Binocular vision and fixational eye movements

by

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Author's declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

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Abstract

Introduction

In observers with amblyopia, abnormal patterns of amblyopic eye (AME) fixational eye movements (FEM) have been associated with monocular (reduced amblyopic eye visual acuity) and binocular sensory deficits (e.g. suppression) of amblyopia. However, is it unknown whether sensory deficits associated with amblyopia cause the FEM abnormalities. The overall goal of this thesis was to investigate the effect of monocular and binocular sensory function on FEM characteristics in observers with normal vision and observers with amblyopia. The specific objectives of this thesis were four-fold. The first objective was to investigate the effect of reduced visual acuity on FEM in observers with normal vision and in amblyopia. The remaining three objectives were experiment specific and were to understand the effect of binocular interaction on FEM in observers with normal vision and amblyopia. In all experiments, participants were instructed to fixate a target that was presented either dichoptically using haploscope or non-dichoptically. Then, the measured FEMs were analyzed in 3 different ways: 1) fixational stability (global bivariate contour ellipse area – BCEA), 2) characteristics of microsaccades and 3) fast Fourier transformation (FFT).

Experiment-I

Monocular visual acuity (VA) of controls was varied from 20/20 to 20/100 using plus lenses. The amblyopia group completed three monocular conditions; a) AME fixating, b) fellow eye (FFE) fixating and c) FFE fixating with VA matched to the AME using plus lenses. The results showed that the AME had significantly less stable fixation than the FFE even when visual acuity was matched between the two eyes. Similar results were noted for microsaccadic amplitude as well. Reduced VA also had no effect on fixational stability and microsaccadic amplitude in controls. Therefore, impaired AME fixational stability could not be explained on the basis of reduced VA.

Experiment-II

The objective of Experiment – II was to study whether is there any advantage of binocular fixation over monocular fixation and if there is any advantage, whether is it noted at all contrast levels. Fixation target contrast was varied from 0% to 100% while control participants fixated monocularly (fellow eye occluded) and binocularly. The results showed that the fixational stability was significantly improved during binocular fixation compared to monocular fixation for all contrasts. FEMs were less stable when the stimulus contrast was 0%, (no central fixation target) during monocular as well as binocular

fixation. Though FS was found to be significantly improved during binocular fixation, microsaccades were found to be not different between monocular and binocular viewing conditions.

Experiment-III

The objective of this experiment was to investigate the effect of binocular interaction on observers with normal vision by introducing different form of binocular interactions such as binocular rivalry and monocular stimulation. FEMs were measured under three dichoptic viewing conditions; 1) binocular rivalry (orthogonal sinusoidal gratings), 2) monocular stimulation (left eye was presented with a grating and the right eye with a blank mean luminance screen), 3) dichoptic fusion (similarly oriented pair of gratings) and one non-dichoptic viewing condition (single grating presented to both eyes). The results showed that except during monocular stimulation viewing condition, there was no significant difference in fixational stability between the right eye and the left eye.

Experiment-IV

The objective of this experiment is to investigate the effect of binocular interaction on observers with normal vision and amblyopia by varying the interocular contrast level. FEMs were measured for both eyes simultaneously while interocular contrast was varied by reducing stimulus contrast to one eye whilst keeping it constant at 100% for the other eye. In controls, fixation stability was unaffected by interocular contrast except for when one eye viewed 0% contrast (no central fixation stimulus). In this case, the eye viewing 0% contrast had less stable fixation than the eye viewing 100% contrast. In observers with anisometropic amblyopia, interocular contrast had no affect for any condition. However, the amblyopia group had less stable fixation than the control group for all conditions. The results suggested that, in amblyopia, AME FEM were consensually controlled by the FFE under dichoptic conditions. However, in controls, the two eyes could behave independently.

Conclusion

Thus, the results of the thesis suggested that monocular sensory deficit (impaired VA) did not influence FEM. However, the relationship between AME VA and AME fixational stability during monocular fixation implied 2 possibilities, 1) abnormal FEM could contribute to impaired VA, and 2) an independent third factor such as positional uncertainty, cortical deficits could mediate both impaired VA and impaired FEM. Similarly, the results of this thesis also suggested binocular sensory deficit (suppression) did not influence FEM. During binocular fixation, AME fixation was consensually

controlled by FFE. However, lack of fixation target influenced FEM which suggested positional uncertainty could have resulted in impaired FEM in AME.

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- Finally, my beloved family members (wife, mom, dad, brother, anni and nieces) for their love and support.
- Last but not least, I thank my God for His blessings.

Dedication

I would like to dedicate this thesis dissertation to my family members.

- Mother (Mrs. Ramadevi Raveendran)
- Father (Mr. Raveendran Ramanathan)
- Brother (Mr. Ramkumar Raveendran)
- Sister-in-law (Mrs. Iswaryaa Ramkumar)
- Nieces, Rakshanaa & Rishetha.

Last but not least, I would like to dedicate this thesis to my beloved wife Jainandhini Srinivasan.

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Chapter 1
Introduction

1.1 Fixational eye movements

The five sensory systems of vision, hearing, touch, smell and taste have a common feature; when the same stimulus is presented for an extended time without changing, adaptation occurs. For instance, let us consider the tactile sense. Assume that I bought a new wrist watch and wore it for the first time. As soon as I wore it, I would feel the presence of the watch on my wrist as my wrist would not be used to the texture and mass of the watch. However, after few hours, that feeling would be gone due to tactile receptor adaptation.

With regard to vision, the best resolution of vision is achieved when images fall on the fovea, the retinal area with the highest density of cones. The main purpose of any eye movement is to align the fovea with the object of interest. However, after bringing the object of interest on to the fovea, if the object is stationary and motionless it begins to fade, particularly in peripheral vision. This phenomenon is called Troxler's effect (named after the scientist who explained it in 1804) [1–4]. To overcome adaptation and the resultant perceptual fading, the eyes exhibit incessant, involuntary micro eye movements called fixational eye movements (Figure 1-1).

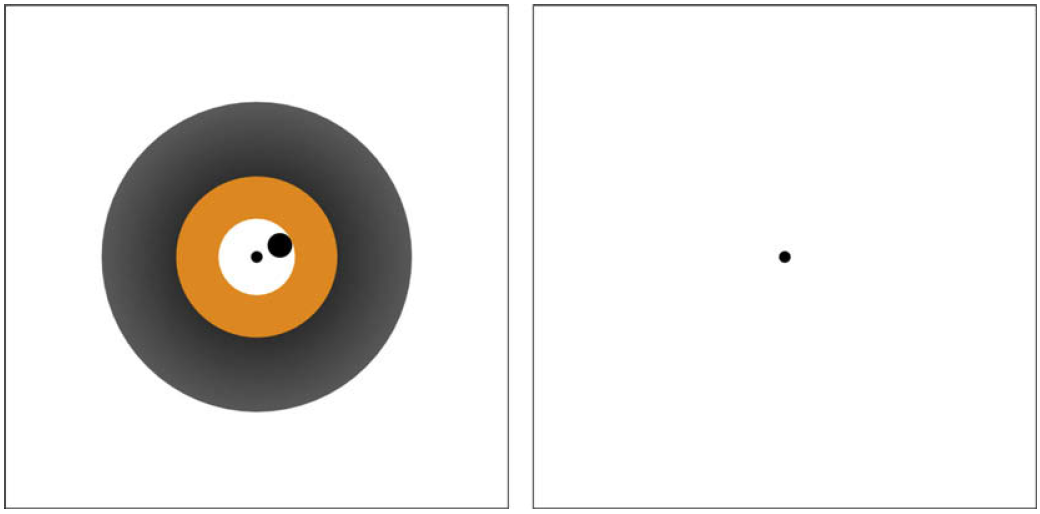


Figure 1-1: Illustration of fixational eye movements

The figure illustrates the fixational eye movements by inducing an after-image. Keep the image at 20cm from you and fixate at the central dot at the left panel for about 30 secs. Then change your fixation to the fixation dot at the right panel, you will perceive an after-image which constantly moves according to your fixational eye movements. Moreover, if you try to control the fixational eye movements, you will notice that the after-image spontaneously fades away (Troxler's effect). Reprinted from Rolfs, 2009, Vision Research, Copyright (2017), with permission from Elsevier (See Copyright permissions#1).

Fixational eye movements were first described in 1599 by a psychologist named du Laurens. He reported that "the eye standeth not still but moveth incessantly" (pg-117 of Wade & Tetler, 2005). However, the first empirical evidence was provided by Robert Darwin (Charles Darwin's father) in 1786 where he used a piece of red silk on a white background and reported that "unsteadiness of the eye a

part of the fatigued retina falls on the white background" (pg-118 of Wade & Tetler, 2005). However, it was Helmholtz in 1924 who reported "it requires an extraordinary effort and attention to focus the gaze perfectly sharply on a definite point of the visual field even for 10 or 20 seconds" and termed these movements as "wandering of the gaze" (pg-205 of Wade & Tetler, 2005).

1.1.1 Types of fixational eye movements

Currently, the consensus is that fixational eye movements are categorized into three types based on velocity, amplitude and frequency. They are, 1) microsaccades, 2) ocular drifts and 3) ocular tremors.

Microsaccades are square wave-like, jerky eye movements that occur at the rate of 1-2 Hz. They are the fastest among the three types of fixational eye movements with peak velocity ranging from 16 to 47 deg/s (Martinez-Conde, Macknik, Troncoso, & Hubel, 2009). Velocity is the most common criterion used to isolate microsaccades from other components of fixational eye movements. Microsaccades have characteristics that are similar to voluntary saccades such as a main sequence. The main sequence is a relationship between amplitude and peak velocity whereby higher amplitudes have a higher peak velocity with the relationship following a saturating

function. In fact, microsaccades fall on the same main-sequence continuum as saccades. Since microsaccades exhibit a main-sequence relationship, they are considered to share the same neural mechanism as voluntary saccades [5,6]. Amplitude is not used for this purpose because the amplitude of microsaccades can vary from a few seconds of arc to 2 degrees [3–5] and can be as large as 5 degrees in some cases e.g. amblyopia [7,8].

Ocular drifts are low velocity eye movements with amplitudes ranging from 1 to 12 minutes of arc (Martinez-Conde et al., 2004) and a velocity typically less than 30 min of arc/sec. The usual method to isolate drifts is to remove microsaccades from the data. Drifts are then measured as "intersaccadic intervals"[9,10]. Cornsweet (1956)[11] suggested that drifts are not under visual control and are as random as Brownian movements.

The third component of fixational eye movements is ocular tremors, small amplitude and high frequency (30 – 100Hz) movements that occur during ocular drifts. Since the frequency of tremors is usually higher than that of critical flicker frequency (about 30Hz) and its amplitude is well within the diameter of a cone photoreceptor, ocular tremors are thought to have a limited effect on vision compared to other two types of eye movements [3,4,9]. Moreover, the modern video-based eye

trackers such as EyeLink-II have high intrinsic noise[12] that is almost equal to the amplitude of tremors and therefore, it is very hard to measure and isolate the tremors from the other components of fixational eye movements or from instrument noise.

Unlike voluntary saccades, microsaccades are typically involuntary. However, there is evidence that microsaccades can be controlled voluntarily during activities that require high visual attention such as threading a needle, aiming a gun etc. Drifts and tremors, on the other hand, cannot be controlled voluntarily. Microsaccades are also considered to be binocular, always conjugate between two eyes.[13–15] Unlike microsaccades, ocular drifts and tremors do not show conjugacy. They are not binocular in nature and have a poor correlation between the two eyes.[14,16]

Therefore, in summary, fixational eye movements are classified into three types based on their amplitude, frequency and velocity. Of these three types, ocular drifts and tremors are mainly random and they take the image off the fovea. Thus, one of the purposes of microsaccades is to correct the error induced by ocular drifts and tremors.

1.1.2 Stability of fixational eye movements

Modern eye trackers provide information on both horizontal and vertical eye positions. Based on this information, the stability of fixation has usually been

quantified by two different methods – 1) standard deviation (SD) of eye positions and 2) bivariate contour ellipse area (BCEA).

Ott, Seidman and Leigh (1992)[17] measured stability of fixational eye movements using scleral coils in observers with normal vision. They noted the mean SD of fixational eye movements to be LE: 0.11±0.05 deg, RE: 0.11±0.06 deg for horizontal; LE: 0.10±0.07 deg, RE: 0.11±0.07deg for vertical and LE: 0.16±0.12 deg, RE: 0.20±0.11 deg for torsional eye movements. Krauskopf et al. (1960)[14] also measured the stability of fixational eye movements using photocell contact lenses and the mean SD was less than 3 minutes of arc for both monocular and binocular viewing conditions.

The former method gives a stability measure for horizontal and vertical eye positions separately whereas the estimation of fixational stability using BCEA gives the area of an ellipse with a major axis dictated by the standard deviation of horizontal eye positions and a minor axis corresponding to the standard deviation of vertical eye positions. However, measures of stability based on BCEA do not differentiate between the underlying micro eye movements (microsaccades and ocular drifts). The detailed method of calculating BCEA is provided in section 2.2.1.

1.1.3 Functions of fixational eye movements

1.1.3.1 Maintenance of ocular fixation (fixational stability)

It remains unclear whether microsaccades or ocular drifts plays an active role in maintaining ocular fixation. There are few studies which suggested that microsaccades play an active role [11,14,16]. Contrarily, few other studies suggested that ocular drifts were capable of controlling fixation [12,18,19]. There are few more studies which suggested that both ocular drifts and microsaccades were error-producing and error-correcting in nature [20,21].

It was Cornsweet (1956) who first suggested that ocular drifts were not under visual control and fixation error was noted be increased during the ocular drift. He also noted that microsaccades reduced those fixation errors induced by ocular drifts. However, this claim by Cornsweet was challenged by Nachmias (1961). First, he noted that microsaccades directions were highly idiosyncratic. Moreover, the author also noted that some corrections were achieved by ocular drifts as well. Steinman and his colleagues noted that microsaccades can be controlled voluntarily. When the microsaccades were controlled, ocular drifts effectively maintained the ocular fixation. Thus, they not only questioned the purpose of microsaccades but also suggested that only ocular drifts are essential for maintaining fixation. Later, Engbert

& Kliegl (2004) showed increase in the variance of FEM after removing microsaccades from the time series. Thus, they concluded that variance in fixation and control in fixation were highly dependent on microsaccades. Later, Chung et al. (2016) showed that using multiple regression model showed that factors such as amplitude and rate of microsaccades were important in predicting fixational stability. An interesting study was done by de Bie (1986) where they shifted the fixation target by about 2.5 min arc and studied the behavior of fixation in response to target shift. They noted that target shift resulted either in ocular drifts or microsaccades towards the target. Therefore, it was concluded that both ocular drifts and microsaccades could be error correcting. This result was consistent with the early findings of Nachmias (1961). Cherici et al. (2012) measured FEM in observers with normal vision in two experimental conditions, 1) marker condition (presence of fixation target) and 2) no-marker condition (absence of fixation target). Then, they quantified the interplay between the microsaccades and ocular drifts by estimating compensatory index, i.e. the direction which an oculomotor event (saccades/drifts) shifted the line of sight in relation to the preceding oculomotor event (saccades/drifts). It was shown that tendency to compensation of drifts was not influenced by presence or absence of fixation target. However, the tendency was significantly reduced when the fixation

target was absent. Moreover, both ocular drifts and microsaccades showed good tendency to compensation when the fixation target was present.

Thus, it could be concluded that though ocular drifts are capable of maintaining ocular fixation without an aid from microsaccades, the latter eye movements are more efficient in precise relocating of the target than the former eye movements. Therefore, a proper interaction between ocular drifts and microsaccades is essential for proper ocular fixation. Factors such as differences in the stimuli, analyses of eye movements could have resulted in these inconsistencies noted in the literature. Therefore, there is a need of objective analysis of fixational eye movements without any bias in definition of eye movements.

1.1.3.2 Prevention of perceptual fading

The other purpose of the fixational eye movements that has been debated for a long time is prevention of perceptual fading. Ditchburn et al. (1959)[1] showed that after stabilizing retinal image motion, perceptual fading occurred the periphery. However, this claim by Ditchburn was opposed by Steinman and his colleagues[12,18,19]. Collewijn and Kowler (2008) [12] argued that in the real world, it is still unclear why we need such micro amplitude eye movements since head movements move the image across larger part of the retina to avoid perceptual fading. They noted that microsaccades are

suppressed efficiently during high visual acuity task such as threading a needle and suggested that microsaccades serve no useful purpose. Moreover, some trained participants can efficiently suppress microsaccades without fading of the visual percept [18,22]. Ditchburn [23] replied to these claims with what has become a famous quotation, "Some acrobats can walk on their hands with amazing agility and most young people can learn to do this tolerably well. Certain tasks, such as following a line marked on the floor can be performed with reasonable accuracy. Yet no one suggests, from these facts, that it is mysterious that feet have evolved. Similarly, the fact that many subjects can perform certain kinds of visual tasks in the absence of frequent saccades does not conflict with the view that saccades play an important and, indeed, an essential part in normal vision" (pp 272 of Ditchburn 1980).

More recently, McCamy et al. 2012 [24] showed that microsaccades play a major role in the prevention of Troxler's effect (Figure 1-2). In this experiment, participants were asked to fixate on a red dot and respond to visibility (intensification) or fading of a low spatial frequency Gabor patch (40% contrast) which was presented at different eccentricities. They noted that the rate of microsaccades was higher during Gabor patch intensification than during Gabor patch fading. Therefore, they concluded that microsaccades indeed play a role in intensification of Gabor patch i.e.

prevention of Troxler's effect. However, it should be noted that the retinal motion due to ocular drifts was not measured during the experiment. Therefore, though it is evident that fixational eye movements are useful in the prevention of perceptual fading, it is still debatable whether ocular drifts or microsaccades play a dominant role.

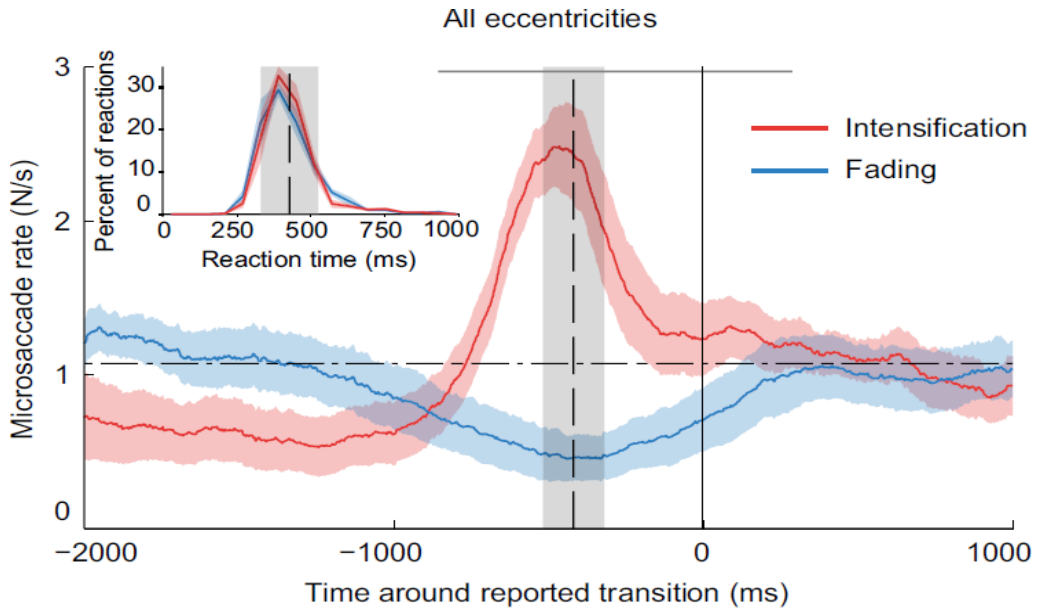


Figure 1-2: Microsaccades prevent perceptual fading

McCamy et al. 2012 showed that fading of Gabor patches presented at different eccentricities was associated with reduction in the rate of microsaccades. They concluded that microsaccades are helpful in preventing perceptual fading. Image from McCamy et al (2012) and copyrights obtained (See Copyright permissions#2)

1.1.3.3 Fine spatial details.

Ko et al. 2010 [25] created a threading a virtual needle experiment. They noted that the rate of microsaccades substantially reduced during high visual attention

demanding tasks and also during finely guided visuomotor tasks. This was consistent with the findings of Steinman & his colleagues [12,18,22]. However, the suppression of microsaccades occured only after the distance between the needle and the thread was less than 5" of arc. Moreover, they also noted that almost every time before adjusting the position of the needle, microsaccades shifted the gaze between the needle and the thread. Therefore, microsaccades were used as an oculomotor strategy to precisely relocate the two objects of interests (the virtual needle and the virtual thread). The purpose of precise relocation and alignment of objects onto the fovea by microsaccades was tested by Poletti et al. (2013)[26]. Within the fovea, the foveola has the highest sensitivity. Using a high precision dual Purkinje image eye tracker and a retinal image stabilization technique, they showed that microsaccades precisely relocate stimuli within the foveola [26].

It was mentioned earlier that ocular drifts are Brownian movement or random walk[27,28].This raises an important question: what is the purpose of smooth intersaccadic ocular drifts? Rucci and Casille (2005)[29] tested the hypothesis that ocular drifts enhance spatial details. Using computational techniques, they showed that image motion on the retina introduces an important component in early visual processing that might contribute to effective representation of natural scenes. In other

words, ocular drifts convert spatial information into temporal information. But the question is why is this important? If the image is static (zero temporal frequency) on the retina, a set of photoreceptors receives averaged luminance of the natural scene. Therefore, the spatial correlation between two adjacent receptors is very high and they can compute only low spatial information. However, if the image is dynamic, i.e. swept across retina by ocular drifts with non-zero temporal frequency, two adjacent photoreceptors would no longer have such a high spatial correlation and can compute a larger range of spatial information. This decorrelated spatial information is essential for early visual processing because retinal ganglion cells [30], LGN cells [29] and V1 neurons [21,31–33] are highly sensitive to decorrelated signals compared to spatially correlated signals. Subsequent studies have provided empirical evidence that decorrelated signals due to ocular drifts result in enhanced perception of high spatial frequencies [32,34,35]. The illustration of how luminance modulation by ocular drifts plays a role in enhancing high spatial frequencies is shown in Figure 1-3.

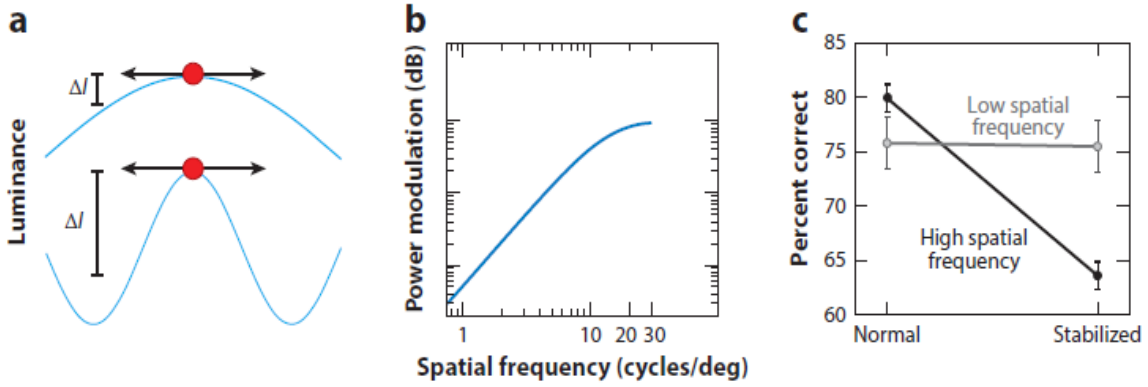


Figure 1-3: Enhancement of high spatial frequency processing due to ocular drifts.

The figure shows the effect of ocular drifts on enhancing high spatial frequencies (image was reprinted from Rucci & Poletti (2015)): a) shows mean luminance modulations that occur due to ocular drifts for low (top) and high spatial frequency gratings (bottom), b) power modulation due to ocular drifts at the level of photoreceptors was plotted as a function of spatial frequency, c) Results from Rucci [34] in which participants were asked to respond to the orientation of gratings, either at low (gray) or high (black) spatial frequency, on a noisy background with and without retinal stabilization. Retinal stabilization resulted in impairment selectively to high spatial frequency. No additional permissions are required to reprint this figure from Annual Reviews.

Mostofi et al. (2015) [35] showed that ocular drifts enhance sensitivity to high spatial frequencies whereas microsaccades enhance sensitivity to low spatial frequencies. Snodderly, 2016[36] provided physiological evidence supporting the results of Mostofi et al (2015) and showed that saccades and drifts selectively activate different populations of V1 neurons that have quite different spatiotemporal characteristics. Ocular drifts selectively activate "positional/drifts cells" in V1 which are sensitive to changes of contrast and high spatial frequencies.

1.1.3.4 Summary

Thus, fixational eye movements are not a mere noise of the oculomotor system. The incessant image motion due to fixational eye movements helps not only in preventing Troxler's fading but also helps in providing decorrelated visual signals for subsequent neuronal processing [5,6,21,25,30,32,34,37–39]. Therefore, optimal excursion (stability) of fixational eye movements maintains the image within the region of fovea and contributes to visual sensory processing by enhancing important spatial characteristics.

The above-discussed purposes of fixational eye movements raise an important question: whether is there any causal relationship between less stable fixation and impaired sensory processing that is present in vision conditions such as amblyopia.[40–44] For instance, amblyopia is associated with poor control of microsaccades i.e. increased amplitude of microsaccades. One of the functions of microsaccades is to precisely relocate preferred retinal locus suggests that increased amplitude might lead to impaired spatial vision. Similarly, ocular drifts were noted to enhance the sensitivity towards high spatial frequency. Therefore, it is logical to expect that if an optimal level of fixation stability enhances spatial vision, then an abnormally increased level of instability may contribute to impaired sensory processing in

conditions such as amblyopia. In other words, there is a possibility of causal (direct) relationship between abnormal fixational eye movements and the impaired spatial vision that is associated with amblyopia.

The following two sections will discuss the sensory deficits, oculomotor deficits and the relationship between these two in amblyopia.

1.2 Amblyopia

Amblyopia is a neuro-developmental disorder in which monocular or binocular vision loss is caused by abnormal visual experience in an early developmental period due to strabismus, anisometropia (or both combined) or visual deprivation.[45,46] The prevalence of amblyopia in developed countries was estimated to be 1 – 5% [47,48] and it still considered to be one of the major reasons for monocular vision loss in adults [46]. It is also considered to be a burden on society due to reduced quality of life. [47]

1.2.1 Sensory deficits of amblyopia

In amblyopia, apart from amblyogenic factors such as strabismus and anisometropia, no ocular structure abnormalities are present. As von Noorden describes it, *"the condition in which the examiner sees nothing and the patient very little"*.[49] Therefore, amblyopia is clinically diagnosed based on a difference of two logMAR lines of visual acuity between the amblyopic eye and the fellow eye and an acuity deficit in the amblyopic eye. The other classical visual deficit of the amblyopic eye is crowding, i.e. poorer visual acuity while measuring with a row of letters than an isolated letter. While clinically diagnosed as a reduction of 20/40 in one eye and a two line difference between the eyes [46] studies show amblyopia also affects many visual

functions including contrast sensitivity[50–54], positional information[55–60] and motion perception[61–65]. These sensory deficits can be broadly classified into local deficits (that occur at the early stage of visual processing) and global deficits (at later stages of visual processing).

1.2.1.1 Local deficits

The sensory deficits such as reduced visual acuity and contrast sensitivity are local spatial deficits and appear to occur at the level of primary visual cortex (V1). Hence, multiple theories have been postulated to explain these spatial deficits based on the behavioral and structural changes in V1 - 1) *reduced contrast sensitivity and resolution in the neurons of V1 or even earlier sites (LGN)* [50,66,67]*, 2) Undersampling (aliasing)* [60,68] *and 3) uncalibrated cortical topography* [59,69]*.*

It has also been reported that there is a significant difference between anisometropic and strabismic amblyopia in terms of visual deficits. Mckee, Levi & Moshovon (2003) [54] measured contrast sensitivity, grating acuity, Vernier acuity (a form of hyperacuity) and stereoacuity (a measure of binocularity) in 427 adult observers with amblyopia (anisometropic, strabismic, mixed and deprivational) and observers without amblyopia but with a risk factor for amblyopia such as anisometropia or strabismus. They showed that the pure strabismics (without

anisometropia) showed overall better contrast sensitivity compared to anisometropes, mixed and deprivational amblyopes. However, despite their better contrast sensitivity, strabismics do exhibit acuity as poor as anisometropes if not even slightly worse. Among all the factors, observers with eccentric fixation had the worst overall contrast sensitivity and acuity levels. Brain imaging studies also found differences between these subtypes of amblyopia. Using MRI and VBM (voxel based morphometry), Mendola et al. 2005 [70] found that anisometropic amblyopia showed more reduced gray matter compared to strabismic amblyopia. fMRI studies showed that for strabismic amblyopes, reduced activity at the calcarine sulcus was noted for low spatial frequency stimuli whereas for anisometropic amblyopia, reduced activity at the calcarine sulcus was noted for high spatial frequency stimuli[71].

However, Bi et al (2011) [72] showed that abnormalities in behavioral responses such as contrast sensitivity were always underestimated at the level of V1 during physiological studies in macaques reared with strabismus. Moreover, they also showed that further downstream in the neurons of V2, abnormalities were found to be much higher than that noted at the level of V1 (Figure 1-4). These results suggested that abnormalities in amblyopia might extend even beyond the striate visual cortex into the extra-striate areas where global processing takes place.

1.2.1.2 Global deficits

The receptive field size of cells within V1 (striate cortex) are smaller in size compared to the cells in extrastriate areas and therefore those cells process information from a much smaller and more limited field of vision. Therefore, information processing respecting the entire field of vision requires integration of local information across multiple V1 receptive fields. This is known as global processing. Global processing occurs within the extra striate areas of the visual cortex that have relatively large receptive sizes. For instance, global processing of motion occurs at dorsal extrastriate areas such as V5 /MT and global processing of form occurs at ventral areas such as V4. There is also a more consistent representation of binocularity across neural populations in extrastriate areas such as V2 [72] and V5/MT [73] (Figure 1-4) than in V1.

It is well established that global motion processing is abnormal in amblyopia [62,65]. However, this abnormality was pronounced only when amblyopes were asked to perform a task that requires segregation of signal/noise but not when performing the task that requires only integration of information [63,64,74]. These findings suggested that deficits of global processing in amblyopes are not due to a simple extension of local deficits. On the contrary, it has been suggested that deficits in amblyopia are a

cascade. In other words, the deficits seem to occur first in V1 and that deficit is amplified further downstream [75,76].

In conclusion, deficits in amblyopia shown to be extended beyond the visual area V1 into the extra-striate areas where the information from both eyes are combined.

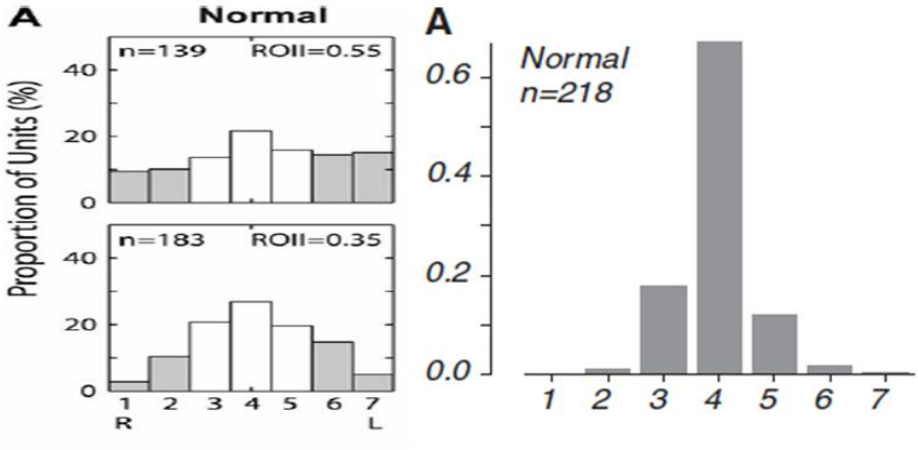


Figure 1-4: Binocular representation is more pronounced in higher visual areas such as V2 and MT/V5.

The figure shows the ocular dominance columns in the scale of 1-7, the extreme numbers 1, 2 or 6, 7 represent that neurons are highly monocular. The figure shows the proportion of types of neurons in V1 (top left), V2 (bottom left) [Bi et al, 2011[72]]and V5/MT (right) [El-Shamayleh et al. 2010 [73]] in monkeys with normal binocular vision. It is clearly shown that more representation binocular cells are noted in higher visual areas compared to V1. [Copyright permissions obtained for both Bi et al. 2011 and El-Shamalayah et al. 2010. See Copyright permissions #3].

1.2.1.3 Suppression

The other common phenomenon that is seen in patients with amblyopia is interocular suppression (*for simplicity sake, it will be noted as suppression hereafter*). To deal with interocular image differences (in cases of anisometropia) or diplopia (in cases of strabismus), the visual system suppresses the visual information from the weaker eye. If the suppression is left untreated, then it may subsequently develop into amblyopia. Two processes were thought to be the basis for suppression; 1) binocular rivalry and 2) dichoptic masking.

In individuals with normal binocular vision, the two foveas are corresponding retinal points. When each fovea is presented separately with a pair of dissimilar objects (that cannot be fused into a single image, e.g. pair of orthogonal gratings), each eye would have their turn to be the dominant eye while the other eye is suppressed. This phenomenon is known as binocular rivalry. It is also considered to be one of the mechanisms behind the physiology of suppression in strabismic amblyopes [77]. It is shown that GABA, an inhibitory neurotransmitter, plays a major role in bi-stable perceptions such as binocular rivalry and, that people with higher GABA had slower alternations. [78]. Sengpiel et al. (2006) also showed that suppression in strabismic cats was mediated by the level of GABA in visual cortex [79]. Therefore, the mechanism

behind suppression in strabismic amblyopia and binocular rivalry may be similar. [80] However, it should be noted that the difference was that binocular rivalry induced in controls, alternates the perception between two eyes. However, in the cases of strabismic suppression, there will be no such alternation of perceptions due to disproportionate differences in the ocular dominance.

Dichoptic masking refers to a phenomenon where presenting an incompatible stimulus to one eye prevents the detection of another stimulus presented briefly to its fellow eye. This also considered to be one of the reasons for suppression, especially in the cases of anisometropia and small-angled strabismus[81]. However, both rivalry and dichoptic masking share common dynamics [82] and dichoptic masking may be an early stage of binocular rivalry [83]. Dichoptic masking can be explained in terms of contrast, whereby presentation of a higher contrast stimulus (pedestal) to one eye influences the detection of lower contrast stimulus presented to the other eye (masking). This method of masking has been used to understand the mechanism behind contrast processing (discrimination)[84–87].

It has been suggested that amblyopes lack binocular summation due to suppression. Meese et al. (2006) [88] used contrast masking to develop a new binocular vision model called the "Two-stage model" (Figure 1-5) that attempts to explain the

mechanism behind suppression in amblyopia. According to the model, there are two stages in binocular contrast summation. In the first stage, two monocular signals are subjected to some inhibitory inputs (red lines in Figure 1-5) from the contralateral eye (interocular suppressive) and also some internal (Gaussian) noise from the ipsilateral eye. Then these two monocular (excitatory – green lines) signals are sent to the second stage for summation. In normal binocular vision, the interocular suppressive inputs are almost equal such that the two monocular signals that reach the second stage for summation are also equal. However, in the cases of abnormal binocular summation as noted in amblyopia (right panel of Figure 1-5), the non-dominant eye is subjected to additional signal attenuation and greater internal noise. Therefore, the suppressive (inhibitory) inputs from the non-dominant eye to the dominant eye would be weaker than that of the dominant eye to the non-dominant eye. Subsequently, when two monocular (excitatory) signals reach the second stage for summation - an imbalance in the two monocular signals leads to a lack of binocular summation.[89] Therefore, this model suggests that the location of suppression in amblyopia might be before the location of summation. Later, Baker et al. (2008) showed that binocular contrast summation in human amblyopia is intact if the monocular signals are balanced between two eyes by reducing the contrast of the signals to the dominant eye.

Therefore, it is considered that imbalanced sensory signal between the amblyopic eye and the fellow eye is the basis for interocular suppression [53,88,89].

Mckee, Levi & Moshovon (2003) [54] measured contrast sensitivity, grating acuity, Vernier acuity (form of hyperacuity) and stereoacuity (measure of binocularity) in 427 adult observers with amblyopia (anisometropic, strabismic, mixed and deprivational) and without amblyopia but possessing one or the other risk factors of amblyopia such as anisometropia, strabismus. They noted that individuals with binocular vision showed better contrast sensitivity and acuity level compared to non-binocular individuals. They argued that the presence or absence of binocularity is a key factor in determining the visual deficits of the amblyopic eye. [54,75]

In light of this evidence, the condition of amblyopia is now considered to be a binocular deficit rather than a monocular deficit. Novel anti-suppression training has been developed based upon adjusting the contrast between the amblyopic and fellow eye. Techniques using this principle have been developed for a number of common devices such as iPod® [90,91] as well as iPad® platforms [92,93]. Numerous investigations now show that prolonged exposure to binocular tasks with balanced contrast reduces the suppressive action of the fellow eye on the amblyopic eye, which is associated with improved visual acuity and in some cases improved stereopsis[63,91,92].

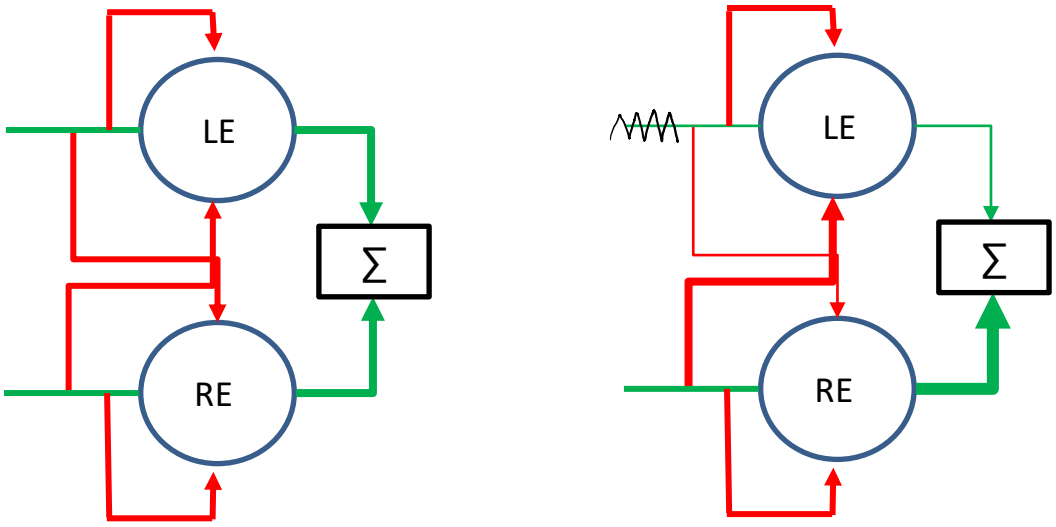


Figure 1-5: Two-stage model of binocular vision.

The left panel represents the normal binocular vision model and the right panel represents the amblyopia model and explains the mechanism underlying the lack of binocular summation in amblyopia. The green lines represent excitatory signals and the red lines represent inhibitory signals. Thickness of lines represents the weight of the signal, i.e. the thinner the line, the weaker the signal. See text for detailed explanation of the model. This is an adapted figure from Meese et al. 2006 and modified (shown only till summation process) for the purpose of easy understanding.

1.3 Oculomotor deficits of amblyopia

Eye movements are broadly classified into 2 types – 1) eye movements that bring the image onto the fovea e.g. saccades, vergence and 2) eye movements that hold the image on the fovea, e.g. vestibulo-ocular reflex and smooth pursuit. Eye movements such as saccades, smooth pursuits, disparity vergence and fixational eye movements have been shown to be abnormal in observers with amblyopia (Tables 1-1 & 1-2). Table 1-1 summaries the studies that reported abnormalities of eye movements such as saccades, vergence and smooth pursuits whereas Table 1-2 summaries the studies that reported abnormal patterns of fixational eye movements in observers with amblyopia. Niechwiej-Szwedo et al. (2010) measured saccadic eye movements in 13 patients with anisometropic amblyopia and found that saccadic latencies are longer when the amblyopic eyes were viewing compared to latencies noted during binocular viewing and fellow eye viewing. Therefore, they concluded that abnormal sensory processing delays the processing of motor commands. Later, McKee et al. (2013) measured saccadic eye movements in 421 observers with amblyopia and without amblyopia but with amblyogenic factors. Anisometropes showed shorter a latency compared to mixed and strabismic amblyopes. Though correlations between interocular saccadic latency and interocular VA, grating acuity

and contrast sensitivity were noted, these deficits could not explain the differences between anisometropic and strabismic amblyopes. Hence, they concluded that the motor deficits could not be attributed to sensory deficits.

A similar uncertainty was noted in binocular eye movements such as disparity vergence (a disconjugate eye movement that occurs when the object of interest moved in depth). Kenyon et al. 1980[94] measured disparity vergence in observers with amblyopia and strabismus. They noted that disparity vergence was absent for observers with amblyopia and strabismus. Similarly, Boman and Kertesz (1985) [95] showed that disparity vergence does not exist in observers with strabismus. They also concluded that disparity blocking mechanisms (suppression) were restricted to central field of vision only. To test the effect of suppression on disparity vergence, Raveendran (2012) [96] [Unpublished work] measured disparity vergence in 6 patients with strabismic amblyopia in two different viewing conditions, 1) with objective angle of strabismus aligned (i.e. bifoveal fixation) and 2) with bifoveal fixation and also with interocular contrast of the visual stimuli balanced (to enhance binocular combination). The results showed that there was no effect of improved binocular combination on disparity vergence in observers with amblyopia.

Therefore, in summary, most of the studies have pointed to the sensory deficits of amblyopic eyes such as visual acuity & interocular suppression for oculomotor deficits[97,98]. However, there are a few studies which suggest that sensory deficits did not influence the motor deficits[99,100].

Table 1-1: Characteristics of different eye movements in amblyopia

Type of eye movements	Deficits in amblyopia
Saccadic eye movement	• Increased latency in the amblyopic eye compared to the fellow eye and to that of control participants and normal latency during binocular or fellow eye viewing [97–100] • Deficits attributed to sensory deficits of the amblyopic eye [97,98]. • Anisometropes showed shorter latency compared to mixed and strabismic amblyopes. Sensory deficits could not explain the differences between anisometropic and strabismic amblyopes.
Smooth pursuits	• Increased latency in the amblyopic eye [101–103] • Normal steady state gain in anisometropic amblyopes [101] and decreased steady state gain in strabismic amblyopes [102,103] • Normal catch-up saccade frequency in anisometropic amblyopia and increased frequency of catch-up saccades in strabismic amblyopia [103] • Deficits attributed to sensory deficits of the amblyopic eye

Disparity Vergence eye movements	• No evidence of disparity vergence eye movements in strabismic amblyopes[104]. In the absence of disparity of disparity vergence, accommodative component of vergence helps in reducing disparity [94]. • Disparity vergence exists in strabismic amblyopes but the disparity blocking mechanism (possibly suppression) is limited to the central visual fields. [95]

1.3.1 Fixational eye movements in amblyopia

Like other eye movements, fixational eye movements are also reported to be abnormal in amblyopia. Table 1-2 summaries the abnormalities noted in fixational eye movements of observers with amblyopia. Though fixational eye movements are classified into three types, information on tremors has not been reported because they are difficult to measure and are believed to serve no useful purpose in the human visual system[41]. Overall, it is evident that amblyopic eyes show reduced fixational stability compared to their fellow eyes. However, reports of the other characteristics of fixational eye movements such as amplitude/rate of microsaccades and ocular drifts have been inconsistent.

For observers with amblyopia, microsaccades were shown to be larger and more frequent [8,105,106]. However, there are other studies which showed no difference in microsaccadic amplitude between observers in amblyopia and controls [40,107]. Moreover, a study by Shi et al. 2012 in observers with anisometropic amblyopia showed that microsaccades were larger and less frequent in the amblyopic eye compared to the fellow eye. Later, Chung et al. 2015 showed that in groups of observers with anisometropia, there was no statistical significance in microsaccadic amplitude between the amblyopic eye and the fellow eye. However, in groups of observers with strabismus, the amblyopic eye showed significantly larger

microsaccadic amplitude compared to fellow eyes. Most recently, Shaikh et al., 2016 also did not find any difference in the microsaccadic amplitude between controls and observers with amblyopia (strabismus and/or anisometropia). Thus, the characteristic of microsaccades were found to be inconsistent in the literature.

Similarly, ocular drifts were also shown to be abnormal in observers with amblyopia. Ocular drifts were found to be larger and faster in the amblyopic eye [105,106,108]. Recently, Chung et al. 2015[41] also showed that the amplitude of ocular drifts was larger in the amblyopic eyes of observers with amblyopia due to strabismus and/or anisometropia. However, they did not find any difference in the speed of ocular drifts. Thus, there are inconsistent findings as far as the characteristics of ocular drifts and microsaccades are concerned. One explanation for these inconsistent results could be the different detection algorithms that these previous studies used to isolate the oculomotor events. Another characteristic of fixational eye movements is that characteristics of ocular drifts and microsaccades cannot portray is overall fixational stability (detailed information about fixational stability was provided in section 1.1.2). Amblyopic eyes show less stable fixation.[40,42–44,106] Since the findings on characteristics of microsaccades/ocular drifts were inconsistent, it remains unclear which type of fixational eye movements contribute to the overall deficit in fixational stability.

1.3.2 Visual acuity and fixational stability

Spatial vision is impaired in the amblyopic eyes. From Table 1-2, it is evident that fixational eye movements are also abnormal in the amblyopic eye. It is unknown whether there is a causal relationship between vision impairments and abnormal fixation stability in amblyopia.

Of the previous studies (listed on Table 1-2), only 5 studies looked at the association between visual acuity (VA) and fixational stability in observers with amblyopia. Srebro (1983)[109] measured monocular fixational eye movements in observers with normal vision and amblyopia (strabismic and/or anisometropia) and noted that characteristics of fixational eye movements such long-term drift, fixational stability, intersaccadic drift interval, amplitude and rate of microsaccades were not correlated with VA of the amblyopic eye. Almost three decades later, Gonzalez et al. (2012)[40] measured fixational eye movements in monocular and binocular viewing conditions and noted that there is no correlation between VA and reduced fixational stability of AME. However, this finding was later challenged by Subramanian et al. (2013)[42] and Chung et al. (2015). Subramanian et al. (2013)[42] measured fixational stability in 89 children using a Nidek MP1 microperimeter. Though overall there was a significant correlation between VA and fixational stability, when the subgroups of

amblyopia were analyzed there was no such relation between VA and fixational stability in anisometropic amblyopes.

Chung et al. (2015) also measured fixational stability in 28 adult observers with amblyopia and concluded that there is a significant correlation between VA and fixational stability irrespective of the subtypes of amblyopia. Later, Shaikh et al. 2016[44] classified observers with amblyopia into three categories as mild, moderate and severe amblyopia based on the visual acuity of the amblyopic eye. They also noted that the fixational stability deteriorated with increasing severity of amblyopia. However, it is important to note that a correlation between the fixational stability and VA does not suggest that VA is the limiting factor on fixational stability or vice versa. Chung et al. (2015) also reported a mediation analysis suggesting that error magnitude, fixational stability, amplitude of microsaccades and amplitude of ocular drifts limit visual acuity in amblyopia. Moreover, no study has investigated the effect of simulated reduction of VA on the amblyopic and normal visual systems.

1.3.3 Binocular interaction and fixational stability

The other sensory class of visual deficits that may be associated with abnormal patterns of fixational eye movements in amblyopia are abnormal binocular interactions such as suppression. Gonzalez et al. (2012)[40] measured fixational eye

movements in monocular and binocular viewing conditions and estimated a binocular summation ratio (monocular BCEA/binocular BCEA). Since no binocular advantage was noted when the amblyopic eye was viewing and, also there was a correlation between interocular visual acuity differences and fixational stability, they concluded that a lack of binocular summation could be responsible for reduced fixational stability of the AME. Similarly, Subramanian et al. (2013)[42] also showed a significant correlation between stereo acuity and fixational stability, i.e. the worse the stereoacuity, the less stable the fixation.

A direct measure of the relationship between binocular interactions and fixational stability in amblyopia was first reported by Raveendran et al. (2014)[43] who showed that in strabismic amblyopia, binocular fixational stability could be improved transiently by aligning the objective angle of strabismus (foveal fixation) and balancing the contrast of the target between the amblyopic eye and the fellow eye (improved binocular interaction). Though, the improved binocular interaction brought the fixational stability of the amblyopic eye to be comparable to that of control participants, it should be noted that aligning the strabismus was the major factor in improving fixation stability.

Even though the consensus is that the amblyopic eye shows less stable fixational eye movements, it remains unclear whether it is the characteristics of microsaccades, ocular drifts or both that contribute to fixational stability. Chung et al. (2015) noted that error magnitude and characteristics of microsaccades are the primary limiting factors in fixational stability (BCEA) in amblyopia. However, there are four studies which showed no abnormalities in microsaccadic amplitude in amblyopia even though the fixational stability was found to be significantly less stable.[40,44,107,109] Schor & Hallmark (1978) suggested that failure of microsaccades to correct for the error induced by ocular drifts was responsible for poor fixational eye movements in the amblyopic eye. Furthermore, Cherici et al. (2012) also noted in observers with normal vision that the interaction between microsaccades and ocular drifts was critical in maintaining stable fixation. They also concluded that characteristics of ocular drifts, not microsaccades, were better predicting factors of fixational stability. Therefore, it remains unclear which type of fixational eye movements contribute to overall fixational stability.

Table 1-2: Fixational eye movements and amblyopia

Table 1-2 summarizes the literature on fixational eye movements in amblyopia. Fixational stability, microsaccades and ocular drifts were considered.

S No	Authors	Fixational stability	Microsaccades	Ocular drifts
1	Schor & Hallmark (1978)	Not measured	Increased rate and amplitude in the AME	Increased rate in the AME of strabismic amblyopia
2	Srebro (1983)	AME showed decreased stability.	Amplitude and frequency normal	Increased drifts in the AME.
3	Ciuffreda, Kenyon & Stark (1979, 1980, 1991)	Not measured	Increased amplitude and rate of were noted in the AME	Increased peak to peak amplitude of drifts and mean velocity were noted in the AME

4	Gonzalez et al. (2012)	Reduced fixational stability of the AME.	Microsaccadic amplitude and rate of microsaccades did not vary between the AME and the control groups.	Ocular drifts were not analyzed
5	Shi et al. (2012)	No measure of stability was quantified	In anisometropic amblyopia, increased amplitude, lower rate of microsaccades were noted in AME compared to FFE	Longer intersaccadic interval was noted in AME
6	Subramanian et al. (2013)	Reduced fixational stability was noted for the AME compared to FFE and controls	Characteristics of microsaccades were not analyzed	Characteristics of ocular drifts were not analyzed

7	Raveendran (2013) & Raveendran et al. (2014)	Reduced fixational stability was noted in the amblyopic eye of strabismic amblyopes compared to fellow eyes.	No significant difference in the microsaccadic amplitude was noted.	Characteristics of ocular drifts were not analyzed
8	Chung S et al. (2015)	Reduced fixational stability was noted for AME of strabismic amblyopes compared to FFE and the control participants. The AME of anisometropic amblyopes did not vary significantly from the controls.	Increased amplitude and increased rate of microsaccades were noted for the AME of strabismic amblyopes compared to FFE and the control participants. The AME of anisometropic amblyopes did not vary significantly from the controls.	The amplitude of ocular drifts in the AME of both groups was significantly higher compared to control participants.

9	Shaikh A et al. (2016)	Reduced fixational stability was noted in the AME during viewing and non-viewing conditions.	No significant difference was noted for microsaccadic amplitude and frequency	No significant difference was noted for ocular drifts as well.

1.4 Goals and objectives of the thesis

Of the nine studies listed in Table 1-2, only four showed a relationship between impaired AME VA and less stable AME fixation [41,42,44,109]. Moreover, these associations were based on correlation between VA and fixational stability in AME. Moreover, there are a few studies which show no relationship between VA and fixational stability [40,109]. Thus, the relationship between VA and fixational stability remains unclear and no study has investigated the effect of simulated reduction of VA on the amblyopic and normal visual systems.

Secondly, there are a few studies [40,42] suggested that abnormal binocular experience could have resulted in less stable fixation of AME. However, again, this has not been investigated directly on the amblyopic and normal visual systems. Thus, the overall goal of this thesis was to investigate the effect of monocular and binocular sensory function on FEM characteristics in observers with normal vision and observers with amblyopia.

The specific objectives of this thesis were four-fold. The objective of Experiment-I was to investigate the effect of reduced visual acuity on FEM in observers with normal vision and in amblyopia. The remaining three objectives were experiment specific and were to understand the effect of binocular interaction on FEM in observers with normal vision and amblyopia. The objective of Experiment–II was

to study whether is there any advantage of binocular fixation over monocular fixation and if there is any advantage, whether is it noted at all contrast levels. The objective of Experiment-III was to investigate the effect of binocular interaction on observers with normal vision by introducing different form of binocular interactions such as binocular rivalry and monocular stimulation. The objective of this experiment is to investigate the effect of binocular interaction on observers with normal vision and amblyopia by varying the interocular contrast level.

The secondary goal of the study was to investigate whether the nature of fixational eye movements can be effectively by converting eye movement data from time domain into frequency domain using fast Fourier transformation. In this thesis, we used fast Fourier transformation to analyze FEM in observers with normal vision and observers with amblyopia to analyze FEM objectively i.e. without isolating the oculomotor events.

Chapter 2
Methods

In this section, methods common to all experiments such as the instrumental arrangement and data analysis techniques will be described.

2.1 Instrumentation

Fixational eye movements were measured under two different viewing conditions, 1) dichoptic viewing using a haploscope and 2) non-dichoptic viewing.

2.1.1 Haploscope

2.1.1.1 Building the haploscope

Two cold mirrors, which transmit infrared light but reflect 96% of visible spectrum light (Edmund Optics, NJ, USA http://www.edmundoptics.com/optics/optical-mirrors/specialty-mirrors/cold-mirrors/1900), were placed orthogonally 15cm from a chinrest. On either side of the mirrors, two 7" LCD monitors (Lilliput®, California, USA http://lilliputweb.net/non-touch-screen-monitors/7-inch-monitors/619gl-70np-c.html) were placed at 25cm. Thus, the total viewing distance was 40cm. The haploscope is shown in Figure 2-1 and a schematic representation is shown in Figure 2-2.

The two haploscopic monitors were controlled by a computer and using an external multi-display adapter (DualHead2Go® from Matrox Graphics Inc., Quebec, Canada http://www.matrox.com/graphics/en/products/gxm/dh2go/analog), the resolution of 1600x600 was split into two such that each monitor had a 800x600 resolution. The luminance of both monitors was found to be approximately around 105cd/m^2 when displaying 50% luminance.

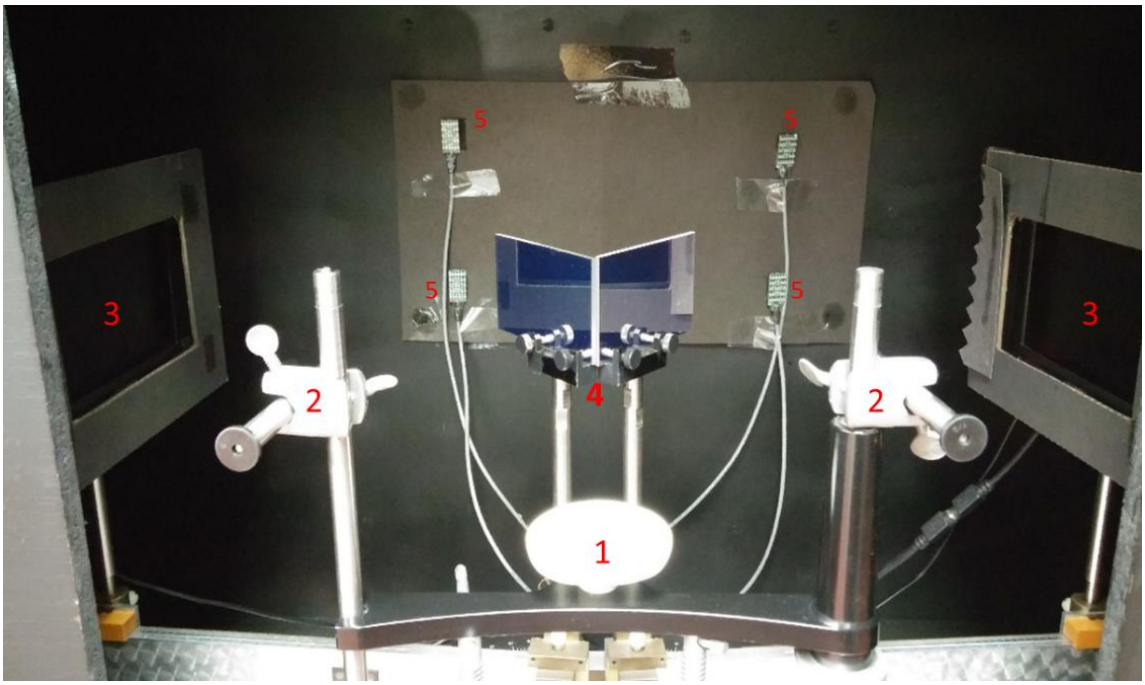


Figure 2-1: The haploscope

The haploscope was constructed from: 1) a chinrest, 2) two clamps that support the head to minimize any lateral movement, 3) two 7" LCD monitors that were placed 25cm from the center of rotation of the instrument, 4) two cold mirrors that were placed orthogonally at the distance of 15cm from the eyes and 5) four IR markers which were placed behind the mirrors, 40cm from the chinrest.

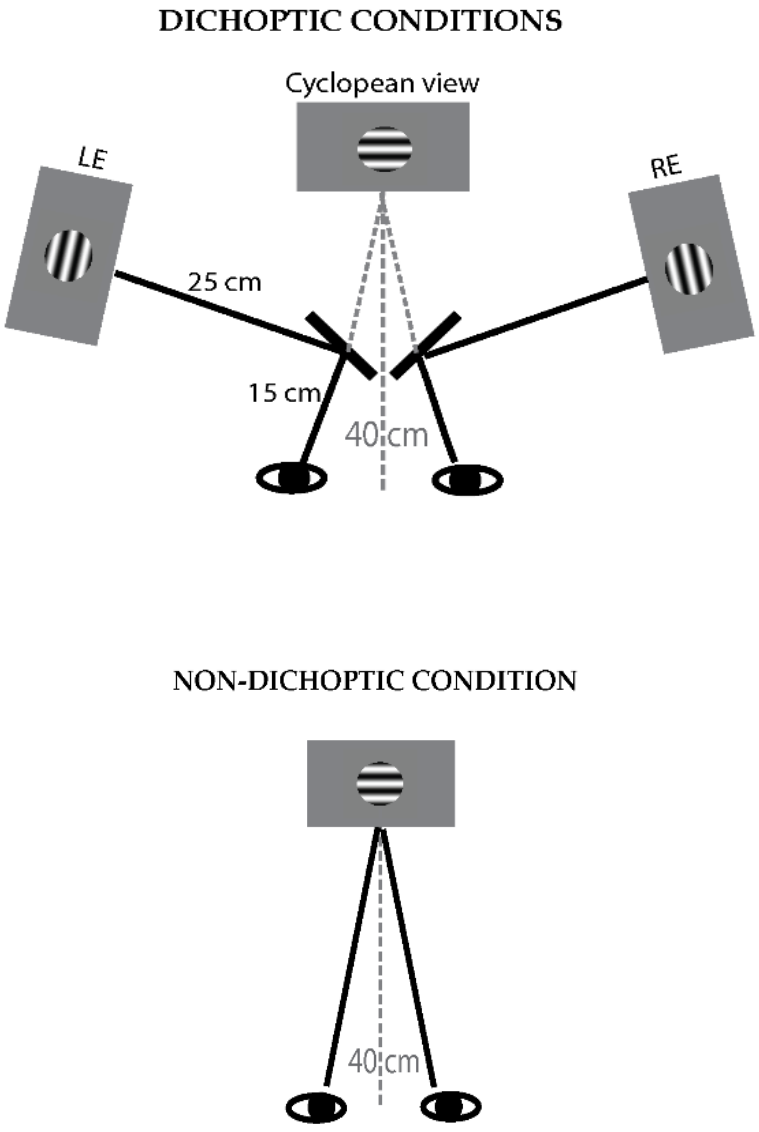


Figure 2-2: Schematic representations of dichoptic viewing (top) and non-dichoptic viewing conditions.

2.1.1.2 Gamma measurement of the screen and the cold mirrors

The gamma function (a non-linear function between the pixel value and its actual luminance) was measured for 1) the LCD screen directly and 2) the reflected image of the screen from the cold mirror using a photometer (Konica-Minolta CS-100A). The result of this calibration is shown in Figure 2-3. The gamma value was found to be 2.2 for both LCD monitors when measurements were taken directly. Similar values were found when the measurement was taken from the reflected image of the screen. This correction factor was then implemented in the MATLAB code for preparing the visual stimuli. The almost identical gamma functions for both conditions suggested that the reflected image through the cold mirror had similar image characteristics to the LCD screen.

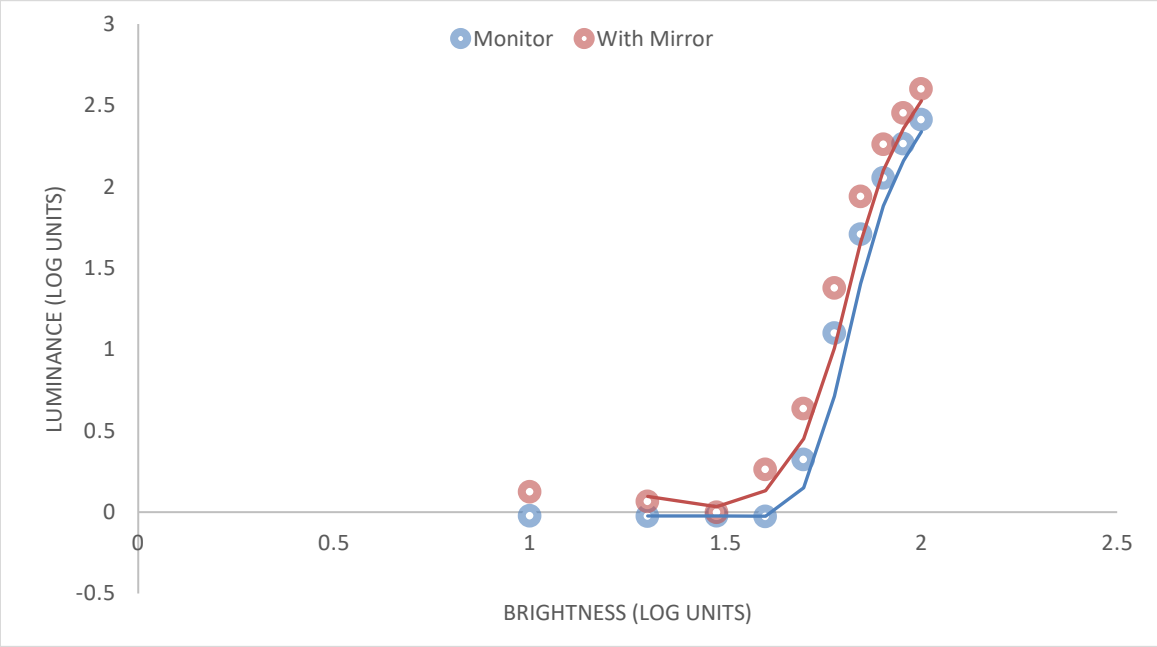


Figure 2-3: Gamma measurement of the LCD screen and the reflected image of the LCD screen on the cold mirror.

The relationship between the brightness (V), luminance (L) and gamma (γ) is defined as $L=aV^{\gamma}$, where 'a' is a constant offset at the brightness value of zero.

For Experiments - I & III, fixational eye movements were also measured in a non-dichoptic viewing condition. The schematic representation of this viewing condition is shown in Figure 3-3. The non-dichoptic viewing condition was created by placing a 7″ LCD monitor (one of the haploscopic monitors) at 40 cm (Figure 1-3) along the midline of the face of participants.

It should be noted that in both dichoptic and non-dichoptic conditions, the planes of accommodation and vergence were at 40cm. Under dichoptic conditions, the arms of the haploscope were rotated to provide a 40cm vergence angle for an inter-pupillary distance (IPD) of 60mm. Participants adjusted the haploscope arms from this starting point to align an "x" presented on one screen with a "+" presented on the other. This ensured that the vergence and accommodation planes were fixed at 40cm for all participants and minimized the contribution of these factors to fixation stability.

2.1.2 Eye tracking

Fixational eye movements were measured using a video-based infra-red eyetracker, EyeLink-II (Figure 3-4) from SR Research, Osgoode, Canada http://www.sr-research.com/EL_II.html) and eye movements were sampled at the rate of 500Hz. The eye tracker has a spatial resolution of 0.01° root mean square. The pupil-only eye tracking mode was used for all experiments.

Figure 2-4: The EyeLink-II infrared eyetracker

The eye tracker consists of 1) two IR LEDs and a video camera for each eye and 2) an IR sensor at the forehead region. Proper alignment of the eyetracker is achieved by adjusting the position of the camera using the pivot (3).

The eye tracking system also involves four infra-red head markers. These head markers were tracked by a sensor at the forehead region of the head mount. The purpose of the head markers is to track head movements which are then compensated for in the eye movement data. Usually, these head markers are placed in the four corners of the monitor which is used to display visual stimuli. For the non-dichoptic conditions, the four markers were placed on the 4 corners of the 7" monitor. However, for the dichoptic conditions, the four head markers were placed behind the haploscope cold mirrors at a distance of 40cm from the eyes (Figure 2-2)

2.1.3 Calibration of the eye tracker

Before measuring fixational eye movements on every participant, monocular calibration of the eye tracker was performed. A custom nine-point calibration procedure was used to calibrate and then validate each eye separately. If the average difference between the calibration and the validation was ≤0.5°, then the calibration was considered acceptable. If not, the calibration procedure was repeated until it was acceptable. After calibration, drift correction was performed.

2.2 Data Analysis

2.2.1 Estimation of fixation stability

The stability of fixational eye movements (fixational stability) was quantified using global bivariate contour ellipse area [BCEA] [19,40,110]. The equation to estimate the BCEA is as follows,

$$BCEA = \pi\chi^2\sigma_x\sigma_y\sqrt{(1-\rho^2)}$$

where χ^2 is the chi-square value (2 degrees of freedom) corresponding to a probability value of 0.682 (i.e.±1SD); σ_x, σ_y correspond to standard deviations of horizontal and vertical eye positions, respectively; ρ corresponds to Pearson correlation coefficient between horizontal and vertical eye positions. Therefore, the formula provides us the

area of the ellipse that comprises fixational positions of 68% of the time of a trial. In other words, the larger BCEA values imply that the fixational positions are highly dispersed and fixational stability is poor (Figure 2-5). The advantage of this method of quantifying fixational stability using BCEA is that it considers the variance of both horizontal and vertical components of fixational eye movements.

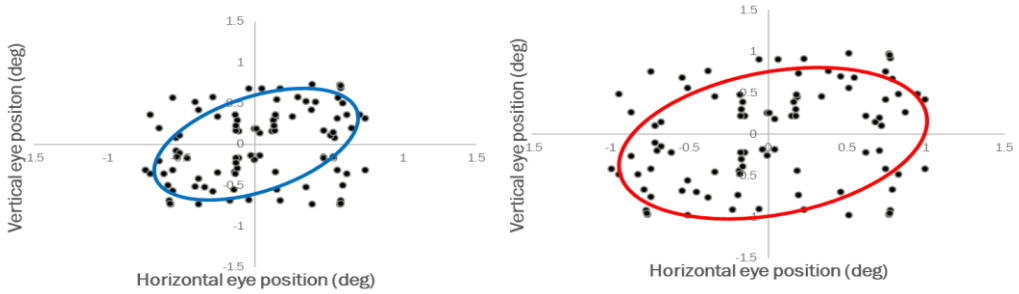


Figure 2-5: Pictorial representation of bivariate contour ellipse area (BCEA)

Representational figures of the BCEA analysis. More dispersed fixational points (right panel relative to left panel), result in a greater ellipse area which indicates reduced fixational stability.

2.2.2 Detection of microsaccades

There are many ways to isolate microsaccades from the data of fixational eye movements. Microsaccades are the largest and the fastest type of fixational eye movements. Though the amplitude of microsaccades is usually smaller than a typical voluntary saccade, the amplitude is not used as a criterion to isolate microsaccades for the following reasons. Firstly, voluntary saccades can be made at amplitudes as small as microsaccades. Secondly, the amplitude of microsaccades can be as large as

2 or 3 degrees in some pathological conditions [5,111] and hence assigning the upper threshold based on amplitude is difficult. Thus, the most well-accepted method is to delineate microsaccades based on a velocity criterion. However, this method has also its own limitation – the velocity threshold to detect microsaccades is highly susceptible to the noise of the measuring device. Though different types of the algorithm [13,41] are available, the "unsupervised cluster method" developed by Otero-Millan et al. 2014[112] was used in these experiments. This method uses a statistical method called cluster analysis to delineate true microsaccades from noise detected as microsaccades. Therefore, the noise of the measuring device has a limited effect on the detection of microsaccades.

The algorithm first detects the potential microsaccadic events by identifying velocity peaks in both the vertical and horizontal components of the eye movement trace. Velocity peaks that are separated by at least 30ms (to avoid detecting overshoots as separate events) will be detected as a potential microsaccade event. After detection, the algorithm uses clustering (a statistical method to group elements with similar properties) to divide the detected events into noise and microsaccades. Thus, this method provides improved accuracy in detecting microsaccades by delineating noise from actual microsaccades and reduces the error of detection by 62%. The other

strength of this algorithm for the experiments described in this thesis is that it does not require microsaccades to be binocularly conjugate. The algorithm is available for free download at http://smc.neuralcorrelate.com/sw/microsaccade-detection/.

2.2.3 Fast Fourier transformation (FFT) of fixational eye movements

Fast Fourier transformation (FFT) is a discrete Fourier transformation where any signal from its original format (here, time domain) will be converted into the frequency domain.[113] In other words, FFT decomposes N data points (usually in the power of 2 e.g. 4, 16, 2048, 4096, etc.) of a signal in the time domain into N data points in a frequency domain. Then it gives a frequency spectrum which identifies the frequency distribution and peak frequencies of the signal. In this study, we used FFT as the tool to analyze the frequency components of fixational eye movements of control participants and participants with amblyopia due to anisometropia and strabismus. Therefore, the idea was that converting the data of fixational eye movements from the time domain to the frequency domain would provide information on the influence of microsaccades and ocular drifts on fixational stability without using criteria to isolate them from other types of eye movements.

The eye movements were measured at a sampling rate of 500Hz. In order to perform FFT, the analysis requires samples at the power of 2 (e.g. 4, 16, 128 etc.). In

this analysis, we chose 4096 samples because the minimum frequency spectra that could be analyzed was 0.12207 Hz and 500/4096 = 0.12207. Therefore, the eye movement data corresponding to initial 4096 points of time domain (approximately 8sec, i.e. 4096/500 = 8.192 initial seconds of eye movement data) was converted into the frequency domain. The analysis was performed using MATLAB (Mathworks©) and a custom program was used. Before performing FFT analysis, the horizontal components of eye positions were detrended in MATLAB to correct for any slow drifts due to mild head tilt during eye movement measurement or due to slow slip of the eye tracker. Then the horizontal component of eye movements was analyzed using FFT.

FFT was used in the eye movements analysis to reveal the dominant frequencies from an eye movement waveform. [114] Simmers et al. (1999)[114] used this method to identify dominant frequencies in the fixation data from the patients with congenital nystagmus. Similarly, in this thesis, FFT was used to identify dominant frequency in the fixational eye movements data of observers with normal vision and amblyopia.

2.3 Clinical details of observers with amblyopia

All participants provided informed, written consent and the study was approved by the Office of Research Ethics, University of Waterloo. The detailed clinical information of all the observers with amblyopia are provided in Table 2-1. Participants were recruited from the lists of participants who were recruited for a clinical trial (a randomized clinical trial for binocular treatment of amblyopia – BRAVO [115]. All participants had VA difference of at least 2 lines between AME and FFE. Participants were classified as anisometropic amblyopia, if the difference of refractive error between AME and FFE ≥1.50DS. From the list of participants, S5 and S8 were classified as observers with mixed amblyopia and the remaining six participants were classified as observers with anisometropic amblyopia. Note that all participants had full refractive correction worn during measurement of FEM.

Table 2-1: Clinical details of observers with amblyopia

S.No	Participant		Refractive error	VA (dist)	VA (near)	Sensory status		Motor status	
	Age	Gender				W4DT	Stereoacuity	Angle of strabismus	EF
S1	38	F	AME: +3.50DS/-1.00DC x 135 FFE: plano	AME: 0.5 FFE: -0.3	AME: 0.66 FFE: -0.1	D: Fusion N: Fusion	60	No strabismus	No EF
S2	48	F	AME: +4.00DS OS: plano	AME: 0.46 FFE: -0.10	AME: 0.46 FFE: -0.04	D: Fusion N: Fusion	400	No strabismus	2Δ nasal
S3	26	M	AME: +3.50DS FFE: plano	AME: 0.3 FFE: 0.0	AME: 0.4 FFE: 0.0	D: Fusion N: Fusion	>800	No strabismus	2Δ nasal
S4	33	F	FFE: plano AME: +5.50DS/-1.50DC x 70	FFE: -0.2 AME: 0.5	FFE: 0.0 AME: 0.4	D: Fusion N: Fusion	100	No strabismus	3Δ nasal
S5	30	M	AME: +5.00DS FFE: +3.00DS	AME: 0.7 FFE: 0.0	AME: 0.8 FFE: 0.02	D: Fusion N: Fusion	>800	8-10Δ intermittent exotropia	No EF

S6	42	M	AME: +1.50/-3.25x170 FFE: plano	AME: 0.4 FFE: 0.02	AME: 0.9 FFE: 0.0	D: Suppression N: Diplopia	>800	No strabismus	2Δ temporal
S7	47	M	FFE: plano AME: +1.75DS	FFE: 0.0 AME: 0.3	FFE: 0.0 AME: 0.4	D: Fusion N: Fusion	200	No strabismus	2Δ nasal
S8	25	F	AME: +3.50DS FFE: plano	AME: 0.56 FFE: 0.0	AME: 0.48 FFE: 0.0	D: Suppression N: Suppression	>800	14-16Δ esotropia	No EF

D – Distance; N – Near; VA – visual acuity; W4DT – Worth four dot test; EF – Eccentric fixation. AME – Amblyopic eye; FFE – Fellow fixing eye; DS – Diopters in sphere; DC – Diopters in cylinder.

Stereoacuity was measured using Randot® stereocuity test. Eccentric fixation was measured by using Haidinger's brushes.

Chapter 3

Effect of visual acuity on fixational eye movements

3.1 Introduction

Visual acuity (VA) is a measure of spatial resolution of the visual system. Tests may involve recognising targets such as letters (recognition acuity) or the ability to detect spatial features (resolution acuity). A clinical diagnosis of amblyopia is made on the basis of VA. Specifically, amblyopia is defined as an interocular difference of at least two 0.2 LogMAR in otherwise healthy eyes. Along with reduced visual acuity, the amblyopic eye (AME) also exhibits abnormal fixational eye movements (FEM) which cause fixation to be less stable than the fellow eye (FFE) and control eyes [40–44]. FEM abnormalities (refer to Table 1-2) include increased microsaccadic amplitude [8,41,116], increased ocular drift amplitude[41,108] and increased ocular drift velocity [105,108,117].

One study has suggested that impaired AME fixational stability is independent from the AME VA deficit [40]. However, a number of larger studies have reported a positive correlation between reduced AME VA and reduced AME fixational stability (S. Chung, Kumar, Li, & Levi, 2015; Shaikh, Otero-Millan, Kumar, & Ghasia, 2016; Srebro, 1983; Subramanian, Jost, & Birch, 2013). Subramanian et al. (2014) measured fixational stability in 89 children using Nidek MP1 microperimeter. Though overall there was significant correlation between VA and fixational stability, when the

subgroups of amblyopia (strabismic and anisometropic amblyopia) were analyzed no significant relationship between VA and fixational stability was found in anisometropic amblyopes. Later, Shaikh et al., 2016 [44] classified observers with amblyopia into three categories as mild, moderate and severe amblyopia based on the visual acuity of the amblyopic eye. Fixational stability was found to deteriorate with increasing severity of amblyopia.

The cause and effect relationship between impaired fixational stability and reduced VA in amblyopia has not been studied directly. It is conceivable that reduced VA could impair fixation stability, perhaps by reducing the spatial resolution of fixation targets. Alternatively, impaired fixation stability could reduce VA by moving images away from the fovea. The latter possibility was supported by Chung et al. (2015), who identified AME fixational stability as a limiting factor on VA using mediation analysis. However, as they point out, establishing whether VA reduces fixation stability or the converse is not clear from the results.

Building on this previous work, the main objective of this experiment was to directly test whether reduced VA induced by plus lenses impacts fixational stability in a similar fashion to the reduced VA and fixational stability found in amblyopia. The rationale was that if in fact reduced VA impairs fixational stability, then

degrading visual acuity in control participants would reduce fixational stability. Similarly, if reduced VA contributes to the fixation stability impairment in amblyopia, reducing FFE VA such that it matches AME VA, should reduce the difference in fixational stability between the two eyes.

3.2 Methods

3.2.1 Participants

13 participants [5 control and 8 observers with amblyopia] took part in this study. All 5 control participants (age: 31 ± 6 yrs) had best corrected visual acuity better than or equal to 0 logMAR in both eyes, stereoacuity of 40″ and no strabismus or anisometropia. Of 8 participants with amblyopia (age: 36 ± 9 yrs), 6 were anisometropic and 2 (S5 and S8) had mixed strabismic/anisometropic amblyopia (Table 2-1). All participants with amblyopia had an interocular VA difference of at least logMAR 2 lines and an FFE VA ≤0.02 logMAR. Anisometropia was defined as an interocular refractive error difference of ≥1.50DS. All participants wore full refractive correction when FEM were measured.

3.2.2 Visual stimuli and instrumentation

The stimulus (Figure 3-1, top panel) consisted of an 8.1° outer box and a 1° central fixation cross presented on a mean luminance background (105 cd/m^2). The

visual stimulus was presented in a haploscope (Figure 3-1, bottom panel). The rationale behind using the haploscope was to permit direct comparisons with other experiments within this thesis. Only monocular fixational eye movements were measured and the fellow eye was occluded completely using a black patch.

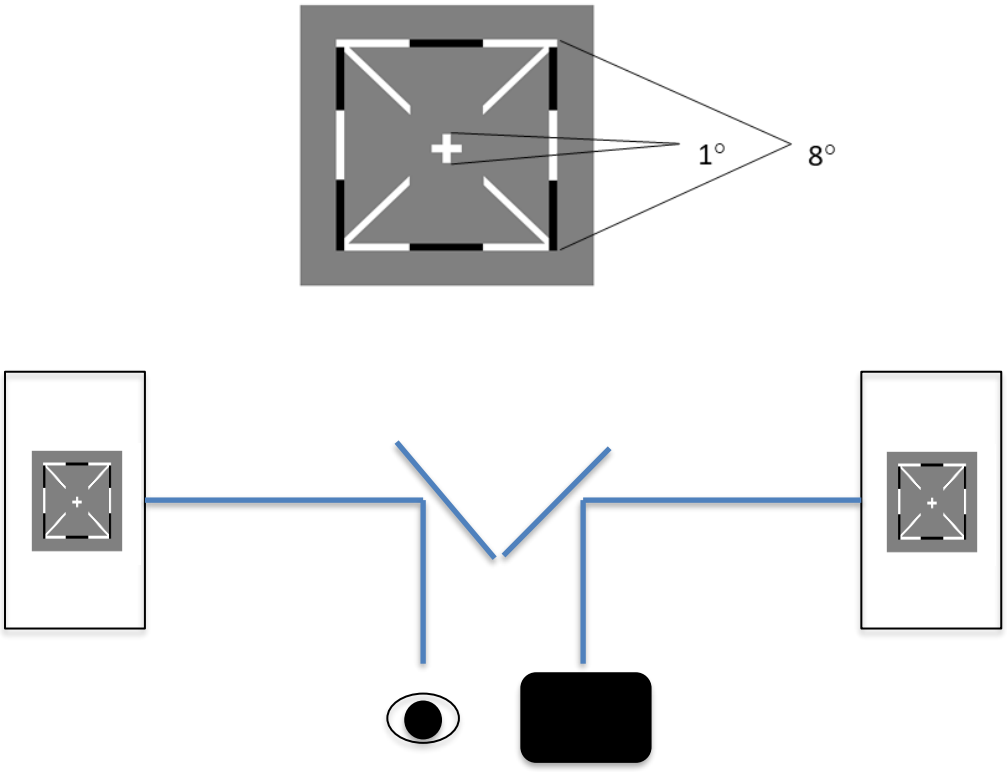


Figure 3-1: Visual stimuli and the schematic representation of stimulus presentation.

3.2.3 Procedure

For the control participants, the right eye or left eye was randomly chosen and then near visual acuity was measured using the standard near visual acuity chart (Precision vision®) at 40cm. The participants were then asked to wear a trial frame

(with refractive error correction in place if any). Monocular visual acuity (measured using the same near VA chart) of control participants was blurred using corrected curve convex (plus) lenses to 0, 0.2, 0.4, 0.6 and 0.7 logMAR. A +2.50D corrected curve convex lens was placed in the trial frame (with refractive error correction in place) to relax accommodation for the working distance of 40cm. All other plus lenses were placed on top of the +2.50D lens until the participant could not read the line below the required VA level. For example, if the required simulated VA level was 0.4 logMAR, then the plus lenses were added until 0.3 logMAR line could not be read. Then, at each simulated visual acuity (blur) level, monocular fixational eye movements were measured for 15sec and each trial was repeated 10 times. The order of the simulated visual acuity levels was randomized across trials.

For the participants with amblyopia, three different monocular viewing conditions were tested with the non-viewing eye occluded; 1) AME fixating, 2) FFE fixating and 3) FFE fixating with visual acuity matched to that of the AE using corrected curve plus lenses. The same procedure used for the control participants was used reduce FFE VA to match AME VA. Then for each viewing condition, fixational eye movements were measured for 15sec and each condition was repeated 10 times. The order of the viewing conditions was randomized across trials.

3.3 Results

3.3.1 Comparison between controls and observers with amblyopia

BCEA analysis revealed that the AMEs showed less stable FEM compared to the FFEs ($t_7 = 3.16$; $p=0.02$). However, the difference in fixational stability between the AMEs and control eyes did not reach significance ($t_{11} = 2.09$; $p=0.06$). Though less fixational stability and larger microsaccadic amplitude were noted in AME compared to FFE, these values failed to reach statistical significance when compared with controls (Figures 3-2 and 3-3). It could be argued that it was due to the relatively small sample size of the control group. However, a study with larger sample size (n=14) by Chung et al., 2015 also showed that there was no statistical significance difference between fixational stability of controls and AME of anisometropic amblyopia. Fixational stability of the FFEs did not differ significantly from controls ($t_{11} = -1.16$; $p=0.21$).

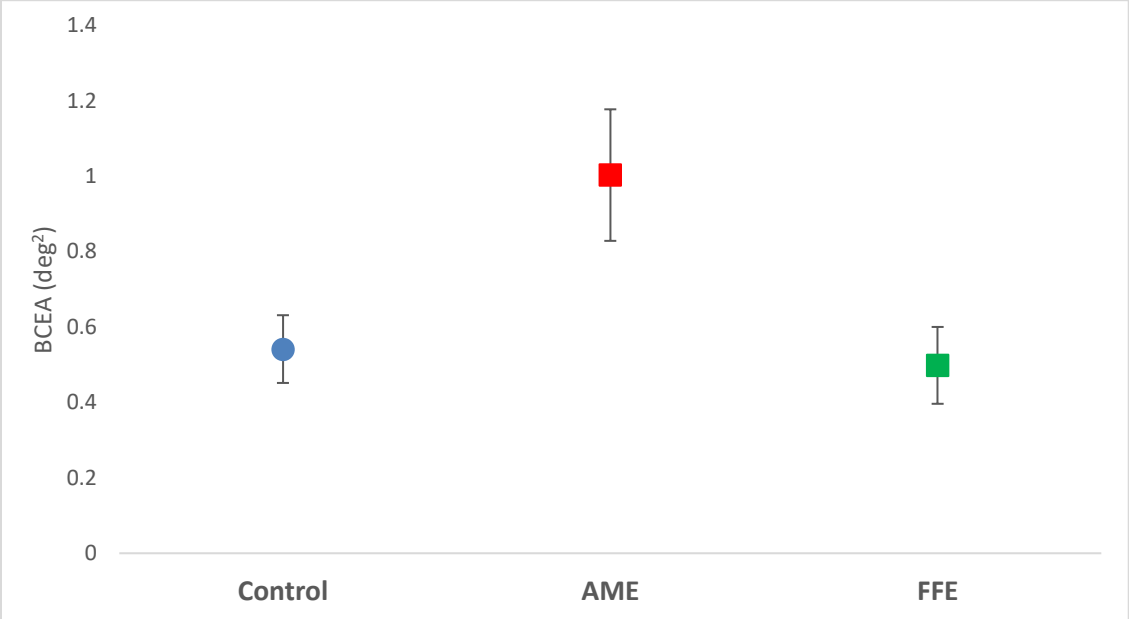


Figure 3-2: Mean fixational stability: Controls vs. amblyopia

Average BCEA of controls (blue), AME (red) and FFE (green). AME showed larger microsaccadic amplitude compared to FFE but not controls. The error bars represent ±1 SEM.

A similar trend was present for microsaccadic amplitudes. The average microsaccadic amplitude was larger in the AMEs compared to the FFEs ($t_7 = 3.16$; $p=0.02$), but did not differ significantly from control eyes ($t_{11} = -1.90$; $p=0.09$). Average microsaccadic amplitude of the FFEs did not differ significantly from controls ($t_{11} = -0.31$; $p=0.77$).

Figure 3-3: Average microsaccadic amplitude: Controls vs. amblyopia

Average microsaccadic amplitude of controls (blue), AME (red) and FFE (green). AME showed larger microsaccadic amplitude compared to FFE but not controls. The error bars represent ±1 SEM.

3.3.2 Effect of VA on fixational stability in control participants

3.3.2.1 Fixational stability

Simulated VA reductions in control participants did not have a significant effect on fixational stability (Figure 3-4). Repeated measures ANOVA revealed no significant main effect of visual acuity (5 levels) on fixational stability quantified using BCEA [$F(4,16) = 0.723; p=0.589$].

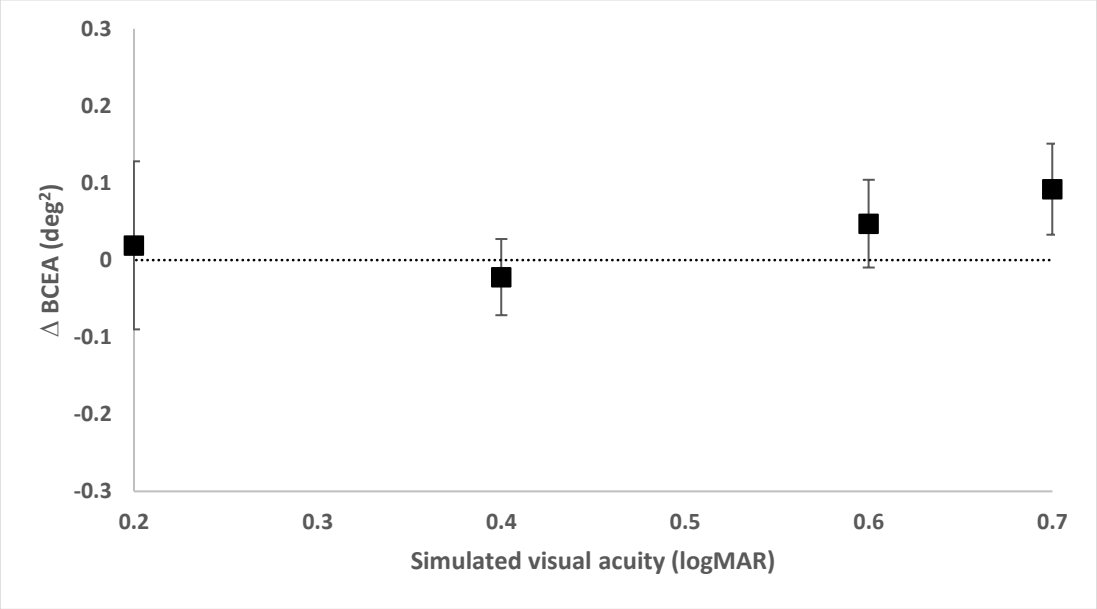


Figure 3-4: Fixational stability of control participants with simulated visual acuity.

The y-axis represents the Δ BCEA values (BCEA values for a simulated VA deficit were subtracted from the BCEA value for the 0 logMAR condition), the x-axis represents the simulated visual acuity level. Simulated visual acuity in control participants did not significantly influence fixational stability.

3.3.2.2 Microsaccadic amplitude

Like fixational stability, microsaccadic amplitude was analyzed using RM ANOVA after log transformation of the values. The analysis showed that there was no significant main effect of visual acuity (5 levels) on microsaccadic amplitude [$F(4,16) = 1.663; p=0.208$] (Figure 3-5).

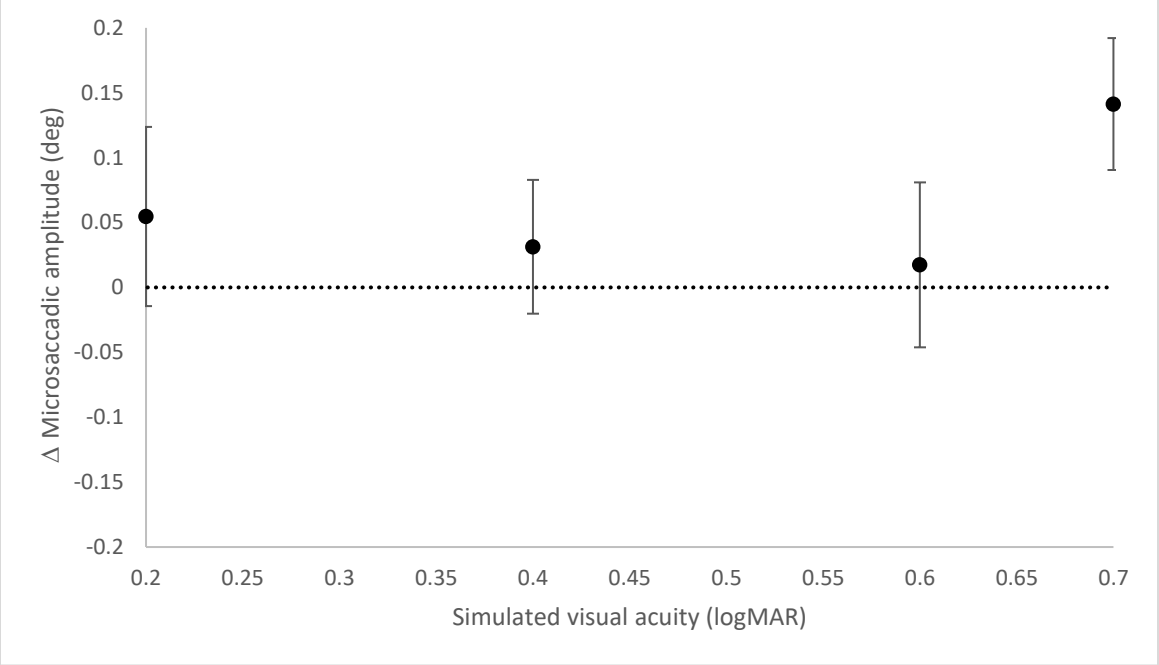


Figure 3-5: Mean microsaccadic amplitude as a function of simulated visual acuity.

The y-axis represents the change in microsaccadic amplitude from the microsaccadic amplitude measured for the 0 LogMar condition. There was no significant influence of reduced visual acuity on microsaccadic amplitude.

However, it should be noted that at the simulated visual acuity of 0.7 logMAR, both fixational stability and microsaccadic amplitude were found to be increasing.

Increasing the simulated VA beyond 0.7 logMAR might have resulted in even less stable FEM and even larger microsaccadic amplitude. However, such high-powered plus lenses (average: +5.00DS) that require to bring the simulated VA beyond 0.7logMAR may deteriorate resolution of the fixation target i.e. high spatial frequency contents of the visual stimuli.

3.3.3 Effect of VA on fixational stability in participants with amblyopia

3.3.3.1 Correlation between VA and BCEA of AME

Before analyzing the effect of VA on fixational stability of observers with amblyopia, the relationship between VA and fixational stability (BCEA) in the AMEs was evaluated. Pearson correlation between VA and BCEA in the AMEs revealed a significant correlation ($r=0.73$; $p=0.038$) [Figure 3-6] whereby less stable fixation was associated with poorer visual acuity.

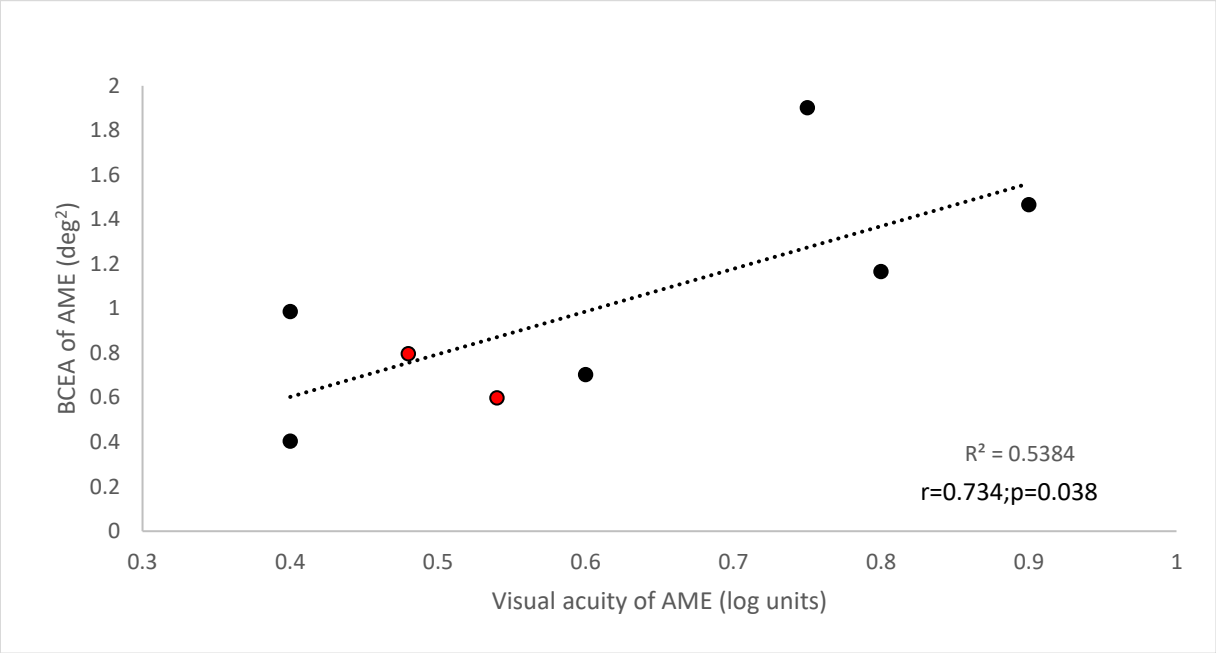


Figure 3-6: Relationship between amblyopic eye visual acuity and the fixational stability.

The figure shows a significant positive relationship between VA and fixational stability (BCEA). The red data points indicate the two participants with strabismic amblyopia.

3.3.3.2 Fixational stability

To examine the role of reduced VA in the relationship between VA and fixational stability in amblyopia, VA of the FFE was reduced to match that of AME on a patient by patient basis. Reducing VA of FFE did not vary its fixational stability quantified using BCEA (t_7 = 0.06; p=0.957). Furthermore, even when the VA was matched between the FFE and AME, the FFE showed significantly more stable fixational eye movements than the AME (t_7 = 3.16; p=0.02) (Figure 3-7).

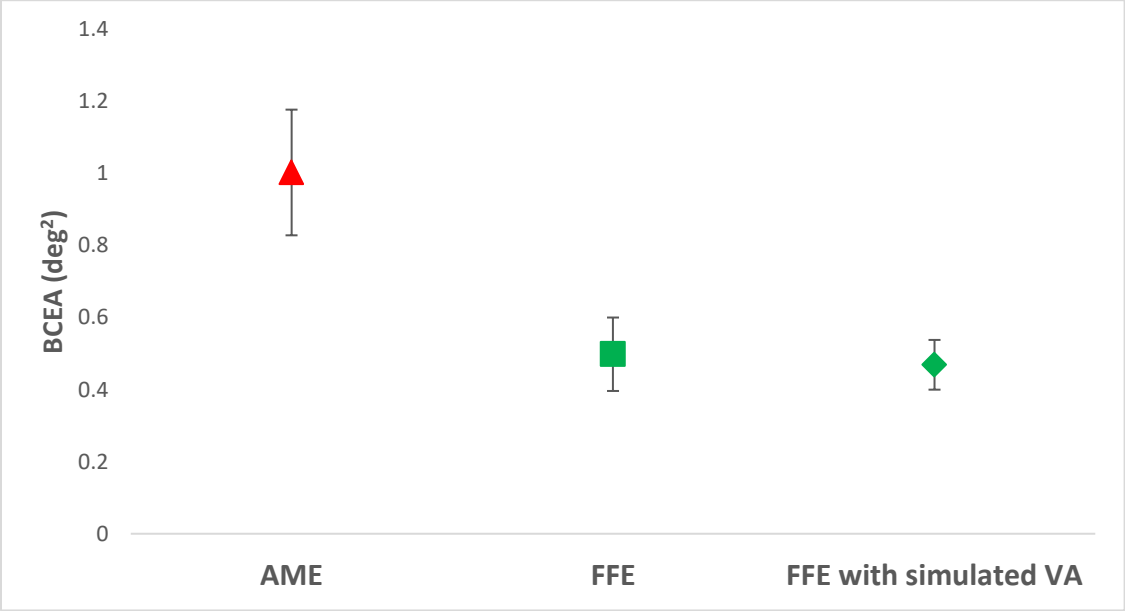


Figure 3-7: Effect of visual acuity on fixational stability in observers with amblyopia.

Fixational stability of the AME (red), FFE (green-square) and FFE with a simulated VA reduction (green-diamond). The AME showed significantly less stable fixation compared to the FFE. Moreover, reduction of FFE VA to match AME VA did not affect FFE fixational stability.

3.3.3.3 Microsaccadic amplitude

Like stability of fixational eye movements, microsaccadic amplitude in the AME was shown to be significantly larger compared to the FFE ($t_7 = 3.16$; $p=0.02$). The microsaccadic amplitude of the FFE did not alter after VA was reduced to match the AME VA ($t_7 = -.042$; $p=0.68$). FFE microsaccadic amplitude was still significantly smaller than that of the AME when VA was matched between the two eyes ($t_7 = 2.93$; $p=0.03$) [Figure 3-8].

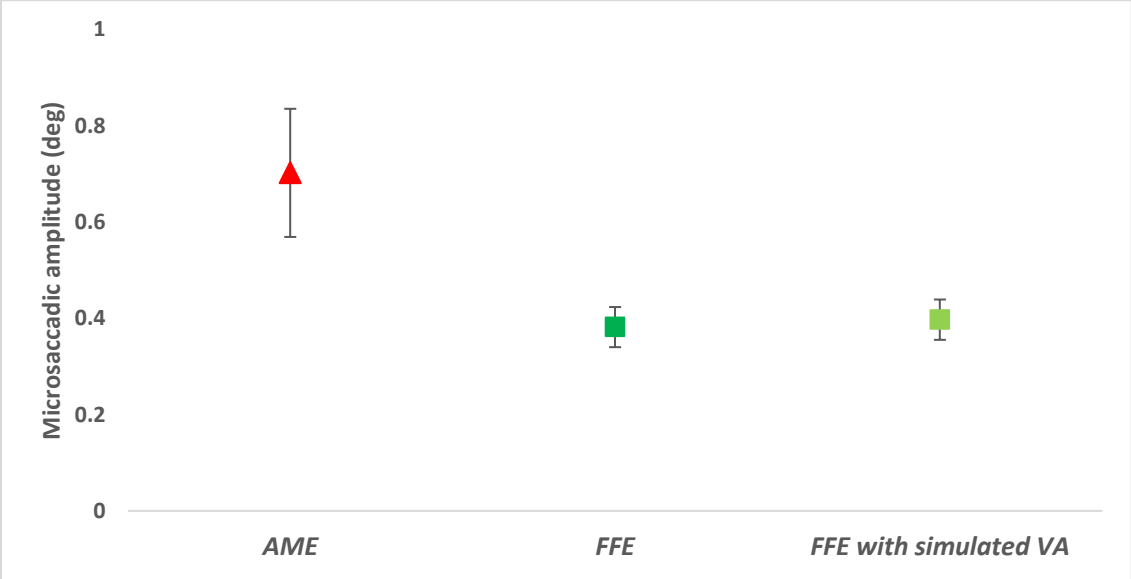


Figure 3-8; Effect of visual acuity on the microsaccadic amplitude in observers with amblyopia.

The mean microsaccadic amplitude of the AMEs (red), FFEs (green-square) and FFEs with VA matched to the AMEs (green-diamond). Microsaccadic amplitude was not influenced by simulated reductions in VA.

3.3.4 Fast Fourier transformation (FFT)

In control participants, a peak in amplitude spectral density was evident in the frequency range of 0.1 to 0.5 Hz which corresponds to ocular drifts. A smaller peak in the range of 0.5 to 1Hz, corresponding to microsaccades, was also present (Figure 3-9).

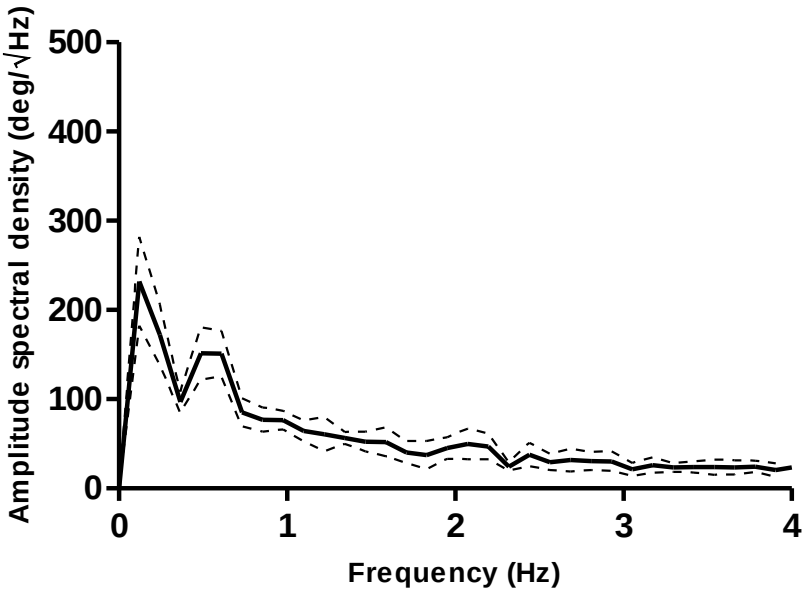


Figure 3-9 :Mean spectral density of fixational eye movements of control participants during monocular fixation.

The solid line and the dotted lines represent Mean ± SEM, respectively. The spectral density indicated that eye movement frequencies in the 0.1 to 1 Hz range were most prominent.

A representational eye position trace and its corresponding amplitude spectral density for one participant (S1) with amblyopia are shown in Figure 3-10. Figure 3-11 shows the averaged amplitude spectral density function of the amblyopic eye (red lines) and the fellow eye (green lines) during monocular fixation. The overall results showed that the amblyopic eye had overall increased average amplitude spectral density compared to the fellow eye across the frequency ranges of 0.1 to 3Hz.

Therefore, both increased drifts and increased microsaccades were responsible for reduced stability of the amblyopic eye.

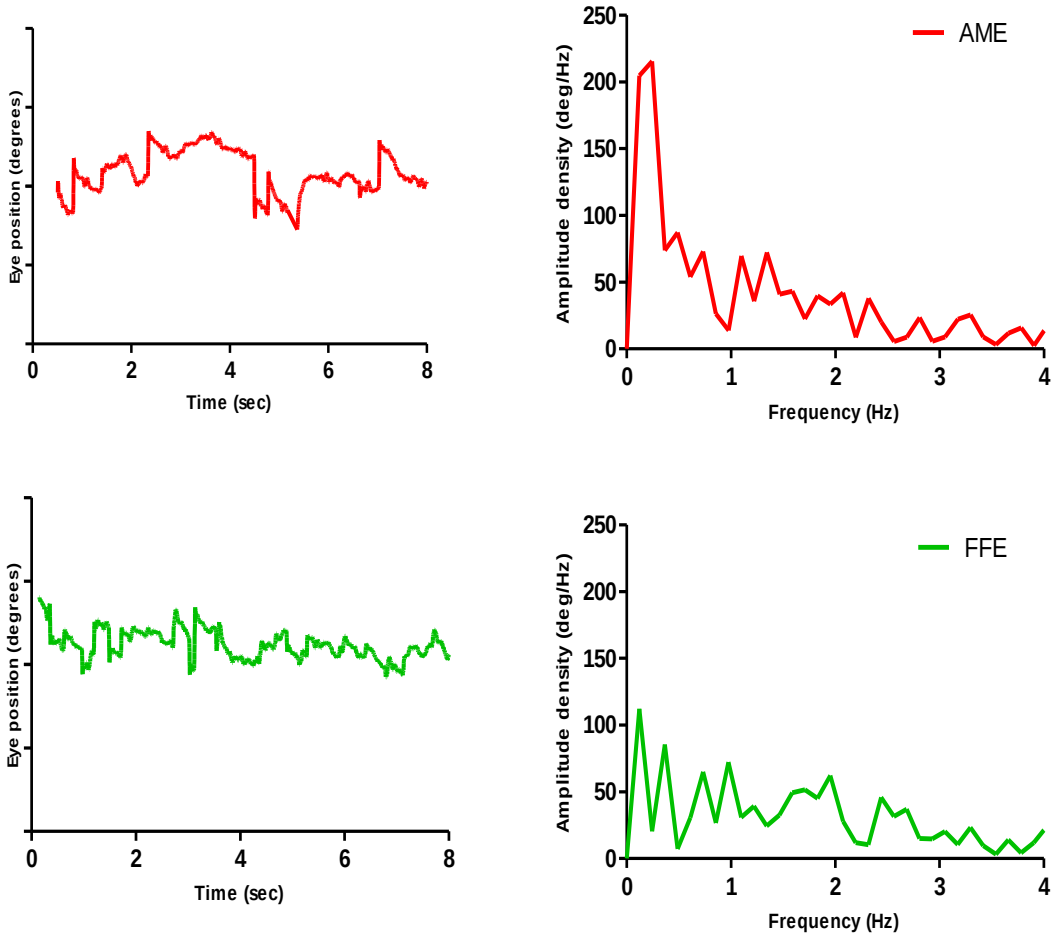


Figure 3-10: Representative eye traces (left column) and their corresponding Fourier transformations (right column).

The top panel shows the representative eye trace (S1) of an AME (left) and its corresponding spectral density function after FFT. The bottom panel shows the same data for the FFE. The FFE exhibited less power in the frequency range of 0.1 to 0.5 Hz compared to the AME.

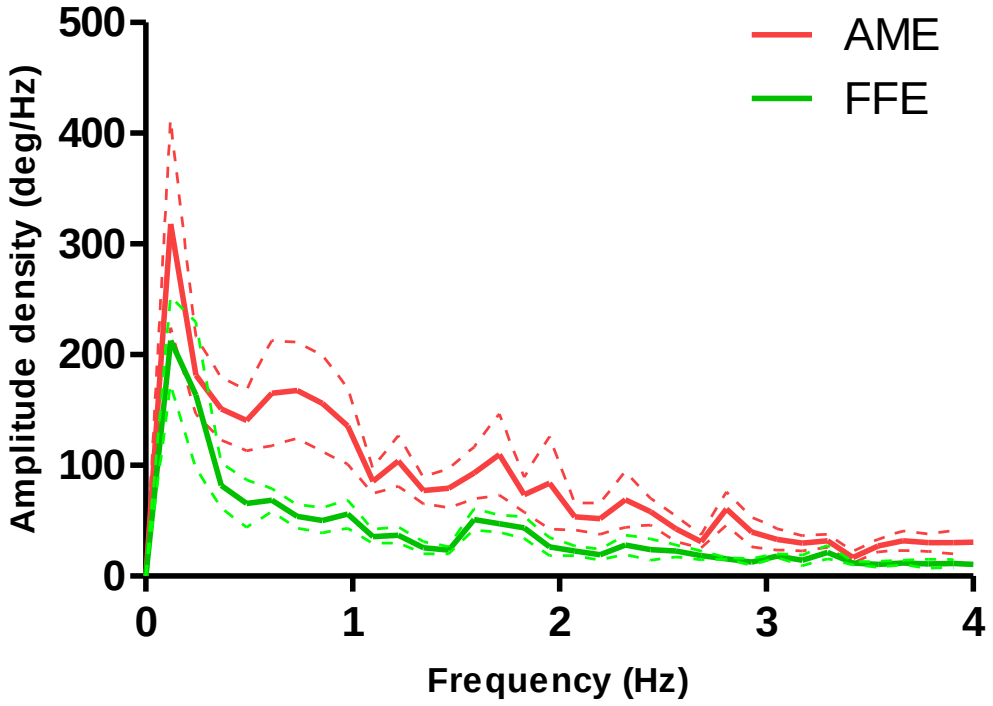


Figure 3-11: Averaged spectral density function of fixational eye movements in observers with amblyopia during monocular fixation.

The red lines and the green lines represent the amblyopic eye and the fellow eye, respectively. The amblyopic eye has increased spectral density across all frequencies ranging from 0.1 to 3Hz during monocular fixation.

3.4 Discussion

The purpose of the experiment was to test for a causal relationship between VA and fixational stability in controls and observers with amblyopia. VA was manipulated in control participants and fixational stability was measured. The results showed that altering VA did not affect fixational stability or microsaccadic amplitude

in control participants. The relationship was also tested in observers with amblyopia by reducing FFE VA to match AME VA. Altering FFE VA did not influence fixational stability or microsaccadic amplitude in observers with amblyopia. Furthermore, the AME still exhibited less stable fixation and greater microsaccadic amplitude than the FFE when the VA was matched between the eyes. The other explanation could be less stable fixation does not arise from a loss of high spatial frequencies induced by lens defocus in either controls or the FFE of observers with amblyopia. This is consistent with the findings of Rucci[9] that that FEM act to enhance high spatial frequencies but not for low spatial frequency. Thus, this study suggests that impaired visual acuity is not responsible for abnormal fixational stability in amblyopia.

Recently, McKee et al., 2016 measured saccadic latency in 66 controls and 393 observers which include participants with amblyopia due to strabismus, anisometropia and combined strabismic-anisometropic, and with participants with only these amblyogenic factor but not amblyopia. They found that interocular saccadic latencies were positively correlated with interocular sensory deficits such as reduced VA, contrast sensitivity. Furthermore, they found that mean saccadic latency of the strabismic amblyopes were longer than that of anisometropic amblyopes. However, the mean of sensory deficits such as VA, contrast sensitivity was not

significantly different between strabismic amblyopia and anisometropic amblyopia. Therefore, they concluded that despite the relationship between saccadic latency and VA, the longer latencies in strabismic amblyopia could not be attributed to reduced VA. They also speculated that the longer latencies could be due to frequent microsaccades and the consequent attentional shifts which result in delaying the processing of visually-guided saccades.

Similarly, in agreement with most [41,42,44,109], but not all [40] prior studies of FEM in amblyopia, we also observed a significant correlation between AME VA and AME fixational stability. Altering VA in observers with normal vision and amblyopia did not influence the FEM, therefore, the relationship seems to exist in only one direction i.e. abnormal FEM may be contributing to the VA deficits in amblyopia. The analysis of FEM using FFT showed that ocular drifts and microsaccades occur at a higher proportion in the AME compared to the FFE. Therefore, the abnormal ocular drifts and resulting larger microsaccades in AMEs may take the image off the fovea causing impaired visual acuity [41]. Another example in which larger image movement on the retina leads to impaired VA is nystagmus. Reduced duration of foveation due to abnormal fixational eye movements in nystagmus contributed to impaired VA [114,118].

An alternate explanation is also possible that FEM and VA are influenced independently by a third variable such as abnormal visual cortex or thalamic development. It is well established that the superior colliculus (SC) is involved in FEM. The SC receives inputs from two different pathways, 1) retino-collicular pathway and, 2) cortico-collicular pathway. Shi et al., 2012, using a mathematical model of the SC, suggested that the increased amplitude of microsaccades noted in the AME during monocular fixation in anisometropic amblyopia was due to an imbalance between the two pathways. However, physiological evidence is needed to support this claim.

3.5 Summary and conclusion

1) during monocular fixation, the AME fixational stability was significantly reduced compared to the FFE.
2) like fixation stability, microsaccadic amplitude was significantly larger in the AME during monocular fixation compared to the FFE
3) Reduced VA due to defocus induced by ophthalmic lenses in control participants and the FFE of observers with amblyopia did not alter the characteristics of FEM such as fixational stability and microsaccadic amplitude

4) A significant correlation between AME VA and fixational stability was observed.
5) FFT analysis of FEM revealed that both ocular drifts and microsaccades were abnormal in AME.

Abnormal fixational eye movements in the amblyopic eye could not be explained by reduced VA. This raises three possibilities, 1) abnormal AME FEM patterns could be independent of sensory deficits such as VA, 2) FEM could contribute to impaired AME VA and, 3) both FEM and VA are influenced independently by a third variable such as abnormal visual cortex development.

Chapter 4
Monocular vs. binocular fixation

4.1 Introduction

In the real world, we use both eyes for any type of eye movements. Unlike other eye movements, attention towards the binocular component of fixational eye movements is not common in the literature. An important question is whether fixational stability is different under binocular vs. monocular viewing conditions. Two studies have shown increased fixational stability under binocular compared to monocular viewing conditions [40,119]. Motter and Poggio (1984) measured the stability of FEM in two rhesus monkeys and showed improved stability during binocular fixation. Gonzalez et al. (2012) quantified fixational stability using bivariate contour ellipse area (BCEA) in normal observers and noted improved fixational stability during binocular compared to monocular fixation. Gonzalez et al. (2012) suggested that binocular summation might be responsible for improved stability during binocular fixation. However, contrasting results were reported by Krauskopf, Cornsweet and Riggs (1960) [14]. They measured FEM during monocular and binocular fixation and found that variance during binocular fixation was higher compared to monocular fixation. Therefore, it is not clear whether there is a binocular advantage to fixational stability. The first purpose of this experiment, therefore, was to determine

whether fixational stability is affected by binocular vs. monocular fixation in observers with normal vision. Moreover, all the above-mentioned studies used only high contrast targets such as a red point on a white screen [40] as fixation targets. Therefore, the current study also investigated whether any binocular advantage was dependant on the contrast of the fixation point, as would be expected for an effect generated by binocular summation of contrast signals.

4.2 Methods

11 observers with normal binocular vision were recruited from the School of Optometry and Vision Science, University of Waterloo. Participants provided informed, written consent and the study was approved by the Office of Research Ethics, University of Waterloo. Measures of best corrected visual acuity, stereoacuity using the Randot Stereotest and phoria using the modified Thorington test were obtained from all participants. All participants had best corrected visual acuity of 20/20 or better in each eye and stereoacuity of <60 secs of arc. A sighting test (Porta test) was used to determine eye dominance [62]. The participants were asked to extend both arms and put one thumb over the other. Then they were asked to align their thumbs to a distant object with both eyes open. Ocular dominance was then

determined by alternatively occluding each eye and asking through which eye the distance between their thumbs and the object was shorter.

The visual stimulus used in this experiment is shown in Figure 4-1. The stimulus consisted of an outer box which subtended 8.1° visual angle at 40cm and a central fixation cross which subtends ≈1° at 40cm, presented on a grey background. Using Weber's contrast ratio, the contrast of the cross and the white portion of the peripheral square was varied from 0 to 100% in seven steps: 0%, 5%, 10%, 20%, 40%, 80% and 100% as shown in Figure 4-2. Note that the contrast of the target was varied by changing the luminance of the white portions of the target in relation to the mean (grey) background luminance. The black portions of the target were never varied. Having high contrast in the peripheral visual field kept the incidence of Troxler's phenomenon constant at all contrast levels and allowed for stable fusion.

Fixational eye movements were measured under three viewing conditions, 1) monocular fixation with the dominant eye (DE) only, 2) monocular fixation with the non-dominant eye (NDE) only, and 3) binocular viewing. Non-viewing eyes were occluded with an opaque, tight-fitting eyepatch. At each contrast level, fixational eye movements were measured for 30 seconds. Breaks were given between each recording period to minimize the effect of fatigue. Each combination of stimulus contrast and

viewing condition was measured 4 times for each participant. The order of stimulus contrast level presentation was randomized.

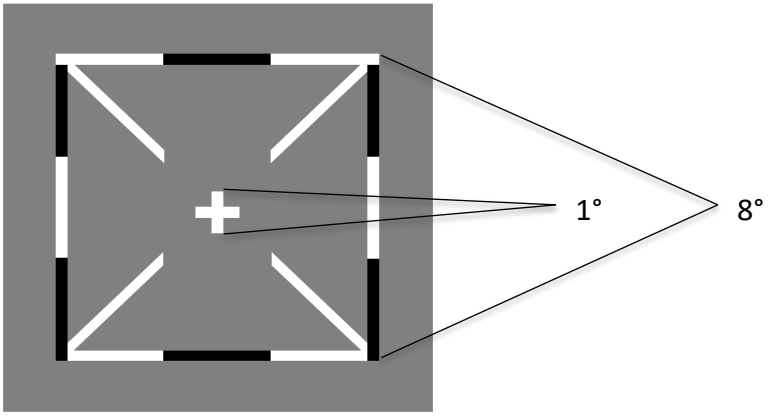


Figure 4-1: Specifications of the visual stimuli

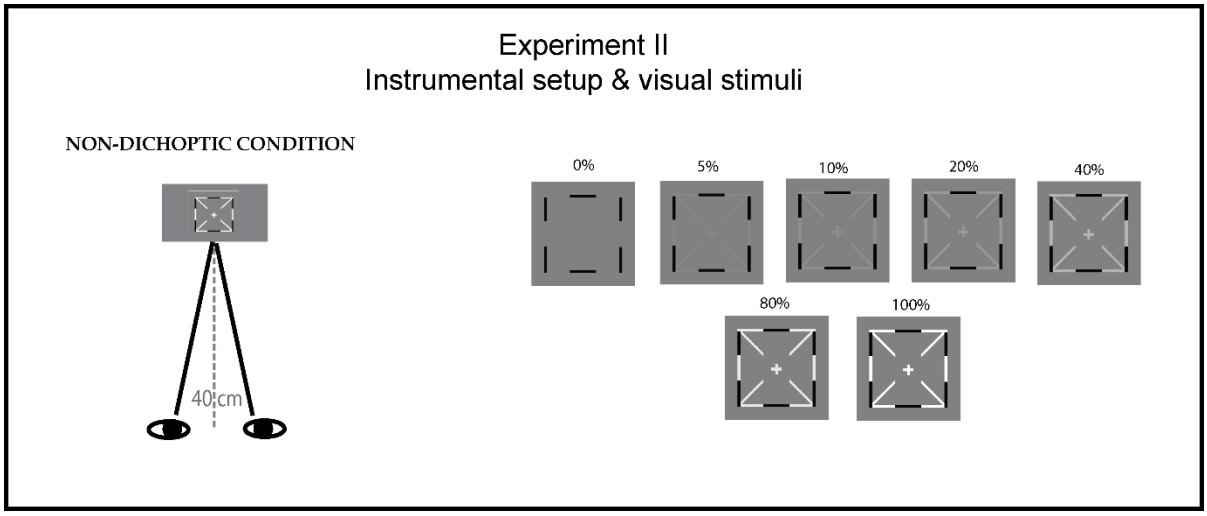


Figure 4-2: Monocular vs. binocular fixation – Instrumental setup and visual stimuli

4.3 Results

4.3.1 Fixational stability

The fixational stability (BCEA values) of the DE and NDE during monocular and binocular fixation are shown in Figure 4-3. After log transformation of BCEA values, the effects of viewing condition (monocular vs. binocular viewing), ocular dominance (DE vs. NDE) and contrast (7 levels) on the stability of fixation were investigated using repeated measures ANOVA. There were significant main effects of viewing condition [$F(1,20) = 7.97; p=0.02$] and contrast level [$F(6,120) = 13.90; p<0.001$]. The significant main effect of viewing condition suggested that fixational stability was significantly improved during binocular fixation compared to monocular fixation (Figure 4-3). Post hoc analysis revealed that the significant main effect of contrast was mainly due to a reduced fixational stability at the contrast level of 0%, as no significant difference was noted in fixational stability from 5 to 100%. No significant effect of ocular dominance was present [$F(1,20) = 0.03; p=0.87$]. Intriguingly, a significant three way interaction was also noted ($F(1,20) = 2.27; p=0.048$). However, on close inspection of the data, the resulting significant interaction effect was most likely due to high variability in the NDE data, as no significant trend was noted to explain the interaction.

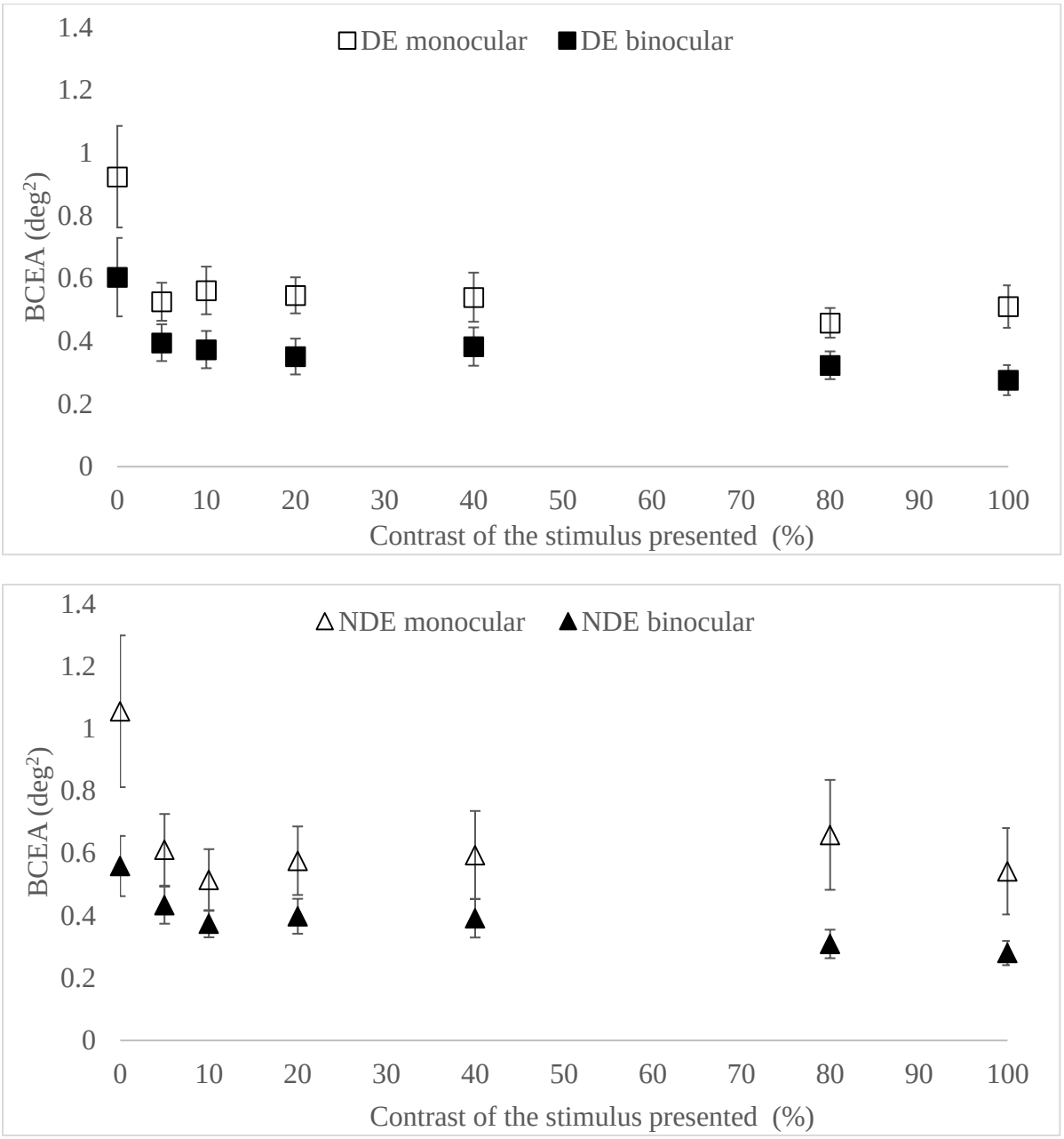


Figure 4-3: Monocular vs. binocular fixational stability

The mean fixational stability of the DE (top) and the NDE (bottom) during monocular (open symbols) and binocular (filled symbols) fixation. Error bars represent ±1 SE. During binocular fixation, both the DE and the NDE showed improved fixational stability across all contrast levels. Moreover, at 0%

contrast, fixational stability was significantly reduced during both monocular and binocular fixation in the DE as well as the NDE.

4.3.1 Estimation of a binocular advantage ratio

A binocular advantage ratio was calculated by determining the ratio between monocular and binocular fixational stability (BCEA). Note that lower values of BCEA indicate better (more stable) fixational stability. Therefore, the ratio was determined as monocular BCEA / binocular BCEA so that a ratio of >1 indicated a binocular advantage.

Since there was no significant main effect of ocular dominance, the BCEA values of the DE and NDE were averaged for the binocular advantage ratio calculation. The binocular advantage ratio values are tabulated in Table 4-1 and it is evident that the ratio is greater than 1.4 (√2) across all the contrast levels and therefore exceeded the effect of binocular summation for contrast detection [85,88]. Interestingly, the advantage was even shown at the contrast level of 0% (i.e. no central fixation target).

Table 4-1: Binocular advantage ratio

Contrast level	Binocular advantage ratio	
	Mean	SE
0	1.85	0.33
5	1.55	0.28
10	1.54	0.24
20	1.84	0.34
40	1.92	0.47
80	1.82	0.27
100	2.15	0.41

The binocular advantage ratio which was calculated by determining the ratio between the fixational stability (BCEA) during monocular fixation and the fixational stability (BCEA) during binocular fixation. Note that a ratio >1 indicates a binocular advantage.

4.3.2 Effect of stimulus contrast

The effect of stimulus contrast on fixational stability was tested during monocular and binocular fixation to assess whether the improved fixational stability during binocular fixation might have been due to increased contrast information. Figures: 4-4a & 4-4b show the effect of stimulus contrast on fixational stability during monocular and binocular fixation, respectively. During binocular fixation, both the DE and NDE showed increased stability as the stimulus contrast increased. Analyzing the data using linear regression revealed that a significant relationship between BCEA

and stimulus contrast was noted during binocular fixation for DE (R^2 = 0.81, p=0.02) and NDE (R^2 = 0.87, p=0.01). However, no relationship between BCEA and stimulus contrast was evident for the monocular fixation conditions.

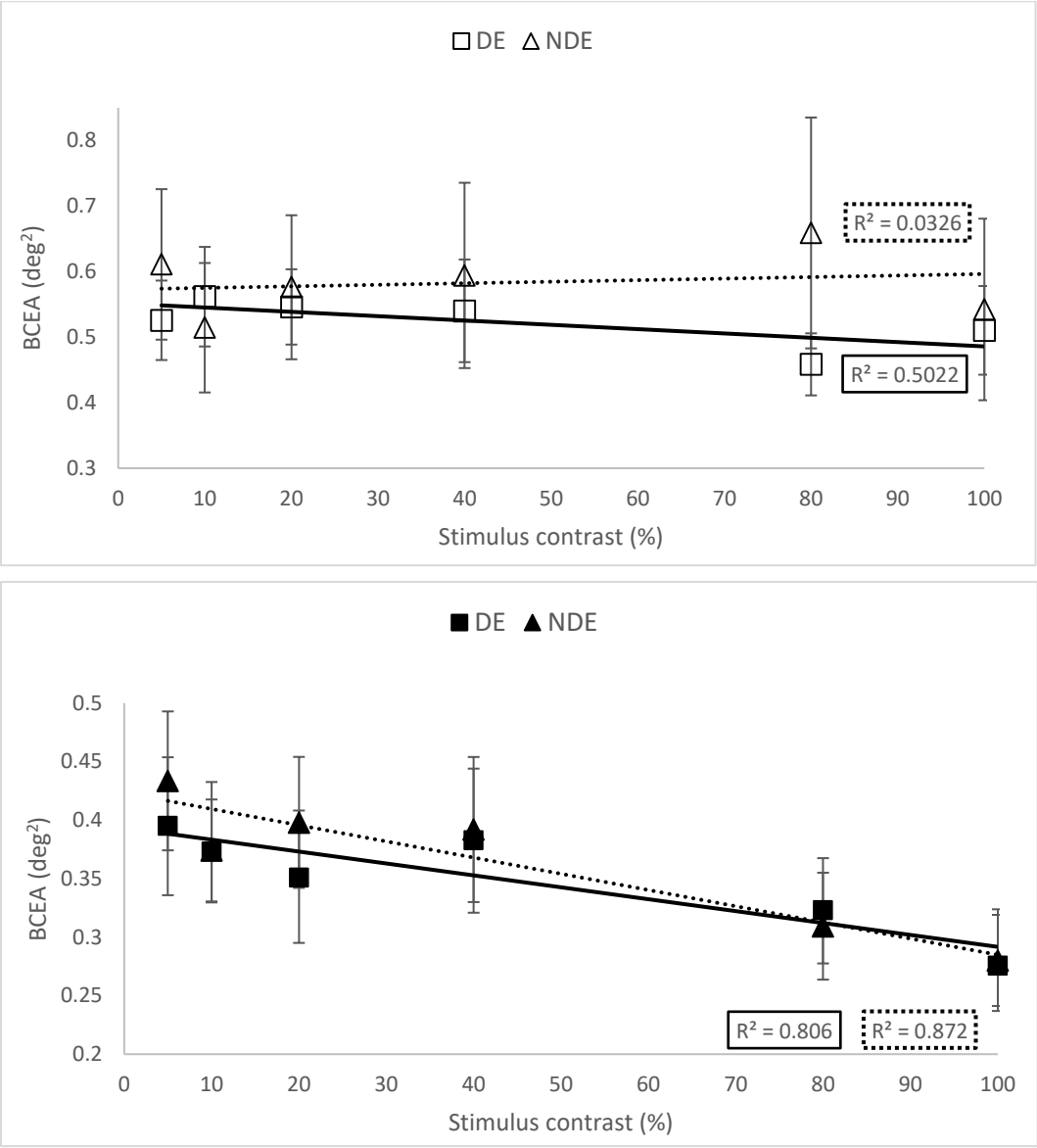


Figure 4-4: Effect of stimulus contrast on fixational stability

The effect of stimulus contrast on fixational stability during monocular fixation (top) and binocular fixation (bottom). A relationship between increasing stimulus contrast and greater fixation stability was only evident for binocular fixation.

4.3.3 Microsaccadic amplitude

The mean amplitudes of microsaccades during monocular fixation and binocular fixation across all contrast levels are shown in Figure 4-5. The amplitude values were log transformed and subjected to a 2x2x7 repeated measures ANOVA (as described above). The analysis showed that there was a significant main effect of contrast [$F(6,120) = 9.128$; $p<0.001$]. As noted in the stability of fixation, the microsaccadic amplitude at the contrast level of 0% was higher than at other contrast levels. However, there were no significant interactions and no significant main effects of viewing condition (binocular vs. monocular) or ocular dominance (DE vs. NDE). Therefore, unlike fixational stability, no binocular advantage was noted for microsaccadic amplitude. Tukey HSD revealed that microsaccadic amplitude of the DE and NDE was significantly greater at the contrast level of 0% irrespective of viewing conditions (binocular or monocular fixation) than all other contrast levels except 5%.

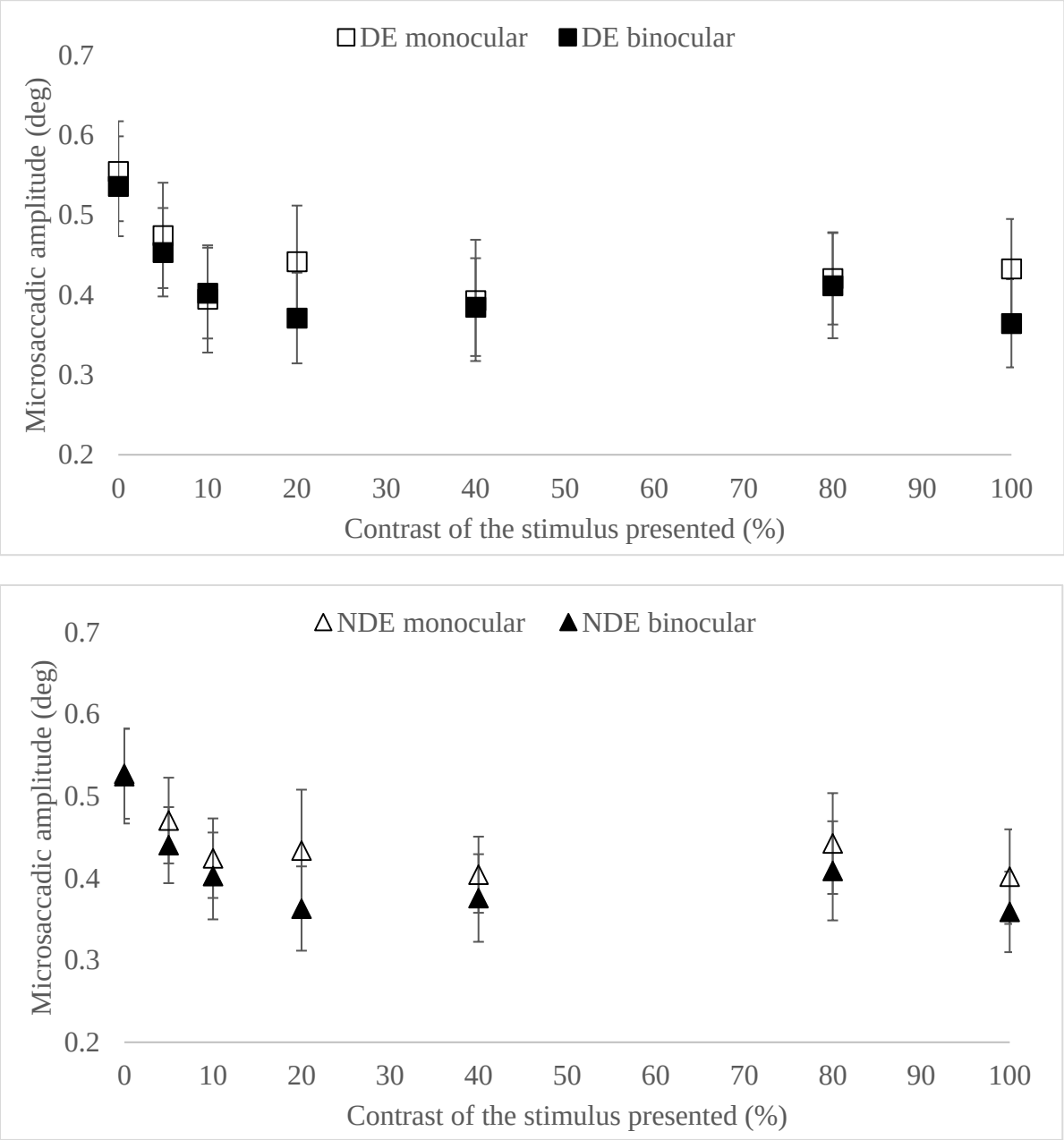


Figure 4-5: Monocular vs. binocular microsaccadic amplitude

The mean microsaccadic amplitude of the DE (top) and the NDE (bottom) during monocular (solid) and binocular (dotted) fixation. Unlike fixational stability, no difference between monocular fixation and binocular fixation was noted. However, microsaccadic amplitude was significantly increased while viewing 0% contrast.

4.3.4 FFT analysis

For every participant, FFT analyses were performed for every trial and the overall mean spectral density function is depicted in Figure (4-6). The amplitude of spectral density was reduced within the frequency range of 0.1 – 1 Hz during binocular fixation compared to monocular fixation. This suggested that the improved fixational stability noted during binocular fixation was due to improved control of ocular drifts and hence microsaccadic occurrence. However, note that there was no difference in microsaccadic amplitude between monocular and binocular fixations.

FFT analysis was also used to compare the spectral density of the 0% contrast conditions with the 100% contrast conditions under monocular viewing because the 0% contrast condition exhibited a pronounced reduction in fixation stability relative to 100% contrast. The analysis revealed an increase in spectral density amplitude within the frequency range of 0.1 – 2Hz for the 0% contrast condition (Figure 4-7). This suggested that the rate of both microsaccades and ocular drifts were increased when there was no fixation target.

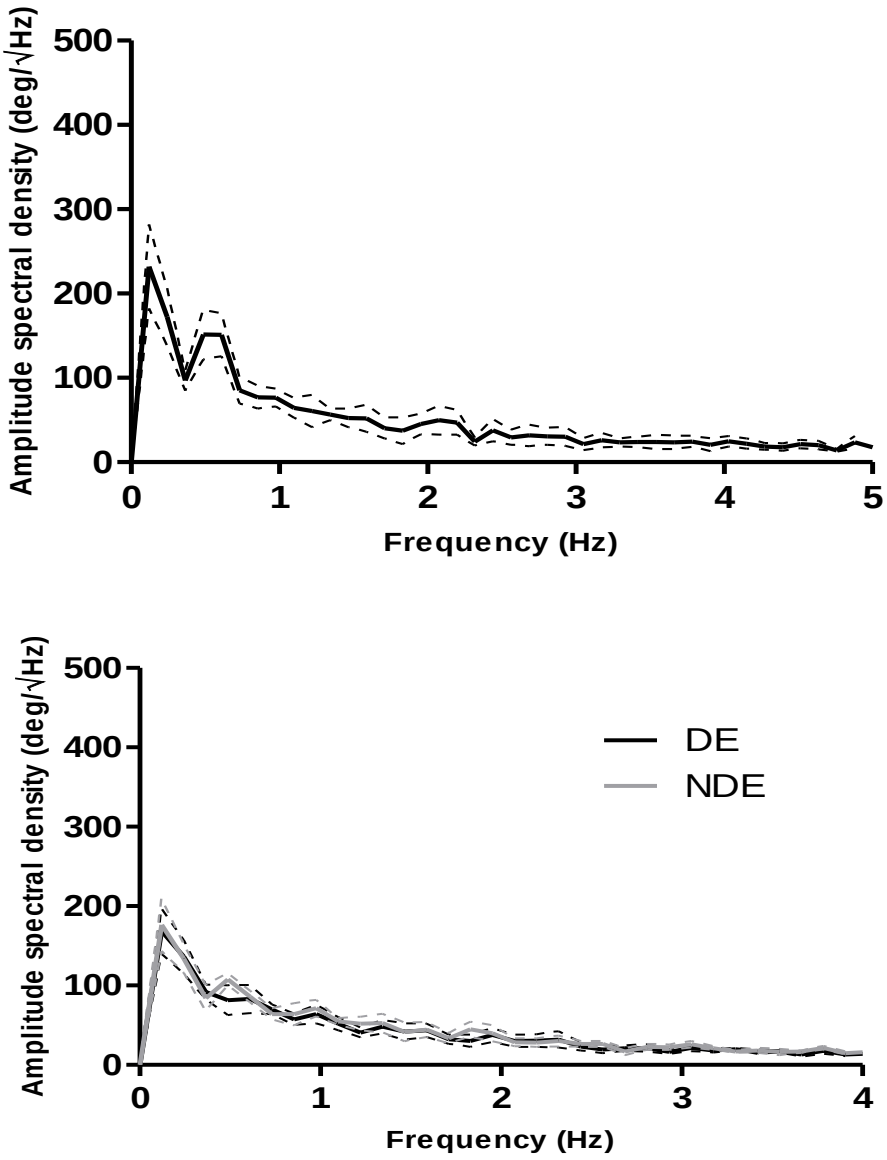


Figure 4-6: Spectral density of fixational eye movements of control participants.

Mean spectral density function of horizontal fixational eye movements during monocular (top panel) and binocular (bottom panel) fixation conditions. The solid lines represent the group mean and the dotted lines ± SEM. The spectral density suggested that the frequency of eye movements in the range of 0.1 to 1 Hz was higher for monocular than binocular fixation. Consistent with the results of fixational

stability, the overall spectral density was shown to have less power during binocular fixation compared to monocular fixation.

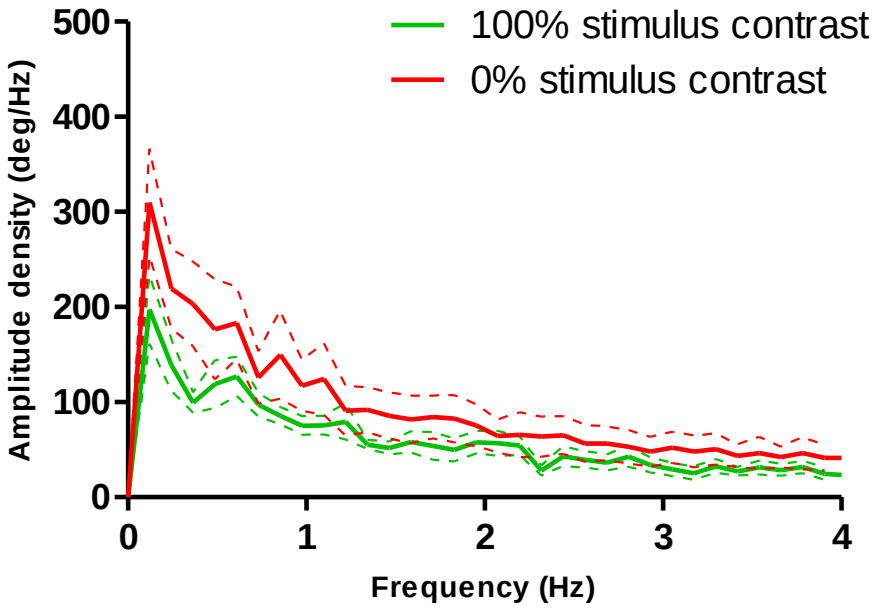


Figure 4-7: Mean spectral density of fixational eye movements of control participants during monocular fixation.

Mean spectral density functions of horizontal fixational eye movements for the 0% contrast condition (red) and the 100% contrast condition (green). The solid line and the dotted lines represent Mean ± SEM. The data indicate that amplitude spectral density was increased across the whole frequency range for the 0% relative to the 100% contrast condition. This suggests that both ocular drifts and microsaccades were increased in the 0% contrast condition.

4.4 Discussion

In this experiment, the advantage of binocular fixation was evaluated by comparing fixational stability during monocular fixation and binocular fixation. The

results showed that the fixational stability during binocular fixation was significantly improved (more stable) compared to monocular fixation. This result is consistent with two previous studies [40,119]. Furthermore, the results of the study showed that both the DE and NDE showed improved fixational stability under binocular fixation across all contrast levels. The calculation of binocular advantage ratio also revealed that binocular advantage was noted at all contrast levels.

Though the improved fixational stability was noted during binocular viewing, there was no difference in microsaccadic amplitude between monocular and binocular fixation. Krauskopf et al. 1960 [14] measured fixational eye movements during monocular and binocular fixation in 2 observers. They noted that microsaccades were larger in amplitude and more frequent during binocular fixation compared to monocular fixation. But there are three studies which suggested that there was no difference between monocular and binocular fixation in terms of microsaccadic amplitude [40,107,120]. Thus, the result suggested that microsaccades are highly binocular and conjugate in nature. This is consistent with previous findings [3–5].

To analyze the effect of binocular fixation further, fixational stability of the DE and NDE was plotted as a function of stimulus contrast during monocular fixation and binocular fixation separately. A relationship between stimulus contrast and

fixation stability was noted for the DE and NDE only during binocular fixation. In particular, the higher the contrast of the stimulus, the better the fixational stability (Figure 1-5). FFT analysis suggested that ocular drifts are better controlled during binocular fixation. Furthermore, ocular drifts were shown to enhance contrast sensitivity of high spatial frequencies [35]. Therefore, increased control of ocular drifts might play a role in processing contrast information during binocular fixation.

Which component of fixational eye movements played a role in improving fixational stability during binocular viewing? FFT analysis revealed that the peak of the amplitude density spectrum within the frequency range of 0.1 to 0.5 Hz during binocular fixation was reduced relative to monocular fixation. This suggested that ocular drifts are better controlled during binocular fixation and might be responsible for more stable fixation during binocular viewing. Cherici et al., 2012 showed that the characteristics of ocular drifts are a better determinant of fixational stability than the characteristics of microsaccades. However, factors such as fusion and proprioception (awareness of both eyes being open) might have played a role in achieving better fixational stability during binocular fixation. These factors require further investigation.

During monocular fixation, contrast had a significant effect on the stability of fixation. However, it should be noted that the main effect was due to 0% contrast as no significant difference in the stability of fixation was noted from 5 to 100% stimulus contrast. Ukwade and Bedell (1993) [121] measured FEM by varying the stimulus contrast from 7 to 84% and showed that there was no effect of stimulus contrast on fixational stability. This result is consistent with the findings of the present study. Cherici et al. (2012) [21] measured FEM under two viewing conditions, 1) marker and 2) no-marker (i.e. without fixation target) conditions and showed that variance of fixational eye movements under the no-marker condition was significantly higher than the marker condition. Gonzalez et al., 2012 and Raveendran et al., 2014 also showed that lack of visual stimulus leads to less stable FEM.

Microsaccadic amplitude was also significantly larger when the contrast of the stimulus was 0%, i.e. when there is no fixation target, compared to other contrast levels. McCamy et al. (2013) [2] also showed significantly larger microsaccadic amplitude and lower microsaccadic rate while fixating at 0% luminance target compared to other luminance levels of the target. Moreover, at higher luminance levels, there were no significant differences in the characteristics of microsaccades.

Thus, the results suggested that presence or absence of the fixation target influences the characteristics of fixational eye movements such as fixational stability and microsaccadic amplitude. The other factors such as contrast or luminance of the fixation target did not influence fixational stability and microsaccadic amplitude.

4.5 Conclusion

- Improved fixational stability was noted during binocular fixation compared to monocular fixation across all contrast levels of the visual stimulus.
- The presence or absence of a fixation target influences fixational stability, microsaccadic amplitude and ocular drifts.
- During monocular fixation, stimulus contrasts from 5% to 100% did not influence fixational stability or microsaccadic amplitude.
- The effect of stimulus contrast was noted only during binocular fixation, i.e. higher the stimulus contrast, better the fixation stability.
- Microsaccadic amplitude did not vary between monocular and binocular fixation. Therefore, the ocular drifts might be responsible for improved fixational stability during binocular fixation. This hypothesis was supported by FFT analyses.

Chapter 5

Effect of different types of binocular interactions on fixational eye movements in control participants

The previous experiments in this thesis showed that during monocular fixation, sensory information such as reduced visual acuity (experiment-I) or stimulus contrast (experiment-II) did not influence fixational stability. However, during binocular fixation, increasing stimulus contrast did correlate with improved fixational stability and fixation was more stable under binocular than monocular viewing conditions. These results combined suggested that interactions between the two eyes might play a role in influencing fixational stability during binocular fixation. To add to support to this idea, prior studies have shown a relationship between fixational stability and binocular measures. Gonzalez et al., 2012 noted that interocular VA difference was correlated significantly with fixational stability, i.e. greater the interocular difference, the less stable the fixational stability in observers with amblyopia. Moreover, Subramanian et al., 2013 also showed a positive correlation between fixational stability and stereo-acuity which is a clinical method of measuring the level of binocular interaction in observers with amblyopia. Therefore, they suggested that abnormal binocular visual experience during visual development could result in abnormal FEM patterns in observers with amblyopia. These results

combined suggested that lack of binocular interaction in amblyopia might play a role in reduced AME fixation stability.

The goal of the following two experiments was to investigate the effect of binocular interaction on fixational stability in control participants and observers with amblyopia.

5.1 Introduction

The objective of this experiment was to study the effect of different types of binocular interactions on fixational stability in control participants. Fixational stability was measured while participants with normal binocular vision were presented with dichoptic grating stimuli that were (1) fused, (2) rivalrous or (3) consisted of a grating presented to the left eye and mean luminance to the other eye (referred to as monocular stimulation). These stimuli were designed to induce (1) fusion, (2) periods of left eye suppression (rivalry) or (3) left eye dominance, respectively.

Though there are no prior studies that have investigated the effect of binocular rivalry on fixational stability, there are studies that have reported the effect of binocular rivalry on microsaccades. Sabrin & Kertesz (1980) [122] showed that there was almost a 50% increase in the rate of microsaccades while viewing rivalrous targets

compared to non-rivalrous targets. They concluded that the increased rate of microsaccades contributed to the alternation of perception during binocular rivalry. If the above statement is true, then the fixational stability should also be reduced (less stable). This is because the rate and amplitude of microsaccades directly affect fixation stability [41].

However, it should be noted that the aim of the current study was not to investigate the effect of binocular rivalry on the characteristics of FEM but to use binocular rivalry as the platform to study the effect of interocular suppression on fixational stability in control participants. A recent study by van Loon [78] suggested that the level of GABA (an inhibitory neurotransmitter) within the human visual cortex influences the alternation rate of binocular rivalry. GABA is also known to mediate interocular suppression in strabismic amblyopia [77,79]. Since binocular rivalry can be easily induced in control participants, it provides an convenient platform to study the effect of interocular suppression on fixational stability in control participants.

5.2 Methods

15 participants with normal binocular vision were recruited. The visual stimulus was a sinusoidal grating (3.6° diameter, 1.1 cpd) with a central fixation target of 0.5°

(Figure 5-1). Three different binocular viewing conditions were presented; 1) *dichoptic fusion*; identically oriented gratings presented to both eyes in the haploscope, *2) binocular rivalry*; a pair of dichoptically presented orthogonally oriented gratings and 3) *monocular stimulation*; a sinusoidal grating was presented to left eye and a mean luminance (grey) blank screen was presented to the right eye. These viewing conditions were compared with a baseline measurement, *non-dichoptic fusion*, whereby a single sinusoidal grating was viewed binocularly without the haploscope. For the non-dichoptic fusion condition, the stimulus was presented using one of the LCD monitors used in the haploscope. Grating orientation was changed every 4 seconds in the dichoptic fusion, monocular stimulation and non-dichoptic fusion conditions. Importantly, the experiment was designed so that the stimulus presented to the right eye varied across conditions whereas the stimulus presented to the left eye was the same in every condition (Figure 5-1).

In our experimental design, participants were asked to respond to changes in perception (horizontal grating, vertical grating or piecemeal) using buttons on a gamepad (Sidewinder®, Microsoft). If a participant perceived a horizontal/vertical grating, he/she held a button (button "LT" for horizontal and "RT" for vertical on the left top and right top of the gamepad respectively) until the perception changed to

another grating or piece-meal. If they perceived piece-meal, did not press any of the buttons. Every button press/release sent a specific message to the eye tracker. If the response was inappropriate (i.e. pressing two buttons simultaneously or the conjunction of a button event with a blink), the associated period of fixational eye movement data was excluded from further analysis.

Under each viewing condition, fixational eye movements were measured for 40 seconds and each condition was repeated 6 times. Presentation order was randomized and breaks were given to minimize the effect of fatigue.

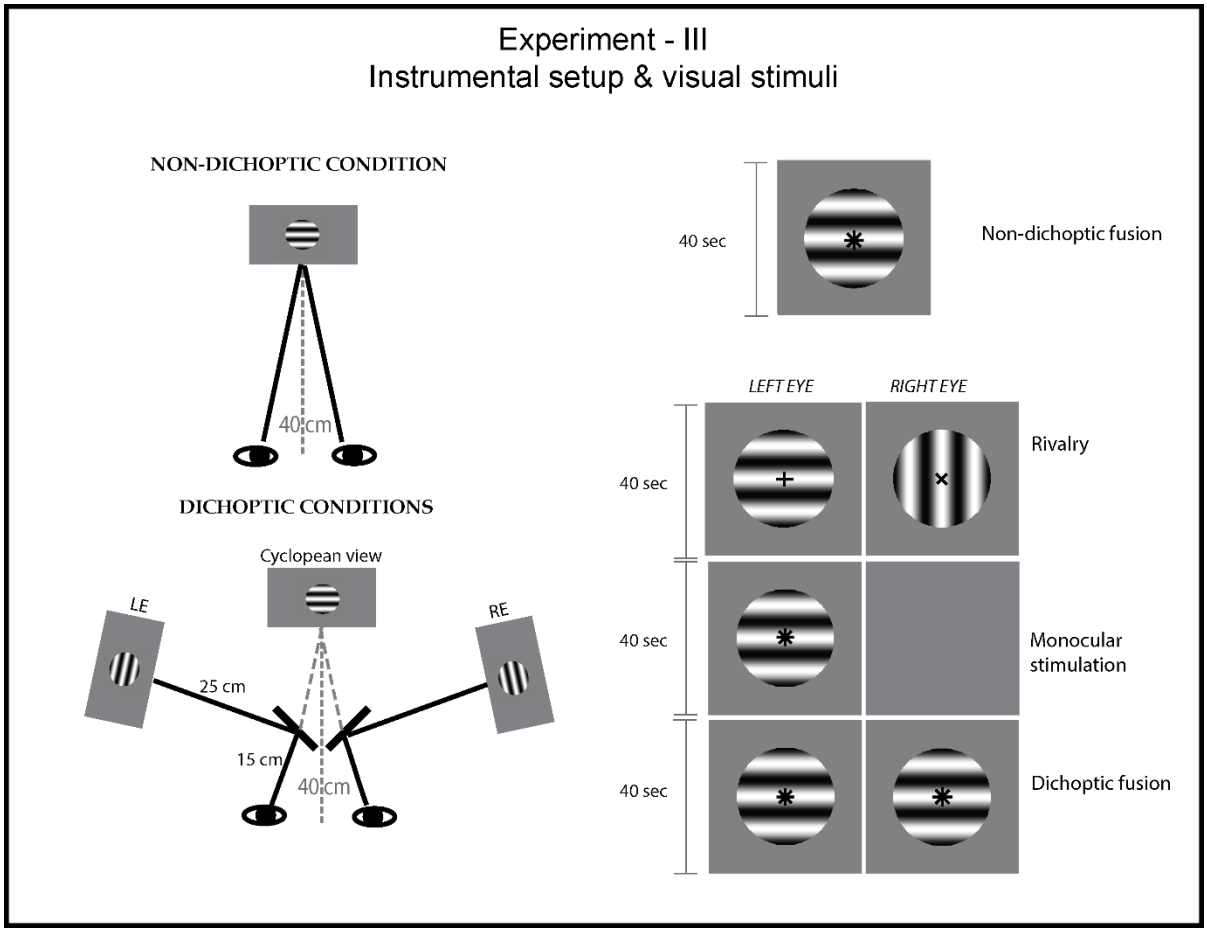


Figure 5-1: Visual stimuli and instrumental setup – Experiment III

Schematic representations of the stimulus displays are shown on the left. The visual stimuli are shown on the right.

5.3 Results

5.3.1 Different dichoptic viewing conditions

BCEA values across all conditions for both left eye and right eye are shown in Figure 5-2. BCEA values were converted into log values and subjected to RM ANOVA (2 eyes & 4 viewing conditions). The analysis showed that there was a significant

interaction between eye (left and right eyes) and the four viewing conditions [$F(3,39) = 5.16$; $p=0.004$]. Post-hoc pairwise analyses (Tukey HSD) revealed the following results; 1) during the non-dichoptic fusion condition, both eyes showed significantly more stable fixation than the three dichoptic conditions ($p<0.001$), 2) comparing fixational stability between the two eyes revealed that viewing conditions such as binocular rivalry, dichoptic fusion and non-dichoptic fusion did not show a significant difference between two eyes. However, during the monocular stimulus condition, there was a significant difference between the fixational stability of two eyes. The right eye that was presented blank screen showed significantly less stable fixation compared to the left eye that was presented the fixation target ($p=0.03$).

It should be noted that the stimulus to left eye was kept constant and the stimulus to right eye was varied. Therefore, statistical analyses were made separately for the left eye and the right eye using repeated measure ANOVA (4 viewing conditions). Analysis on the left eye showed that there was a significant main effect of viewing condition [$F(3,39) = 19.67$; $p<0.001$]. However, this main effect was due to the non-dichoptic fusion condition, as no significant differences were noted between three dichoptic viewing conditions ($p > 0.05$). Similarly, the right eye which was presented with different viewing conditions showed the same pattern [$F(3,39) = 16.61$;

p<0.001], i.e. the stability of right eye under non-dichoptic fusion condition was significantly better compared to all three dichoptic conditions (p<0.001) and there were no statistically significant differences noted between the dichoptic conditions (p > 0.05).

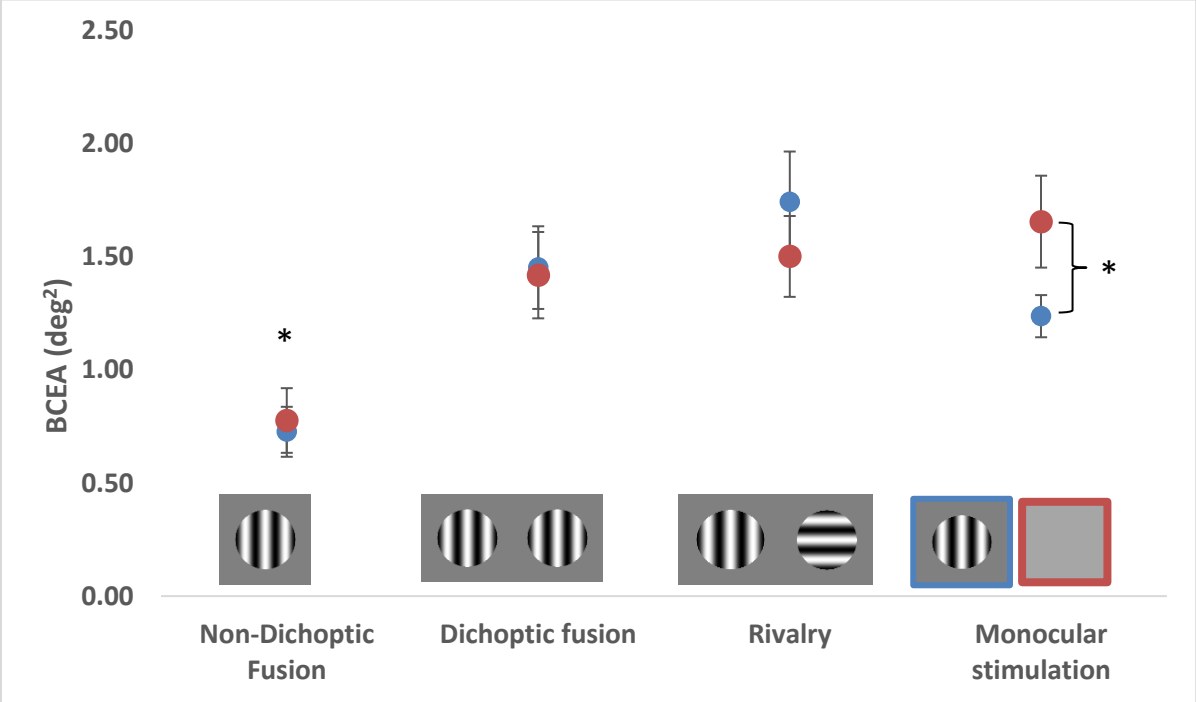


Figure 5-2: Effect of different binocular viewing conditions on fixational stability

Fixational stability of the left eye (blue) and the right eye (orange) is shown for non-dichoptic fusion (NDF), dichoptic fusion (DF), binocular rivalry (BR) and monocular stimulation (MS). Error bars represent ±1 SE. Fixational stability was significantly different between two eyes only during monocular stimulation condition. The asterisk symbol represents statistical significance.

5.3.2 Effect of rivalry suppression

In the binocular rivalry condition, perceptual dominance switched between the two eyes. The two possible percepts were 1) suppression (i.e. perceiving only one of the gratings while suppressing the other) or 2) piece-meal (i.e. perceiving a mixture of both gratings). This allowed the rivalry data to be separated into periods of suppression and periods of piece-meal. BCEA data were then calculated for each period of suppression and piece-meal. To test the hypothesis that suppression would influence fixational stability, BCEA of the left eye when it was the dominant eye was compared with the left eye when it was the suppressed eye. The same analysis was done for the right eye. After segregating the data, the mean and SD of a single period of suppression was 1.86±1.3 sec and 1.91±1.05 secs for the right eye and the left eye, respectively. Figure 5-3 shows that there was no significant effect of suppression on fixation stability. Moreover, fixational stability during piece-meal was significantly less stable compared to fixational stability during the period of suppression or dominance.

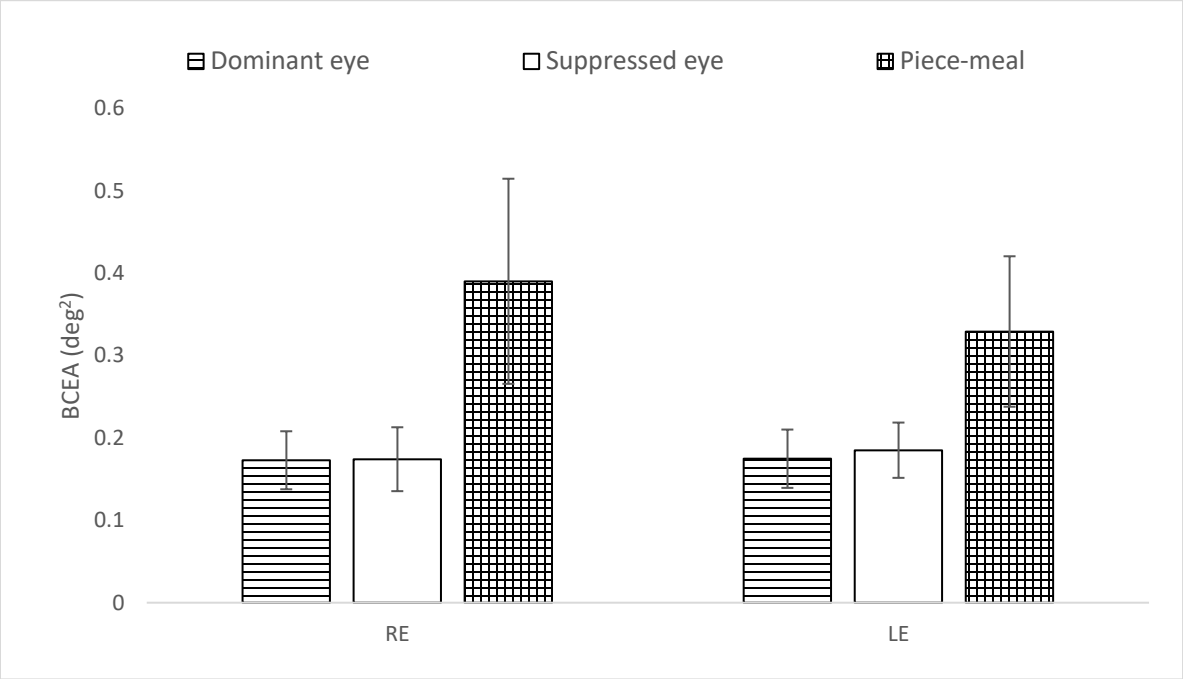


Figure 5-3: Effect of rivalry suppression on fixational stability.

The mean fixational stability values of the left eye and right eye during periods of dominance (horizontal stripes), suppression (blank) and piece-meal (checkered). Error bars represent ±1 SE. There was no significant effect of rivalry suppression on fixational stability. Moreover, fixational stability during periods of piece-meal perception was less stable compared to fixational stability during periods of suppression or dominance.

5.3.3 Characteristics of microsaccades

5.3.3.1 Microsaccadic amplitude

Figure 5-4 shows the amplitude of microsaccades across different viewing conditions for the left eye and the right eye. Repeated measures ANOVA (2 eyes & 4 viewing conditions) was performed after log transforming the amplitude and it

showed that there was a main effect of viewing condition [F (3,33) = 5.87; p=0.003]. Post hoc analyses (Tukey HSD) showed that under non-dichoptic fusion, the microsaccadic amplitude in the left eye was significantly lower compared to other three dichoptic conditions ($p<0.001$). However, there was no statistically significant difference between the three dichoptic conditions. The same effect was present for the right eye. This result is consistent with the fixation stability data where the non-dichoptic fusion showed significantly more stable fixation compared to all three dichoptic conditions. However, unlike the fixational stability data, microsaccadic amplitude showed no difference between the right and the left eyes for any of the viewing conditions.

When the microsaccadic amplitudes for the left eye and the right eye were analyzed separately (in the same fashion as performed for fixational stability), similar results were noted. For the left eye, there was a significant main effect of viewing condition (4 factors) $F(3, 33)=8.34$, $p<0.001$. Post-hoc analyses showed that microsaccadic amplitude was significant larger in the non-dichoptic fusion condition compared to the other dichoptic conditions. No significant differences were noted between the three dichoptic conditions.

For the right eye, a significant main effect of viewing conditions was noted $F(3, 33)=3.6850$, $p=.02$. Though the similar trend of results was noted, post-hoc analysis revealed that microsaccadic amplitude was found to be significantly larger in the binocular rivalry condition compared to non-dichoptic fusion condition ($p < 0.05$). No other significant differences were found.

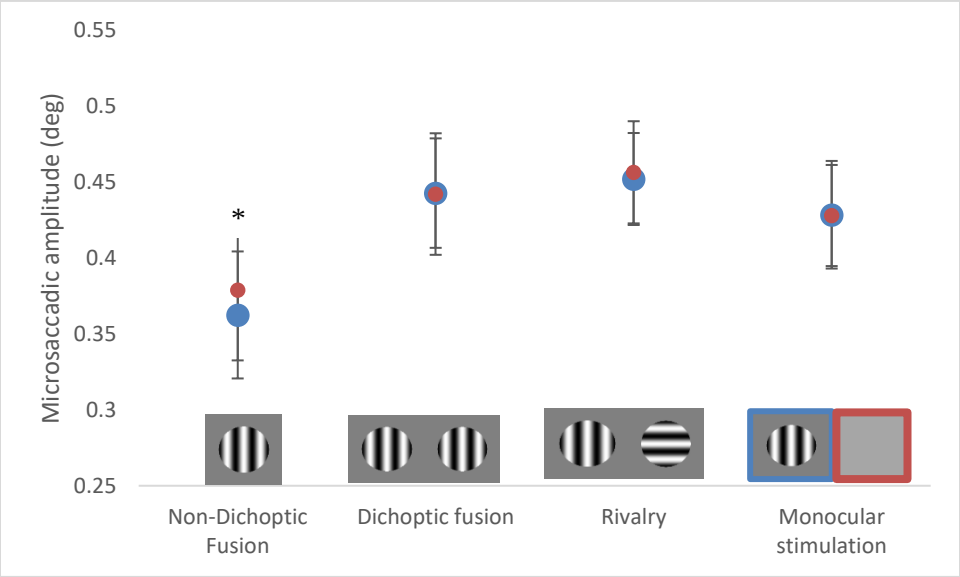


Figure 5-4: Effect of different binocular interactions on microsaccadic amplitude

Microsaccadic amplitude of the left eye (blue) and the right eye (orange) during non-dichoptic fusion (NDF), dichoptic fusion (DF), binocular rivalry (BR) and monocular stimulation (MS). Microsaccadic amplitude during non-dichoptic viewing was significantly decreased compared to the three dichoptic conditions. No significant differences between the right and left eyes were present. The asterisk symbol represents statistical significance.

5.3.3.2 Frequency of microsaccades

Figure 5-6 shows the frequency (rate) of microsaccades across different viewing conditions. Repeated measures ANOVA (4 viewing conditions) showed a significant main effect of viewing conditions [$F(3,33) = 16.765$; $p<0.001$]. Tukey HSD was used to perform post hoc analysis. Under the non-dichoptic viewing conditions, the frequency of microsaccades was lower compared to the other three dichoptic conditions.

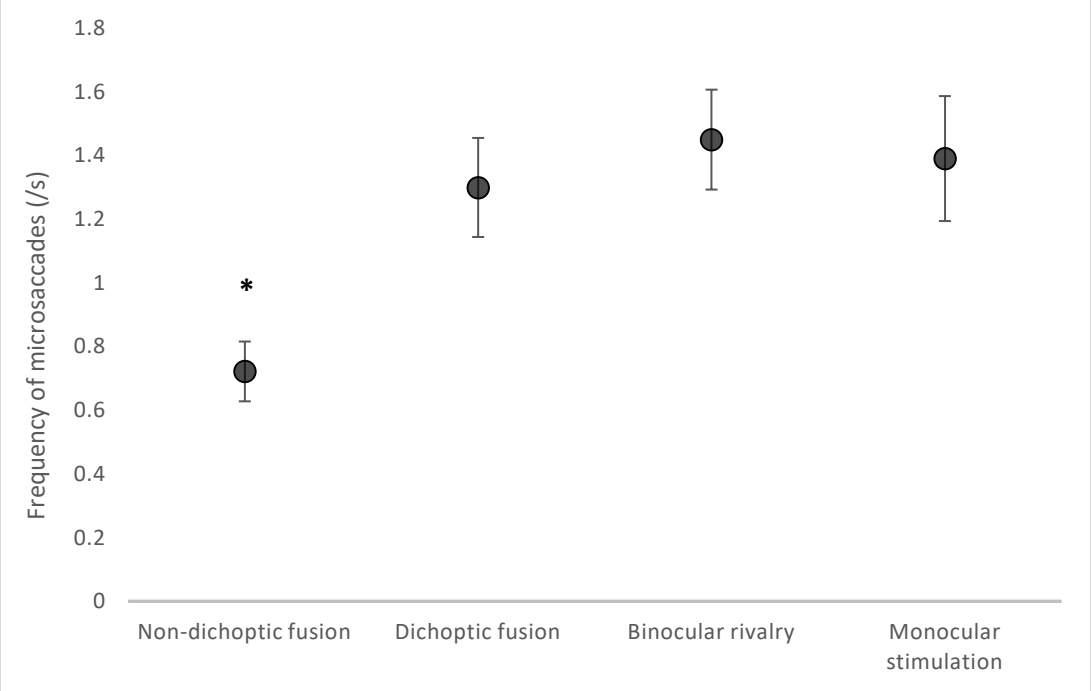


Figure 5-5 Frequency of microsaccades.

The frequency of microsaccades was significantly lower in the non-dichoptic condition than the other conditions. The error bars represent ±1 SE. The asterisk symbol represents statistical significance.

5.4 Discussion

Since the results of the previous experiment (Chapter-4) showed that fixational stability was much improved under binocular fixation, it was hypothesized that any change in binocular interaction would influence fixational stability. Therefore, to study the effect of binocular interaction on fixational stability, using a dichoptic viewing arrangement, the left eye was always presented with the same stimulus whilst the right eye was presented with different images such as an orthogonally oriented grating (binocular rivalry), a mean luminance screen (monocular stimulation) or an identical image (dichoptic fusion) to introduce different binocular interactions. Thus, the primary outcome of the study was left eye fixational stability. If binocular interaction played a role in influencing the fixational stability, then viewing conditions such as binocular rivalry and monocular stimulation would be expected to effect fixational stability of left eye. However, the results suggested that the fixational stability of left eye did not differ significantly between the different dichoptic stimuli.

The binocular rivalry data were further explored by segregating the data into periods of suppression and periods of piece meal. BCEA was then estimated for each eye separately during these periods. The results showed that there was no difference

between the suppressed and dominant eyes during the periods of suppression. However, fixational stability was significantly less stable during periods of piece-meal compared to the periods of suppression. This suggested that rivalry suppression did not influence fixational eye movements. Moreover, the increased instability during the periods of piece-meal could be due to the fact that neither eye was dominant. Therefore, there was not a single strong signal to hold fixation stable.

The results of experiments I & II suggested that the lack of a fixation target influences fixational stability more than reduced VA or contrast of the fixation target. To investigate further the effect of an absent fixation target on fixational stability, a 'monocular stimulation' viewing condition was tested. The results of this condition also suggested that the presence of a fixation target is crucial for stable FEM even if the other eye is viewing a target. Moreover, this experiment also suggested that under dichoptic viewing conditions, each eye can behave independently, i.e. the eye that was viewing no fixation target showed significantly less stable fixation that the eye viewing a target. This raises the question of whether FEM are conjugate. It is well established that microsaccades are conjugate [6,14,16,31]. It is also evident from the results of this study that microsaccadic amplitude or frequency did not vary significantly

between the eyes during the monocular stimulation condition. Thus, it could be speculated that it was ocular drifts that differed between the two eyes.

The other intriguing result of this experiment was a significant difference in the characteristics of FEM between the dichoptic and non-dichoptic fusion conditions. Factors such as disparity vergence, accommodative vergence, phoria, and the use of reflected images in the haploscope could not explain the differences between these conditions (Appendix-B). The cause of this difference remains unresolved.

Microsaccadic amplitude showed similar results to fixation stability whereby the dichoptic fusion condition showed a significantly decreased amplitude of microsaccades compared to all three dichoptic viewing conditions. However, unlike fixational stability, there was no difference in the microsaccadic amplitude between two eyes during the monocular stimulation viewing condition. A previous study showed that the frequency of microsaccades was increased during binocular rivalry compared to a non-rivalrous target [122]. However, in the present experiment, an increased rate of microsaccades was noted in all dichoptic conditions compared to the non-dichoptic fusion condition. Therefore, an increased rate of microsaccades might be attributed to dichoptic presentation of visual stimuli but not rivalry per se. This is

consistent with the findings of van Dam & van Ee, 2006 [123] where they showed that bistable perceptions and eye movements were not related.

5.5 Conclusion

- Abnormal binocular interaction simulated through binocular rivalry did not influence fixational stability or microsaccadic amplitude.
- In agreement with the results of experiments 1 and 2, the absence of a fixation target (monocular stimulation) influenced fixational stability. This result also suggested that eyes of controls can behave independently during fixation.
- Though perception is believed to be the same, dichoptic viewing showed less stable fixation compared to non-dichoptic fusion condition.

Chapter 6

Effect of different degrees of binocular interaction on fixational stability in participants with normal vision and amblyopia

The advantage of the experiment described in (Chapter-5) was that using binocular rivalry, suppression could be simulated easily in observers with normal binocular vision to study the effect of suppression on fixational eye movements. However, the simulated suppression through binocular rivalry might not have been maximally effective due to the short period of the binocular rivalry alternation cycle. Also, the effect of these different forms of binocular interactions cannot be tested in the participants with amblyopia who have natural suppression. Therefore, additional experiments that enable a simulation of different degrees of binocular interaction were needed to study the effect of binocular interaction on characteristics of fixational eye movements in control participants as well as the observers with amblyopia.

6.1 Introduction

Contrast can be used as a factor to induce different degrees of binocular interaction by varying the interocular contrast ratio, i.e. keeping the contrast constant to one eye whilst varying the contrast to the other eye. The method of varying interocular contrast ratio has been widely used in the field of amblyopia to measure

the degree of interocular suppression [62,86] and is also used in the binocular treatment of amblyopia [91,92]. To the best of our knowledge, the experiment described in this chapter was the first study to evaluate the effect of varying interocular contrast on fixational eye movements in control participants and observers with amblyopia.

The hypothesis was that if binocular interaction influences fixational stability, then 1) in control participants, degrading binocular interaction by inducing interocular contrast differences would make fixation less stable and, 2) in anisometropic amblyopia, improving binocular interaction by introducing interocular contrast differences would make fixation more stable.

6.2 Methods

13 observers (8 with normal binocular vision and 5 with anisometropic amblyopia – S1, S2, S3, S6 & S7, Table 2-1) were recruited. The visual stimulus for this experiment was the same as used in the previous experiments. Visual stimuli were presented dichoptically using the haploscope. In control participants, there were 2 viewing conditions (Figure 6-1); 1) the contrast of the visual stimulus presented to the dominant eye (DE) was varied across 7 levels (0%, 5%, 10%, 20%, 40%, 80% and 100%) while the contrast the non-dominant eye (NDE) was kept constant at 100% and 2) the contrast was varied in the NDE while keeping the contrast constant in the DE. In

observers with amblyopia, only one viewing condition was tested, the contrast of the visual stimulus presented to the fellow eye (FFE) was varied across 7 different levels (0%, 5%, 10%, 20%, 40%, 80% and 100%) while the to the amblyopic eye (AME) was kept constant at 100%. In observers with amblyopia, a condition where the AME saw 0% and the FFE saw 100% measurements was also measured. For each trial, the contrast level presentation order was randomized. At each interocular contrast level, fixational eye movements were measured for 30 seconds in both eyes simultaneously. A set of seven different interocular contrast levels were considered as one trial. Trials were repeated four times per participant.

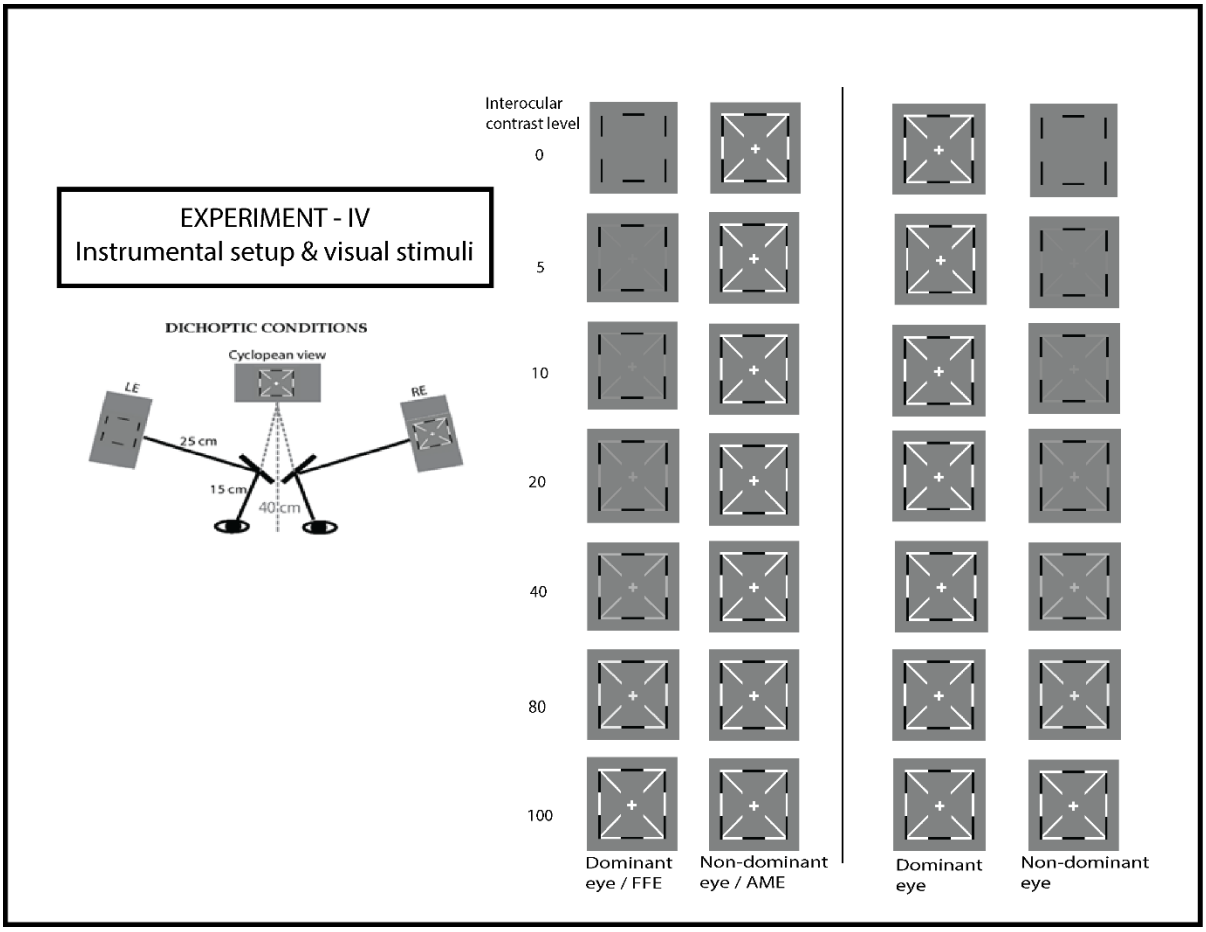


Figure 6-1: Visual stimuli and instrumental setup of Experiment-IV.

The left panel shows a schematic representation of stimulus presentation. The right panel shows the visual stimuli used in the experiment. Interocular contrast was varied to induce different degrees of binocular combination.

6.3 Results

6.3.1 Control participants

6.3.1.1 Contrast varied to the dominant eye

Figure 6-2 shows the relationship between interocular contrast levels (when the contrast was fixed at 100% to the NDE and varied from 0 – 100% to the DE) and the stability of FEM. The BCEA values were log transformed and analyzed with repeated measures ANOVA with two factors; contrast level (7 levels) and eye (dominant vs. non-dominant). There was a significant interaction between contrast level and eye [$F(6,42) = 3.78$; $p=0.004$]. Tukey HSD revealed that except at the interocular contrast level of 0%, there were no significant differences between the DE and NDE. When the contrast of the NDE was fixed at 100% and the DE at 0%, the DE showed significantly reduced fixational stability compared to NDE ($p<0.001$).

Comparing fixational stability of the DE across different contrast levels, the DE showed significantly less stability when it was presented with 0% contrast (i.e. no fixation cross) compared to all other contrast levels ($p<0.001$). Moreover, DE at the interocular contrast level of 20% showed improved fixational stability (more stable) compared to the fixational stability at the contrast of 0%, 10%, and 80%. The NDE also

showed significantly improved FEM stability at the interocular contrast level of 20% compared to 0%, 10%, 80% and 100%.

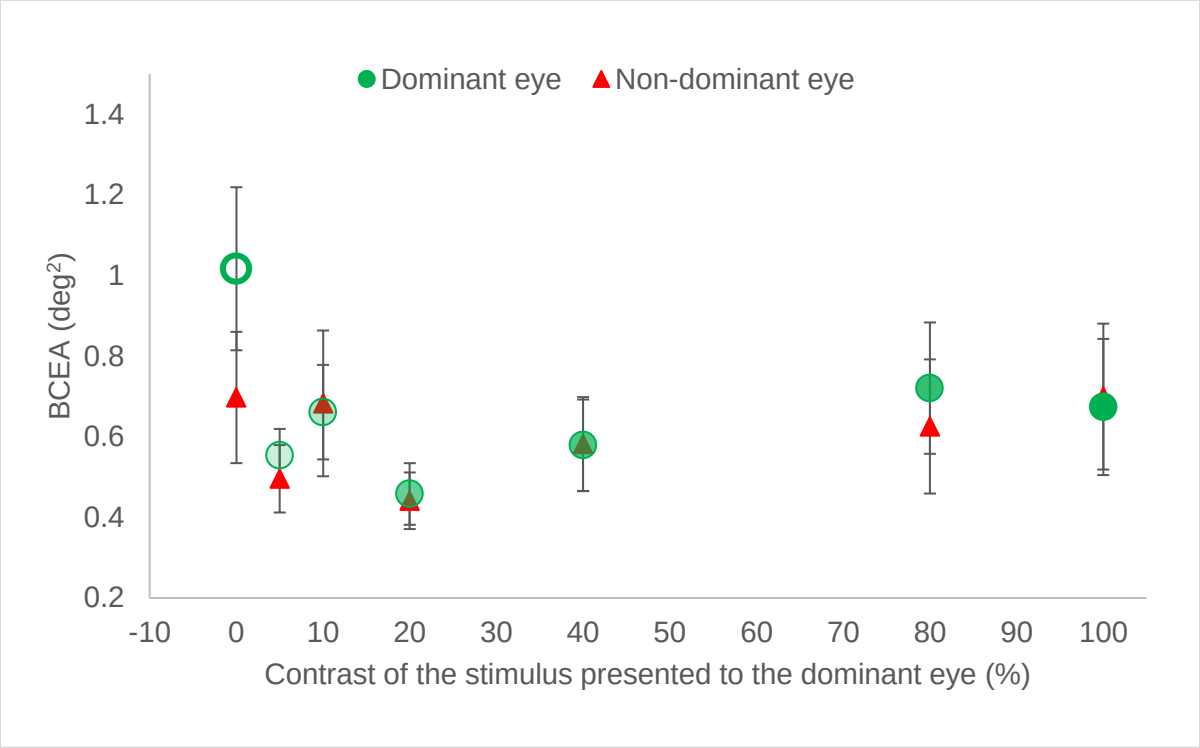


Figure 6-2: Fixational stability of control participants when the contrast was varied to the dominant eye.

The fixational stability of the dominant eye (DE – green data points) and the non-dominant eye (NDE – red) when the contrast was varied to the DE and kept constant at 100% for the NDE. The datapoints and error bars represent Mean ± SEM. The stability of FEM was significantly different between two eyes only when the DE was presented with 0% contrast (empty green) and the NDE with 100% contrast. In all other interocular contrast levels, there were no significant differences between DE and NDE. Significantly improved FEM stability of both eyes was present at the interocular contrast difference of 20%.

6.3.1.2 Contrast varied to the non-dominant eye

Figure 6-3 shows the relationship between fixational stability and the interocular contrast level when the NDE contrast was varied from 0-100% and the DE contrast was fixed at 100%. BCEA values were log transformed and analyzed with repeated measures ANOVA as described in section 1.3.1.1. The analysis showed a significant interaction [$F(6,42) = 3.298$; $p=0.009$] and significant main effect of 7 contrast levels [$F(6,42) = 2.416$; $p=0.031$]. Tukey HSD revealed that at the interocular contrast level of 0%, i.e. when the contrast of the NDE was at 0% and the DE at 100%, NDE showed significantly less stable FEM compared to DE ($p<0.001$). Moreover, fixational stability of the DE and NDE at the interocular contrast level of 20% showed improved stability compared to 0%, 5%, 40%, and 80% interocular contrast levels.

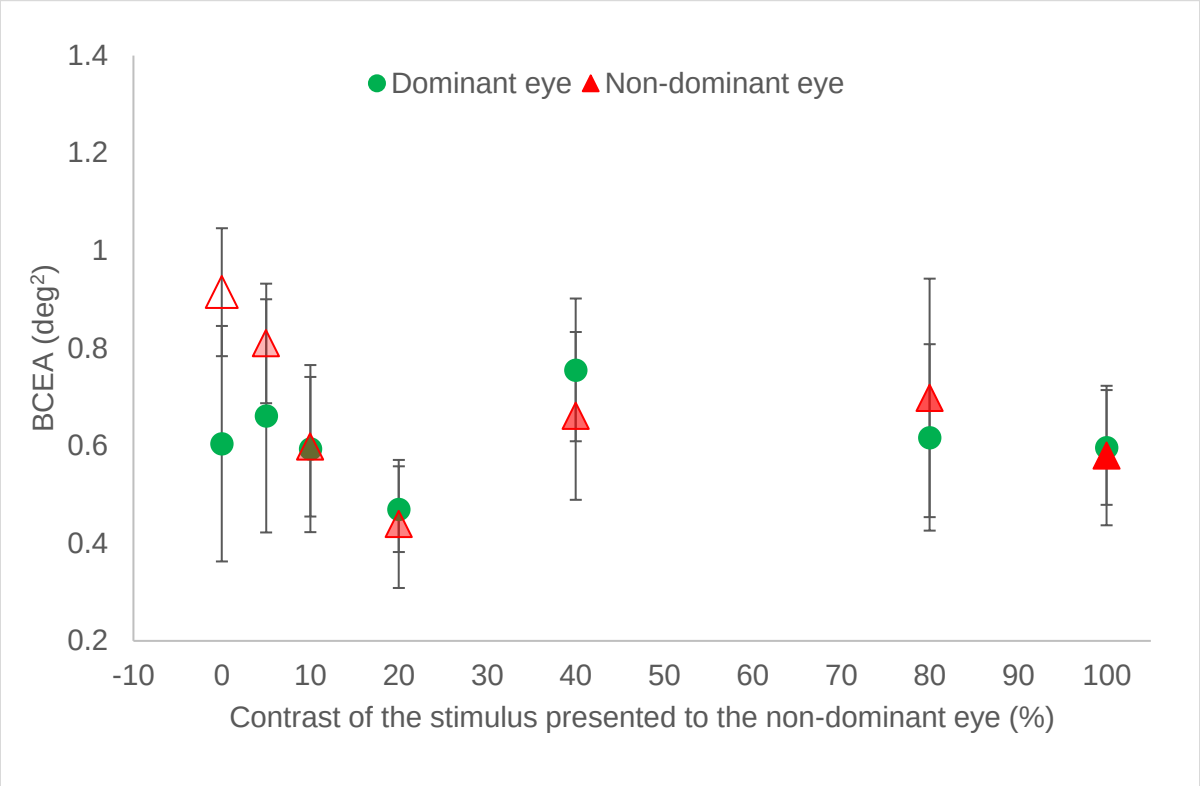


Figure 6-3: Fixational stability of control participants when the contrast was varied to the non-dominant eye

The figure shows the fixational stability of the dominant eye (DE – green data points) and the non-dominant eye (NDE – red data points) when the contrast was varied to NDE and kept constant for DE. The datapoints and error bars represent Mean ± SEM. A similar pattern of result was noted when the contrast was varied to NDE. The stability of FEM was significantly different between two eyes only when the NDE was presented with 0% contrast (empty red) and the DE with 100% contrast. In all other interocular contrast levels, there were no significant differences between DE and NDE. Significantly improved FEM stability of both eyes was present at the interocular contrast difference of 20%.

6.3.1.3 Microsaccadic amplitude

Figure 6-4 shows the amplitude of microsaccades across different interocular contrast ratios when the contrast was varied to the dominant eye (DE) (top) and non-

dominant eye (NDE) (bottom). The values of microsaccadic amplitudes were log transformed and subjected to repeated measure ANOVA. Microsaccadic amplitudes, when the contrast was varied to DE, showed a significant main effect of contrast level [$F(6,36) = 3.16$; $p=0.013$] and no significant interaction [$F(6, 36) = 1.52$; $p=0.20$]. Furthermore, no significant main effect of ocular dominance was noted [$F(1, 6) = 1.01$; $p=0.35$]. Tukey HSD revealed that at the interocular contrast level of 0%, both the DE and NDE showed significantly higher microsaccade amplitude compared to each of the other contrast levels ($p<0.001$). Moreover, there was no statistical significance between DE and NDE at any other contrast ratios.

When the contrast was varied to the NDE, microsaccadic amplitudes showed a significant interaction between contrast level and ocular dominance [$F(6,36) = 2.40$; $p=0.047$]. But no main effect of ocular dominance [$F (1, 6)=1.1961$, $p=.316$] or contrast levels [$F(6,36) = 0.52$; $p=0.787$]. Post-hoc analysis revealed that at the interocular contrast level of 0%, i.e. 0% to NDE and 100% to DE, the microsaccadic amplitude of DE was significantly larger compared to NDE ($p=0.01$).

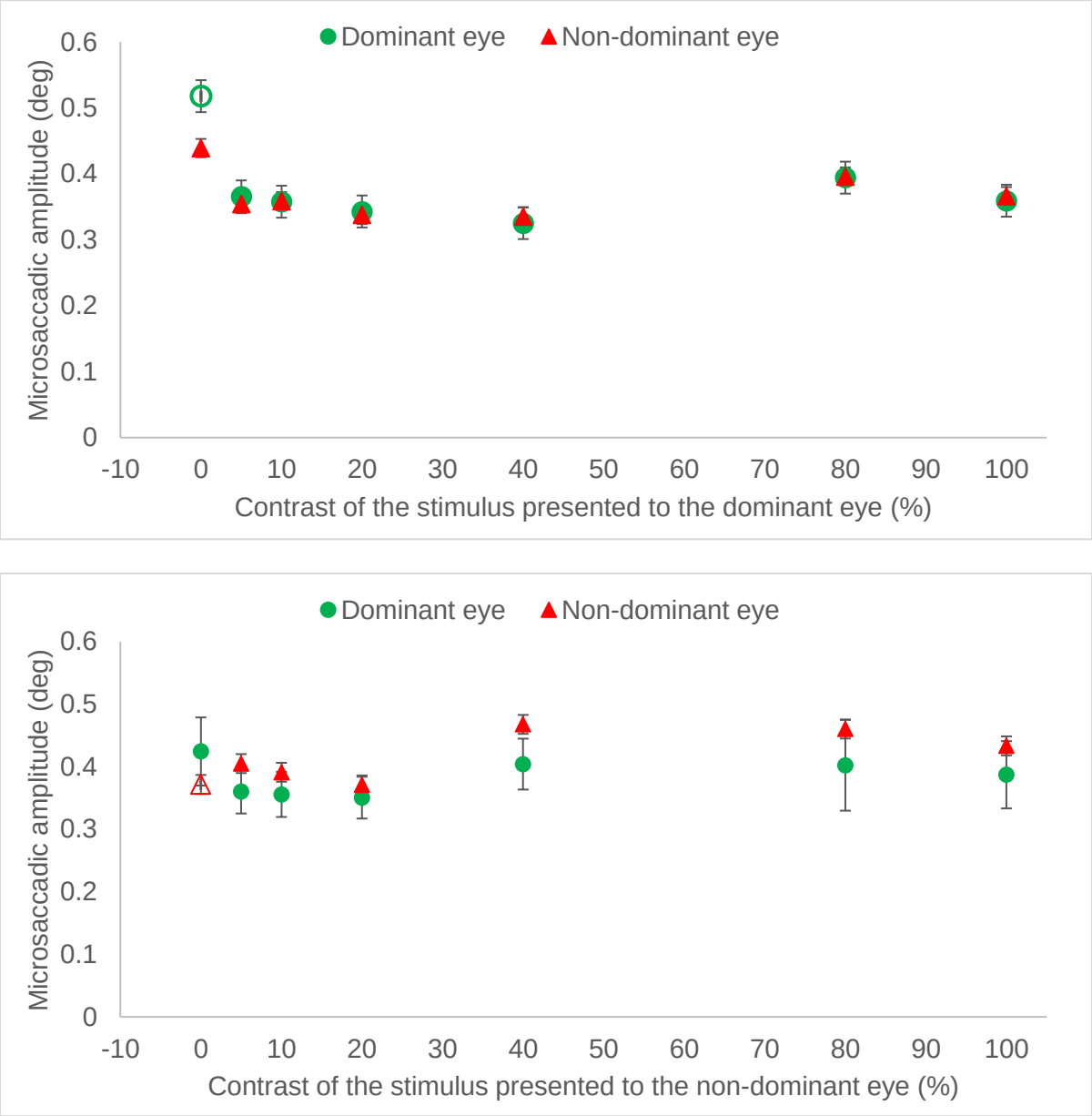


Figure 6-4: Effect of interocular contrast level on microsaccadic amplitude.

The top panel shows mean microsaccadic amplitude plotted as a function of interocular contrast (contrast varied to the DE and kept constant for the NDE). The bottom panel is mean microsaccadic amplitude plotted as a function of interocular contrast (contrast varied to the NDE and kept constant for the DE). The datapoints and error bars represent Mean ± SEM. It should be noted that there was a

significant difference in the microsaccadic amplitude between DE and NDE with DE (viewing 0% contrast) showed larger amplitude compared to NDE. However, such difference between NDE and DE was not noted when NDE was viewing 0% and DE 100% contrast targets. This suggested that there might some effect of ocular dominance (though there was no significant main effect).

6.3.1.4 Fast Fourier transformation

In control participants, a significant difference in fixational stability between the two eyes was present only at the interocular contrast level of 0%. Therefore, FEM of both eyes at the interocular difference of 0% were analyzed using to FFT to determine which combination of FEM components were responsible for less stability in the eye that was presented with 0% contrast. The results are shown in Figure 6-5 and it revealed that, for the eye that was viewing the 0% contrast target, there was an increase in the spectral density amplitude within the frequency range of 0.1 – 0.5Hz (red lines) relative to the eye that was presented with 100% contrast (green lines). This frequency range corresponds to ocular drifts.

Thus, to summarize, larger BCEA values (less stable fixation) in the eye that was presented with 0% contrast (no fixation target) is associated with larger drifts in control participants. It should also be noted that microsaccadic amplitude was noted to be larger in DE when it was viewing no fixation target compared to NDE.

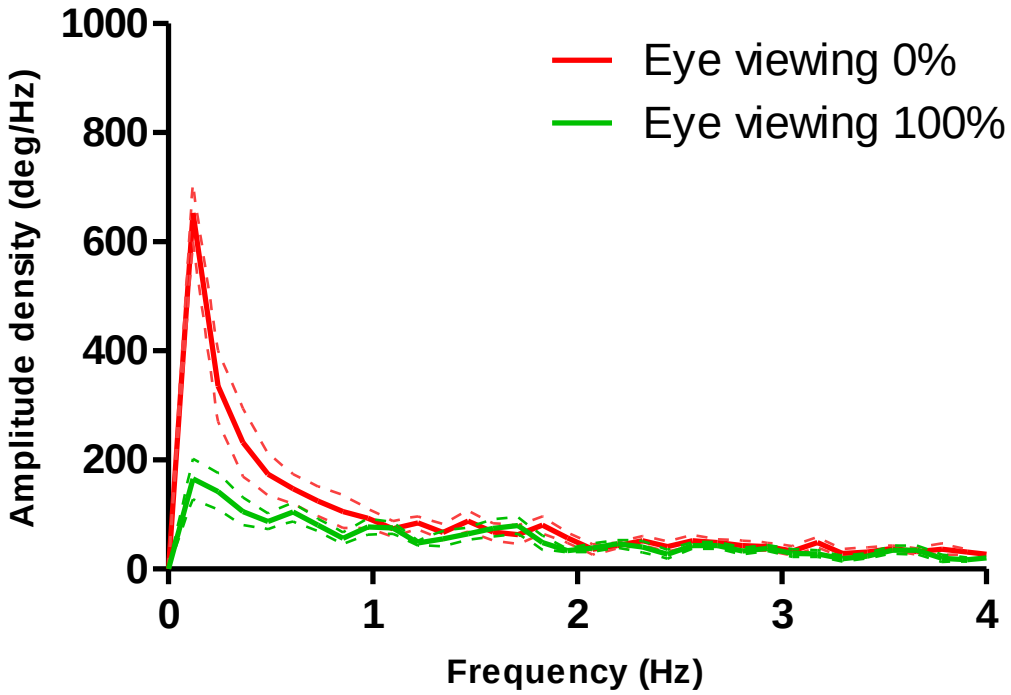


Figure 6-5: Spectral density of fixational eye movements of control participants during binocular fixation

Mean spectral density of FEM of control participants at the interocular contrast level of 0%. The dotted lines represent ±1 SEM. The eye that was presented with 0% contrast target (red lines) showed increased spectral density at the frequency range of 0.1 – 0.5Hz compared to the eye viewing the 100% contrast target. The frequency range of 0.1 – 0.5Hz corresponds to ocular drifts.

6.3.2 Observers with amblyopia

6.3.2.1 Fixational stability

Figure 6-6 shows the effect of interocular contrast levels on the stability of fixation in observers with anisometropic amblyopia. Stability of the AME and FFE

was not different at any interocular contrast level. The results were analyzed using repeated measures ANOVA which revealed a significant main effect of contrast (7 levels) [$F(6,24) = 2.843; p=0.031$]. However, there was no significant main effect of eye (AME vs. FFE) [$F(1,4) = 0.230; p=0.656$] and no significant interaction (eye vs. contrast) [$F(6,24) = 0.570; p=0.750$]. At the interocular contrast ratio of 0%, i.e. 0% stimulus contrast to FFE and 100% to AME, both the FFE and AME became less stable ($p<0.001$). This implied that the FFE influenced the fixation stability of the AME.

In order to further assess whether the FFE was determining the fixation stability of the AME, 0% contrast was presented to the AME and 100% was presented to the FFE. Figure 6-7 shows the fixational stability of the FFE and the AME under two conditions: 1) AME viewing 100% contrast (filled red bar) and FFE viewing 0% contrast (open green bar) and 2) FFE viewing 100% contrast (filled green bar) and AME viewing 0% contrast (open red bar). The AME exhibited significantly more stable fixational eye movements when it viewed 0% contrast and the FFE viewed 100% contrast than vice versa ($p=0.03$). This also suggests that fixational eye movements of the AME are influenced by the FFE under binocular viewing conditions.

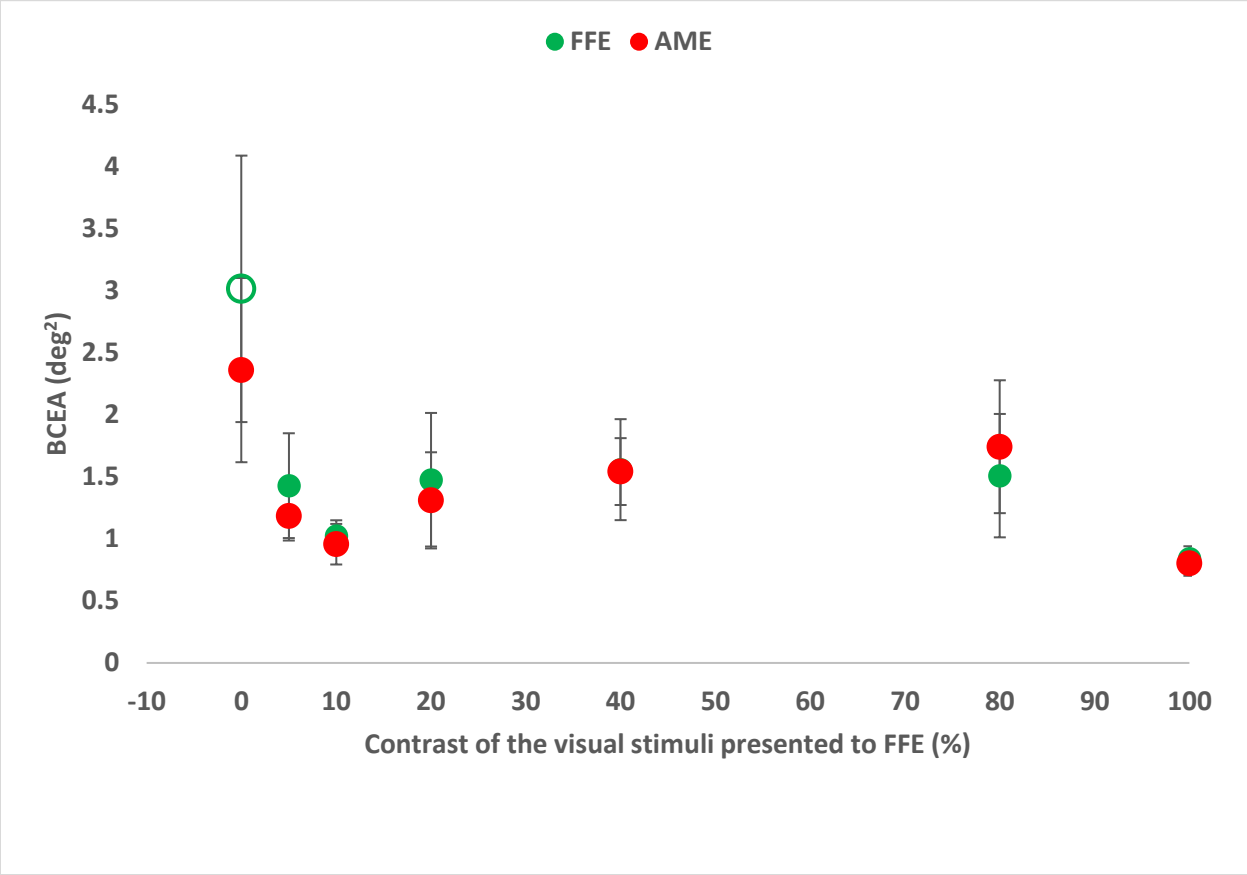


Figure 6-6: Fixational stability (BCEA) in observers with amblyopia when contrast presented to the FFE was varied.

Fixational stability of both eyes was significantly reduced when the fellow eye was presented with 0% contrast. Otherwise there was no effect of interocular contrast on fixational eye movements for either eye.

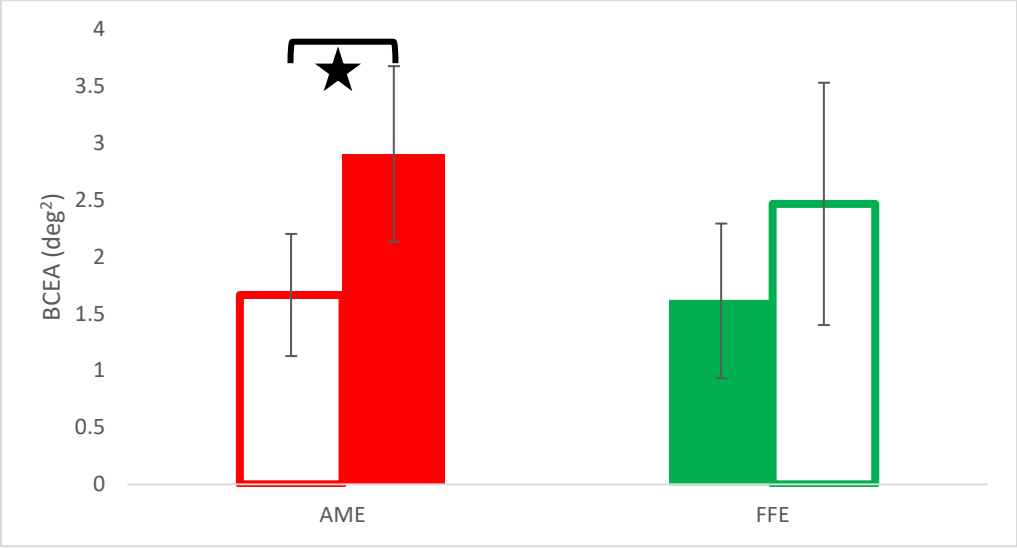


Figure 6-7: Effect of the presence of a target on the stability of fixation

Red bars indicate AME data and green bars FFE data. Filled bars indicate that the eye was viewing a 100% contrast stimulus and open bars a 0% contrast stimulus. When one eye was presented with 100% contrast, the other was presented with 0% contrast. The data indicate that when the FFE viewed the 100% contrast fixation target, the AME, which viewed 0% contrast, showed significantly more stable fixation than when the AME viewed the 100% contrast fixation target and the FFE viewed 0% contrast.

6.3.2.2 Microsaccadic amplitude

Figure 6-8 shows the mean microsaccadic amplitude of the AME and the FFE across different interocular contrast levels. The values were log transformed and subjected to repeated measures ANOVA which revealed no significant main effect of eye (AME vs. FFE) [$F(1,4) = 2.137; p=0.218$] and no significant interaction (eye vs. contrast) [$F(6,24) = 0.885; p=0.521$]. However, there was significant main effect of contrast (7 levels) on microsaccadic amplitude [$F(6,24) = 2.843; p=0.031$]. Even pair-

wise comparison (paired t-test) did not show statistical significance between AME and FFE at any interocular contrast levels.

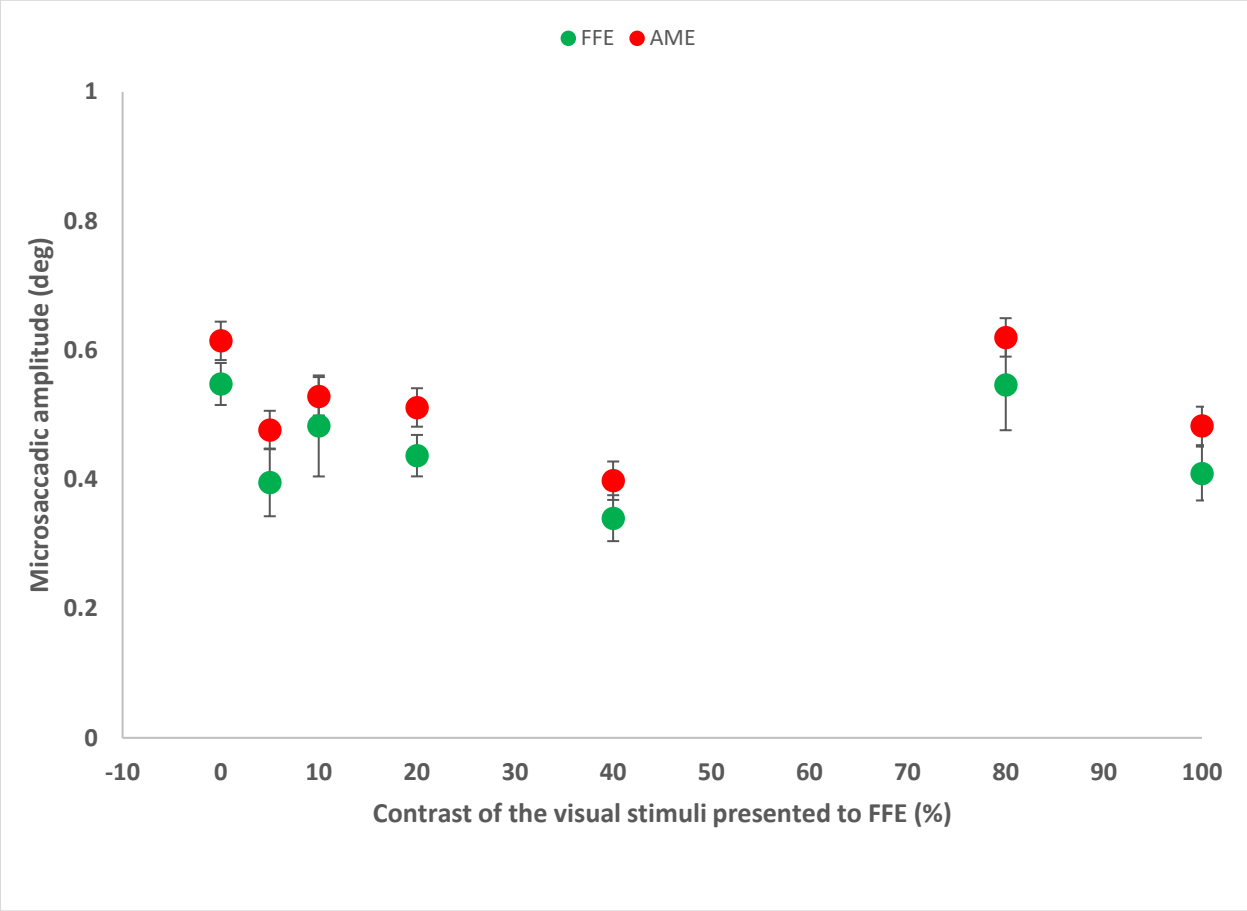


Figure 6-8: Microsaccadic amplitude plotted as a function of contrast presented to the FFE

Mean microsaccadic amplitudes of FFE (green) and AME (red) were plotted as a function of contrast presented to FFE. Though the mean microsaccadic amplitude of AME was numerically larger than that of FFE at all interocular contrast levels, there were no statistically significant differences between the two eyes.

6.3.3 Controls vs. anisometropic amblyopia

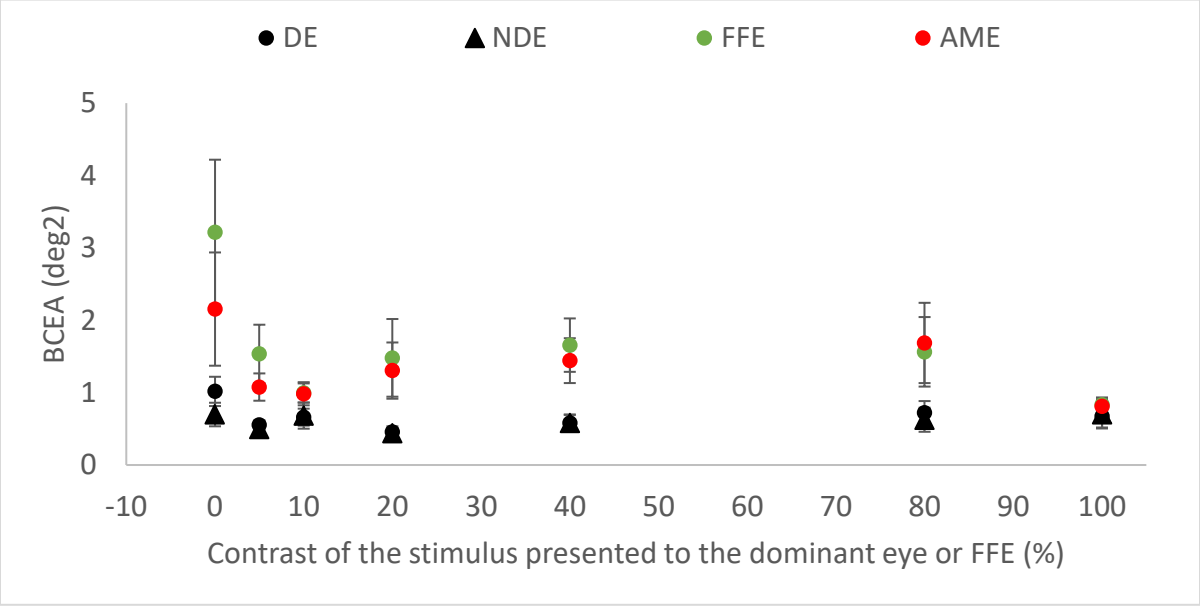
6.3.3.1 Fixational stability and microsaccadic amplitude

It should be noted that in control participants, the condition where the contrast of the stimulus presented to DE was varied and the contrast of the stimulus presented to NDE was kept constant at 100% was used for the comparison. Therefore, in both groups, the contrast of stimulus presented to the DE (FFE in observers with amblyopia) was varied from 0 to 100% whereas the contrast of stimulus presented to NDE (AME in observers with amblyopia) was kept constant at 100%.

Figure 6-9a shows the fixational stability of control participants and observers with anisometropic amblyopia. The figure shows that at all interocular contrast levels, the fixational stability of the AME and FFE was numerically higher (less stable) than that of control participants. In terms of fixational stability, there were significant main effects of group (controls vs. anisometropic amblyopia), contrast (7 levels) and an interaction between Eye (FFE/DE & AME/NDE) x Contrast (7 levels). This suggested that though there was no significant difference between AME and FFE, the overall fixational stability of both FFE and AME of the anisometropic amblyopia group was less stable compared to the control participants group. However, at the contrast level

of 100% to FFE, the fixational stability of the observers with amblyopia was as similar to that of controls.

Similarly, Figure 6-9b shows the microsaccadic amplitude of control participants and observers with anisometropic amblyopia. The results suggested that though microsaccadic amplitude in the amblyopia group was shown to be numerically larger compared to that of control participants, no significant differences were noted. Full statistical comparisons are shown in Table 6-1.



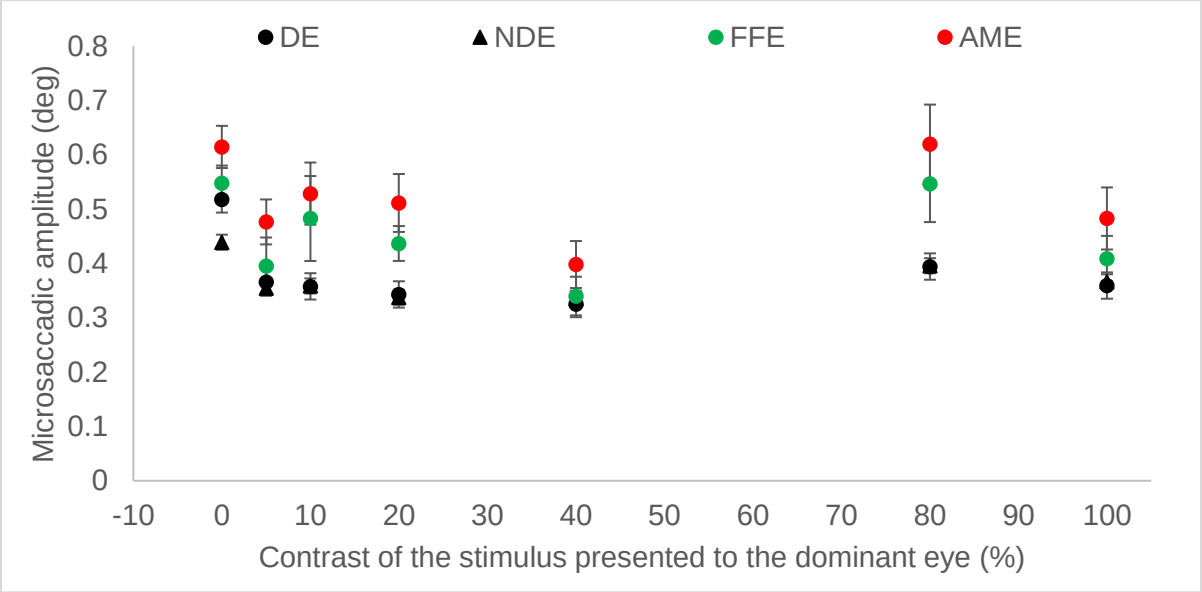


Figure 6-9: Comparison between controls and anisometropic amblyopia (AA)

Comparison of a) fixational stability and b) microsaccadic amplitude between the AME (red), FFE (green), DE of controls (black circle) and NDE of controls (black triangle). The fixational stability of the AME and FFE was significantly less stable than controls. The statistical values are tabulated in Table 1-1.

Table 6-1: Comparison between controls and anisometropic amblyopia (AA)

Comparisons	***F-values***
Fixational stability	
Main effect: Group (Controls vs. AA)	F(1, 11)=7.86, p=0.011*
Main effect: Contrast (7 levels)	F(6, 66)=2.23, p=0.050*
Main effect: Eye (FFE/DE x AME/NDE)	F(1, 11)=5.14, p=.045*

Interaction: Eye x Contrast	F(6, 66)=3.18, p=0.008*
Interaction: Group x Eye	F(1, 11)=0.38, p=0.85
Interaction: Group x Contrast	F(6, 66)=0.68, p=0.67
Interaction: Group x Eye x Contrast	F(6, 66)=0.58, p=0.74
Microsaccadic amplitude	
Main effect: Group (Controls vs. AA)	F(1, 10)=2.58, p=0.14
Main effect: Contrast (7 levels)	F(6, 60)=6.38, p<0.001*
Main effect: Eye (FFE/DE x AME/NDE)	F(1, 10)=1.98, p=0.14
Interaction: Eye x Group	F(1, 10)=3.77, p=.081
Interaction: Eye x Contrast	F(6, 66)=1.27, p=0.29
Interaction: Group x Contrast	F(6, 66)=0.83 p=0.56
Interaction: Group x Eye x Contrast	F(6, 66)=0.95, p=0.47

6.3.3.2 FFT analysis of FEM in observers with amblyopia

FFT analysis of FEM of observers with anisometropic amblyopia at the interocular contrast level of 100% is shown in Figure 6-10. The figure shows that the AME (red lines) showed increased spectral density in the frequency range of 0.1 to 0.5Hz which corresponds to ocular drifts compared to FFE (green lines). It should be noted that similar pattern of amplitude density spectrum was noted in control

participants as well, when one of the eyes presented with 0% and the other eye was presented with 100% contrast (Figure 6-5). The control eye that was presented with the 0% stimulus contrast showed increased spectral density in the frequency range of 0.1 to 0.5Hz similar to the AME of observers with anisometropic amblyopia when both eyes were presented with 100% contrast. In other words, the AME viewing 100% contrast showed a similar pattern of FEM to a control eye viewing 0% contrast.

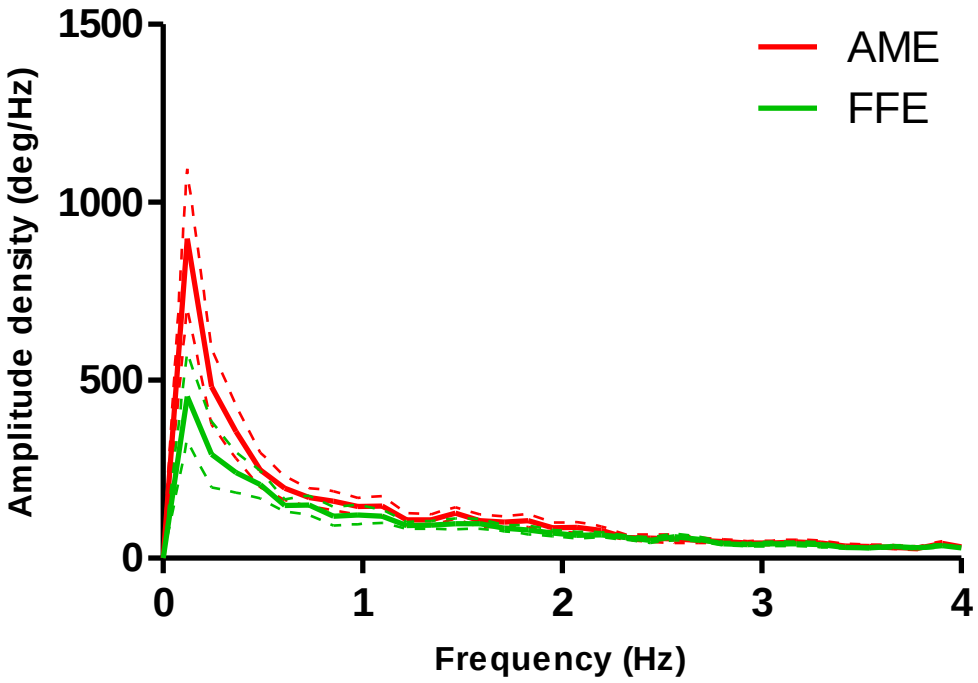


Figure 6-10: Spectral density function of fixational eye movements in observers with amblyopia during binocular fixation.

Mean amplitude spectral density of AME (red) and FFE (green) at the interocular contrast level of 100%. The dotted lines represent ±1 SEM. The amblyopic eye showed increased spectral density in the frequency range of 0.1 to 0.5Hz which corresponds to ocular drifts.

6.4 Discussion

6.4.1 Binocular interaction and fixational stability

It is suggested that in amblyopia, binocular contrast summation can be achieved by attenuating the signals to the fellow fixing eye (by reducing the contrast) to balance monocular inputs from the amblyopic eye and the fellow eye and overcome suppression of amblyopic eye signals [86]. Thus, varying the contrast levels between the dominant eye and the non-dominant eye is a good platform for studying the effect of suppression on fixational stability in observers with anisometropic amblyopia. The technique can also be applied to controls. This experiment showed that, except at the interocular contrast level of 0%, there was no difference in the fixational stability between two eyes at any of the interocular contrast levels in control participants. This result is consistent with the results of the previous experiment of this thesis (Chapter-5, section 5.3.2) where the suppression was induced by binocular rivalry in control participants. Moreover, the eye that was presented with 0% stimulus contrast (i.e. no central fixation target) showed less stable fixation compared to the eye that was presented with 100% stimulus contrast. This result is also consistent with the result of

the previous experiment of this thesis (monocular stimulation condition in Experiment-III).

In anisometropic amblyopia, at all contrast levels, the fixational stability of the fellow eye and the amblyopic eye did not vary significantly between two eyes. Thus, abnormal binocular interactions such as interocular suppression did not appear to influence fixational stability in control participants as well as in observers with amblyopia in this experiment.

6.4.2 Microsaccadic amplitude

The results of this experiment also suggested that microsaccadic amplitude was not significantly different between the FFE and AME during dichoptic viewing conditions. Chung et al. (2015) also noted that the amplitude of microsaccades was not significantly different between the AME and FFE in participants with anisometropic amblyopia under monocular viewing conditions. But, in the study by Chung et al. (2015), although the measurements were monocular, both eyes were remained open in an otherwise dark room. However, it should be noted that Shi et al. (2012) reported that microsaccadic amplitude was larger in the AME of observers with anisometropic amblyopia compared to the FFE. Shi et al. (2012) measured fixational eye movements in observers with anisometropic amblyopia monocularly, i.e. the

fellow eye was occluded while taking AME measurements and vice versa. Even in the previous study of this thesis (Chapter-3) where fixational eye movements were measured monocularly, there was a significant difference in fixational stability and microsaccadic amplitude between the AME and FFE. Therefore, the discrepancy between the findings of previous studies might be due to monocular vs. binocular viewing.

6.4.3 Absence of a fixation target in controls and observers with amblyopia

Previous experiments within this thesis showed that the absence of a central fixation target had a greater influence on fixational stability than optical blur or contrast. In this experiment, in control participants, the eye that was presented with the 0% contrast stimulus showed less stable fixational eye movements compared to the other eye that was presented with the 100% contrast stimulus. This agrees with findings reported in earlier chapters of this thesis (Chapters – 4&5). However, in observers with anisometropic amblyopia, at the interocular contrast ratio of 0% (i.e. the FFE was viewing 0% and the AME 100% contrast stimuli), the fixational stability of both the FFE and AME became significantly less stable compared to the other interocular contrast differences. This suggests that under binocular viewing, fixational stability of the AME was dependent on the fixational stability of the FFE. To

test this possibility further, the AME was presented with a 0% contrast stimulus and a 100% contrast stimulus was presented to the FFE. AME stability was increased in this new condition compared to the FFE 0%, AME 100% condition. Together, the results from this experiment suggest AME fixation stability is consensually controlled by FFE fixation.

6.5 Conclusion

- Abnormal binocular interactions such as interocular suppression have a limited role in influencing the stability of fixational eye movements in control participants and in observers with amblyopia.
- Consistent with the results of previous experiments, presence of a fixation target influenced fixation stability more than the contrast of the target in controls as well as in the observers with amblyopia.
- Both AME and 0% contrast in controls showed a relatively increased proportion of ocular drifts compared to the FFE or the eye with 100% contrast in the case of controls. This suggested that lack of positional certainty could be associated with unstable fixational eye movements.

Chapter 7
General discussion

Amblyopia is a neuro-developmental disorder which is associated with sensory deficits such as reduced visual acuity [45,124], crowding (due to contour interaction) [125–127], reduced contrast sensitivity for high spatial frequencies [50,66,128], reduced stereo-acuity [93,129], global deficits in motion perception [61–63,65] and form perception [61]. In addition to these sensory deficits, amblyopia is also associated with oculomotor deficits such as increased saccadic latency (Table-1) and abnormal fixational eye movements e.g. increased microsaccadic amplitude and increased ocular drifts (Table-2). Therefore, amblyopia is a condition which shows both impaired visual functions and impaired (less stable) fixational eye movements. Previous studies reported a positive relationship between impaired fixational stability and monocular sensory deficits such as impaired VA [41,42,44,109] and binocular deficits such as suppression [40,42,43]. The cause and effect relationship between impaired fixational stability and these sensory deficits in amblyopia has not been studied directly. Therefore, the objectives of this thesis were to understand the effect of simulated and real monocular and binocular sensory deficits on the characteristics of FEM such as fixational stability, microsaccadic amplitude and ocular drifts.

7.1 Monocular sensory deficits and fixational eye movements

To study the relationship between the visual acuity and fixational stability, experiment–I was conducted in control participants and observers with amblyopia. It is evident from the results that simulated reduced visual acuity in control participants did not alter fixational stability or microsaccadic amplitude. In observers with amblyopia, a positive relationship between fixational stability and reduced VA was noted for AMEs which was consistent with the findings of previous studies[41,42,44]. Moreover, significantly reduced fixational stability was noted in AME compared to FFE. Nonetheless, when VA of the FFE was reduced and matched to that of the AME, fixational stability was unaltered in the FFE. Thus, the results of this experiment suggested that impaired VA could not explain the impaired fixational stability of the AME.

7.2 Binocular interaction and fixational eye movements

Recent evidence suggested that suppression is an important component of amblyopia and it should be treated first for successful amblyopia management.[130–132] It should be noted that suppression is a binocular phenomenon and therefore, before checking the effect of suppression on fixational eye movements, we need to understand whether there is any advantage of binocular fixation over monocular fixation. The results of Experiment-II showed that the fixational stability was always

much improved during binocular fixation compared to monocular fixation. The binocular advantage in the stability of fixation was not only noted for high contrast targets also across all contrast levels range from 0 to 100%. Moreover, the estimation of binocular advantage ratio (Table 4-1) also suggested that the ratio was greater than typical binocular summation ratio (1.414) across contrast levels. Therefore, it was logical to hypothesize that any abnormal binocular interactions such as suppression would influence fixational eye movements.

To understand the causal relationship between abnormal binocular interactions and the characteristics of fixational eye movements, two different experiments were conducted. In experiment – III, different binocular interactions such as binocular rivalry, monocular stimulation and dichoptic fusion were compared with non-dichoptic fusion. The results showed that non-dichoptic viewing resulted in significantly more stable fixation, decreased amplitude of microsaccades and decreased frequency of microsaccades compared to the three dichoptic conditions. The dichoptic conditions did not differ from one another, although there was a significant difference between the two eyes for the monocular stimulation condition, whereby the eye seeing the target had more stable fixation than the eye with no target.

Then, experiment – IV was conducted where the interocular contrast was varied to generate different degrees of binocular interaction in controls and patients with amblyopia. Like experiment III, this study also showed that expect at the interocular contrast level of 0%, there was no significant difference between the dominant and the non-dominant eyes in control participants. In observers with amblyopia, the fixational stability of the FFE was reduced significantly when it was presented with 0% contrast and it was comparable to fixational stability of the AME.

Thus, the results of Experiments – III & IV did not show any effect of abnormal binocular interactions such as binocular rivalry or modification of interocular contrast on the characteristics of fixational eye movements in observers with normal vision. Even in observers with amblyopia, modification of interocular contrast did not influence fixational stability and microsaccadic amplitude. Therefore, from the results of these experiments, it could be concluded that abnormal binocular interactions such as suppression do not influence fixational stability.

Based on these results of these experiments, it could be concluded that neither interocular suppression nor impaired VA could explain the less stable FEM of AME. In other words, sensory deficits of amblyopia could not explain the abnormal patterns of fixational eye movements of the amblyopic eye.

7.3 Absence of a fixation target

A consistent result across several of the experiments reported in this thesis was that less stable fixational eye movements were noted when an eye was presented with a 0% contrast target or a mean luminance screen, i.e. no fixation target. This suggested that the presence or absence of a fixational target is a crucial factor influencing fixational stability. Other factors such as target contrast, optical blur, different types of binocular interaction (binocular rivalry) did not influence fixational stability. This is consistent with previous studies which reported less stable fixation in the absence of a fixation stimulus [2,21,40,43]. However, the major difference between these previous studies and the current experiments was that the previous studies used either complete black screen [21,43] or occlusion by IR filter (which blocks visible light) [40] whereas in this study, a mean luminance screen was always presented and the fixation target was removed or the luminance of the bright part of the fixation target was varied. The other major difference is that the current experiments were first to assess the effect of removing the fixation target under monocular, binocular and dichoptic viewing conditions.

These results provided insights in the nature of fixational eye movements in controls and patients with amblyopia, as described below.

7.3.1 Fixational eye movements in controls

The lack of a fixation stimulus always resulted in less stable FEM, irrespective of viewing condition i.e. whether recordings were made during monocular, binocular or dichoptic fixation. During monocular fixation, less stable FEM (high values of BCEA) were associated with a larger amplitude of microsaccades. This was also found when both eyes were viewing no fixation target; the microsaccadic amplitude was larger for both eyes. However, when only one of the eyes was presented with no fixation target during dichoptic viewing, there was no significant difference in the microsaccadic amplitude between two eyes (although the eye with no fixation stimulus had less stable fixation). Further analysis using FFT revealed that slow, low frequency ocular drifts were more pronounced for eyes that did not have a fixation target for all viewing conditions. These results collectively suggested that ocular drifts are independent between the two eyes because they were increased in one eye but not the other under dichoptic viewing. Furthermore, microsaccades seem to be highly conjugate because showing one eye a stimulus but not the other results in the same microsaccadic amplitude in each eye that is driven by the eye with the stimulus. These results are partly consistent with the theory postulated by Krauskopf, Riggs and Cornsweet (1960) which states that *"each eye would trigger saccades in response to their*

own error and since the ocular drifts in the two eyes seem to be independent". The results of this study showed that ocular drifts are independent between the two eyes but not microsaccades.

The cause of reduced fixational eye movement stability in the absence of a fixation target is unclear. McCamy et al. (2013)[2] showed that the rate and amplitude of microsaccades were influenced by the size of the fixation target. They showed that microsaccades became less frequent and increased in amplitude with increasing target size. Similar characteristics of microsaccades were noted when there was no fixation target as well. Therefore, they concluded that the lack of a fixation target was equivalent to a very large fixation target which led to increased microsaccadic amplitude and consequently less stable fixational eye movements.

An alternative explanation for less stable fixational eye movements with no fixation target was given by Cherici et al. (2012). They measured FEM in observers with normal vision in two experimental conditions, 1) marker condition (presence of fixation target) and 2) no-marker condition (absence of fixation target). Then, they quantified the interplay between the microsaccades and ocular drifts by estimating a compensatory index, i.e. the direction which an oculomotor event (saccades/drifts) shifted the line of sight in relation to the preceding oculomotor event (saccades/drifts).

Figure 5e in Cherici et al. 2012[133] shows the average compensatory indices for saccades-to-drifts and drifts-to-saccades events for marker and no-marker conditions. It was shown that a to compensate for drifts was not influenced by the presence or absence of a fixation target. However, the tendency to compensate for microsaccades was significantly reduced when the fixation target was absent. Moreover, both ocular drifts and microsaccades showed compensation when the fixation target was present. Thus, they concluded that lack of interplay between saccades and drifts was responsible for less stable fixation during a no-target condition.

Thus, in this thesis less stable fixation noted during lack of fixation target could be due to lack of proper interconnection between microsaccades and ocular drifts. i.e. lack of compensating fixation error. Cherici et al. (2012) showed that in both marker and no-marker conditions, characteristics of ocular drifts such as speed and curvature had significant relationship with fixation stability. Therefore, they concluded that characteristics of ocular drifts was a better predictor of accurate fixation than microsaccades. Moreover, microsaccades lacked tendency to compensate fixation error by ocular drifts. This could have lead to highly pronounced ocular drifts. The

results of the thesis confirmed this that ocular drifts were always noted to be highly pronounced during lack of fixation target viewing conditions.

7.3.2 Fixational eye movements in amblyopia

Interestingly, the fixational eye movements observed in controls viewing no fixation target resembled the fixation patterns noted in the amblyopic eye. Figure 7-2 shows that the fixational stability of control participants, during monocular fixation when the eye was presented with no fixation target, had a similar mean value to that of the amblyopic eyes when viewing a target. The same was true for the amplitude of microsaccades. The analysis of amblyopic eye fixational eye movements using FFT also revealed that during monocular fixation, the frequencies associated with ocular drifts as well as microsaccades had a higher peak in the amplitude density spectrum compared to FFE.

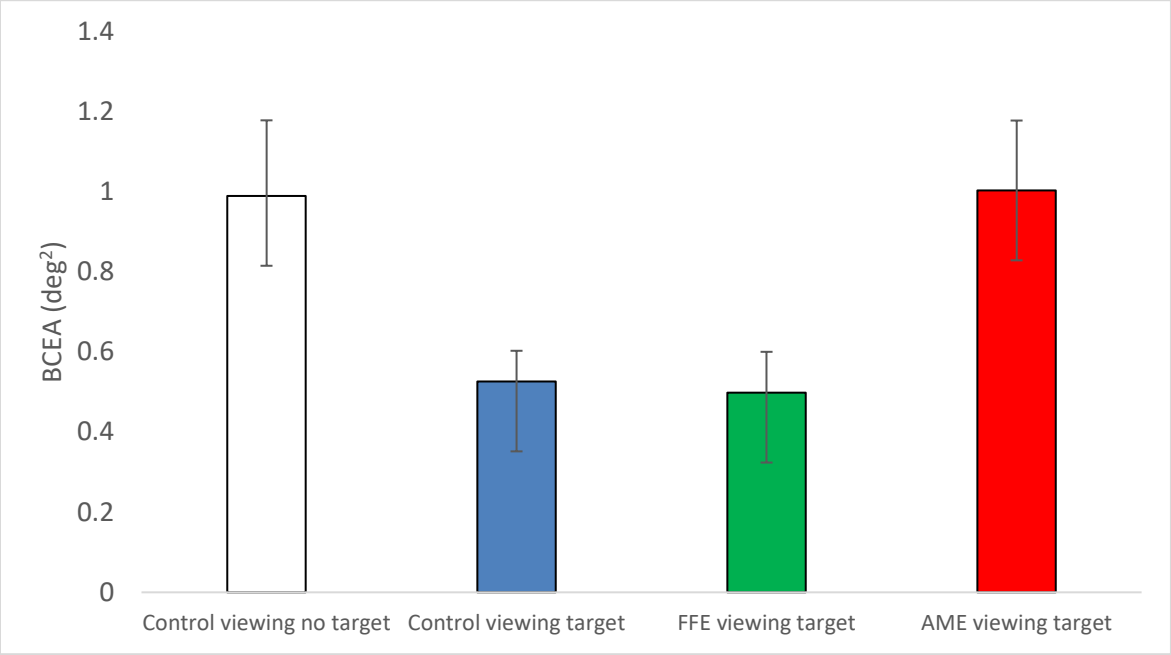


Figure 7-1: Fixational stability in controls viewing no target and the AME

Monocular fixational stability of control participants viewing no fixation target (white) and viewing a target (blue), the fellow eye (green) and the amblyopic eye (red). Error bars represent ±1 SEM.

During dichoptic viewing, when one of the eyes of control participants was presented with a 0% contrast target or a mean luminance screen, and the other with a 100% target, the eye with no target showed less stable fixational eye movements than the eye viewing the target. In this situation, FFT revealed that only ocular drifts (not microsaccades) were different between the two eyes. Similarly, in the amblyopia group when both eyes viewing 100%, FFT revealed that only ocular drifts (not microsaccades) seem to be different between the AME and FFE. In order to test

whether the same pattern would be noted in strabismic amblyopia as well, FEM of an observer with strabismic amblyopia measured under the same dichoptic viewing conditions was analysed using FFT. Figure 7-3 shows the results of FFT analysis of the observer with strabismic amblyopia. It was intriguing to note that, for the AME, the frequencies associated with ocular drift were higher in proportion compared to the FFE. Thus, the pattern of fixational eye movements seen in amblyopia could be simulated by a lack of fixation target in control participants.

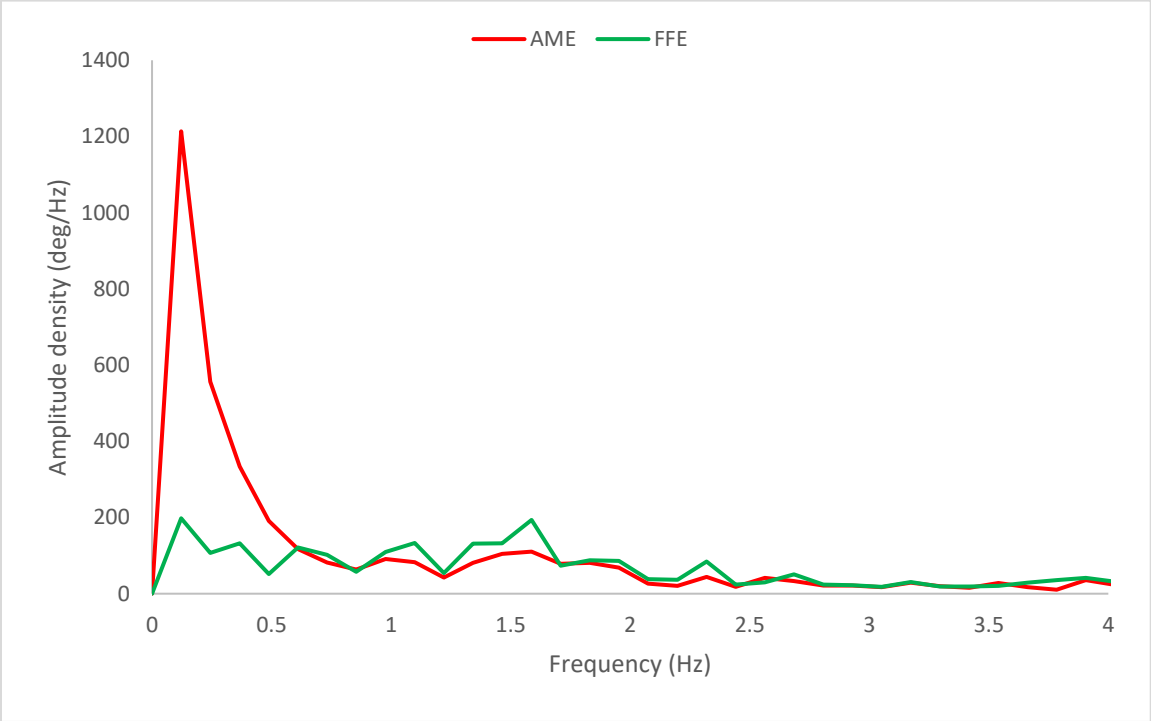


Figure 7-2: FFT of an observer with strabismic amblyopia (S8)

FFT analysis of FEM of an observer with strabismic amblyopia (S8) during dichoptic viewing with both eyes presented with 100%. As noted in Figure 6-10 for anisometropic amblyopia, observer with

strabismic amblyopia also showed similar pattern of FEM, showing higher proportion of low frequency eye movements which correspond to ocular drifts.

Moreover, FFT analysis also suggested that ocular drifts were the only factor that was consistently shown to be different between the FFE and AME in amblyopia. Thus, the results of this thesis support the claim of Cherici et al. (2012) that ocular drifts were better determinants of fixational stability than microsaccades. Gonzalez et al. (2012) also suggested that less stable fixation of the AME can only be attributed to slow and low frequency ocular drifts, which is consistent with our results. Shaikh et al. (2016) noted that ocular drifts were not only noted to be larger in the AME but also in the FFE. The results of this thesis were consistent with the findings of Shaikh et al. (2016). FFT analysis also showed that frequencies 0.1 -0.5 Hz that correspond to ocular drift shown to be larger for both AME and FFE compared to controls.

Less stable fixation during lack of fixation target might be due to uncertainty in positional control of fixation[21]. AME also exhibits positional uncertainty[57–59,134–136] which may be related to the sensory deficits of the amblyopic eye. The results of this study suggest that there may be a relationship between positional uncertainty and abnormal fixational eye movements in amblyopia.

In summary, the lack of a fixation target resulted in less stable fixation that was due to larger amplitude of microsaccades and ocular drifts during monocular fixation and larger ocular drifts only during dichoptic fixation. Finally, the fixation pattern of controls in the absence of a fixation target resembles the pattern of amblyopic eye fixation with a fixation target. Previous studies showed that less stable fixation in controls during lack of fixation might be due to positional uncertainty. Since, it is well established that AME exhibit positional uncertainty

Recent evidences suggest that fixational eye movements are purposeful and act to provide feature detectors at the retinal level acting to convert spatial information into temporal. Normal fixational eye movements enhance processing high spatial frequency but not low spatial frequency. The results from both defocus (experiment-I) and contrast reduction (Experiments II and IV) seem to fit this model in that both act to reduce the degree of high spatial frequencies available to the eye. No effect results until there is a loss of fixation.

7.4 Implications for the management of amblyopia

In control participants, fixation was more stable under binocular viewing than monocular viewing. Similar results occurred for observers with amblyopia. Under monocular fixation conditions, the AME showed significantly less stable FEM

compared the FFE. Also, under dichoptic viewing conditions, AME stability was driven by the FFE. In particular, AME fixational stability became worse (less stable) only when the FFE was either occluded or presented with no-fixation target. These results collectively imply that treatments which involve binocular viewing would enable more stable amblyopic eye fixation during treatment. However, it should be noted that even during binocular fixation, AMEs showed a higher proportion of ocular drifts compared to FFEs. Therefore, treatment strategies that target better control of ocular drifts and binocular viewing would be beneficial. Schor and Hallmark (1978) [106] and Flom, Kirschen, and Bedell [137] used auditory feedback to train the observers with amblyopia to maintain steady and foveal fixation. However, it was cumbersome method in those early days to execute such training regimens in clinical setups. With great advances in technology these days, it is possible to execute such training regimens.

Chapter 8
Summary & Conclusion

To summarize, the results of this thesis showed that

- In observers with normal vision and amblyopia, artificially simulated VA impairment did not influence the characteristics of FEM such as fixational stability, microsaccadic amplitude. However, a positive relationship noted between less stable fixation and reduced AME VA suggested that 1) abnormal FEM could contribute to impaired VA in AME, 2) there might be a third factor such as positional uncertainty which could result in impaired FEM as well as impaired VA.
- A binocular advantage in terms of fixational stability was present in control participants. Furthermore, effect of stimulus contrast on fixational stability was noted only during binocular fixation. This result led to the hypothesis that binocular interaction could play a role in influencing FEM. However, different binocular interactions such as binocular rivalry in controls did not influence FEM. Similarly, different degrees of binocular interaction induced by varying interocular contrast levels in controls and observers with amblyopia did not influence fixational stability. This suggested that abnormal binocular

interaction such as suppression did not influence characteristics of FEM such as fixational stability and microsaccadic amplitude.

- Moreover, in observers with anisometropic amblyopia, AME FEM were noted to be consensually controlled by the FFE.
- The most consistent result of this study was that the absence of a fixation target resulted in less stable fixation, irrespective of viewing condition.
- FFT analysis revealed that ocular drifts can be independent between the two eyes. However, microsaccades were found to be conjugate and binocular in nature.

Thus, to conclude, the results of this thesis provided evidence that both monocular and binocular sensory deficits of amblyopia could not explain the abnormal fixational eye movements in observers in amblyopia.

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Title of the article or chapter the portion is from	Microsaccadic Efficacy and Contribution to Foveal and Peripheral Vision
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Appendix A
Instrument calibration

During my Master's thesis, I used a haploscopic setup and an eye tracker from Arrington Research, Scottsdale, USA. However, the eye tracker had spatial resolution of 0.15° and temporal resolution of 60Hz. Moreover, there was no facility of monitoring head movements to ensure that the data was confounded by head movements. Therefore, for my PhD thesis, an eye tracker with spatial resolution of 0.01° and the temporal resolution of 500Hz, EyeLink – II from SR Research, Osgoode, ON, Canada was used. The latter eye tracker has also the facility of head tracker which enables us to monitor head movement during the measurement of eye movements.

The eyetrackers were compared by two methods, 1) comparing the voluntary saccades of known amplitudes (5, 10, 15 deg) and 2) comparison of characteristics of microsaccades.

Comparison of voluntary saccades

The results are shown in the following figures. Figure-1 shows the mean gains of 5, 10 and 15 degrees of voluntary saccades for Viewpoint (red) and EyeLink-II (blue). It was evident that the average amplitude of voluntary saccades did not vary

significantly at any degree of eye movements. Figure -1b shows the main sequence relationship between the amplitude and the peak velocity of voluntary saccades. It was clearly shown that for a given amplitude of saccade, the peak velocity was shown to be always larger when measured using Eyelink-II compared to that of Viewpoint. This was an expected result because the Viewpoint has low sampling frequency (60Hz) compared to that of EyeLink-II (500Hz).

Comparison of microsaccades:

The following results are comparison of characterisitcs of microsaccades measured while using Viewpoint and EyeLink-II eye tracking systems. Table-1 shows the descriptive statistics of microsaccadic characteristics. It was evident that the microsaccades that were detected using the Viewpoint showed larger amplitude, lower peak velocity, lower mean velocity and larger duration compared to that of measured using EyeLink-II. Moreover, since the spatial resolution of Viewpoint is 0.2°, the data points of microsaccades from the Viewpoint had equal spacing of 0.2°. In addition, as noted in the main sequence for voluntary saccades, the peak velocity of microsaccades measured using the EyeLink-II was always higher for any given amplitude of microsaccade.

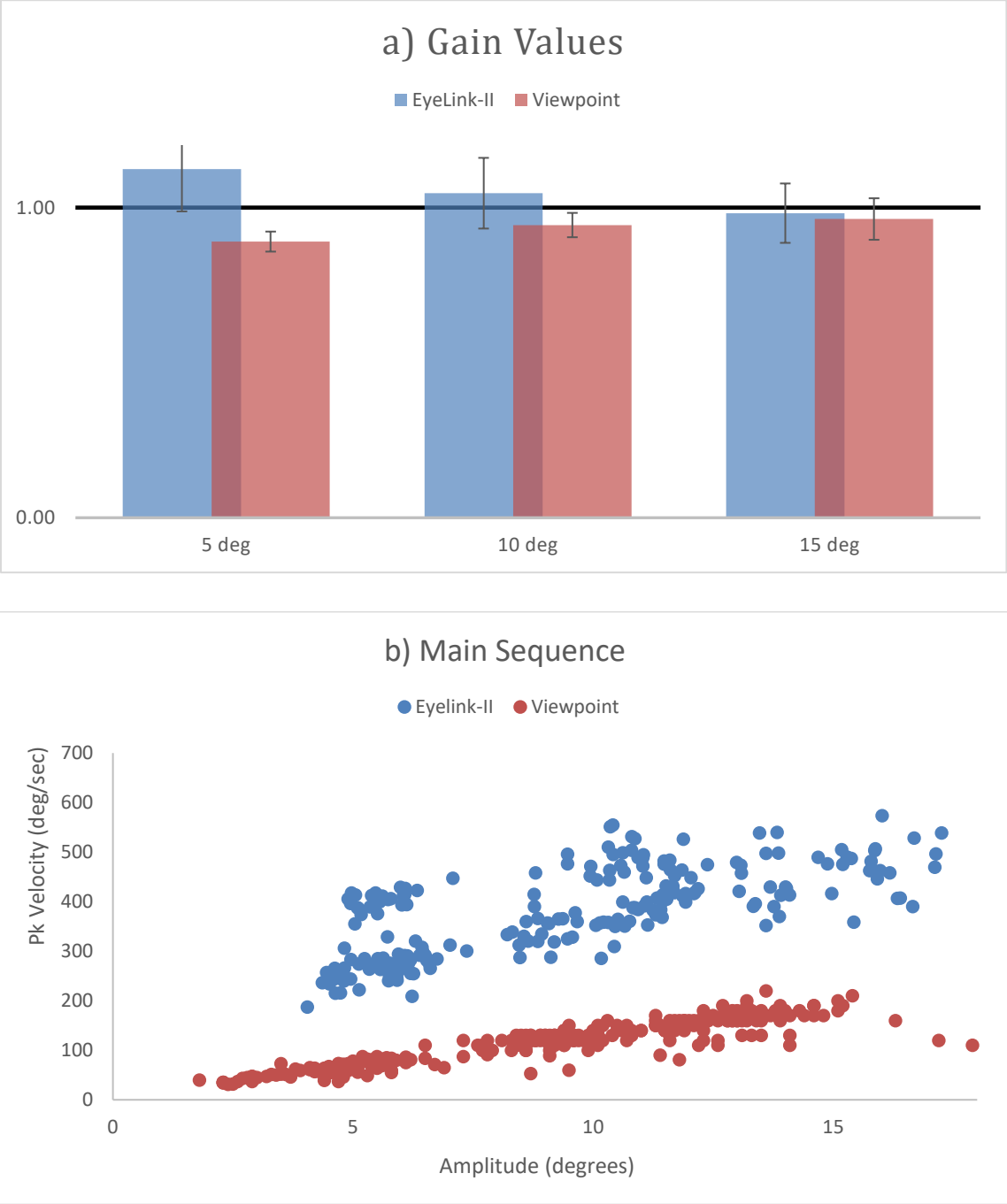

Figure A-1: Comparison of voluntary saccades: EyeLink-II vs. Viewpoint

Table A - 1: Characteristics of microsaccades: EyeLink-II and Viewpoint.

Microsaccades Dynamics	**Eye trackers**			
	Eyelink-II		Viewpoint	
	OD	OS	OD	OS
Mean Amplitude (deg)	0.69	0.70	1.62	1.09
Mean Velocity (mean) (deg/sec)	42.58	33.72	10.47	10.08
Mean Duration (ms)	36.67	37.01	171.88	103.24
Mean Peak Velocity (deg/sec)	121.08	130.18	22.39	23.09

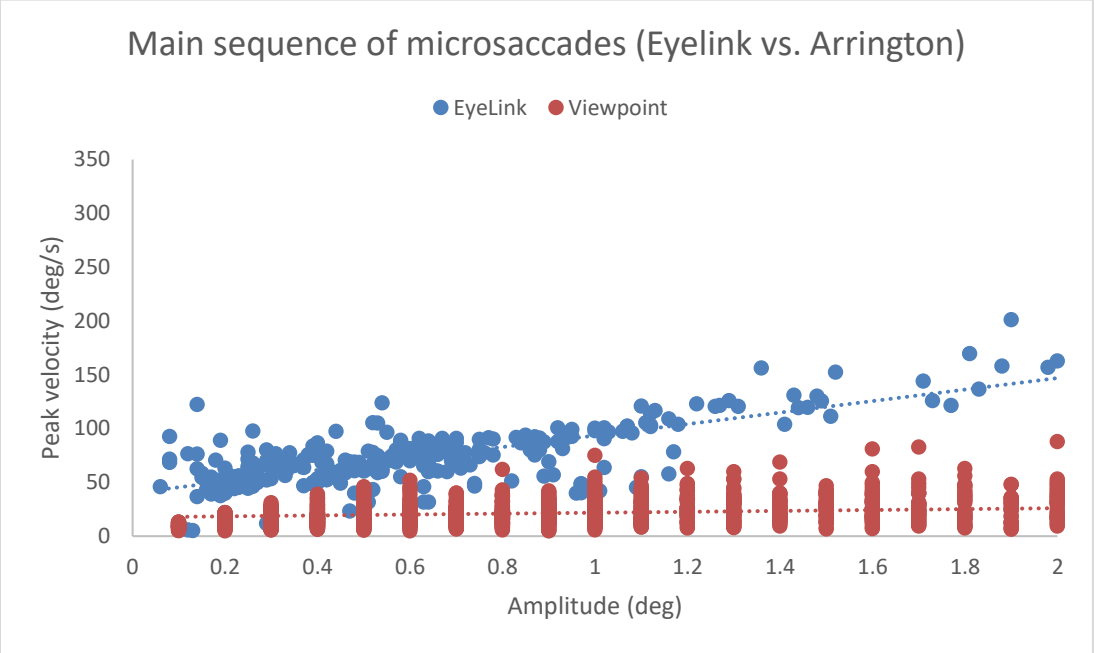

Figure A- 2: Comparison of microsaccades: EyeLink-II vs. Viewpoint

Therefore, in conclusion, the EyeLink-II provided much better datasets of microsaccades compared to the Viewpoint eye tracker.

Calibration of the head markers placed behind the mirrors in the stereoscope

The four IR markers used to sense head movement were placed behind the mirror setup such that the four markers match the physical size of two monitors of the haploscope. In order to check whether such placement of the markers would provide accurate measure of eye movement, we measured known degrees of saccadic eye movements under two conditions, 1) with markers placed at the usual position i.e. at the four corners of the monitor and 2) markers behind the cold mirror setup.

Figure A-3 shows the saccadic amplitude under the above-mentioned two viewing conditions. It is evident from the figure that there is no significant difference between the two viewing conditions. The values are tabulated in Table A-3.

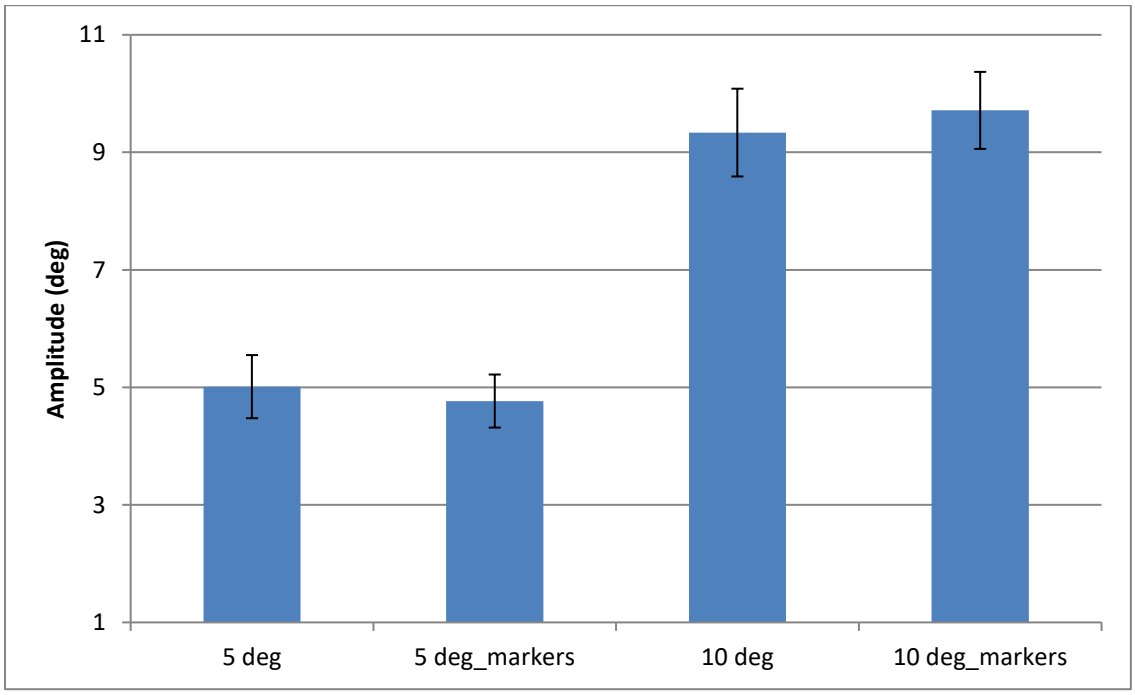

Figure A- 3: Saccadic amplitude across viewing conditions – calibration of markers' position

Table A - 2: Saccadic amplitude with and without markers

	5 deg	**5 deg_markers**	**10 deg**	**10 deg_markers**
Mean	5.012333	4.7674	9.336143	9.714286
SD	0.537377	0.451621	0.746712	0.655292

Measurement of eye tracker's noise

It is very important to measure the noise of the eye movement measuring systems, especially when it involves measuring miniature eye movements such as fixational eye movements. In order to estimate the noise of the eyetracker, we used a model eye. However, the eye tracker had difficulty in marking the pupillary margin. Therefore, to overcome this situation, a black dot was drawn over the pupillary region. Then the eye movements of two model eyes which were considered to the right eye and the left eye were measured for continuous 30 secs and repeated for 9 times. The average standard deviation of horizontal and vertical components is tabulated in Table A-4. It is evident from the table that the noise of eye tracker is very minimal.

Table A - 3: Noise of the eye tracker.

	RE_X	RE_Y	LE_X	LE_Y
Average SD	0.00000	0.00000	0.02068	0.00000
SD of SD	0.00000	0.00000	0.00106	0.00000

Conclusion

The novel method of measuring eye movements under dichoptic viewing conditions was stable. Moreover, this novel method also allows the user to keep monitoring the head movement while measuring eye movements.

Appendix B
Dichoptic vs. non-dichoptic conditions

It was surprising to note that when a single grating was presented to both eyes in a non-dichoptic setup, the fixational stability of both eyes improved significantly (Figure 5-2) compared to all other dichoptic condition viewing conditions ($p<0.001$) (refer to Chapter-5 and section 5.3). This result was very intriguing given that perception of the visual stimuli must be similar under both dichoptic and non-dichoptic viewing. A similar pattern was noted in average microsaccadic amplitude as well. Here, the following factors were analyzed to test whether they explained the difference between these two viewing conditions.

Instrumental factors

The difference in the stability of FEM between dichoptic and non-dichoptic viewing could be due to cues like proximal or reflected images and fusional vergence. To test the effect of these factors, FEM were measured in the same haploscopic setup but under monocular viewing conditions, i.e. occluding the right eye using a patch. The rest of the methods (the orientation of gratings, 40 sec per trial) were unaltered. This experiment was done in 3 normal observers who participated in the real experiment. Figure-3 shows the comparison of stability of FEM for those 3 participants

under the conditions of dichoptic fusion, non-dichoptic fusion and the monocular viewing under dichoptic setup. The result showed that stability of FEM under monocular viewing condition was very similar and statistically not different from the non-dichoptic condition (p=0.599). This implied that neither reflected image perception (proximity) nor the haploscopic setup would have caused the difference.

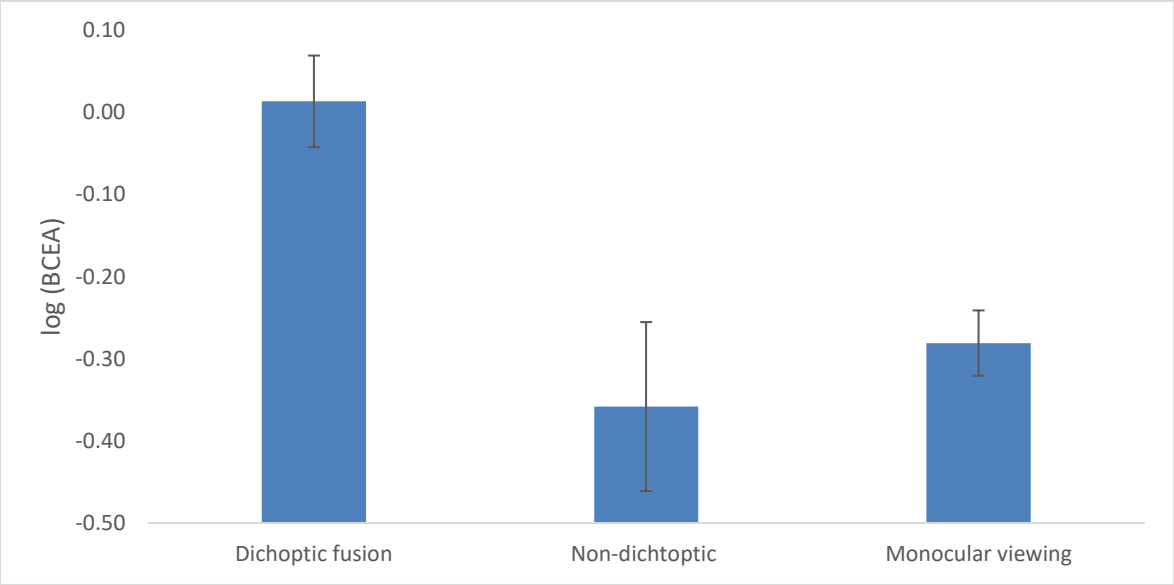

Figure B - 1: Effect of reflected image during dichoptic viewing.

Influence of fusion vergence

The other important factor that could have caused a difference between dichoptic and non-dichoptic fusion conditions is fusional vergence (disjunctive eye movements). The influence of fusional vergence on fixational stability was determined by estimating conjugacy of FEM which was determined by calculating

Pearson correlations between horizontal positions of the two eyes for each trial of all conditions. For this analysis, a positive 'r' value suggests that an eye movement is conjugate e.g. a saccade, whereas a negative 'r' value suggests that an eye movement is disjunctive e.g. vergence. Figure B-2 shows the distribution of conjugacy for the horizontal component of FEM. All the dichoptic conditions showed a higher amount of conjugate FEM. However, the condition which produced the most stable fixation, non-dichoptic fusion, showed lesser conjugate FEM. This result implied that increased instability noted in all dichoptic conditions might be due to increased influence of microsaccades which are conjugate.

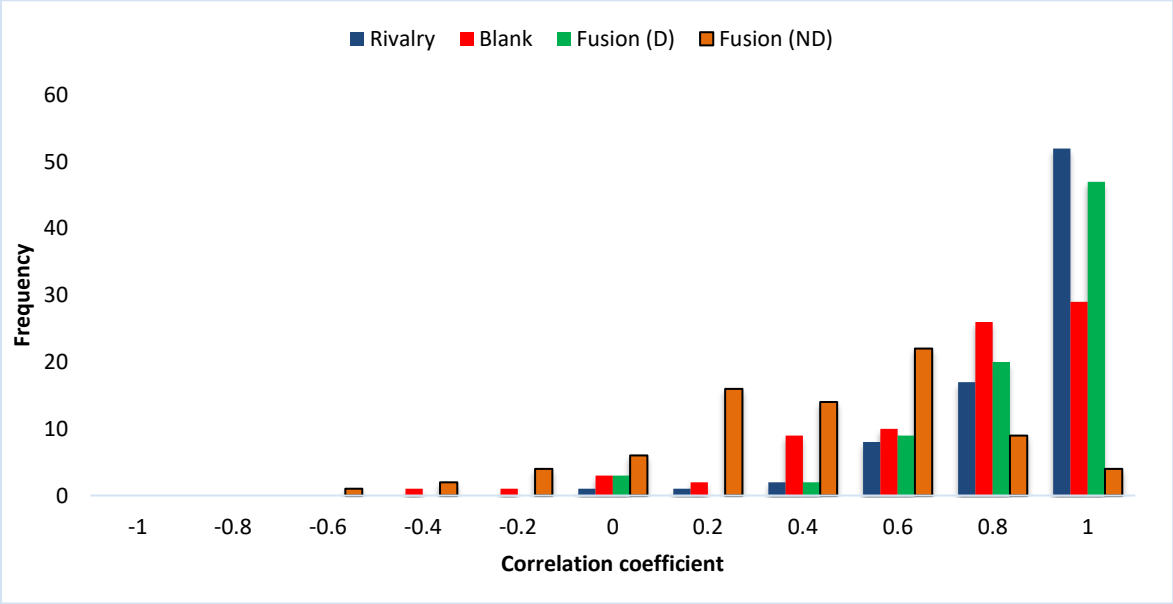

Figure B - 2: Distribution of conjugacy of FEM measured in all conditions.

Conjugacy was determined by finding Pearson correlation coefficient between horizontal eye positions of the left eye and the right eye. Non-dichoptic fusion (fusion (ND)), the condition which showed the most stable fixation, had a less amount of conjugate FEM and revealed that fusional vergence might not the factor for reduced stability in the dichoptic conditions.

Heterophoria

The other factor that could have contributed to increasing the stability of FEM in dichoptic conditions is heterophoria. Figure-5 shows the difference in BCEA values between dichoptic and non-dichoptic fusion of the left eye plotted as a function of heterophoria (measured using modified Thorington's scale) of all the participants and it revealed that there was no relationship between the stability of FEM and heterophoria. Note that phoria was aligned in all dichoptic measurements (refer 3.2.3) to ensure that participants would not experience double vision in the rivalry condition.

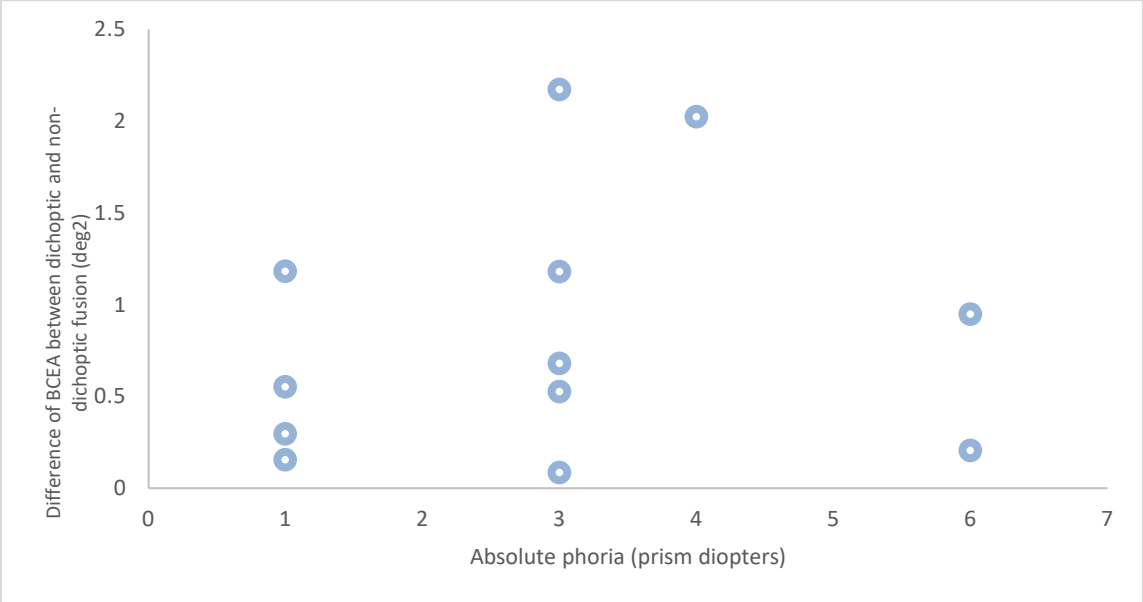

Figure B - 3: Relationship between heterophoria and fixational stability

The difference in the stability of FEM (BCEA) between dichoptic and non-dichoptic viewing plotted as a function of phoria.

Moreover, the results of experiment I and experiment III (where similar a fashion of visual stimuli was used) also showed that the fixational stability was significantly improved during non-dichoptic binocular viewing.

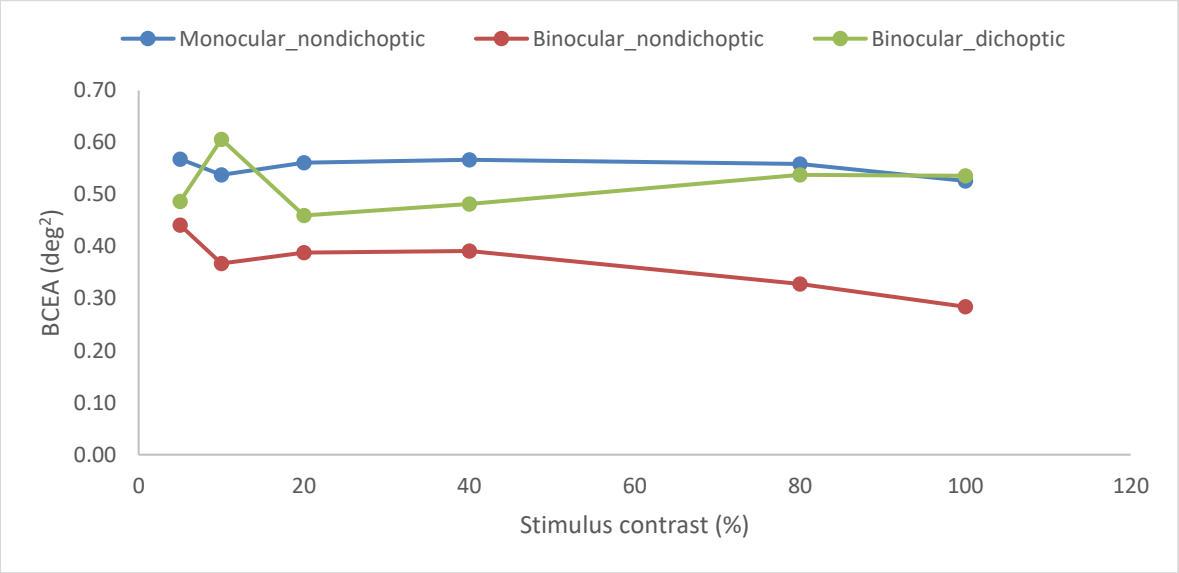

Figure B - 4: Fixational stability – dichoptic vs. non-dichoptic viewing

What is responsible for the difference between non-dichoptic and dichoptic viewing?

The result of voluntary saccades in Appendix – A suggested that saccadic amplitude did not vary significantly between the dichoptic and the non-dichoptic viewing conditions. Therefore, the difference in the fixational stability that was noted between these two viewing conditions must be attributed to the nature of fixational eye movements only, especially to ocular drifts. It was evident from the results of fixational stability and FFT analysis that ocular drifts are independent between the two eyes. Therefore, when the viewing condition is dichoptic, ocular drifts become even more independent and in turn result in increased microsaccadic amplitude and

more frequent microsaccades as noted in Experiment – II. However, further experiments are required to answer this speculation.

Appendix C

MATLAB codes

Estimating Bivariate contour ellipse area (BCEA)

%{ Data Analysis Script for pilot experiment BR_all

Input data:
1. Sample Index
2. Sample Message
3. R_Gaze_X (right eye gaze X position)
4. R_Gaze_Y (right eye gaze Y position)
5. L_Gaze_X (left eye gaze X position)
6. L_Gaze_Y (left eye gaze Y position)
7. Left eye in blink (0 = no blink, 1 = blink)
8. Right eye in blink (0 = no blink, 1 = blink)
Output data

1. Viewing condition (1 = Fusion, 2 = Rivalry, 3 = Blank, 4 = Control)
2. Right Eye (RE) horizontal standard deviation
3. Right Eye (RE) vertical standard deviation
4. Correlation between RE horizontal and vertical standard deviation
5. RE bivariate contour ellipse area (BCEA)
6. Left Eye (LE) horizontal standard deviation
7. Left Eye (LE) vertical standard deviation
8. Correlation between LE horizontal and vertical standard deviation
9. LE bivariate contour ellipse area (BCEA)
10. Horizontal conjugacy (Fusion): correlation of H eye position between the eyes
11. Vertical conjugacy (Fusion): correlation of V eye position between the eyes
%}

%%
clear;
% Read input file and store in workspace

```
prompt = 'Insert filename:';
result = input(prompt, 's');
filename = strcat(result, '.xlsx');
table2 = xlsread(filename);


% Remove blinks


% RE X position blink removal
RX_blink = isnan(table2(:,3));
RX_blink2 = find(RX_blink(:,1)==1);
num = size(RX_blink2);
if num == 0
   q = 1;
elseif num > 0
   if RX_blink2(1,1) > 10
      for b=1:(num(1,1))
         for d=1:10
            RX_blink((RX_blink2(b,1)-d),1) = 1;
            RX_blink((RX_blink2(b,1)+d),1) = 1;
         end
      end
   elseif RX_blink2(1,1) <= 10
      for b=1:(num(1,1))
         for d=1:(RX_blink2(1,1)-1)
            RX_blink((RX_blink2(b,1)-d),1) = 1;
            for f=1:10
               RX_blink((RX_blink2(b,1)+f),1) = 1;
            end
         end
      end
   end
end

% RE Y position blink removal
```

```
RY_blink = isnan(table2(:,4));
RY_blink2 = find(RY_blink(:,1)==1);
num = size(RY_blink2);
if num == 0
   q = 1;
elseif num > 0
   if RY_blink2(1,1) > 10
      for b=1:(num(1,1))
         for d=1:10
            RY_blink((RY_blink2(b,1)-d),1) = 1;
            RY_blink((RY_blink2(b,1)+d),1) = 1;
         end
      end
   elseif RY_blink2(1,1) <= 10
      for b=1:(num(1,1))
         for d=1:(RY_blink2(1,1)-1)
            RY_blink((RY_blink2(b,1)-d),1) = 1;
            for f=1:10
               RY_blink((RY_blink2(b,1)+f),1) = 1;
            end
         end
      end
   end
end

% LE X position blink removal
LX_blink = isnan(table2(:,5));
LX_blink2 = find(LX_blink(:,1)==1);
num = size(LX_blink2);
if num == 0
   q = 1;
elseif num > 0
   if LX_blink2(1,1) > 10
      for b=1:(num(1,1))
         for d=1:10
            LX_blink((LX_blink2(b,1)-d),1) = 1;
```

```
            LX_blink((LX_blink2(b,1)+d),1) = 1;
         end
      end
   elseif LX_blink2(1,1) <= 10
      for b=1:(num(1,1))
         for d=1:(LX_blink2(1,1)-1)
            LX_blink((LX_blink2(b,1)-d),1) = 1;
            for f=1:10
               LX_blink((LX_blink2(b,1)+f),1) = 1;
            end
         end
      end
   end
end

% LE Y position blink removal
LY_blink = isnan(table2(:,6));
LY_blink2 = find(LY_blink(:,1)==1);
num = size(LY_blink2);
if num == 0
   q = 1;
elseif num > 0
   if LY_blink2(1,1) > 10
      for b=1:(num(1,1))
         for d=1:10
            LY_blink((LY_blink2(b,1)-d),1) = 1;
            LY_blink((LY_blink2(b,1)+d),1) = 1;
         end
      end
   elseif LY_blink2(1,1) <= 10
      for b=1:(num(1,1))
         for d=1:(LY_blink2(1,1)-1)
            LY_blink((LY_blink2(b,1)-d),1) = 1;
            for f=1:10
               LY_blink((LY_blink2(b,1)+f),1) = 1;
            end
```

```
        end
      end
   end
end

% LE blink removal
LE_blink = table2(:,7);
LE_blink2 = find(LE_blink(:,1)==1);
num = size(LE_blink2);
if num == 0
   q = 1;
elseif num > 0
   if LE_blink2(1,1) > 10
      for b=1:(num(1,1))
         for d=1:10
            LE_blink((LE_blink2(b,1)-d),1) = 1;
            LE_blink((LE_blink2(b,1)+d),1) = 1;
         end
      end
   elseif LE_blink2(1,1) <= 10
      for b=1:(num(1,1))
         for d=1:(LE_blink2(1,1)-1)
            LE_blink((LE_blink2(b,1)-d),1) = 1;
            for f=1:10
               LE_blink((LE_blink2(b,1)+f),1) = 1;
            end
         end
      end
   end
end

% RE blink removal
RE_blink = table2(:,8);
RE_blink2 = find(RE_blink(:,1)==1);
num = size(RE_blink2);
if num == 0
```

```
   q = 1;
elseif num > 0
   if RE_blink2(1,1) > 10
      for b=1:(num(1,1))
         for d=1:10
            RE_blink((RE_blink2(b,1)-d),1) = 1;
            RE_blink((RE_blink2(b,1)+d),1) = 1;
         end
      end
   elseif RE_blink2(1,1) <= 10
      for b=1:(num(1,1))
         for d=1:(RE_blink2(1,1)-1)
            RE_blink((RE_blink2(b,1)-d),1) = 1;
            for f=1:10
               RE_blink((RE_blink2(b,1)+f),1) = 1;
            end
         end
      end
   end
end

table2(:,7) = RX_blink + RY_blink + LX_blink + LY_blink + LE_blink + RE_blink;
total2 = find(table2(:,7) < 1);


% Make table for data
table = zeros((size(total2,1)),7);

for a=1:(size(total2,1))
   for b=total2(a,1)
      table(a,1) = total2(a,1);
      table(a,2:7) = table2(b,2:7);
   end
end

% Compute running time from initial timestamp
```

```
table(:,1) = table(:,1)./500;

% Convert H and V pixel coordinates to degrees
table(:,3) = table(:,3)./46.14;          % H 46.14 pixels/deg
table(:,4) = table(:,4)./46.22;          % V 46.22 pixels/deg
table(:,5) = table(:,5)./46.14;
table(:,6) = table(:,6)./46.22;

% Get event row numbers
fusion = find(table(:,2) == 1);
control = find(table(:,2) == 4);

% Determine block numbers
%% Compute BCEA for the fusion event

   max = size(fusion);
   fusiontable = table(fusion(1,1):fusion(max,1),:);

   % Write events numbers to output table - Fusion = 1; Rivalry = 2;
   % Blanks = 3; Control = 4;
   output(1,1) = 1; %For Fusion

   % Compute standard deviation of horizontal and vertical
   SD_RE_H(1,1) = std(table(fusion(1,1):fusion(max(1,1),1),3));
   SD_RE_V(1,1) = std(table(fusion(1,1):fusion(max(1,1),1),4));
   SD_LE_H(1,1) = std(table(fusion(1,1):fusion(max(1,1),1),5));
   SD_LE_V(1,1) = std(table(fusion(1,1):fusion(max(1,1),1),6));

   % Compute correlation between horizontal and vertical components of fixation and
BCEA

LE_correl=corr((table(fusion(1,1):fusion(max(1,1),1),5)),(table(fusion(1,1):fusion(max(
1,1),1),6)));

RE_correl=corr((table(fusion(1,1):fusion(max(1,1),1),3)),(table(fusion(1,1):fusion(max(
1,1),1),4)));
```

```
   RE_BCEA = pi*2.291*SD_RE_H*SD_RE_V*sqrt((1-((RE_correl^2))));
   LE_BCEA = pi*2.291*SD_LE_H*SD_LE_V*sqrt((1-((LE_correl^2))));

   % Write horizontal and vertical standard deviation, correlation and BCEA values
to output table
   output(1,2) = SD_RE_H;
   output(1,3) = SD_RE_V;
   output(1,4) = RE_correl;
   output(1,5) = RE_BCEA;
   output(1,6) = SD_LE_H;
   output(1,7) = SD_LE_V;
   output(1,8) = LE_correl;
   output(1,9) = LE_BCEA;
   output(1,10)                                                                    =
corr(table(fusion(1,1):fusion(max(1,1),1),3),table(fusion(1,1):fusion(max(1,1),1),5));
   output(1,11)                                                                    =
corr(table(fusion(1,1):fusion(max(1,1),1),4),table(fusion(1,1):fusion(max(1,1),1),6));

%% Compute BCEA for the alternating event

   max = size(control);
   controltable = table(control(1,1):control(max,1),:);

   % Write rivalry events to output table
   output(2,1) = 4;

   % Compute standard deviation of horizontal and vertical
   SD_RE_H(1,1) = std(table(control(1,1):control(max(1,1),1),3));
   SD_RE_V(1,1) = std(table(control(1,1):control(max(1,1),1),4));
   SD_LE_H(1,1) = std(table(control(1,1):control(max(1,1),1),5));
   SD_LE_V(1,1) = std(table(control(1,1):control(max(1,1),1),6));

   % Compute correlation between horizontal and vertical components of fixation and
BCEA
```

```
LE_correl=corr((table(control(1,1):control(max(1,1),1),5)),(table(control(1,1):control(m
ax(1,1),1),6)));

RE_correl=corr((table(control(1,1):control(max(1,1),1),3)),(table(control(1,1):control(
max(1,1),1),4)));
   RE_BCEA = pi*2.291*SD_RE_H*SD_RE_V*sqrt((1-((RE_correl^2))));
   LE_BCEA = pi*2.291*SD_LE_H*SD_LE_V*sqrt((1-((LE_correl^2))));

   % Write horizontal and vertical standard deviation, correlation and BCEA values
to output table
   output(2,2) = SD_RE_H;
   output(2,3) = SD_RE_V;
   output(2,4) = RE_correl;
   output(2,5) = RE_BCEA;
   output(2,6) = SD_LE_H;
   output(2,7) = SD_LE_V;
   output(2,8) = LE_correl;
   output(2,9) = LE_BCEA;
   output(2,10)                                                                    =
corr(table(control(1,1):control(max(1,1),1),3),table(control(1,1):control(max(1,1),1),5));
   output(2,11)                                                                    =
corr(table(control(1,1):control(max(1,1),1),4),table(control(1,1):control(max(1,1),1),6));

%% Output new table

newfilename = strcat('A_', filename);
xlswrite(newfilename,output,'Sheet1');
xlswrite(newfilename,fusiontable,'Sheet2');
xlswrite(newfilename,controltable,'Sheet3'
```