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The Effect of Training on Eye Movement While Learning to Use a Non-Foveal Retinal Locus

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THE EFFECT OF TRAINING ON EYE MOVEMENTS WHILE LEARNING TO USE A NON-FOVEAL RETINAL LOCUS

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ABSTRACT

Vision is our most far-reaching sense. It allows us to quickly detect information about the environment and enhances our ability to interact with the world around us. Accordingly, many neural areas are devoted to obtaining, processing, and interpreting visual information. When vision is impaired through normal aging or disease processes, the functional implications for a person can be quite significant. This is particularly true when a person is deprived of high acuity, central vision.

Many people with bilateral central visual impairments learn to compensate for vision loss by adopting a viewing strategy that involves the use of the peripheral retina. This strategy allows them to detect detailed visual information with greater resolution than normally experienced with their condition. In some cases, individuals develop a new point of oculomotor reference called a preferred retinal locus (PRL) that is used in a manner similar to the defunct fovea for planning saccadic eye movements and fixating upon targets of interest.

How certain individuals develop and learn to effectively use a PRL is still debated. The process can take months to years to occur in a natural setting. Research has shown that individuals with healthy vision can be trained to develop a PRL in a relatively short period of time. Inducing a PRL in a controlled, laboratory setting offers the ability to continuously record and analyze eye movements as an individual experiences simulated central vision loss and learns to effectively utilize a PRL.

This dissertation aims to quantify how oculomotor behaviors change as a person undergoes training to use a PRL for everyday tasks. The first aim was to understand how peripheral vision training influences eye movements. The second aim was to understand how such eye movement changes relate to changes in behavior. This dissertation presents three main findings: 1) training results in improvements in all oculomotor metrics, 2) the rate of learning is similar for all oculomotor metrics but slightly faster for saccadic precision as compared to fixation stability, and 3) training results in increased accuracy on behavioral tasks. These results suggest that laboratory training may prove useful for patients who wish to accelerate their acquisition of a stable PRL for improved vision.

Keywords: eye movements, macular degeneration, visual training, fixation stability, saccadic precision, rate of learning

DEDICATION

This work is dedicated to my father Charles Eugene Vice, who inadvertently started me on this journey many years ago, and to my family Claire, Stella, and Vivian, who supported me along the way. May you never have to silence your footsteps again.

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LIST OF ABBREVIATIONS

AMD	Age-related macular degeneration
BCEA	Bivariate contour ellipse area
BN	Burst neurons
FEF	Frontal eye fields
KDE	Kernel density estimator
MD	Macular degeneration
OPN	Omnipause neurons
PPRF	Paramedian pontine reticular formation
PRL	Preferred retinal locus
RPE	Retinal pigmented epithelium
RSVP	Rapid serial visual presentation
SC	Superior colliculus
TRL	Trained retinal locus

CHAPTER 1

INTRODUCTION

The research described in this dissertation examines how human oculomotor control changes following impairment to the central visual system. Specifically, the outlined research provides data on how oculomotor control is learned when individuals with healthy vision undergo peripheral vision training. This approach was selected in order to categorize and describe eye movement behavior in a controlled setting as a person is first learning to use peripheral vision for everyday tasks. The results of this research will add to the existing evidence base to help guide clinical decision-making when working with persons with central visual impairment.

This chapter begins with a review of the relevant literature which motivates the work, starting with an overview of the anatomy and physiology of the human retina. This will be followed by a discussion on how visual functions ascribed to the retina are associated with eye movements, how eye movement control develops across the lifespan, and how eye movement control changes with central vision defects. Finally, common clinical and laboratory intervention strategies for developing an alternative retinal locus will be compared.

Overview of the Retina

The human retina is a light-sensitive layer of tissue approximately 0.3 mm thick that lines the back of the eye (Kolb, 1995). Its purpose is to receive light that has entered the eye and transduce it into neural electrical signals that are transmitted to and interpreted by the cortex. For light to reach the retina, it must pass through a series of focusing structures, along with the many layers of the retina itself until it reaches the light sensing photoreceptors are located in the outermost layer. The photoreceptors, known as rod and cone cells, are very different in terms of quantity, distribution, and function. Rod cells are numerous and outnumber cone cells by nearly 20:1, with some 120 million rods present in the retina (Kolb, 1995). As such, rods are present in a much higher density than cones throughout most of the retina. This relationship changes, however, as one approaches the center of the retina. This location contains a small (5.5 mm) but anatomically distinct region known as the macula (Yamada, 1969). Here, the ratio of rods to cones is much lower than what is found in the periphery. The center of the macula contains a small pit (1.5 mm) of densely packed cone cells and very few rod cells, known as the fovea centralis or 'fovea'. The center of the fovea, or foveola, is an avascular zone that contains only cone photoreceptors (Curcio et al., 1990). Rod and cone cells are specialized for different aspects of vision. Rod cells have low spatial acuity but are very sensitive to light. They are the primary contributor to scotopic vision which allows for vision in low-light environments. Cone cells are present in three different types, each of which responds with peak sensitivity to different wavelengths of light, allowing for color vision. Cone cells function best with higher levels of light and have higher spatial acuity, particularly in the fovea.

To understand how the retina contributes to visual function, it is important to consider how the photoreceptor cells are arranged. The high density of cone photoreceptor cells within the macula contributes to high-acuity vision. In particular, cone cells within the foveal region can have a one-to-one relationship with bipolar and retinal ganglion cells (Kling et al., 2019), which allows for fine spatial discrimination. The fovea and the macula make up approximately 5° and 17° of the visual field respectively. The area beyond the macula from 18° to 30° is termed paracentral or sometimes near-peripheral vision, although the entire inner 30° of the monocular visual field is commonly referred to as central vision (Spector, 1990).

Visual acuity decreases with eccentricity from the fovea, due to a combination of a decline in cone density (Curcio, 1990) and increasing convergence of photoreceptor signals onto retinal ganglion cells (Yu et al., 2018), and approaches one-sixteenth of its foveal value at 30° (Westheimer, 1987). The majority of vision, which is outside of the macular region, has less spatial discrimination but is more sensitive to movement and brightness (Hirsch & Curcio, 1989). The retinal zone beyond 30° up to 60° of the visual field is termed mid-peripheral vision with the remaining retinal area known as far-peripheral vision (Strasburger et al., 2011).

Eye Movements and Function

The visual functions ascribed to central and peripheral vision can be used to explain behavioral characteristics of human eye movements. Peripheral vision is responsible for detecting threats or unidentified objects of interest where a person is not directly looking, whereas central vision is responsible for inspecting those objects with

high acuity, providing information on shape, color, and other fine details (Wang & Cottrell, 2017). This is accomplished by directing the fovea, via head and eye movements, towards an object of interest. This response can be reflexive, as in the case of detecting surprise movement in the periphery, or voluntary, as when inspecting a photograph or reading. Quickly bringing the image of an object of interest onto the fovea involves a type of eye movement known as a saccade. Saccades are quick, conjugate eye movements that shift the fovea of both eyes from one location in the visual field to another. Once the fovea has been accurately positioned toward the object of interest, it is important that the direction of gaze remain steady to allow the visual system to inspect the target in greater detail. The time period when the eye is maintaining gaze at a single location is known as fixation. Normal, involuntary eye movements do occur even when attempting to maintain stable fixation (Ditchburn & Ginsborg, 1953). Slow drifts (slow motions of the eye) and microsaccades (or flicks) make up the majority of fixation time (Yarbus, 1967; Rolfs, 2009). Humans frequently produce saccades and fixations in rapid succession in order to investigate a visual scene or read a line of text with the fovea acting as a locus of fixation.

Neural control of saccadic eye movements arises from a complimentary pathway between an area of the frontal cortex known as the frontal eye fields (FEF) and the superior colliculus (SC) of the midbrain, both of which are important for initiation and accurate planning of saccadic eye movements (Sparks, 2002; Pouget, 2015; Skalicky, 2016). The FEF, which also plays a role in the allocation of covert attention, exerts influence on saccade production via projections to the ipsilateral SC, basal ganglia, and to the cerebellum by way of the pontine nuclei (Schall, 2009). The FEF contributes to both

the selection of targets of interest and the shifting of attention before initiation of an eye movement. The SC contains superficial layers which are retinotopically organized due to projections from retinal ganglion cells and deeper layers containing premotor neurons which project to gaze centers in the reticular formation of the brainstem (Berson & Stein, 1995; Liu et al., 2022). Each gaze center is associated with eye movements along a discrete axis: the paramedian pontine reticular formation (PPRF) which produces horizontal eye movements and the rostral interstitial nucleus which is responsible for vertical eye movements (Bender, 1980; Fukushima, 1991). In a typically developed visual system, stimulation of a particular location in the FEF or SC produces a saccadic eye movement in a specified direction and with sufficient amplitude such as to align the fovea with the location in visual space associated with the corresponding stimulus (Vernet et al., 2014). In many cases, this may be accompanied by a certain degree of head movement. However, the generation and contribution of head movements will not be further addressed in this discussion.

Neural commands which drive saccadic responses are typically velocity-driven commands, meaning they generate eye movement toward a new location but then they are terminated (Becker, 1989). Saccades are mostly ballistic, meaning that they are not modified between initiation and termination of movement (Costella & Woods, 2019). Once a saccade has been completed to a designated location, the addition of a tonic signal is required to hold the eye in the new position. This is because elastic forces from passive extraocular muscles and other connective tissues would cause the eye to drift away from the target location (Quaia et al., 2009; Schneider et al., 2013).

Describing fixational eye movements requires an understanding of reciprocally behaving neurons within the superior colliculi which are also associated with saccade generation: burst neurons (BN) and omnipause neurons (OPN). Signals from the rostral SC neurons relay excitatory signals through monosynaptic pathways to exciting OPNs for fixation. Tonic activity is maintained while the eyes are stationary on a target but stops immediately prior to and throughout a saccade (Cohen & Henn, 1972). Termination of tonic activity is achieved by signals from the caudal SC neurons which excite inhibitory BNs, which in turn directly inhibit and suppress OPN activity for the initiation and duration of saccades (Takahashi, 2005; Takahashi et al., 2022).

Development of Eye Movement Control

Eye movement control is present but immature at birth, relating to both the developmental status of neural circuitry and the lack of sufficient visual experiences. Saccadic reaction time or latency is shown to be longer and saccadic amplitude or accuracy to be less precise in children as compared to adults (Warren et al., 2013). Oculomotor learning occurs throughout childhood and into adulthood through a process known as saccadic adaptation (Alahyane et al., 2016; Huang et al., 2017). As is common with most types of learning, saccadic adaption occurs in response to errors, in this case those resulting from inaccurate saccadic landing positions. Adjustments in saccadic amplitude occur with repetitive errors, such that accuracy is nearing adult levels by 8-years of age (Alahayne et al., 2016) and latency in initiating saccades is near adult levels by 12-years of age (Fukushima et al., 2000).

Visual fixation, which is described above as an active process, is not fully developed at birth in humans and follows maturation of the fovea and central nervous system with control improving significantly by 6-months of age (Von Noorden & Campos, 2002). However, development continues to occur with the number of intruding saccadic movements decreasing, and duration of stable fixation increasing from 4 to 15-years of age (Aring et al., 2007). The ability to effectively shift and maintain attention toward a selected target is also shown to be associated with development of the fixational system with younger children more frequently breaking fixation when distracted by peripheral stimuli (Paus et al., 1990).

Beginning in middle age and continuing into old age, the visual system experiences a series of normal, age-related changes which result in reduced visual acuity, contrast sensitivity, visual processing, and eye movement control (Ross et al., 1985; Salthouse, 2010; Owsley, 2011). Increased latency of saccadic movements and decreased smooth-pursuit gain are both common with age (Moschner and Baloh, 1994; Ross et al., 1999). Fixation stability was previously thought to remain relatively unchanged in older adults when compared to younger adults (Kosnik et al., 1986), however normalized data acquired using microperimetry shows that mean fixation stability decreases starting in the fourth decade and continuing into old age (Morales et al., 2016). Age-related declines in attention, motor control, and mechanical efficiency are also likely factors contributing to decreased eye movement control (Clark & Demer, 2002; Noiret et al., 2017).

Macular Disease and Central Vision Loss

Loss of peripheral vision due to a lesion or disease is often not immediately obvious and goes undetected until advanced, however loss of central vision is generally detected quickly as fine details become obviously harder to see for a patient. One disease that has a significant impact on central vision is macular degeneration (MD). MD is one of the leading causes of visual impairment worldwide. It is most frequently encountered in adults over age 55 with incidence increasing with advancing age (Klein et al., 2004), however juvenile forms do exist such as Stargardt's disease, Best disease, and juvenile retinoschisis (Altschwager et al., 2017). It is estimated that the global prevalence of MD will rise to nearly 300 million cases by 2040 (Wong et al., 2014) and therefore constitutes a significant public health concern. MD is a complex eye disease characterized by the degeneration of retinal support structures such as the retinal pigment epithelium (RPE) and choriocapillaris which directly nourish the RPE and photoreceptors of the macula (Blasiak, 2020). The exact mechanism of pathogenesis is unknown but likely attributable to metabolic dysregulation and oxidative stress in the retina (Ding et al., 2009; Hadziahmetovic & Malek, 2021). The eventual result is the death of photoreceptor cells in the macula.

MD typically progresses through stages. Early stages begin with a build-up of a soft, fatty lipoprotein between the RPE and underlying choroid, known as drusen (Curcio, 2018). Larger drusen continue to accumulate during the intermediate stage until the late stage when widespread geographic atrophy of photoreceptors begins to occur (Ferris et al., 2013). These stages are collectively referred to as the "dry" form of the disease and account for the majority of cases (Friedman et al., 2004). In the "wet" form or

neovascular form of the disease, abnormal blood vessels proliferate into the macula. The fragility of the vessels results in serous fluid exudate or blood leaking out which can lead to additional photoreceptor death. Approximately 10-20% of people with the dry form of the disease progress to the wet form (Friedman et al., 2004), however the wet form accounts for approximately 60% of advanced cases of MD (Klein et al, 2008) and the majority of central vision impairment associated with the disease (Ferris et al., 1984).

In advanced stages, the atrophy of photoreceptors in the macula leads to the development of scotomas (blind spots) in the central visual field. Scotomas ultimately impact the functioning of the fovea and result in a permanent loss of central visual acuity. When vision has degenerated such that bilateral central scotomas affect the foveae, looking directly at an object causes its image to fall within the boundaries of the scotomas. The result is that the person experiences missing, blurry, or distorted images, difficulty distinguishing colors, and trouble detecting low-contrast environmental features, all of which have significant implications on functional performance (Gopinath et al., 2014).

There is currently no cure for macular degeneration. Existing medical treatments are designed to delay the onset or slow the progression of the disease. Dietary modification and vitamin supplementation may reduce the risk of developing advanced age-related macular degeneration (Age-Related Eye Disease Study Group, 2001) and intravitreal anti-VEGF agents are able to block the growth of aberrant blood vessels for some individuals in the neovascular form of the disease (Solomon et al., 2019). The eventual result of progression is loss of central visual acuity which impairs the person's ability to effectively perform tasks such as reading text, recognizing faces, and locating

objects in the environment. Central vision loss impacts instrumental activities of daily living so much that many individuals become more dependent on others and experience decreased quality of life (Massof, 1998; Gopinath et al., 2014).

Central Vision Loss and Eye Movement Control

Bilateral damage to the macula and fovea not only impairs visual functions such as acuity and contrast, but it also impairs the person's ability to plan and direct eye movements given the loss of the fovea as an oculomotor reference point. When this occurs, the person adopts one of many alternative retinal location for binocular fixation known as a preferred retinal locus or PRL (White & Bedell, 1990; Fletcher & Schuchard, 1997). The PRL corresponds to a relatively healthy area of the spared retina located eccentrically to the fovea. The PRL acts as a 'pseudo-fovea' allowing people to eccentrically direct their gaze to view targets in such a manner that light from the object avoids the scotomatous region and contacts an area of greater residual acuity in the more peripheral retina (Figure 1). Some individuals become very skilled at using their PRL, such that the coordination of eye movements become re-referenced to this location. This means that eye movements are no longer planned with the fovea as the locus of fixation, but with the PRL instead.

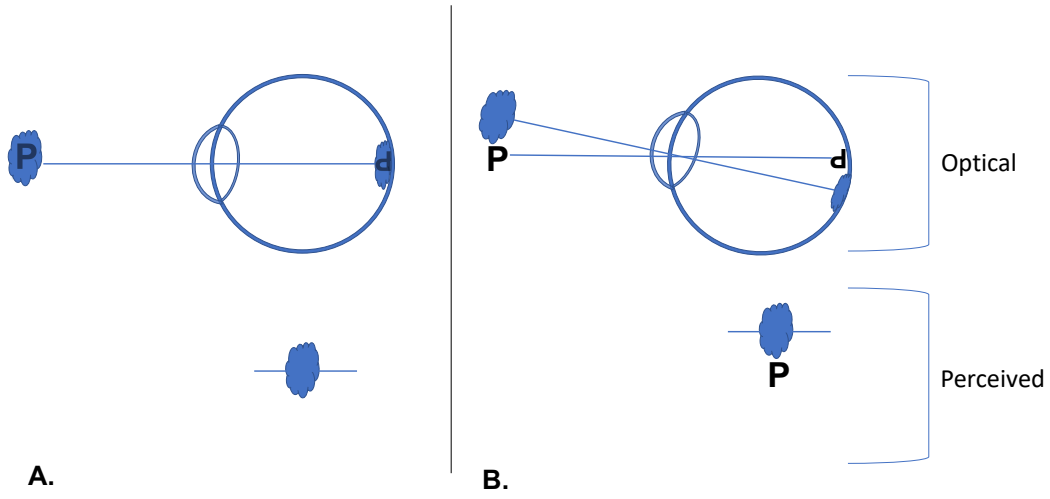

Figure 1. Eccentric viewing. A.) Central fixation using the fovea places the image from the letter 'P' within the macular scotoma. B.) Directing gaze upward results in the scotoma moving anatomically downward, allowing the image of the 'P' to land on a residual healthy area of the retina.

The mechanisms underlying PRL development are still under investigation, including why some individuals independently develop a PRL and others do not. In a 2005 study, 25 patients with recent onset macular disease spontaneously developed a PRL within 6 months (Crossland et al., 2005), however most of the patients were unaware that they were using the area for non-foveating fixations. Few other longitudinal studies of PRL development have been completed. It is known that the PRL tends to develop near the border of the scotoma (Fletcher & Schuchard, 1997) and that it is not always the retinal area with greatest residual acuity (Bernard & Chung, 2019). The PRL also tends to remain along the same meridian, even with the expansion or progression of the scotoma (Barraza-Bernal et al., 2018, Tarita-Nistor et al., 2020).

A typical saccade brings a target of interest onto the fovea and is therefore called a foveating saccade. A non-foveating saccade requires the person to not fixate the target with their fovea but rather eccentrically fixate it with the PRL. For those who do not

spontaneously develop a PRL, it can take a considerable amount of time to adopt the PRL as a point of oculomotor reference, that is, to re-reference saccades to this location (White & Bedell, 1990; Whitaker et al., 1991; Crossland et al., 2005). Initially, persons with MD may continue to use foveating saccades even when a PRL is present (Whitaker et al., 1991; Tarita-Nistor et al., 2009). When they do attempt to use a PRL, the planning and execution of eye movements to this location are often deficient. Renninger & Ma-Wyatt (2011) compared the eye movements of participants using typical foveating saccades to those using a PRL. Both groups attempted to fixate a radial target by making a saccade from a central fixation point. While healthy controls made a saccade directly to the target, individuals using a PRL made saccades that curved toward the target at the end of the saccade and required multiple small, corrective saccades in order to reach the target. They also found that participants using a PRL made saccades with lower peak velocity and longer duration than those using a fovea. These findings are consistent with other research which has found increased saccadic latency and landing dispersion (Whitaker et al., 1991; Van der Stigchel et al., 2013) and an increase in the number of saccades necessary to locate a target (refixations) using a PRL (White & Bedell, 1990; McMahon et al., 1991). Once the target is successfully placed at the PRL the stability of fixation is often profoundly impaired. Using a common metric for calculating the area and orientation of an ellipse which encompasses a defined percentage of fixation points during a task (called the bivariate contour ellipse area or BCEA), people with bilateral central vision impairment can have a BCEA as large as 10 to 20 deg^2 (White & Bedell, 1990; Crossland et al., 2011) whereas a person using foveating fixation may have a BCEA from 0.022 to 0.36 deg^2 (Kosnik et al., 1986; Rohrschneider et al., 1996). A larger

BCEA indicates decreased fixation stability. Research also indicates an increase in the amplitude of slow drifts and microsaccades in the population with central vision impairment (Kumar & Chung, 2014).

Identifying the Location of a Preferred Retinal Locus

Estimation of PRL Location Using Traditional Techniques

There are two strategies that can provide insight into the location of a preferred retinal locus, and both can be performed without the need for special equipment. These are known as face-field evaluation and the clock face method (Wright & Watson, 1995; Sunness, 2008). People who develop macular degeneration later in life generally have experience with the usual arrangement of human facial features and with an analog clock. Using one of these methods, the examiner asks the patient to look at a particular location, such as the examiner's nose or the center of a clock and describe any locations on those objects which may appear missing, blurry, or distorted. The patient may describe certain facial structures or certain numbers on the clock as being obscured by their vision. This provides insight into the location of the scotoma (Sunness, 2008). Asking the patient to redirect their gaze toward other facial structures or, in the case of the clock method, different numbers on the clock allows the patient to test different areas of the retina where a PRL might be located. The direction of gaze when the desired target becomes visible (e.g., nose or center of clock) corresponds to the location the eyes must move in order to align the PRL with the desired target (Figure 2).

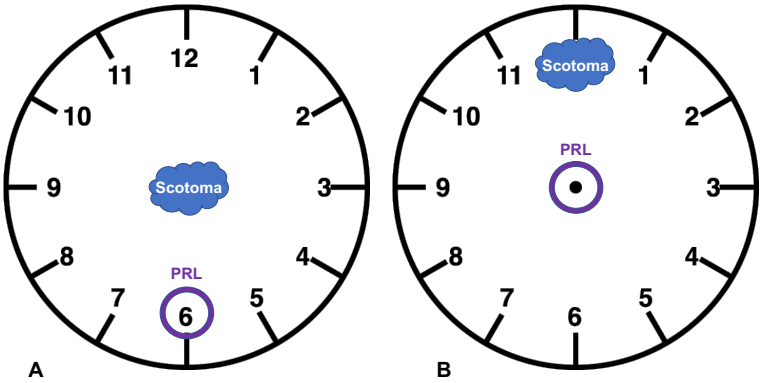

Figure 2. Clock method of PRL location. A.) Patient is fixating on the center of the clock which is obscured by central scotoma. PRL is located below the scotoma in the visual field. B.) Patient redirects gaze toward "12:00" moving the scotoma upwards and bringing the PRL onto the center of the clock, making the previously obscured center visible.

Estimation of PRL Location Using Microperimetry

Microperimetry or fundus-controlled perimetry is a type of visual field test that maps the visual sensitivity of the central retina. It is particularly useful in characterizing visual function and identifying small scotomas in conditions such as AMD. The first commercially available device dedicated to clinical microperimetry use was the Micro Perimeter 1 (MP-1, NIDEK Technologies Srl, Padova, Italy) in 2004. Advantages of microperimetry over previous types of perimetry testing include the ability to image the fundus, adjust parameters such as stimulus size and duration, and create customizable test grid patterns, all while controlling for eye movement through the use of eye tracking technology (Pfau et al., 2021). The inclusion of eye-tracking technology allowed for improved follow-up examination reliability and the ability to calculate and compensate for user fixation stability during an individual session (Midena et al., 2004). Release of the Macular Integrity Assessment device (MAIA, CenterVue, Padova, Italy) improved image quality and anatomical retinal landmark tracking (Barkana,et al., 2021).

Microperimetry examination begins with imaging of the fundus. The patient is asked to fixate on a central target and hold the eye steady as a series of light stimuli appear on the screen. The patient responds via button press when a light stimulus is detected, thus creating a map of retinal sensitivity which is plotted onto the imaged fundus. During the examination, anatomical landmarks on the retina are tracked and the stimuli locations are adjusted correspondingly to compensate for any movement of the eye. The result is a map that identifies not only the scotoma location but also a cluster of fixation points that indicate the portion of the retina used to see the fixation stimulus. These fixation points can be quantified using the bivariate contour ellipse area (BCEA). Fixation stability is quantified by the size of the BCEA with lower values indicating better stability. The PRL is indicated as a circumscribed area containing a majority of fixation points across the examination (Figure 3).

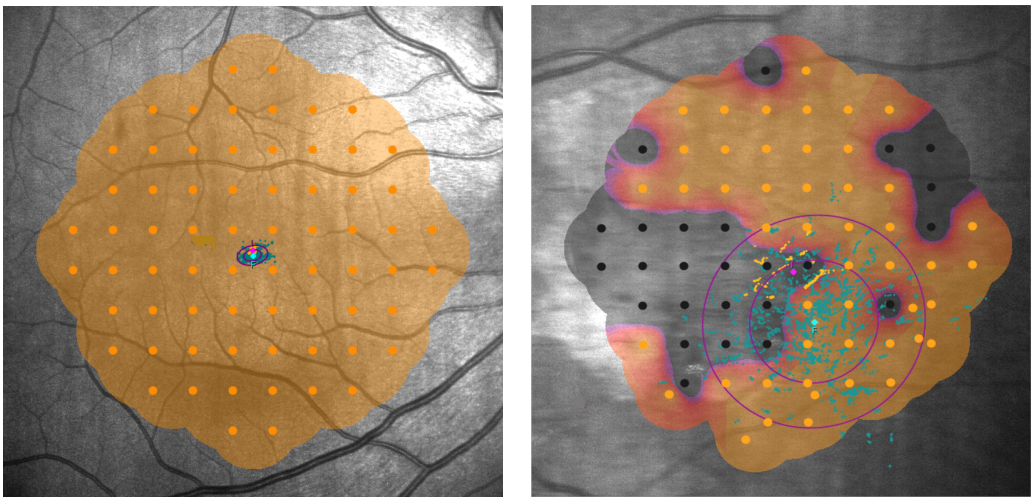

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Figure 3. Preferred retinal locus (PRL) and fixation stability as assessed using microperimetry. Orange indicates areas where the visual stimulus was detected. Green dots indicate fixation points. Purple ellipses indicate the BCEA encompassing 63% and 95% of fixation points respectively. The center of the ellipse demarcates the PRL. A.) Healthy eye showing steady, foveal fixation. B.) Diseased eye showing unsteady fixation and eccentric PRL. (MAIA, CenterVue S.p.A., Padova, Italy)

Training a Preferred Retinal Locus in Clinical Settings

Traditional Training Techniques

Historically, techniques for treating functional visual impairments in patients with macular degeneration have included magnification and enhanced lighting. These techniques play an important role in maximizing the use of the residual healthy retina and may be sufficient alone when scotomas are small, relative, or only impair foveal vision in a single eye. They continue to be important tools for persons with more advanced stages of central vision loss, however they must be combined with training that increases scotoma awareness and teaches the person to efficiently use the PRL as a reference for eye movement control. Such approaches have traditionally been referred to as eccentric viewing training and have existed in various forms since the 1970s, beginning with published work by Holcomb and Goodrich (1976). Two training techniques were developed. The first approach uses the generation of an afterimage on a prescribed peripheral area of the retina. In the second approach, the person was trained to identify single letters by moving the eye to the preferred retinal location. The technique was then advanced by moving to more complex combinations of words, sentences, and paragraphs for mastery (Holcomb & Goodrich, 1976). The afterimage technique, while effective, was found to be unpleasant due to increased photophobia for the patients (Goodrich & Mehr, 1986) and the second technique became more mainstream in clinical settings, culminating in a comprehensive training manual (Quillman, 1980) which was readily adopted by low vision clinicians.

Clinical approaches for increasing the effective use of the PRL have continued to rely on the second approach with only minor modification, including the introduction of

additional training resources, such as Pre-Reading and Writing Exercises for Persons with Macular Scotomas (Warren, 1996) and Learn to Use Your Vision for Reading Workbook (Wright & Watson, 1995), which include printable training exercises designed to allow the user to practice eccentric viewing techniques (Figure 4). Clinical training sessions are typically completed one-on-one with the patient and clinician for up to 60 minutes over the course of several training sessions, including the dispensation of printable home exercises for the patient.

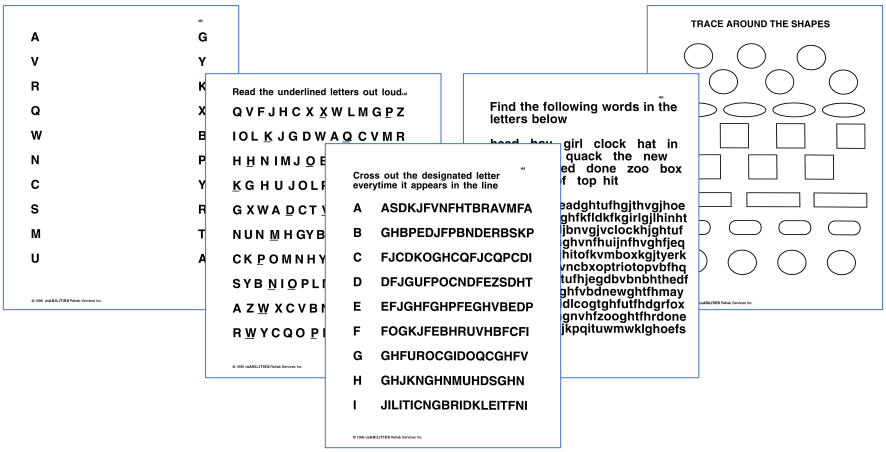

Figure 4. Eccentric viewing exercises. Printable exercises allow the patient to practice eccentric viewing techniques in the clinic and at home. The exercises become increasingly more challenging with alterations to letter spacing, line spacing, and print size. Adapted from "Pre-Reading & Writing Exercises for Persons with Macular Scotomas" by Mary Warren. Copyright 1996 by visABILITIES Rehab Services Inc. Adapted with permission.

Challenges with Traditional Training Techniques

The clinical approaches described are successful for about 60% of individuals, but not for all (Seiple et al., 2005; Vukicevic & Fitzmaurice, 2009; Jeong & Moon, 2011). The literature remains inconclusive regarding the relationship between patient characteristics, type of training provided, and outcomes. If sufficient fixation and

saccadic eye movement control are required to adopt a PRL as a point of re-referencing, it may be that current clinical strategies are less effective in monitoring the progression of oculomotor changes as they occur. Reading outcomes, such as error rate and words-per-minute, are the common objective measures in clinical training, however quantitative information regarding eye movement changes themselves is lacking and mostly based upon observation by the clinician or subjective report of the patient (Stelmack et al., 2004; Nilsson et al., 2003). The lack of objective data on eye movement performance using the PRL may limit the clinician's ability to adequately monitor performance, make appropriate modifications to the training, and/or lead to premature termination of training if it does not appear improvements in performance or accuracy are occurring.

Newer Training Techniques

A newer approach that does provide limited data on eye movement control is biofeedback training with microperimetry. Biofeedback methods allow a patient to become aware of variations in physiological functions using systems that utilize audio or visual stimuli and make changes to those functions through training (Silvestri et al., 2021). Biofeedback training with microperimetry capitalizes on the ability of the device to quantify fixation stability. It includes the addition of a modulating, acoustic tone which is used to re-educate the patient's fixation while they are being directed to gaze at an eccentric location. The tone varies from beeping to continuous as the patient's gaze approaches and fixates at the pre-selected training location. The training can be for the same area as an existing PRL or another retinal area to train a new PRL (sometimes called a trained retinal locus or TRL). As poor fixation stability has been correlated with

decreased visual acuity and reading speed (Crossland et al., 2005; Macedo et al., 2011; Krishnan & Bedell, 2018), the goal of biofeedback training is to improve fixation stability at the PRL or TRL over the course of training sessions. The clinician is then able to monitor improvements in fixation stability by tracking changes in BCEA across the training sessions. Biofeedback training has been shown to improve fixation stability in patients with central scotoma by almost 50% at a TRL (Tarita-Nistor et al., 2009; Daibert-Nido & Markowitz, 2018; Morales et al., 2020; Sahli et al., 2020), however fixation stability is the only eye movement metric that is measured as the software does not have the functionality to train saccadic eye movements.

Training a Preferred Retinal Locus in Laboratory Settings

The question of how oculomotor changes contribute to the functional acquisition of PRL control is important from both a clinical and basic science perspective. It is important to understand how oculomotor changes contribute to improved visual perception and which eye movement training strategies support this process. Limitations exist in studying the natural course of oculomotor changes and adaptation to a PRL in patients with MD. The rate of lesion progression is variable and could run the span of decades. The older age of onset introduces confounding variables, such as comorbid disorders and natural age-related changes to the eye and brain. Therefore, simulation can be used to study these changes as an alternative model system. This can occur in a laboratory setting.

One way to do this is by using an artificial scotoma which is generated using a gaze-contingent eye tracking system. Gaze contingency is a technique where images on a

computer screen are generated or changed in response to where the viewer is looking (Reder, 1973; McConkie & Rayner, 1975). The eye tracking system can continuously monitor and collect eye movement data as a participant progresses through various behavioral assessments or training exercises. Typically sighted individuals can develop a stable and persistent PRL in the presence of an artificial scotoma during oculomotor training in a relatively short period of time (Kwon et al., 2013). This study also reported significant improvements in certain eye movement metrics, including decreased saccadic latency and a decrease in the number of saccades per trial. It was later demonstrated that a TRL could be induced at any intended retinal location using gaze-contingent simulation as a model system (Liu & Kwon, 2016). In this experiment which incorporated both oculomotor and perceptual learning paradigms, significant improvements were noted in accuracy, fixation stability, and first saccade landing locations using the PRL.

The ability to not only monitor but characterize oculomotor strategies as they change over time during peripheral viewing activities is essential for understanding how re-referencing to the PRL develops and for improving therapeutic approaches for clinical interventions. It is expected that different aspects of eye movements would change with PRL development. For example, participants might become more precise at making saccades to the PRL, become better at keeping their eye at this location while fixating a target, or even re-referencing their saccades to the PRL. A recently developed strategy is able to characterize different aspects of eye movements that might be expected to change with training. These eye movement metrics are saccadic landing dispersion, saccadic precision, saccadic latency, saccadic re-referencing, and fixation stability (Maniglia, Visscher et al., 2020; Maniglia, Jogin et al., 2020).

No study to date has examined, in a strong sample size or with consistent training protocols, how these different aspects of eye movements change with experience. The research described here investigates how eye movement metrics change as a person learns to use a trained PRL. A gaze-contingent eye-tracking system was used to display a simulated scotoma, obscuring the participant's central field of view no matter where they looked on the screen. A behavioral training task required that participants attend to a pre-selected peripheral 'clear window' which acted as a PRL, make eye movements to center the PRL on visual stimuli presented at different locations on the screen, and accurately respond to what they see. Eye movements were recorded throughout 12 training sessions, characterized into different eye movement metrics, and analyzed to see how they changed over the course of training.

The work described herein is significant because the approach using a simulated scotoma in the laboratory setting allows for control over the degree of vision available and the ability to apply it equally to each participant. Collecting and characterizing eye movement data as a person learns to use an eccentric retinal locus will allow us to look for associations between changes in eye movement control and changes in performance. We anticipate this information will provide valuable insight into how a person learns to use a PRL and will translate into improved clinical intervention strategies and outcomes.

CHAPTER 2

OCULOMOTOR CHANGES FOLLOWING LEARNED USE OF AN ECCENTRIC RETINAL LOCUS

by

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Abstract

People with bilateral central vision loss sometimes develop a new point of oculomotor reference called a preferred retinal locus (PRL) that is used for fixating and planning saccadic eye movements. How individuals develop and learn to effectively use a PRL is still debated; in particular, the time course of learning to plan saccades using a PRL and learning to stabilize peripheral fixation at the desired location. Here we address knowledge limitations through research describing how eye movements change as a person learns to adopt an eccentric retinal locus. Using a gaze-contingent, eye tracking-guided paradigm to simulate central vision loss, 40 participants developed a PRL by engaging in an oculomotor and visual recognition task. After 12 training sessions, significant improvements were observed in six eye movement metrics addressing different aspects involved in learning to use a PRL: first saccade landing dispersion, saccadic re-referencing, saccadic precision, saccadic latency, percentage of useful trials, and fixation stability. Importantly, our analyses allowed separate examination of the stability of target fixation separately from the dispersion and precision of the landing location of saccades. These measures explained 50% of the across-subject variance in accuracy. Fixation stability and saccadic precision showed a strong, positive correlation. Although there was no statistically significant difference in rate of learning, individuals did tend to learn saccadic precision faster than fixation stability. Saccadic precision was also more associated with accuracy than fixation stability for the behavioral task. This suggests effective intervention strategies in low vision should address both fixation stability and saccadic precision.

Introduction

Macular degeneration (MD) is one of the leading causes of visual impairment worldwide (Wong et al., 2014). Progression of the disease commonly impacts the fovea, the area of highest visual acuity and the location traditionally utilized as a point of reference for directing eye movements and inspecting objects of interest. The development of scotomas, or blind spots, in the central visual field can impact functioning of the fovea and result in permanent loss of visual acuity. Some individuals with bilateral central scotomas adopt compensatory viewing strategies that involve the use of portions of the peripheral retina. In certain cases, individuals develop a new point of oculomotor reference called a preferred retinal locus (PRL) (Fletcher & Schuchard, 1997; Sunness et al., 1996). The PRL corresponds to a relatively healthy area of the retina located eccentrically to the fovea, often near the border of the scotoma (Fletcher & Schucard, 1997).

The mechanisms by which an individual learns to effectively control a PRL are not completely understood (Legge & Chung, 2016; Chen et al., 2019), however the oculomotor system and its relationship to typical behavior is relatively well-established. Eye movements can be classified into two main types: those that shift gaze (saccades) and those that stabilize gaze (fixations) (Leigh & Zee, 2015). Saccades are ballistic eye movements that shift the line of sight, which allows the image of an object of interest to fall within the foveae. Saccades require precise planning so that the endpoint of the movement does not place the target outside of the foveal region (Leigh & Kennard, 2004). Vision is suppressed during a saccade (Matin, 1974), leading to the need for fixations. Fixations allow for the accumulation of detailed visual information about an

object of interest. They require that the foveae remain directed toward an object for the highest acuity vision to occur (Foulsham, 2015). The systems that control these movements are distributed across cortical structures, with different neural circuits responsible for different eye movements. The ability to fixate is present early in life, but continues to develop into adolescence, with improvements in both stability and duration (Luna et al., 2008). The ability to land a saccade in an optimal location for foveation is evident in infancy and improves into childhood (Luna et al., 2008).

Reduced visual acuity and impaired oculomotor control can make learning to use a PRL difficult. Abnormal fixational eye movements have been associated with increased amplitude in oculomotor drifts and microsaccades (Kumar & Chung, 2014), increased saccadic latency and landing dispersion (Whitaker et al., 1991; Van der Stigchel et al., 2013), and an increase in the number of saccades necessary to locate a target (re-fixations) (White & Bedell, 1990; McMahon et al., 1991). Research suggests that fixation stability using a PRL is highly dependent upon changes in oculomotor control that develop after central vision loss (Shima et al., 2010; Tarita-Nistor et al., 2009). Persons with MD may continue to use foveating saccades even when a PRL is present (Whitaker et al., 1991; Tarita-Nistor et al., 2009). A 2005 study of patients with recent onset macular disease observed PRL development within 6 months of onset, however, most of the patients were unaware of using the area for fixation (Crossland et al., 2005).

Low vision specialists, such as ophthalmologists, optometrists, and occupational therapists, commonly use oculomotor training to teach individuals with MD how to view eccentrically and avoid their scotomas by using a PRL or other parafoveal area with greater visual acuity (Hooper et al., 2008; Pijnacker et al., 2011). Training a retinal

location other than the PRL could be more appropriately termed a trained retinal locus (TRL) (Vukicevic et al., 2012). Researchers also use this approach in laboratory settings to study compensatory strategies following simulated central vision loss using gaze-contingent displays controlled in real time by a high-resolution eye tracker (Barraza-Bernal et al., 2017; Kwon et al., 2013; Liu & Kwon, 2016; Maniglia et al., 2020; Walsh & Liu, 2014). The ideal outcome is a shift in oculomotor reference from the fovea to the PRL so that the PRL acts as a "pseudofovea" allowing for eccentric fixation and planning of saccadic eye movements. Many of the recent intervention studies have focused on using rapid serial visual presentation (RSVP) tasks and biofeedback training with microperimetry to enhance fixation stability of the PRL (Chung, 2011; Kaltenegger et al., 2019; Vingolo et al., 2018; Morales et al., 2020).

This is an important avenue of research as decreased fixation stability is shown to be a limiting factor in peripheral visual performance (Crossland et al., 2004; Rubin & Feely, 2009; Kumar & Chung, 2014; Agaoglu & Chung, 2020). However, tasks such as reading require a rapid succession of horizontal saccades to progress across lines of text and fixations to accurately identify letters and numbers (Rayner, 1998; Chung, 2020). Static eye training alone has been shown to be less effective than gaze shift exercises in improving reading speed with a PRL (Seiple et al., 2011). This suggests that focusing on fixation stability alone, without eye movement training, might not be sufficient for promoting functional outcomes. Reading, a common goal of low vision rehabilitation, requires more than just stable fixation. Reading fluency requires the oculomotor systems for fixation stability and saccades to work together. Clinical interventions that focus

exclusively on fixation stability for PRL training might fail to develop the saccadic precision skills necessary for more than just stationary reading.

Translating research into clinical interventions requires acknowledging limitations that exist in clinical settings, including restrictions on time and number of visits, the need for assistance with transportation, missed appointments, and follow-through on home assignments. Importantly, individuals with macular disease are often unaware of the location or boundaries of the scotomous region, making it difficult for them to re-reference to a new retinal location during viewing activities (Schuchard, 1993; Ramachandran & Gregory, 1991). These limitations make efficient training regimens essential. Because multiple types of eye movement control are necessary for functional outcomes, the relative rates of learning of these types of eye movements during PRL training could influence the efficiency of any given training regimen. A better understanding of the rate of learning for different aspects of eye movement control during PRL training could provide insight on the timeline of development of these skills in relation to each other. Knowing this information could support better clinician decision-making on when and where to focus interventions. In this paper, we describe how eye movements change as an individual learns to control an eccentric retinal locus.

Methods

Participants

Forty healthy participants (10 male, 30 female), mean age 24.8 years (age range 18–31 years) with normal or corrected-to-normal vision as assessed using a Snellen chart (visual acuity range as tested with both eyes 20/10–20/20) and no known ocular,

cognitive or neurological impairments were recruited from the University of Alabama at Birmingham (USA) and greater Birmingham metropolitan area.

Participants received monetary compensation for their participation. Written informed consent was obtained from all participants and experimental protocols were approved in accordance with the Institutional Review Board (IRB) of the University of Alabama at Birmingham.

Stimuli and Apparatus

Stimuli were generated and controlled using MATLAB version 8.4 and Psychophysics Toolbox and Eyelink Toolbox extensions (Brainard, 1997; Pelli, 1997; Cornelissen et al., 2002). An ASUS M38 desktop computer was used to run the training program in one of two training rooms; one ran Windows 8, the other Windows 10, but otherwise all software and hardware were identical. Visual stimuli were displayed on a 32-inch liquid crystal monitor (Cambridge Research Systems Display++; refresh rate: 120 Hz; resolution: 1920x1080) located at a viewing distance of 57cm. The SR Research head and chin stabilizer was used to minimize head movements and trial-to-trial variability in estimation of gaze position. Eye movements were monitored (monocular tracking using the dominant eye) using an infrared video-based eye-tracker sampling at 500 Hz (EyeLink 1000 Plus/Desktop Mount, SR Research Ltd., Ontario, Canada.) A nine-point calibration/validation sequence was performed at the beginning of each training block. The gaze position error (i.e., difference between the target position and computed gaze position) was estimated during the nine-point validation procedure. The

calibration and validation were repeated until the validation error was smaller than 1° on all or most points.

Procedure

A gaze-contingent display simulating a scotoma was used to occlude central vision during each training session. The scotoma was a gray circular patch with a radius of 6° and a luminance of 37 cd/m^2 set against a textured parchment background with luminance of 68 cd/m^2 (Figure 1). During a training session, gaze position was monitored in real-time and sent to the display computer via high-speed Ethernet link. The continuous gaze information was used to draw the artificial scotoma on the visual display monitor. To reduce the impact of a mismatch in position of the artificial scotoma and the actual gaze position, which could occur were the participant to blink or squint, the system was designed to turn the entire display screen gray as soon as it detected a blink or a decrease in pupil size to a threshold value (Aguilar & Castet, 2011). Median system latency found using a method described by Saunders and Woods (2014) was 18 ms, which is sufficient to support training task performance.

Training

The training protocol using the simulated scotoma was previously described in detail by Liu and Kwon (2016). This protocol was selected as it was demonstrated to induce a PRL in normally sighted subjects in a relatively short period of time. In addition to the simulated scotoma, the background of the screen was blurred by applying a Gaussian filter that eliminated detailed visual information but allowed for the detection of

motion and color. A single clear window, circular in shape and with radius of 2.5°, was centered 8.5° to either the left or right of the center of the simulated scotoma and served as the location in which to develop a TRL. The left and right windows were selected to be used as training loci as previous studies have shown a higher incidence of natural PRL development occurring at those locations (Sunness et al., 1996; Fletcher & Schuchard, 1997).

The training protocol included three conditions which are relevant to activities of daily living and often identified by persons with central scotoma as being difficult to perform: Face Recognition, Object Recognition, and Word Recognition (Figure 1) (Schucard, 1995; Bullimore et al., 1991; Kleen & Levoy, 1981). The stimuli used for the discrimination tasks were also of different sizes, as it has been suggested that greater learning occurs when using multiple stimulus conditions and tasks (Maniglia & Sitz, 2018; Xie & Yu, 2020). Faces used in the task were cropped using an oval mask and set to 4.3°. The height of both objects and words was set to 1.6° with words being displayed in a lower-case Courier font. Each training session included one block of each condition. Each block consisted of 30 trials. Each trial included three phases: target following and recognition, gaze centering, and visual search. This study focuses specifically on target following and recognition, as this is the phase that requires the greatest oculomotor control and accuracy.

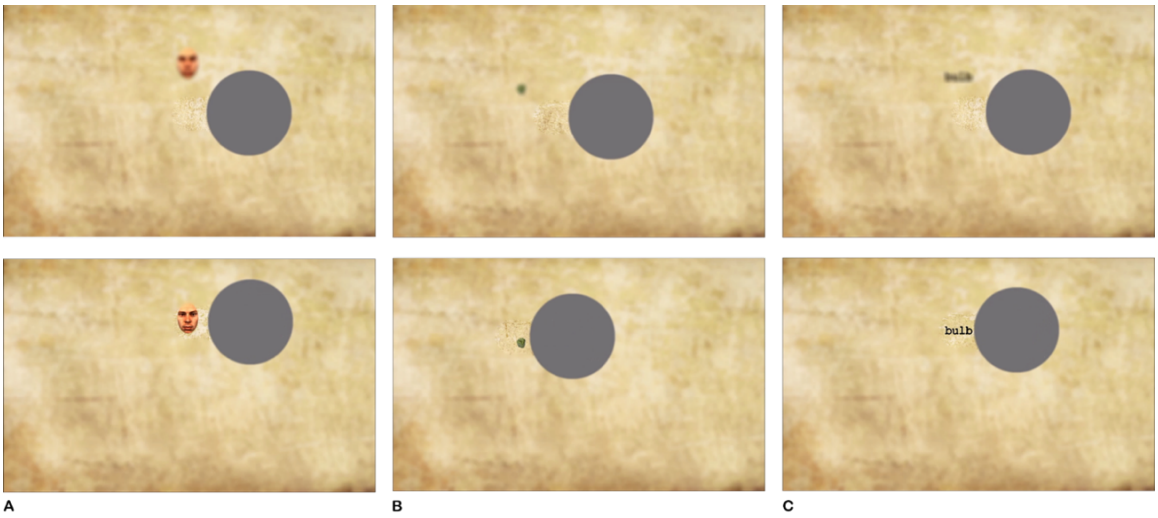

Figure 1. Training task used in the study. Participants were asked to recognize a target as it changed location and identity by directing the TRL clear window (located in this example to the left of the simulated scotoma) onto the target. This was performed under three conditions: A.) Face Recognition, B.) Object Recognition, and C.) Word Recognition. In each case, the target was obscured (top image) until revealed (bottom image) by directing the trained TRL over the target. In A, a face is shown. In B, a bell pepper is shown. In C, the word "bulb" is shown.

During the target recognition phase, participants were asked to visually direct the clear window over the current target (i.e., face, object, or word) which was obscured by the background filter. Participants were tasked with reporting as quickly and accurately as possible whether the target was a male face or female face (Face Condition), a real-world object or non-object (Object Condition), or a real- word or non-word (Word Recognition) by making a keyboard press. The target changed and moved to a new location only when either a valid keypress was detected or when the simulated scotoma did not occlude the target for at least 2.5 seconds. Each training block consisted of 180 trials, after which the participant was provided with onscreen feedback regarding (mean accuracy and task- completion time) for motivation. All participants completed the three training blocks in each session. The order of the training blocks was randomly assigned

to each participant prior to the first session; however, the assigned order was maintained throughout training. Participants were assigned a clear window location (to the left or to the right of the artificial scotoma) prior to initiation that was maintained throughout training. Each training session took approximately 45 minutes to 1-hour to complete. Participants completed a total of 12 training sessions over the course of 4 to 6 weeks.

Six different oculomotor metrics were characterized to assess development of the TRL, as previously described in Maniglia et al. (2020). These metrics aim at describing different oculomotor aspects involved in the development of a TRL, specifically: *First saccade landing dispersion*, the across-trial distribution of landing locations of the first saccade made after target appearance; *Saccadic re-referencing*, the percentage of trials in which the first fixation placed the target in a visible position outside of the simulated scotoma; *Saccadic precision*, the across-trial distribution of landing locations of first fixations that placed the target outside of the scotoma (similar to *First saccade landing dispersion*, but not confined to the first 'absolute' saccade of the trial); *Percentage of useful trials*, the proportion of trials in which at least one saccade placed the target outside of the scotoma; *Latency of target acquisition,* the time interval between appearance of the target and the first fixation outside the scotoma; and *Fixation stability*, the dispersion of eye positions within a trial after a first saccade, normalized for the average TRL location across trials. Figure 2 provides an illustration of each of the oculomotor metrics and a brief description.

The bivariate contour ellipse area (BCEA) was calculated for first saccade landing dispersion, saccadic precision, and fixation stability and expressed in deg^2. In our study, the BCEA is the size of an ellipse that encompasses fixation points (Steinman, 1965) for

68% of eye positions during a trial (Crossland, 2004); a smaller BCEA indicates improvement.

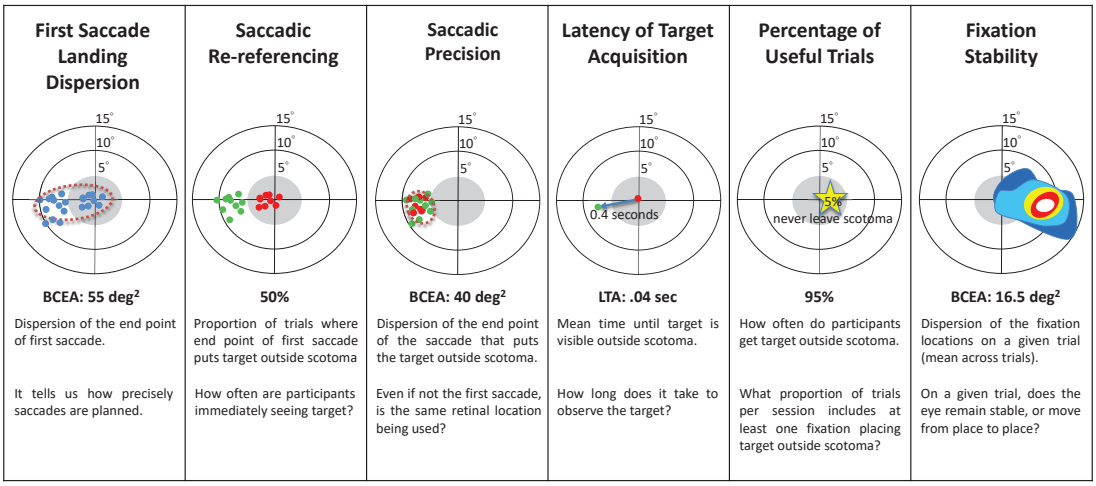

Figure 2. Overview of the oculomotor metrics used in the study (adapted from Maniglia, Visscher and Seitz, 2020). These metrics were extracted from the eye movement data collected during each training block. *First saccade landing dispersion:* blue dots represent the end points of absolute first saccades during each trial of a training block. The BCEA is represented by a red ellipse and encompasses 68% of total eye positions. *Saccadic re-referencing:* green dots represent 'absolute' first fixations of a trial that place the target outside of the scotoma, red dots are 'absolute' first fixations of a trial that place the target within the scotoma. *Saccadic precision:* dots represent the end points of saccades that first place the target outside of the scotoma. A green dot means the saccade was an 'absolute' first saccade (same as Saccadic re-referencing), whereas a red dot means that location was from a second or later saccade. *Latency of target acquisition:* reflects how long it takes to make a saccade which places the target in a visible location. *Percentage of useful trials:* indicates what percentage of trials include at least one saccade placing the target in a visible location. *Fixation stability:* a within-trial measure of dispersion after the first saccade of each trial, normalized to center each trial starting point to the average across-trial TRL location. It is visually represented using a kernel density estimator (KDE).

Results

Oculomotor Changes

Figure 3 shows the mean change in performance for each of the six oculomotor metrics as a function of training between the first training session (Block 1) and the last

training session (Block 12). A comparison of performance at the first and last training session using paired samples t-tests shows a significant improvement in performance in all of the metrics: Overall, participants showed a significant decrease in the spatial distribution of first saccades across trials (First saccade landing dispersion, $t(39) = 17.92, p = 9.95 \times 10^{-21}$), a significant increase in the percentage of trials in which the first absolute saccade placed the target outside of the scotoma (Saccadic re-referencing, $t(39) = 8.84, p = 3.68 \times 10^{-11}$), a significant decrease in the spatial distribution of first saccades that did not obscure the target (Saccadic precision, $t(39) = 14.15, p = 2.99 \times 10^{-17}$), a significant increase in the proportion of trials in which at least one fixation placed the target in a visible position outside the scotoma (Percentage of trials that are useful, $t(39) = 3.46 , p < 0.01$), a significant decrease in the time interval between appearance of the target and the end point of the first useful fixation (Latency of target acquisition, $t(39) = 9.35, p=8.28 \times 10^{-12}$), and a significant decrease in eye position dispersion within trials after the first saccade (Fixation stability, $t(39) = 10.63, p = 2.47 \times 10^{-13}$). Improvement in all six oculomotor metrics demonstrates that participants learned how to improve control after developing a TRL at their assigned clear window.

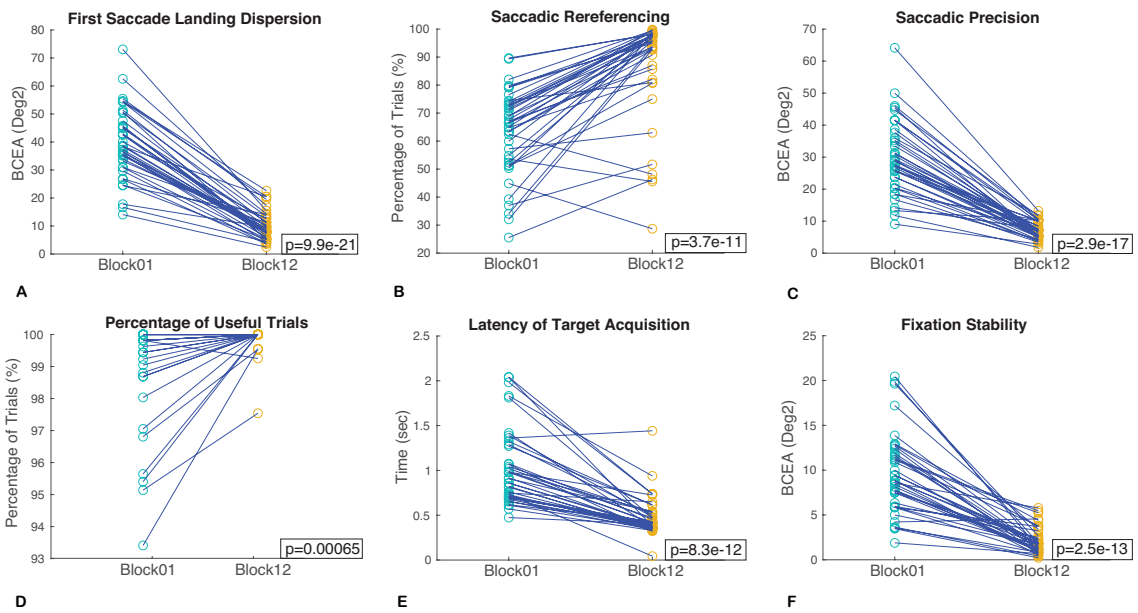

Figure 3. Oculomotor changes with training. Block average of metrics scores for each of the six oculomotor metrics as a function of training (comparison between the first training session (Block 1) and the last training session (Block 12)).

A principal components analysis (PCA) was conducted on the oculomotor metrics from the last training session to better understand how eye movement behaviors were related to each other. Figure 4 shows a plot of the first two principal components; red dots represent scores for individual participants and blue dots represent the weighting of each metric. Principal Component 1 is shown to weigh heavily on a cluster of three metrics that are highly correlated with each other: Fixation stability, Saccadic precision, and First saccade landing dispersion. The proportion of variance explained by the first two principal components was 49.74% and 27.67%, respectively.

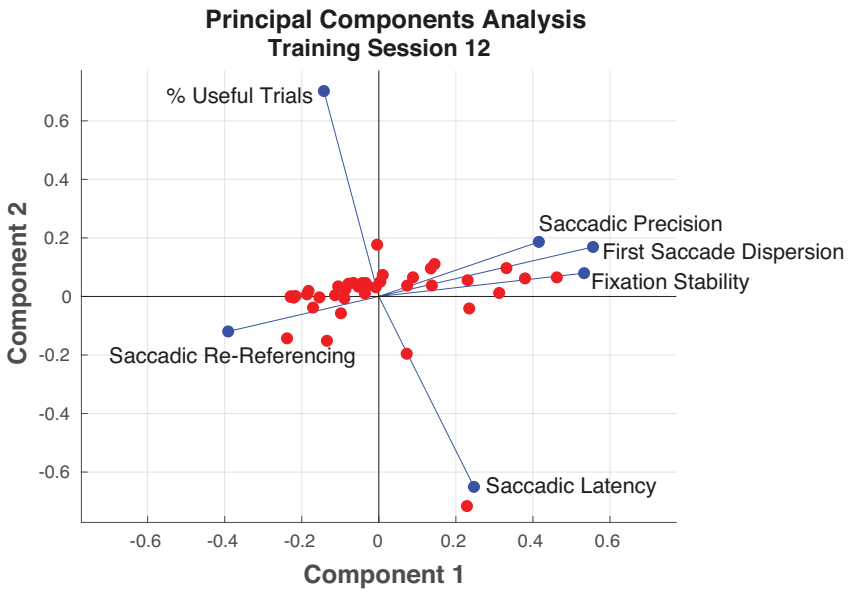

Figure 4. Principal components analysis on the oculomotor metric scores. Plot of the two principal components; red dots represent scores for individual participants and blue dots represent the weighting of each metric. Principal Component 1 weighs heavily on a cluster of three metrics that are highly correlated with each other: fixation stability, saccadic precision, and first saccade landing dispersion.

Behavioral Changes

Table 1 shows a comparison of the mean change in accuracy between the first and last training sessions (Block 1 vs. Block 12). Accuracy is expressed as percentage of correct trials, with higher values indicating better performance. The p-value column shows the p-value of a paired samples t-test comparing Block 1 to Block 12. For the Letter Task, Object Task, and Face Task participants improved performance significantly by 19.78% $(t(39) = -12.97, p = 1.02 \times 10^{-15})$, 18.38% $(t(39) = -13.33, p = 4.22 \times 10^{-16})$, and 20.88% $(t(39) = -12.08 \times 10^{-15})$, respectively.

Mean Changes in Accuracy				
	Block01 (%)	Block12 (%)	Mean Change (%)	*p*-value
Letter Task	72.45	92.23	19.78	1.0×10^{-15}
Object Task	69.93	88.20	18.38	4.2×10^{-16}
Face Task	59.85	80.73	20.88	9.3×10^{-15}

Table 1. Mean changes in accuracy. Comparison of the mean change in accuracy between the first and last training sessions (Block01 vs. Block12). Accuracy is expressed as percentage of correct trials, with higher accuracy indicating better performance.

A correlation analysis (Figure 5) measured the strength and direction of association between the oculomotor metrics post-training and the overall mean accuracy between the three tasks. Fixation stability had a strong, positive correlation with First saccade landing dispersion *($r(38) = .87$, $p = 5.6 \times 10^{-13}$)* and Saccadic precision *($r(38) = .63$, $p = 1.2 \times 10^{-5}$)*. As fixation stability improves, saccadic precision also tends to improve. There was a moderate, negative correlation between saccadic precision and accuracy *($r(38) = -.36$, $p = 0.022$)*. As saccadic precision improves accuracy tends to improve.

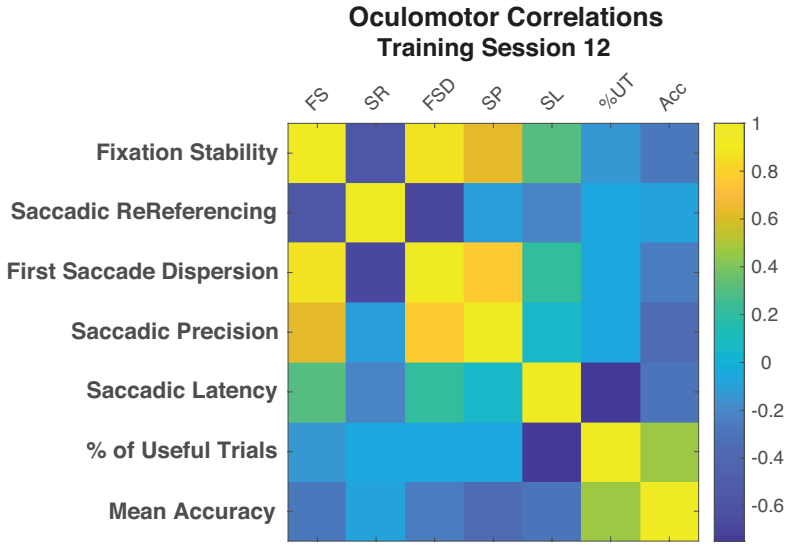

Figure 5. Correlation matrix of oculomotor metrics and mean accuracy. A correlation analysis was completed to measure the strength and direction of association between the oculomotor metrics at the last training session and the overall mean accuracy between the three tasks. Colors indicate Pearson's R.

Learning Rates

An analysis of learning rates was completed to compare the proficiency of each eye metric or behavioral task with increasing levels of experience. The learning curves for metrics where improvements resulted in increases (for example, accuracy) were modeled to fit the form $y = A\left(1 - e^{-k(x-1)}\right) + B$ (Equation 1) where *y* is the value at session x. *A+B* is the value *y* can take at its plateau, *A* is a measure of the amount of learning, and *k* corresponds to the learning rate. Metrics where improvements in performance resulted in decreases (for example, fixation stability where a lower BCEA is better) were fit to the form $y = \mathrm{A}e^{-k(x-1)} + B$ (Equation 2), where the variables have the same meaning, but *B* is the smallest value of *y* at its plateau.

Eye Movement Metrics Learning Rates

Figure 6 shows in orange lines the training curves for all six of the eye metrics for each participant. The blue line represents the mean value across all participants at each training session. The fastest rate of learning was seen in First saccade landing dispersion (*k=1.49*), followed by Percentage of useful trials (*k=1.33*), Saccadic precision (*k=1.14*), Saccadic re-referencing (*k=1.07*), Fixation stability (*k=0.99*), and Saccadic latency (*k=0.61*).

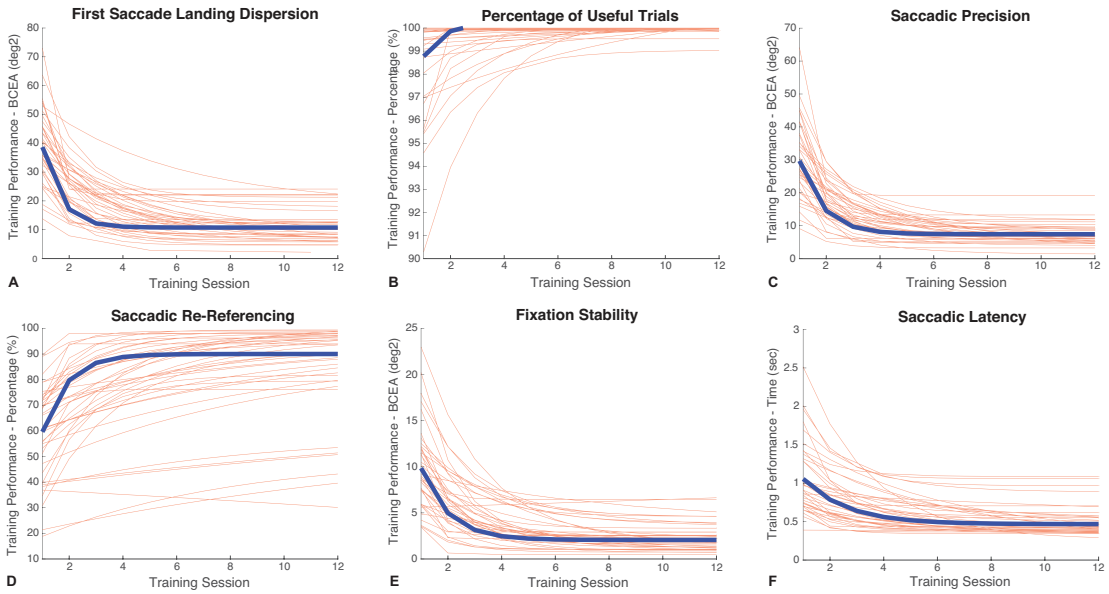

Figure 6. Learning curves of the six oculomotor metrics. The blue line represents the mean value of a given metric as a function of training session. Orange lines represent the learning curves for each participant. A.) First saccade landing dispersion, B.) Percentage of useful trials, C.) Saccadic Precision, D.) Saccadic re-referencing, E.) Fixation stability, and F.) Saccadic latency.

Accuracy Learning Rates

Figure 7 shows in orange lines the training curves for each of the three behavioral training tasks (face, object, and letter) for each participant. The blue line represents the mean value across all participants at each training session. The fastest rate of learning was seen for the Letter task ($k=1.04$), followed by Object ($k=0.48$), and Face ($k = 0.45$). Table 2 shows the differences in learning rates (Δk) between the behavioral training tasks and each of the six eye movement metrics. Statistical significance (p-value) was calculated using paired samples t-tests.

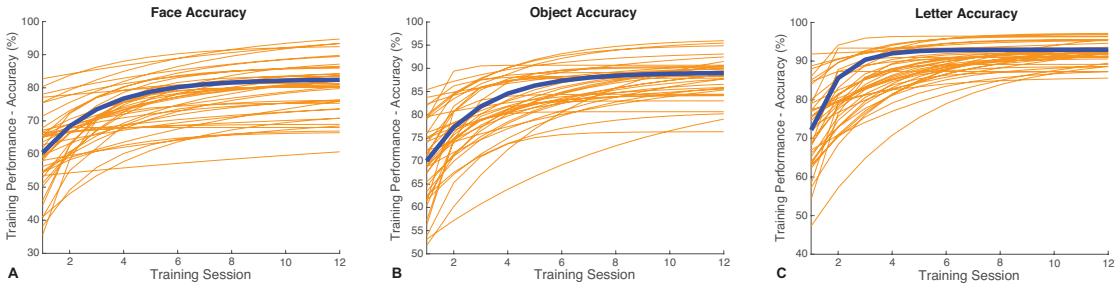

Figure 7. Learning curves of the three behavioral tasks. The blue line represents the mean accuracy value of a given behavioral task as a function of training session. Orange lines represent the learning curves for each participant (fit to Equation 1). A.) Face accuracy, B.) Object accuracy, C.) Letter accuracy.

Eye Metric	*k*	Difference from face rate ($k = 0.45$)	Difference from object rate ($k = 0.48$)	Difference from letter rate ($k = 1.04$)
First saccade landing dispersion	1.49	Δk= -1.04, $p = 0.07$	Δk= -1.01, $p = 0.06$	Δk= -0.45, $p = 0.50$
Percentage of useful trials	1.33	Δk= -0.88, $p = 0.08$	Δk= -0.85, $p = 0.07$	Δk= -0.29, $p = 0.60$
Saccadic precision	1.14	Δk= -0.69, $p = 0.06$	Δk= -0.66, $p = 0.06$	Δk= -0.10, $p = 0.84$
Saccadic re-referencing	1.07	Δk= -0.62, $p = 0.24$	Δk= -0.59, $p = 0.24$	Δk= -0.03, $p = 0.94$
Fixation stability	0.99	Δk= -0.54, $p = 0.01$	Δk= -0.51, $p = 0.03$	Δk= 0.05, $p = 0.90$
Saccadic latency	0.61	Δk= -0.16, $p = 0.32$	Δk= -0.13, $p = 0.19$	Δk= 0.43, $p = 0.28$

Table 2. Differences in learning rates. Comparison of the differences in learning rates between each of the behavioral tasks (face, object, letter) and each of the eye movement metrics. P-values reflect a within-subject t-test comparing the eye metric learning rate to the behavioral test learning rate.

Effect of Eye Metric and Task on Performance

Additional analyses were completed to examine how day-by-day improvements in performance related to improvements in eye metrics. Percent correct scores for each of the 12 blocks for each participant was correlated to their eye metrics for each of the 12 blocks. This gave a Pearson correlation for each participant for each task. These Pearson

correlations were converted to Fisher Z-transformed correlations for further analysis. A two-way repeated measures ANOVA was performed on these scores to assess whether different metrics had different relationships to behavior with factors of eye metric (First saccade landing dispersion, Saccadic precision, Saccadic re-referencing, Fixation stability, Saccadic latency) by task (face, object, letter). Percentage of useful trials was excluded since values were unreliable across subjects (some subjects had 100% useful trials on all blocks, making correlations meaningless). Results revealed a significant main effect of eye metric on Z-transformed correlations to performance ($F_{(4,156)}$=8.96, p<0.0001). There was also a significant main effect of task ($F_{(2,78)}$=4.387, p=0.016). There was no significant interaction of eye metric by task ($F_{(8,312)}$=1.316, p=0.235). Follow-up tests showed that Z-transformed correlations were strongest for First saccade landing dispersion (mean=1.048), Saccadic precision (mean=1.008), and Fixation stability (mean=0.978) followed by Saccadic latency (mean=0.890) and Saccadic rereferencing (mean=0.739). Targeted post-hoc t-tests did not indicate significant differences between first saccade landing dispersion, saccadic precision, or fixation stability (all p>0.05). Post hoc t-tests indicated that participants performed similarly when completing the Letter (mean=1.127) and Object (mean=1.060) tasks, but differently when completing the Face (mean=0.934) task as compared to Letters (p-0.004) or Objects (p=0.039).

Discussion

In this paper we examined eye movement changes and their time course in healthy participants trained to use a peripheral retinal location while performing a visual task in conditions of simulated scotoma. Participants were assigned a specific locus outside the simulated scotoma (a trained retinal locus [TRL], in analogy with the preferred retinal locus [PRL] found in patients suffering from central vision loss). In particular, we extracted six oculomotor metrics (previously described in Mangilia et al., 2020) from the eye movement data recorded during the 12 training sessions. Our results support the hypothesis that eye movement control is influenced by peripheral vision training, which is consistent with previous literature (Tartia-Nistor et al., 2009; Kwon et al., 2013; Janssen & Verghese, 2016; Maniglia et al., 2020). The majority of participants demonstrated significant improvements in Saccadic precision, meaning the ability to place the peripheral target in a consistent retinal location, and in Fixation stability, meaning the ability to maintain steady fixation once the peripheral target is acquired. We also observed statistically significant improvements in First saccade landing dispersion, Saccadic re-referencing, Saccadic latency, and Percentage of useful trials. Interestingly, Fixation stability, Saccadic precision, and First saccade landing dispersion were strongly correlated with each other and explained a great deal of across-subject performance variance post-training. These results, together with previous literature, suggests that training improved these particular eye movement metrics (Seiple et al., 2005; Mandelcorn et al., 2013; Xie et al., 2020). Although there was a strong, positive correlation between Fixation stability and Saccadic precision, the rate of learning for these two metrics was similar, with Saccadic precision being learned slightly faster than

Fixation stability. This supports the idea that learning was occurring separately but simultaneously between neurological systems; those which initiate saccades (including the parietal cortex, caudal superior colliculus, and horizontal and vertical brainstem gaze centers) and those which inhibit saccades or maintain fixation (including the suppression center of the frontal eye fields, rostral superior colliculus, nucleus raphe interpositus, and the medio-posterior cerebellum) (Takahashi et al., 2022; Stewart et al., 2020; Mirpour et al., 2018; Kraulis et al., 2017; Gancarz & Grossberg, 1999).

In addition to examining the learning rates for the eye movement metrics, we also looked at the learning rates for each of the three behavioral tasks. While not statistically different, the learning rates for the eye movement metrics were faster than those for the behavioral tasks in almost all cases. This supports the idea that learning eye movement control of the TRL is a prerequisite for learning to accurately complete a behavioral task, as suggested by previous studies associating increased TRL control with greater accuracy on behavioral tasks (Seiple et al., 2005; Tarita-Nistor et al., 2009; Rose & Bex, 2017). While we demonstrated associations between certain eye movement metrics and task performance across subjects, we also showed these associations to be true within subjects. Day-by-day performance on a given discrimination task is best predicted by First saccade landing dispersion, followed by Saccadic precision, and then by Fixation stability. This adds additional support to the importance of addressing Saccadic precision when providing peripheral or eccentric viewing training.

In this experiment, participants with healthy vision learned to use an eccentric retinal locus over the course of 12 weeks, a timeline that can be different from the lived experience of a person with MD. Progression from the initial diagnosis of MD to

advanced stages of geographic atrophy can occur over a period of many years (Klein et al., 2008), with first appearance of foveal involvement at 2.5 years on average (Linblad et al., 2009). Functional visual changes, however, can begin to occur much earlier (Sunness et al., 1997; Midena et al., 2007; Dimitrov et al., 2011). Considering that MD is often a gradual progression of vision loss, the timing of learning compensatory eye movements in patients diagnosed with MD is much slower (White & Bedell, 1990; Rohrschneider et al., 1997; Crossland et al., 2005; Tarita- Nistor et al., 2008) and adjustments continue to be needed as scotoma size increases (Whitaker et al., 1988; Renninger et al., 2008). Additionally, there exist a number of differences between training healthy participants to perform visual tasks with an artificial scotoma and visual rehabilitation in MD, such as the much clearer location, consistent size and even awareness of the scotoma and clear window in this training paradigm compared to the lived experience of many individuals with MD (Walsh & Liu, 2014).

An important question is whether laboratory-based training strategies, such as the one used in this study, are translatable to clinical settings and generalizable to activities of daily living. Outside of microperimetric biofeedback training, there is limited ability to accurately track or monitor eye movements during traditional clinical eccentric viewing training and many of the laboratory studies utilize on-screen visual aids (Maniglia et al., 2020; Astle et al., 2015) . In addition, previous literature is not clear on differences in the rate of learning for specific types of eye movements using a PRL for persons diagnosed with MD, however, knowing how training in a laboratory environment influences eye movements may help advance understanding of what is possible in patients living with MD and promote future experiments with the MD population which intentionally

demarcate the location of the individual's anatomical scotoma in the visual field. This type of experiment will facilitate better understanding of the similarities or differences in the MD and healthy populations and whether these types of training paradigms have a place in the clinic.

Fixation stability has been an important outcome measure in recent years (Mandelcorn et al., 2013; Vingolo et al., 2018) as it is positively correlated with visual acuity at the PRL (Tarita-Nistor, 2009; Erbezci & Ozturk, 2018) and with reading speed (Crossland et al., 2004; Falkenberg et al., 2007; Amore et al., 2013). However, the naturally selected PRL is often not the peripheral area with highest visual acuity (Bernard & Chung, 2018), and many of these studies succeeded in training a new retinal locus rather than only improving fixation at the existing location (Chung, 2020). It is necessary to consider the influence of this change when drawing conclusions about the importance of fixation stability alone in improving outcomes.

In nature, the eye is regularly completing visual search and smooth pursuit movements, therefore training that targets multiple forms of oculomotor control better simulates the real-world learning experience for persons living with bilateral central vision loss. In the present study, we have demonstrated that saccadic precision has a moderate association with accuracy and can be learned almost simultaneously with fixation stability when training utilizes a method that requires more than just static eye gaze. Given the importance of saccadic eye movements in reading and visual search, clinical interventions that focus on fixation stability should also include opportunities for developing saccadic precision to improve performance.

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CHAPTER 3

DISCUSSION

Despite progress being made in slowing the progression of macular degeneration, no cure for the disease currently exists and new cases are only expected to rise (Wong et al., 2014). It becomes much more important, from that perspective, to understand the process of PRL development and how a person is able to use a PRL to perform everyday activities that require eye movements once guided by the fovea. This work provides insight into how eye movements change as a person learns to use a PRL and how those changes are associated with changes in behavior. It also helps to better inform clinicians and researchers on important metrics which should be incorporated into current and future therapeutic interventions.

The participants in this study all had high-contrast and low-contrast visual acuities within typical, normal limits. Because macular degeneration characteristically progresses over years (Klein et al., 2008), population-based studies do not provide much guidance on how a PRL develops or how the person is learning to use the PRL in a functional manner. Using a healthy population, we induced PRL development in a controlled setting and closely monitored the participant's eye movements and behaviors as they changed over a series of weeks. We used tasks designed to replicate real-world complaints of persons with MD, such as reading words, recognizing faces, and identifying objects in the environment. Analyzing eye movement data collected in real time during the training provided additional insight into the PRL development process as it occurred.

Eye Movements

Quality eye movement control is required for obtaining and maintaining a high-spatial acuity image on the retina. From birth, the brain recognizes the fovea as the location where visual acuity is the highest and begins to plan and direct eye movements to this location accordingly (Van Noorden & Campos, 2002). This process is reinforced through daily repetition, becoming quick and effortless in childhood and throughout adulthood. When foveal integrity is disrupted later in life through disease or trauma, the visual system might be slower to adapt than it was during critical periods of development. However, research using perceptual learning demonstrates that visual plasticity is possible in older adults (Ball et al., 1988; Andersen et al., 2010; Bower & Andersen, 2012) and that older adults show improved eye movement control with training (Seiple et al., 2005; Janssen & Verghese, 2016). With both natural development and PRL training, repetition is key to learning and maximizing motor memory (Merzenich & Sameshima, 1993; Karni et al., 1998). Quality eye movement control is experience-dependent and requires practice.

In this study, the average participant demonstrated improvements with training in all eye movement metrics. Saccadic precision and fixation stability at the PRL were highly correlated and of particular importance for further investigation given their association with eye movements needed for performing visual tasks, such as reading. BCEA for saccadic precision improved by an average of 23 deg^2 ($p=2.99 \times 10^{-17}$) and fixation stability by 8 deg^2 ($p=2.47 \times 10^{-13}$) between the first and last training sessions, however the improvements were not linear. Fluctuations in average BCEA were seen from session to session with scores trending towards improvement by the last training

session (Figure 1). This supports the importance of practice and repetition for developing precision and stability with a PRL.

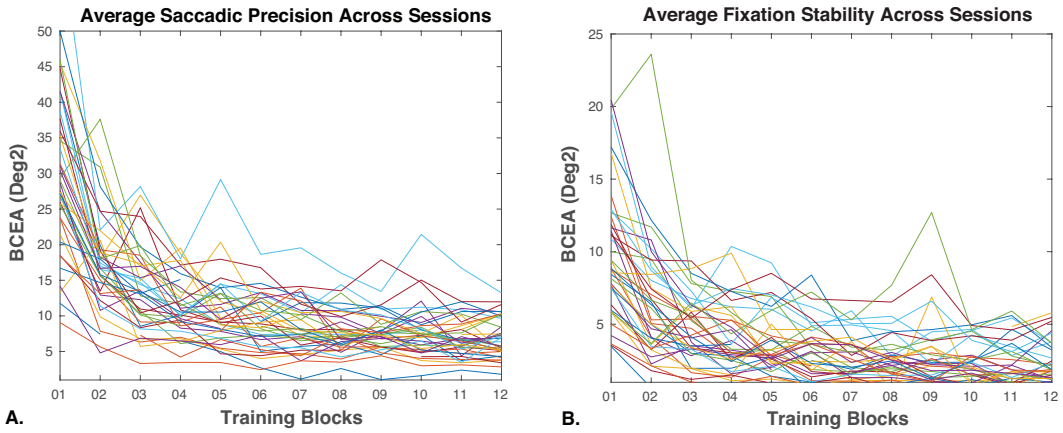

Figure 1. Average eye-movement metrics across training sessions. This figure shows the average BCEA value for each training session for all forty participants across twelve training sessions for A.) Saccadic precision and B.) Fixation stability.

We also found that the eye movement metrics were not learned in isolation. Meaning that no one eye movement metric was learned statistically faster than another. Although fixation stability has been a target of clinical intervention, it does not appear that it is necessary to learn fixation stability before learning saccadic precision. In fact, saccadic precision was learned slightly faster than fixation stability. Since these metrics are strongly correlated with one another and appear to be learned in tandem, it would seem logical that opportunities to practice both skills should be incorporated into clinical interventions. Saccadic exercises were incorporated more into traditional eccentric viewing trainings (Warren, 1996; Wright & Watson, 1995), but have been abandoned in newer biofeedback trainings. Biofeedback training shows strong promise in improving fixation stability at the PRL (Morales et al., 2020). Future researchers and clinicians using this method should consider providing opportunities to practice making saccades

with the PRL, a function not currently available using the MAIA microperimetry system programming. This could take the form of clinical biofeedback training with the inclusion of home eccentric viewing training exercises described in Chapter 1.

Behavior

Being proficient with eye movement control at a PRL is meaningless unless using the PRL increases participation in desired occupations. One way to measure the efficacy of PRL development is to look at how accurate a person is when using the PRL to complete functional activities. In this study, participants demonstrated performance improvements on all three behavioral tasks (*letter, object, face*) with training. In most cases, learning rates for the behavioral tasks were slower than those for eye movement metrics which suggests that increased accuracy follows and may be dependent upon improved eye movement control. Behavioral task accuracy during any given training session was best predicted by eye movement performance during that session, in particular for first saccade landing dispersion, saccadic precision, and fixation stability metrics. This is another example that supports the recommendation for inclusion of saccadic eye movement exercises during peripheral vision training.

Of the three behavioral tasks, performance on the letter task appeared to be the easiest for most participants with the average mean accuracy starting near 73%. This was followed by the object task at 70%, and face task at 60%. This pattern also follows the rate of learning seen for the behavioral tasks with the letter task being the fastest learned and the face task being the slowest. This is interesting in that, while the stimuli in the letter and object tasks were the same size, the faces were much larger. It might be that

while the overall face size was large, the details on the faces which distinguished male from female were lower in spatial resolution or contrast. This is consistent with the real-world experiences of people with MD who report great difficulty recognizing people based upon facial features (Bullimore et al., 1991). As the learning rate for the face task was the slowest of all, this particular task might require more control of saccadic precision and fixation stability in order to be completed accurately. Future trainings which use a similar paradigm might consider starting with a letter task and then advancing to an object and face task as eye movement metrics improve and accuracy on the preceding task plateaus.

Limitations

There are several differences in how a PRL was induced in this study and the lived experience of the typical person with MD. Scotomas generally develop over a period of years, often asymmetrically between the two eyes (Schuchard et al., 1999). Differing monocular scotoma locations means that with two eyes together, the person may not notice a disturbance in visual imagery if the scotoma locations do not overlap in visual space. This concept is like that of the physiological blind spots created by the optic discs. In this study, participant's central vision was immediately occluded at the beginning of training by an artificial scotoma at the same retinal location in both eyes.

Even in cases of monocular vision, most individuals do not notice the physiological blind spot due to perceptual completion (Abadi et al., 2011). Perceptual completion or the 'filling in' of vision occurs when visual features are perceived in an area of missing visual field even though those attributes really exist in the surrounding

local field (Gerrits & Timmerman, 1969). This phenomenon occurs for people with macular scotomas who do not notice black holes in visual space, merely distortions at the location of a scotoma or, in some cases, nothing abnormal at all (Zur & Ullman, 2003). This means the border of a scotoma is typically not clearly defined, as seen on microperimetry, and the person may not be aware they exist (Fletcher et al., 2012). In this study, we used a clearly defined central scotoma with a radius of 6° which was lower in luminance from the background. It is possible that a participant could use the boundary of the scotoma as a landmark for locating and placing the PRL at a desired location (Walsh & Liu, 2014). However, one of the initial goals in clinical settings is to increase awareness of the location and boundaries of central scotomas for this very reason.

It is noteworthy that in this study, the participants were able to return to typical foveal vision following the end of a training session. While we were successful in inducing a PRL in these participants, as evidenced by eye movement and behavioral performance changes, a natural scotoma in a person with MD does not resolve. In many cases, the size of the scotoma increases overtime and the location of the PRL may have to change accordingly (Whitaker et al., 1988). In this study, the size and locations of the scotoma and PRL were constant in relation to one another. Individuals with MD may demonstrate use of a retinal area which houses multiple PRLs that may be used for different functional purposes (Shima et al., 2010; Costella et al., 2017). The PRL trained in this study was a single window located to the left or right of the scotoma.

A final consideration is the effect of age on both learning and eye movement control. In this study, all participants were in early-adulthood. Even in the absence of neurological disease processes, normal age-related structural changes occur in the brain

which contribute to cognitive decline in multiple domains, including reductions in sensory perception and processing speed (Salthouse, 1996; Cavazzana et al., 2018), selective and divided attention (Ball et al., 1988; Groth & Allen, 2000), and learning ability, particularly in the form of explicit learning (Midford & Kirsner, 2007; Verneau et al., 2014). This means that older adults, who are more at risk for developing age-related macular disease, might have greater difficulty modifying eye movement control through learning designed to increase knowledge about the skill. However, the performance changes necessary to redirect eye movements to the PRL might still be learned implicitly through regular participation in training which promotes motor learning, as implicit learning is believed to be relatively independent of age (Jongbloed-Pereboom et al., 2019) and motor learning abilities generally persist across the lifespan (Voelcker-Rehage, 2008; Pauwls et al., 2018). Aging is also shown to impact eye movement control with increases in saccadic latency beginning in middle-age and continuing into old age (Tedeschi et al., 1989; Irving et al., 2006). These changes are believed to be correlated with decreases in processing speed (Klein et al., 2000).

Future Directions

While characteristics of this training paradigm differed in some respects from the real-world experiences of a person with MD, information gained from the study could be used to enhance the biofeedback training methodology and adapt the gaze-contingent training paradigm for people living with MD. Instead of adding home saccadic reading exercises as an adjunct to biofeedback training, software for the MAIA device could be updated to include both a fixation and a saccade training mode. In this way, the clinician

or researcher would continue to receive objective data on how the patient or participant's eye movement metrics are changing in response to training. This information would be invaluable for estimating the efficacy of training. For clinicians, it would also aid in determining whether training effects have plateaued and whether treatment should be continued or terminated. As the MAIA is widely distributed to low vision settings, a simple upgrade to the software would make this feature immediately available to many clinicians.

A second approach would be to use actual microperimetry examination results, which contain anatomical scotoma and PRL location data, to create an individualized gaze-contingent training like the one used in this study. In the individualized training paradigm, the artificial scotoma and PRL window would be placed in on-screen locations that correspond to those in the patient's actual visual field. The patient would then complete a behavioral training task using these features. If having a clearly defined scotoma truly allows a user to access and re-reference from the PRL more readily, this training method has the potential to expedite patient awareness of their scotoma location and begin making changes to their eye movements at the PRL accordingly. Using either scenario would provide clinicians with additional objective information that could be used to potentially improve outcomes for people living with MD.

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