "Low Vision Program: Central Blind Rehabilitation Center." Journal of Vision Impairment and Blindness **5**(3): 19-24.

Stelmack, J. A., R. W. Massof and T. R. Stelmack (2004). "Is there a standard of care for eccentric viewing training?" Journal of Rehabilitation Research and Development **41**(5): 729-738.

Tarita-Nistor, L., M. Eizenman, N. Landon-Brace, S. N. Markowitz, M. J. Steinbach and E. G. Gonzalez (2015). "Identifying Absolute Preferred Retinal Locations during Binocular Viewing." Optom Vis Sci **92**(8): 863-872.

Timberlake, G. T., M. A. Mainster, E. Peli, R. A. Augliere, E. A. Essock and L. E. Arend (1986). "Reading with a macular scotoma I. Retinal location of scotoma and fixation area." Investigative Ophthalmology & Visual Science **27**(7): 1137-1147.

Trauzettel-Klosinski, S., C. Dieling and B. Pietsch (2003). "The influence of visual field defects and other clinical parameters on reading performance: A retrospective study in a low vision population." Visual Impairment Research **5**(2).

Van de Velde, F. J. (1997). "Quantitative SLO microperimetry for clinical research in age related maculopathy." OSA TOPS **11**: 42-47.

Von Noorden, G. K. and G. Mackensen (1962). "Phenomenology of eccentric fixation." American Journal of Ophthalmology **53**: 642-660.

Wallis, T., C. Taylor, J. Wallis, M. L. Jackson and P. J. Bex (2014). "Characterization of field loss based on microperimetry is predictive of face recognition difficulties." Investigative Ophthalmology & Visual Science **55(1)**: 142-153.

Watson, G. R., R. A. Schuchard, W. R. De l'Aune and E. Watkins (2006). "Effects of preferred retinal locus placement on text navigation and development of advantageous trained retinal locus." Journal of Rehabilitation Research & Development **43**(6): 761-770.

White, J. M. and H. E. Bedell (1990). "The oculomotor reference in humans with bilateral macular disease." Investigative Ophthalmology and Vision Science **31**(6): 1149-1161.

Wolffsohn, J. S. and A. L. Cochrane (1999). "The changing face of the visually impaired: the Kooyong low vision clinic's past, present and future." Optometry and Vis. Science **76**: 747-754.

Zeifle, M. (1998). "Effects of display resolution on visual performance." Human Factors Soceity **40**: 554-568.

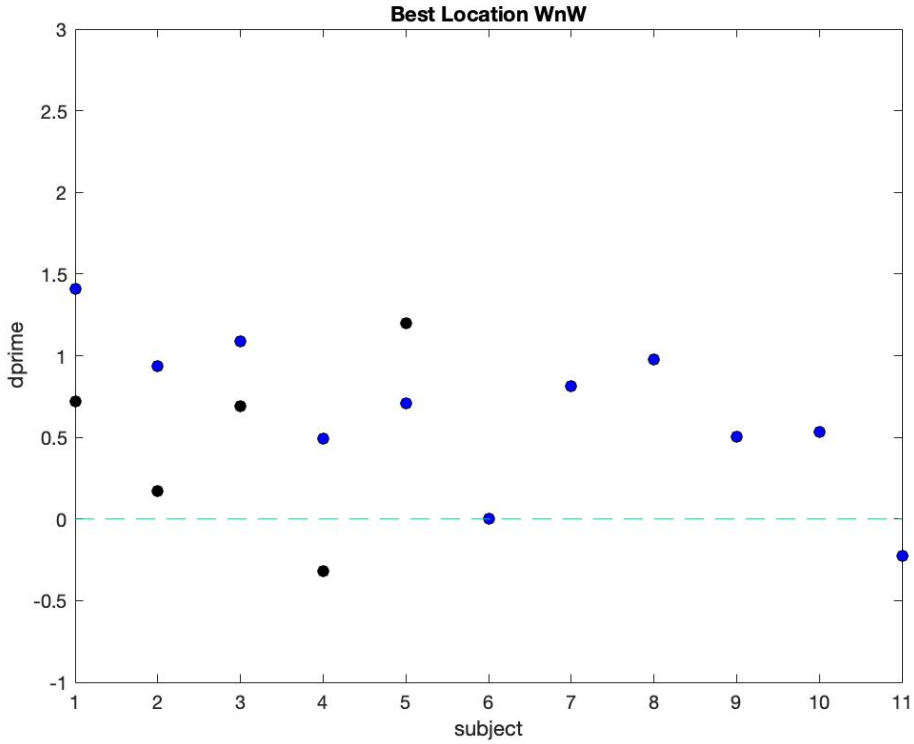
Zheng, D. D. (2012). "Increased mortality risk among the visually impaired: The roles of mental well-being and preventive care practices." Investigative Ophthalmology & Visual Science **53**: 2685-2692.

Appendix 1 – Word Non-Word in Patients

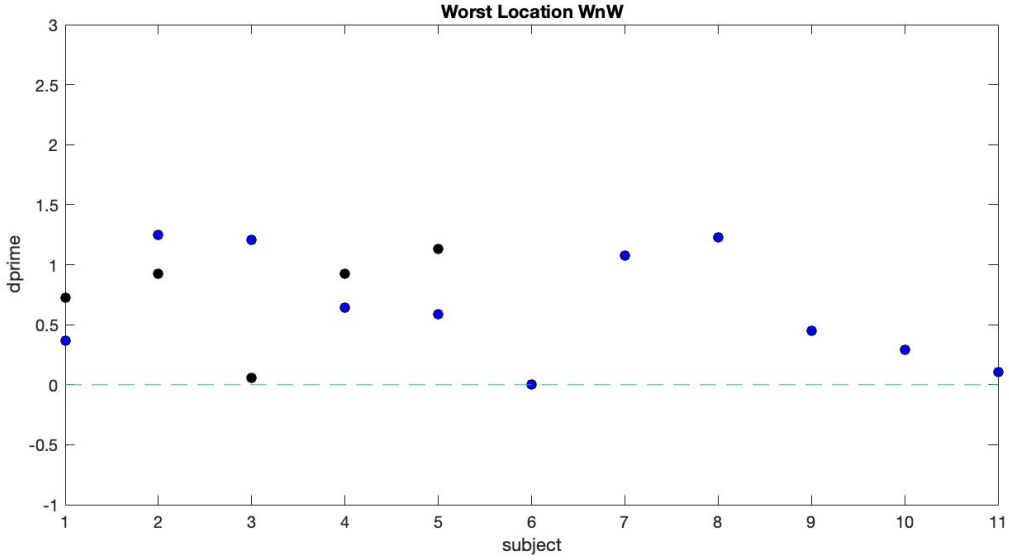
The data below demonstrate both the dprime and rate of hits and false alarms in both normally sighted individuals with simulated central scotomas (in blue) participants and in participants with bilateral central vision loss due to macular disease (in black). The dprime, or sensitivity index, separates appropriate performance of the task from inappropriate performance of the task. It was believed that perhaps the Phase 2 participants with bilateral central vision loss due to macular disease, rather than those with normal vision and simulated central scotomas, were unable to adequately perform the task, and therefore assumed each presented word or non-word was in fact a word. The current analyses of the dprime demonstrates that this was not the case; both participant groups performed equally well with regards to the dprime, that is, both groups assumed each presented trial was a word or not a word at approximately the same rate (Figures a and b).

We also evaluated the rate of hits and false alarms for both participant groups to determine whether this can explain the inadequate results in the participants with bilateral central vision loss due to macular disease. As demonstrated below, both groups did not differ in their rate of hits or false alarms in the performance of the Word Non-Word task (Figures c and d).

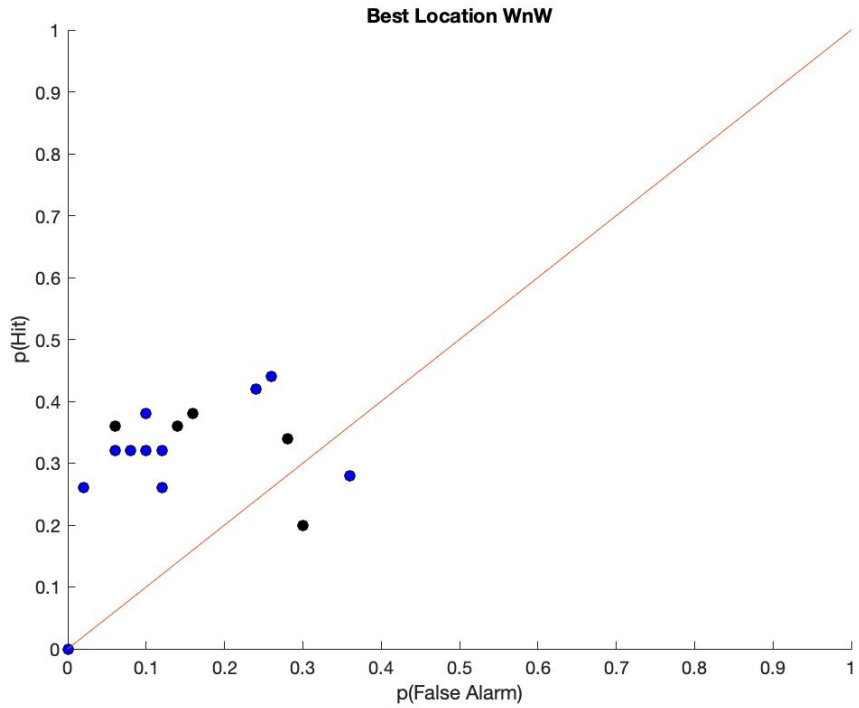
We conclude that the findings of the participants with bilateral central vision loss due to macular disease being unable to perform the task cannot be explained by either of the current theories. We determined that it may simply be that the Word Non-Word task was too difficult for that population. There was no testing bias, or bias in their responses as well.


Best Location WnW
dprime
subject
3
2.5
2
1.5
1
0.5
0
-0.5
-1
1
2
3
4
5
6
7
8
9
10
11

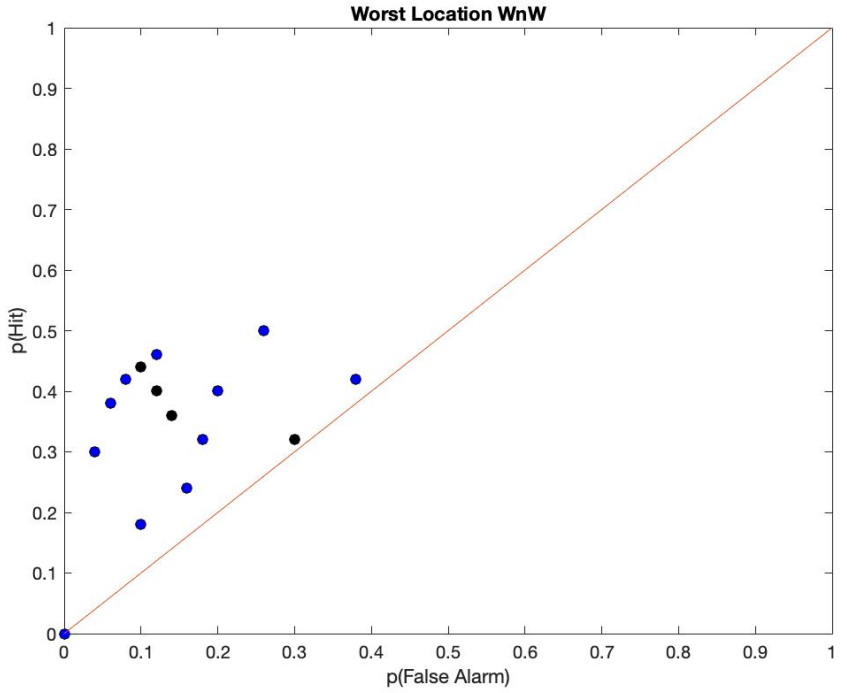
(a)


Worst Location WnW
dprime
subject
3
2.5
2
1.5
1
0.5
0
-0.5
-1
1
2
3
4
5
6
7
8
9
10
11

(b)



(c)



(d)

Figure 14. Word / Non-Word in Patients. Blue data points represent normally sighted individuals with simulated central scotomas and black data points represent participants with bilateral central vision loss due to macular disease.
(a and b) The dprime, or sensitivity index, separates appropriate performance of the task from inappropriate performance of the task. Both participant groups performed equally well with regards to the dprime, that is, both groups assumed each presented trial was a word or not a word at approximately the same rate. **(c and d)** Evaluation of the rate of hits and false alarms at the location with the smallest BCEA (c) and location with the largest BCEA (d): both groups did not differ in their rate of hits or false alarms in the performance of the Word Non-Word task.