The Effects of Deprivation Amblyopia on Fixation Stability and Optokinetic Nystagmus

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

Vision and oculomotor control play an essential role in visual perception and motor coordination. Individuals born with unilateral cataracts ultimately develop deprivation amblyopia, which is associated with sensory deficits. By measuring two fundamental eye movements, fixation stability and optokinetic nystagmus, this study aims to understand how congenital cataracts impact oculomotor control.

Fixation stability and OKN were evaluated using the Eyelink eye tracker during binocular and monocular viewing. An infrared filter was used in the monocular condition to block the visible light (i.e., open loop condition) but allowed recording of eye position. The fixation stability experiment utilized a 3° fixation crosshair, while the OKN test involved a black-and-white vertical square-wave grating moving at 10 deg/s. Eye dispersion during fixation was quantified using bivariate contour ellipse area (BCEA), as well as microsaccades rate, amplitude, and slow drifts. OKN response analysis involved calculating the slow-phase gain based on the velocity of the stimulus, and subsequently determining if the response in the fellow eye was symmetrical across nasalward and temporalward stimulus directions.

The findings of 18 control participants showed that fixation stability was best during binocular viewing, as indicated by the lowest BCEA value. Fixation stability was poorer during monocular viewing, where the covered eye (open loop condition) exhibited the largest dispersion. Further data analysis revealed that the poorer fixation during monocular closed-loop viewing was explained by increased microsaccade rate and higher slow drift velocity, while the poorer fixation during the open-loop condition was explained by the increase in microsaccade amplitude. The patient group included 7 participants. The fellow eye had fixation that was similar to the control group across binocular and closed-loop monocular viewing, while it was poorer during monocular viewing for the open-loop condition. Amblyopic eye viewing was

poorer compared to all viewing conditions in the control group. The OKN response was asymmetrical for 2 of the patients, with one patient showing no response in the temporalward direction, while all 18 control participants exhibited a symmetrical response that was similar for the nasalward and temporalward trials.

This study has provided insight into oculomotor control in unilateral deprivation amblyopia. Further research that investigates the underlying neural mechanisms disrupted in oculomotor control in unilateral deprivation amblyopia can help to uncover more effective treatment options to improve the quality of life and sensorimotor deficits in individuals with deprivation amblyopia.

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List of Abbreviations

- Optokinetic Nystagmus → OKN
- Visual Cortex 1 → V1
- Intraocular Lens → IOL
- Bivariate Contour Ellipse Area → BCEA
- Mean Slow-phase Velocity → MSPV
- Fusion Maldevelopment Nystagmus Syndrome → FMNS
- Nucleus of Optic Tract → NOT
- Slow Wave Jerk → SWJ

1. Introduction

Vision provides critical sensory input for performing everyday tasks. Not only is vision important for perception, but it is also involved in guiding actions, such as driving, navigating through the environment, and reaching out to grab a cup of coffee. Performing everyday visual and motor tasks efficiently is disrupted in many neurological conditions. For example, deprivation amblyopia develops when babies are born with cataracts in one or both eyes (Blair et al., 2023). Although the cataracts can be removed, the brain's development of the visuomotor system is disrupted. The critical periods of visual development are approximately the first seven years of a child's life, and both eyes must receive adequate visual stimulation during this time (Press, 2008).Disruption of vision during the early years of development is associated with a visual acuity deficit, loss of binocularity, and other higher-order deficits such as motion processing or contour integration (Mitchell & Maurer, 2022). Vision also provides important sensory input to guide movement planning and execution. However, surprisingly little is known about the effects of deprivation amblyopia on eye movements and visuomotor control, and the impact on everyday activities that involve hand-eye coordination. Oculomotor and visuomotor deficits have been characterized in other types of amblyopia (Niechwiej-Szwedo et al., 2019) but not in deprivation amblyopia, which is rare but has the most significant potential to disrupt brain development and impact one's ability to engage in meaningful everyday activities. Thus, it is essential to understand the mechanisms that contribute to the visuomotor deficits that could impact an individual's ability to perform routine daily activities. The proposed research will examine the effect of deprivation amblyopia on oculomotor control, specifically focusing on fixational eye movements and optokinetic nystagmus (OKN). In the long run, this work will

provide foundational knowledge that might help develop therapies that could improve the day-to-day experiences of people living with deprivation amblyopia and other neurological conditions.

1.1 Critical Periods of Visual Development as Revealed by Deprivation

1.1.1 Structural Changes due to Deprivation in Animal Models

The critical period of visual development was initially brought to light in a series of studies where the eyelid of a kitten was sutured shut after birth, and the neuronal activity was measured in the visual cortex (Wiesel & Hubel, 1963), which was later also investigated in non-human primates (Hubel et al., 1977)(Le Vay et al., 1980). The key finding was the discovery of multiple critical periods of development for the visual cortex which required normal visual experience to ensure normal cortical development. Daw et al. (1992) deprived kittens unilaterally of visual input and determined that there was no change in ocular dominance if deprivation occurred after 12 months, indicating that the critical period occurs until 12 months for kittens (Daw et al., 1992) . After measuring neuronal activity, it was found that there was a significant reduction in the number of neurons that received inputs from both eyes, as most neurons were only activated by the previously non-deprived eye (Hubel & Wiesel, 1970). This finding was termed ‘ocular dominance’ and introduced the idea that visual input to the previously deprived eye is being suppressed leading to monocular sensory deficits, such as reduced visual acuity as well as poor binocular fusion (Farivar et al., 2011). Animal models have shown that these ocular dominance columns are only partially developed at birth but undergo rapid development during the first few weeks of the postnatal period (Le Vay et al., 1980). The changes of ocular dominance columns due to visual deprivation have allowed us to map out the critical periods of development in primates, where it has been seen that the highest sensitivity to changes in the columns is post-natal, and it decreases as the species matures indicating a tight temporal

relationship between the maturation of ocular dominance structure and balanced visual inputs during the critical periods (LeVay et al., 1980).

1.1.2 Deprivation Amblyopia: A Model for Visual Deprivation in Humans

Although previous studies investigating visual deprivation during critical periods have used primates and kittens, deprivation amblyopia can be used as a model to study neuroplasticity in humans. Deprivation amblyopia develops when there is a pathology, such as congenital or developmental cataract(s), which can be unilateral or bilateral, that disrupt visual processing during the early years of life (Blair et al., 2023). The hallmark of amblyopia is decreased visual acuity in one or both eyes (Blair et al., 2023). Deprivation amblyopia has been severely understudied due to low prevalence, as it is only present in less than 3% of people with amblyopia, which is a condition affecting 1% to 5% of the population (Blair et al., 2023) Although current recommendations emphasize the importance of removing the cataract as soon as possible after the infant is born and the cataract has been found, residual deficits persist throughout life.

Cataract(s) are diagnosed when it is clear that the infant is unable to fixate or follow a light stimulus and when an ophthalmologist is unable to see the retina through the cataract with an ophthalmoscope (Mitchell & Maurer, 2022). The cataract(s) impede image clarity and reduce visual acuity during the postnatal period from birth until the cataract(s) is surgically removed (Lambert, 2010). Upon surgical removal of the cataract(s), artificial intraocular lens (IOL) or contact lenses are implanted with the goal of providing clear visual input to one or both eyes (Lambert, 2010). Teller acuity cards are used at 12 months and the HOTV visual acuity test is used at 4.5 years to determine the change in visual acuity post-operatively (Lambert, 2010). Clinical guidelines for clinicians' state that if a child has an acuity in either eye of 20/40 or worse

at age 3 to 5 or 20/30 or worse after 6 years, they should be referred to an ophthalmologist for further evaluation as this may indicate a risk of amblyopia (Doshi & Rodriguez, 2007).

These cases can differ based on whether the patient experienced a unilateral or bilateral cataract(s). Bilateral cases can be asymmetric, where the visual acuity in one eye is worse than the other, or symmetric, where both eyes have similar visual acuities (Shoshany et al., 2020). In unilateral cases, the amblyopic eye has reduced visual acuity, but the fellow eye has clinically normal visual acuity, which may be lower compared to healthy controls (Varadharajan & Hussaindeen, 2012). These differences are important to note when planning a treatment regimen, such as occlusion therapy.

Post-operatively, occlusion therapy (patching of the eye(s)) can be used to improve visual acuity and lessen the deficits of amblyopia (Flynn et al., 1999). In unilateral cases, it is the non-deprived eye that is patched to force the child to only use their deprived eye (Flynn et al., 1999). In symmetrical bilateral cases, patching is usually applied to one eye at a time on alternative days, with the goal of providing both eyes with equal visual input (Loudon & Simonsz, 2007). In asymmetric bilateral cases, it is the eye with poorer visual acuity that receives additional patching. Studies focusing on the effectiveness of this treatment have reported improvements in visual acuity, however, these improvements vary based on the frequency of patching. For example, one study reported that 53% of unilateral participants improved their visual acuity to 20/80 or better (Birch & Stager, 1988). Lundvall & Kugelberg. (2002) reported 20% of unilateral participants improved to 20/25 visual acuity in their amblyopic eye. Finally, Shoshany et al. (2020) focused on asymmetric bilateral cases finding that the amblyopic eye improved by 4 lines and the stronger eye improved by 2 lines. A significant contributor to better results of occlusion therapy includes adherence to strict and consistent patching (Santos et al., 2020). Overall, there

are improvements in visual acuity in both unilateral and bilateral cases, however, other sensory and perceptual deficits continue to persist and can present differently in both cases.

Deprivation amblyopia is not just a visual acuity deficit, but there are also defects in other sensory capabilities. Recent research has shown that these visual deficits continue to persist even after occlusion therapy. More importantly, however, some of these sensory deficits can present differently in unilateral and bilateral cases. This is an important finding as it has been proposed that although bilateral cataracts affect the development of the visual system by depriving visual input to both eyes, a unilateral cataract affects the development of the visual system by depriving one eye and by biasing interocular competition (Meier & Giaschi, 2017). The unequal inputs during the early months of life can affect the visual system to the point where some sensory deficits may present differently in these patients (Meier & Giaschi, 2017). These sensory deficits include global motion, contrast sensitivity and binocular fusion, and will be discussed in the next section.

Global motion is defined as the ability to integrate local motion signals to extract an overall trend (Furlan & Smith, 2016). Deficits for unilateral cases in comparison to healthy controls for perceiving the direction of global motion increase 1.5-fold, while it increases 4.9-fold for children with bilateral amblyopia (Ellemberg et al., 2005). Furthermore, Maurer & Lewis. (1993) and Tytla et al. (1988) found a difference in contrast sensitivity in unilateral and bilateral cases. Contrast sensitivity is defined as the ability to perceive difference in luminance (Kaur & Gurnani, 2023). The contrast sensitivity function describes the ability of the visual system to detect differences in the contrast of vertical grating at different levels of spatial frequency (Kaur & Gurnani, 2023). Beazley et al. (1980) measured contrast sensitivity at 7 different spatial frequencies in participants of varying age groups. They found that the ability to

detect contrast changes across all spatial frequencies increases until early adolescence (Beazley et al., 1980). Those with a history of unilateral and bilateral cataracts, showed increased deficits in contrast sensitivity with increasing spatial frequency, however, the deficits were much greater for the unilateral participants. Binocular fusion is one's ability to perceive depth by integrating information from both eyes. In humans, stereoacuity starts to develop at 2-6 months post-nataly (Birch et al., 1993), and then continues to gradually improve into adulthood (Giaschi et al., 2013). A key component underlying binocular fusion development or maldevelopment is the V1 horizontal axonal connections (Tychsen & Burkhalter, 1995). These connections are immature during the first 4 months in humans (Tychsen & Burkhalter, 1995). Maturation of these connections relies on correlated inputs from the left and right eyes (Löwel & Singer, 1992). If these inputs are not correlated, the horizontal connections can be lost, and binocular integration does not develop (Lowell & Singer, 1992). Therefore, normal visual input through both eyes is a prerequisite for the normal development of ocular dominance columns and binocular neurons that support spatial vision. Without this normal input, the non-amblyopic eye will dominate and suppress the visual input from the amblyopic eye (Farivar et al., 2011). Visual deprivation during this early post-natal period due to a cataract(s) result in deficits to the binocular visual system. Notably, binocular fusion is more likely to develop in patients with bilateral cataracts in comparison to monocular cases (Meier & Giaschi, 2017) (Hamm et al., 2014). This highlights that balanced input from both eyes is necessary for the normal development of the visual system and binocular fusion.

By understanding the sensory deficits of deprivation amblyopia beyond acuity, we can get a better understanding of the disruption that occurs to the visual system. Animal models and studies with humans with deprivation amblyopia have shown that there are physiological and

functional sensory deficits associated with visual deprivation during the critical period, while there have been very few studies focusing on the visuomotor behavior in deprivation amblyopia. Studying the development of the visuomotor system in individuals with deprivation amblyopia can provide an insight into neuroplasticity of the sensorimotor system (Puderbaugh & Emmady, 2023). In the case of deprivation amblyopia, congenital cataracts are associated with the structural changes, such as ocular dominance caused by the unbalanced visual inputs, and functional brain reorganization, as extrastriate visual cortex also becomes affected by impacting cross-modal interactions (Mitchell & Maurer, 2022).

Oculomotor control is a fundamental component of all visuomotor behaviors and plays an important role in visual perception (Luna et al., 2008). Oculomotor control refers to various types of eye movements which are controlled by 6 extraocular muscles and 4 cranial nerves (Becker, 2009). Broadly speaking, eye movements can be classified as fixational (i.e., maintaining stable fixation), gaze holding (VOR, OKN, and smooth pursuit) and gaze shifting (saccades and vergence) (Becker, 2009). Very little is currently known about oculomotor control in deprivation amblyopia, however, deficits have been shown in patients with other forms of amblyopia. For example, patients with anisometropic, strabismic or mixed amblyopia have poorer fixation stability, slower saccade latency, lower precision in target localization during amblyopic eye viewing, and difficulties with vergance eye movements due a disruption in disparity processing (reviewed in Niechwiej-Szwedo et al., 2019).

The proposed research will focus on investigating two aspects of oculomotor control in adults with unilateral deprivation amblyopia, namely fixation stability and optokinetic nystagmus (OKN) response. Although the key sensory capability lost in the visual system in these patients is visual acuity, the loss of binocular fusion due to the suppression of input from the previously

deprived eye and the shift in ocular dominance imposed by the fellow eye may impact oculomotor control (Meier & Giaschi, 2017). The characteristics of fixation stability and OKN and the effects of amblyopia due to causes other than deprivation on these functions are summarized in the next section.

1.2 Fixation Stability

An individual's ability to hold a steady fixation with their eyes is an essential aspect of a functional visual system. During a period of fixation, the omnipause neurons located in the nucleus raphe interpositus of the paramedian pontine reticular formation fire continuously and this tonic firing inhibits the firing of saccadic premotor burst neurons(Krauzlis et al., 2017). If the omnipause neurons stop firing, then the saccade-related burst neurons, which receive input from the superior colliculus drive the oculomotor neurons that are responsible for innervating the extraocular muscles (Krauzlis et al., 2017). It is important to note that when an individual attempts to fixate on a target, involuntary eye movements occur and include microsaccades, ocular tremors, and slow drifts (Martinez-Conde, 2006).

Microsaccades are smaller amplitude saccades that occur approximately one to three times per second while fixating (Rolfs, 2009). They tend to have an amplitude of less than 0.5 degree in the vertical and horizontal directions (Rolfs, 2009). It has been generally agreed that microsaccades are conjugate, meaning they are only considered to be true microsaccades when they occur in both eyes, while their magnitudes tend to be very similar as well (Otero-Millan et al., 2014). Although 95% of microsaccades are correlated between eyes, there are some that differ in amplitude, which can be attributed to the correction of errors in vergence (Otero-Millan et al., 2014). Ocular slow drifts are the slow eye movements that occur during the period of fixation between microsaccades. Typically, drifts have a lower amplitude than microsaccades

(Rolfs, 2009). Ocular microtremors are small wave-like movements that are just of a few seconds of arc in amplitude and have a frequency of about 90 Hz (Martinez-Conde, 2006). Since they have smaller amplitudes and a fast frequency, this behavior has been difficult to measure with most eye tracking systems (Martinez-Conde, 2006).

Fixation stability can be quantified with the bivariate contour ellipse (BCEA) measure, the rate and amplitude of microsaccades and the velocity of ocular drifts. The BCEA is an important measure of assessing fixation stability that has been used commonly in recent studies. It provides an overall measure of the general dispersion of the eyes during the period of fixation (Castet & Crossland, 2012). A larger BCEA value represents poorer fixation stability, which can be attributed to an increase in microsaccades or ocular drifts during the fixation interval (Tarita-Nistor et al., 2009). Fixation stability can be impacted by visual impairments, the type of fixation target (Thaler et al., 2013) and the age of the participant.

The functional relevance of the fixational eye movements is an area of active investigation, however, some studies have shown that visual impairments that impact visual acuity can also lead to poorer fixation stability. Age-related macular degeneration is characterized by a gradual decline in photoreceptors sensitivity at the macula, which leads to a central scotoma (Altinbay & Idil, 2022). This condition results in deficits in visual acuity and fixation instability (Tarita-Nistor et al., 2009). As a result, individuals experience challenges performing tasks that require them to fixate on a target. Fixation stability can also be impacted by the type of target used in the experiment. Thaler et al. (2013) conducted a key study that assessed how fixation stability can differ based on the size and the shape of the fixation target. By assessing the microsaccade rate and dispersion of the eye position, they found that fixation stability was highest for a shape that looked like a combination of a cross hair and a bullseye

(Thaler et al., 2013). The fixation stimuli recommended by Thaler et al will be used in the proposed experiment in this thesis. Fixation stability has also been shown to be minimally affected by age in a study Kosnik et al. (1986). They revealed that older adults (65-74 years old) had a greater dispersion of their eyes in the vertical direction in comparison to younger adults (19-28 years old) (Kosnik et al., 1986). However, the difference was not statistically significant as no change in BCEA was detected across the groups (Kosnik et al., 1986). It is also important to understand the relationship between fixation stability and visual acuity. Chung et al. (2015) used multiple linear regression models to determine whether fixation stability is impacted by visual acuity or whether a poorer fixation stability worsens visual acuity. Their model suggested that the oculomotor behavior (magnitude of microsaccades) is the independent variable to visual acuity, while fixation stability is the mediator (Chung et al., 2015). To summarize, fixation stability is an important measure of oculomotor control, and as a result, this study will investigate and quantify the fixation stability in people with deprivation amblyopia.

Since there has been no research on fixation stability in humans with deprivation amblyopia, this section will review fixation stability in other types of amblyopia and in animal models of visual deprivation at birth. Fusion maldevelopment nystagmus syndrome (FMNS) is a pathological nystagmus seen in human and nonhuman primates (Tychsen, 2007). It is a pathology that is linked to binocular maldevelopment during infanthood and can result from either strabismus or deprivation of vision (amblyopia) (Tychsen et al., 2010). The feature of FMNS is a characteristic eye movement with a nasal-ward drift, followed by a corrective eye movement in the temporalward direction (Dell'Osso, 1985). The severity (i.e., larger amplitude and frequency) becomes worse when one eye is covered (Tychsen et al., 2010). Animal studies have shown that FMNS is worse in unilateral amblyopia in comparison to bilateral cases

(Tychsen et al., 2010). This may be due to unbalanced inputs from both eyes during the early postnatal period, which is associated with a more severe disruption of the excitatory connections and persistence of inhibitory connections in the V1 resulting in fewer binocular cells (Löwel & Singer, 1992). This behaviour can subsequently result in poor fixation stability due to the greater and more frequent dispersion of eye position.

Fixational eye movements have been used to as a method to determine the effectiveness of an occlusion therapy regimen (Scarmuzzi et al., 2019). Scarmuzzi et al. (2019) categorized patients with amblyopia into those without a nystagmus, those with FMNS, and those with nystagmus but no FMNS. It was found that children with FMNS required more treatment than children without nystagmus, based on their performance on a fixation stability task. This supports the utility of fixation stability measures as a predictor for future treatment plans.

A series of studies have investigated fixation stability in amblyopia. Gonzalez et al. (2012) investigated fixation stability in adults with various types of amblyopia, however, patients with deprivation amblyopia were not included. Results showed that patients had poorer fixation stability under both binocular and monocular viewing conditions in comparison to healthy controls. In the control group, binocular viewing was associated with a BCEA of 0.28 degrees, indicating more stable fixation compared to monocular viewing. Examining fixation stability of the covered eye revealed reduction in fixation stability. During binocular viewing in the amblyopic group, the fellow eye was similar to the control group, but the amblyopic eye had a BCEA that was 0.48 degrees higher than the controls (i.e., greater fixation instability). The amblyopic eye during monocular viewing was 0.40 degrees less stable than the monocular viewing of the healthy controls. The number and amplitude of microsaccades was similar across groups and viewing conditions. Thus, it was assumed that the difference in BCEA was attributed

to an increase in speed and amplitude of ocular slow drifts, since the ocular slow drifts were not actually quantified. Chung et al. (2015) also investigated fixation stability in people with strabismus and anisometropia amblyopia. They quantified fixation stability with microsaccade amplitude and frequency, and the amplitude and speed of the ocular slow drifts. They found that the fellow eye in the amblyopia group had similar fixation stability to the control group. Furthermore, they found that fixation was more unstable in the amblyopic eyes in comparison to control and fellow eyes. Based on Chung et al. (2015) and Gonzalez et al. (2012), fixation stability is poorer in individuals with amblyopia, further emphasizing the importance of studying fixation stability in people with deprivation amblyopia, which is the aim of this study.

1.3 Optokinetic Nystagmus (OKN)

Optokinetic nystagmus (OKN) reflex response refers to a stereotypical eye movement pattern triggered by a large moving stimulus in the visual field (Krauzlis et al., 2017). The purpose of this reflex is to allow for the stabilization of retinal images when an individual is viewing a moving visual field (Knapp et al., 2013). The OKN response consists of two phases– the slow phase in the same direction as the moving stimulus followed by a fast phase where the eyes rapidly reverse (i.e., saccade) in the opposite direction to the stimulus motion.

The OKN response can be triggered by horizontal and vertical stimuli. In all cases, the OKN consists of the slow-phase and quick phase but differs based on the direction of the stimulus and speed of the stimulus (Knapp et al., 2013). If the neural pathways are intact, the slow-phase component of the response will gradually increase in velocity until it reaches the velocity of the stimulus in the visual field. Neural damage in the visual system can affect this response.

In mammals, the key nuclei involved in the OKN response are the nucleus of the optic tract (NOT) and the dorsal terminal nucleus (Distler & Hoffmann, 2011). These nuclei have motion direction sensitive neurons that receive information from the contralateral eye (Distler & Hoffmann, 2011). When a retinal slip (slow-phase) occurs in response to a moving visual field, neurons in the NOT and the dorsal terminal nucleus encode the velocity error between the stimulus displacement and eye position in a direction-selective manner (Distler & Hoffmann, 2011). Afferent fibers in response to temporalward motion go indirectly to the NOT via the ipsilateral visual cortex, while the afferent fibers in response to nasalward motion goes directly to the contralateral NOT (Hoffmann, 1979).

The OKN response to a moving visual field differs based on the size of the target, speed of the visual field, and visual deficits. The OKN response is typically characterized by comparing the velocity of the eye movement during the slow phase to the stimulus target velocity. This is known as the gain of the OKN response and is a widely used outcome measure to characterize the OKN response. Furthermore, Honrubia et al (1968) showed that there are two types of OKN responses in humans, and they can be revealed depending on the instructions given to the participant. The two types of OKN responses are the “stare” response and the “look” response. In the “stare” response, the participant is instructed to stare straight ahead at the moving stripes. This produces a reflexive OKN response as the eyes follow the stripes (i.e. slow phase), and a quick phase shifting the gaze back to the center. Under this instruction, participants produced lower amplitude but higher frequency OKN responses. In the “look” condition, the participant is instructed to follow the stripes as they move across the screen, and then shift their gaze back to the start of the screen. Under these instructions, the participant performs a smooth pursuit response, which has a higher amplitude but lower frequency. It has been proposed that

the “look” condition is under cortical control, whereas the “stare” condition is under subcortical control. To investigate the neural correlates of OKN response with different instructions, Kashou et al (2010) conducted a fMRI study while participants were instructed to “look” or “stare” (Kashou et al., 2010). Results revealed significantly greater cortical activation during the ‘look’ condition in areas responsible for voluntary eye movements, including the cingulate gyrus (voluntary smooth pursuit) and the precuneus (voluntary saccadic and voluntary pursuit eye movements). Additionally, since “look” produces a greater amplitude of OKN response, there was increased activation in the occipital cortex, and increased activation in the parietal cortex due to the increased attention required for the voluntary “look” OKN response. This study shows that OKN instructions influence the type of response elicited, thus, should clearly be provided to the participants.

Literature has shown that during the early postnatal period, humans and kittens have a nasalward OKN bias (Naegele & Held, 1983). The bias can be assessed during monocular viewing by comparing the velocity of the slow phase OKN component when the stimulus moves towards the nose (nasalward) or towards the temple (temporalward) (Naegele & Held, 1983).Research shows that the OKN response to a temporalward stimulus has a lower velocity compared to a stimulus moving nasalward (Westall et al., 1989). The bias occurs between birth and 3 months and has been attributed to immature pathway from the binocular cells in the visual cortex to the horizontal gaze center in the brainstem (Westall et al., 1989). The pathway that is responsible for the nasalward motion is subcortical and is considered independent from the binocular neurons in the cortex (Braddick, 1996). In contrast, the pathway mediating OKN response to temporalward motion is an indirect pathway which projects to the ipsilateral nucleus of the optic tract’s binocular neurons. As the cortex matures and the binocular neurons develop

between 3 to 5 months of age, the OKN movement becomes symmetrical. The asymmetrical OKN response is a common sign of impaired visual development if it persists into adulthood.

Westall et al. (1989) investigated the OKN response in adults with anisometropia and strabismic amblyopia. They found that the OKN response was present in the temporalward direction, however, the response had a lower gain in comparison to the nasalward direction (Westall et al., 1989). The OKN asymmetry was also evident in a study by Lewis et al. (1986) where they tested the OKN response in 9 years old children who had a unilateral congenital cataract that were removed surgically at a median age of 5.5 months (2 to 28 month) (Lewis et al., 1986). The OKN response was quantified by counting how many trials contained the OKN response. They found that when the stimulus moved in temporalward direction, the OKN response was absent on all 15 trials across all participants. To determine whether a participant was exhibiting OKN, the experimenter observed the participant's eye movements while the OKN stimulus was presented. This is an issue because a subjective measure was used to determine if the OKN response was present. By implementing an eye tracker in the proposed experiment, the response can be quantified by assessing the gain of the slow-phase component. Although this study gives us insight into the effects of cataracts on OKN response during childhood, it is important to investigate the response in adulthood as well. In summary, it is clear there the OKN response is abnormal in children with deprivation amblyopia, and thus, it is important to investigate this population into adulthood.

1.4 Rationale for Study

There are sensory deficits in individuals with unilateral deprivation amblyopia. Since sensory processing impacts the planning and execution of motor output, including eye movements, it is vital to learn more about oculomotor control of these patients. Previous

literature has shown that people with amblyopia have poorer fixation stability due to an increase in ocular drifts. Additionally, a study investigating OKN in children who had unilateral cataracts during infanthood has shown that the normal symmetrical response did not develop. Therefore, this study addressed an important gap in the literature by investigating the OKN response and the fixation stability in adults with unilateral deprivation amblyopia.

1.5 Fixation Stability Hypotheses

1. Binocular viewing: it was hypothesized that the fellow eye of the patients will have comparable fixation stability to the control group, however, the amblyopic eye will have poorer fixation stability. This is because it has previously been shown that patients with amblyopia experience greater position uncertainty (Levi et al., 1987).

2. Monocular viewing - Fellow eye

a) closed loop: it was hypothesized that the fellow eye with normal visual acuity will have similar fixation stability to the control group's monocular viewing.

b) open loop: it was hypothesized that the fellow eye will have poorer fixation stability under open-loop in comparison to closed- loop recording because of the lack of visual feedback.

3. Monocular viewing - Amblyopic eye

a) closed loop: it was hypothesized that the amblyopic eye under closed-loop viewing will have poorer fixation stability due to increase in the amplitude of microsaccades and an increase in the velocity of slow drifts.

b) open loop: it was hypothesized that the amblyopic eye will have poorer fixation stability in comparison to closed loop recording due to the lack of visual feedback.

1.6 OKN Response Hypothesis

It was hypothesized that during fellow eye viewing condition there will be a nasalward bias (asymmetrical OKN response). This is because the patients will not have binocular fusion and binocularity has been associated with a symmetrical OKN response.

2.Methods

2.1Participants

Healthy controls were recruited from advertisements at the University of Waterloo, while people with deprivation amblyopia were recruited from a database housed at McMaster University. Informed consent was obtained from all the participants and the project was approved by the University of Waterloo Office of Research Ethics and the Research Ethics Board at The Hospital for Sick Children in Toronto.

Control Group

The cohort included 18 adults (9 females; mean age = 30.2 ±7.25 years) with normal or corrected to normal visual acuity (-0.15 ± 0.11 logMAR) assessed using the Lovie-Bailey visual chart, and steroacuity of at least 40 arc seconds (25.15 ± 8.12 arc sec) measured using the Randot Stereotest.

Patient Group

Seven participants with unilateral deprivation amblyopia were recruited (5 females; mean age = 34.8 + 8.75 years). The history of each patient in regards to their cataract as well as other clinical information is summarized in table 1. The demographics and clinical characteristics of the patient population are summarized in table 2.

Table 1. *Summary of the clinical history of the 7 patients.*

ID	Cataract Diagnosis Age (days)	Cataract Removal Age (days)	Clinical History Notes
P1	160	183	• Strabismus diagnosed at 6 years • Received extensive patching • Interocular lens inserted at 16 years
P2	0	827	No history was available
P3	N/A	140	• Interocular lens in amblyopic eye • Received extensive patching • Strabismus correction procedure at 19 years
P4	75	110	• Several procedures for strabismus correction in both amblyopic and fellow eye • Goniotomy at 8 years
P5	0	10	• Strabismus correction procedure at 16 years

P6	21	42	• Strabismus correction procedure at 5 years
P7	2	45	• Strabismus correction procedure at 1 year

Table 2. *Summary of the demographics and clinical characteristics of the 7 patients.*

ID	**Sex**	**Age**	**Fellow Eye Acuity (logMAR)**	**Amblyopic Eye Acuity (logMAR)**	**Stereoacuity (arc sec)**	**Visible Strabismus (Y/N)**	**Worth 4 Dot Test**
P1	F	29	0.10	Count fingers @ 30 cm	>400	Y	Suppress
P2	F	51	0.10	Hand wave @ 30 cm	>400	N	Suppress
P3	F	29	-0.10	1.00 @ 30 cm	>400	N	Suppress
P4	F	41	-0.30	0.80 @ 1 m	>400	Y	Suppress
P5	M	25	0.00	0.80 @ 1 m	>400	N	Alternator
P6	F	31	0.10	1.00 @ 70 cm	>400	Y	Suppress
P7	M	34	0.40	0.70 @ 60 cm	>400	Y	Suppress

2.2 Apparatus

The control group was tested at the University of Waterloo. Eye position was recorded using the EyeLink 2 eye tracker (SR Research Ltd, Mississauga, Ontario, Canada) at a sampling frequency of 250 Hz using the pupil and corneal reflection tracking. The patient group was tested at SickKids using the EyeLink 1000 eye tracker (SR Research Ltd, Mississauga, Ontario, Canada) at a sampling frequency of 250 Hz using the pupil and corneal reflection tracking. For both sites, the calibration protocol was performed using binocular viewing and a five-point calibration. The fixation stimulus and the OKN stimulus were presented on a "Benq" LCD monitor (1920 x 1080) at SickKids, and on a "Samsung" LCD monitor (1920 x 1080) at the University of Waterloo.

2.3 Fixation Stability Procedure

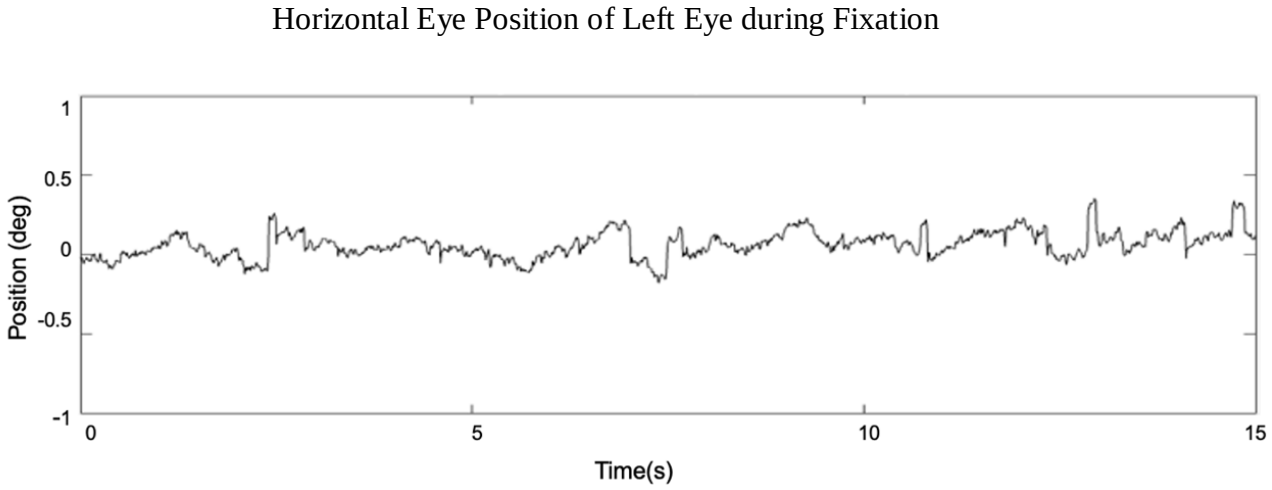
Participants were seated 60cm from the monitor screen and placed their chin in a chinrest. The test was conducted in a well illuminated room. The monitor at the University of Waterloo testing center had a luminance of 175 cd/m^2 and the monitor at the SickKids had a luminance of 178 cd/m^2. The fixation stimulus consisted of a black 3-degree target which is a combination of a bull's eye and a crosshair presented in the center of the monitor screen on a white background (Thaler et al., 2013)

The fixation stability procedure included three viewing conditions: 1. binocular, 2. dominant (fellow) eye, 3. non-dominant (amblyopic) eye. An infrared (IR) long-pass filter was used such that the eye tracker recorded the eye position of the covered eye. This is known as open-loop recording (closed-loop recording is when the eye is uncovered during monocular viewing) and allows for the measurement of fixation stability when the eye is not receiving

visual feedback. The protocol consisted of 3 trials under each viewing condition, where the sequence of viewing condition was randomized. Participants were instructed to fixate at the center of the fixation target by keeping their eyes steady. Each trial was 20 seconds long with a minimum of 20 seconds to rest between trials.

All trials were visually inspected to ensure signal quality. When blinks were detected, 250 ms of the signal was removed before and after to eliminate blink associated noise. This blink criteria was deemed suitable after determining this was the smallest interval that could eliminate blink associated noise. In addition to this, the first 5 seconds of each fixation period were removed from the analysis, therefore, only 15 seconds were included in the analysis.

A)



B)

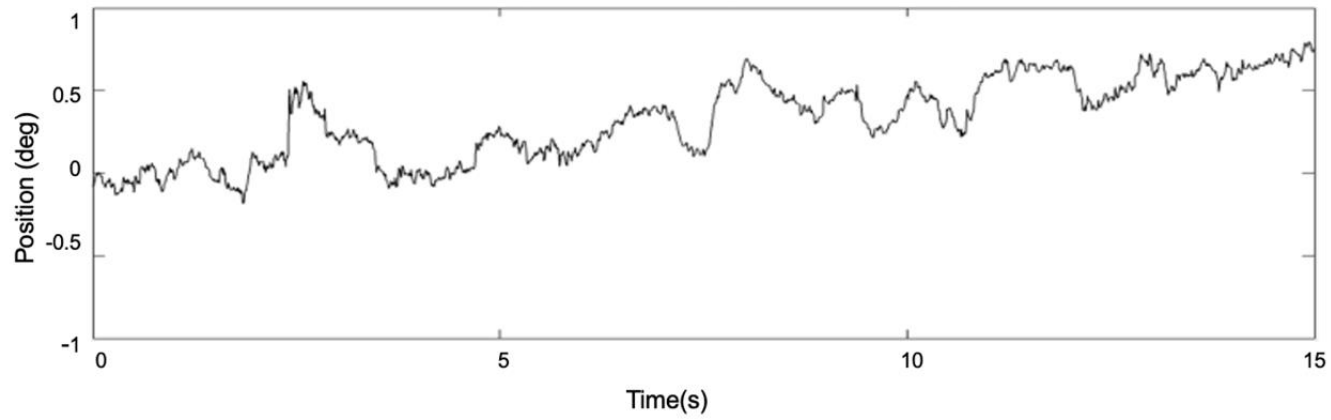


Figure 1. Recording of the left eye position for a control participant during the 15 second fixation interval after blinks have been removed a) horizontal, b) vertical.

Eye fixation stability was quantified by calculating the bivariate contour ellipse area (BCEA). Following this, the amplitude and frequency of microsaccades, as well as the speed of ocular slow drifts were quantified during the 15 seconds interval.

The BCEA represents the area in which the eyes are found over 68.2% of the recording period (Castet & Crossland, 2011). It is calculated using the following formula:

$$\textbf{BCEA} = \pi X^2 \sigma_x \sigma_y \sqrt{1 - p^2}$$

where $\sigma_{x\ and}\ \sigma_y$ represent the standard deviation of eye position across the vertical and horizontal axis, p represents the product moment coefficient, and $X^2 = 2.291$ is the chi-squared value (Caster & Crossland, 2011).

The amplitude of microsaccades and number of microsaccades per second for each trial were also analyzed. Microsaccades were detected using the following criteria: velocity greater then 20 deg/s and an amplitude greater than 0.1 degrees (González et al., 2012). For this study, only the conjugate microsaccades were analyzed for the control group since it has been found that over 95% of microsaccades are conjugate (Otero-Millan et al., 2014). Using only conjugate microsaccades ensured that only real microsaccades were included in the analysis. However, for the patient data, each microsaccaade detected was visually inspected to confirm it was a real microsaccade since it is possible that there can be unconjugated microsaccades in the patient group due to the differences between the fellow and amblyopic eyes.

In quantifying the ocular slow drift, the mean velocity was analyzed. A trial was included in the analysis if it had a minimum of 8 seconds of total slow drift duration across the 15 seconds of the trial. Furthermore, it was required that a duration of slow drift (fixation period between successive microsaccades) should be a minimum of 100 ms for it to be included in the analysis.

2.4 Optokinetic Nystagmus (OKN) Procedure

The OKN test was conducted in a dark room. The OKN stimulus was a black-and-white vertical square-wave grating of a spatial frequency of 0.5 cycles/degree and a velocity of 10 degrees/second moving to the left or to the right. Only the monocular viewing condition was tested with the dominant (fellow) eye. The protocol consisted of 3 trials where the stimulus was moving in the nasalward direction and 3 trials where the stimulus was moving in the temporalward direction. Participants were instructed to look at the center of the screen and maintain clear vision without following the stripes. These instructions elicited the "stare" OKN response. Eye movements were recorded for 15 seconds in each direction. Participant were allowed to rest for approximately 1 minute between trials.

All trials were inspected visually to ensure signal quality. When blinks were detected, 250 ms of the signal was removed before and after blinks. A trial was included in the analysis if it had minimum of 10 OKN slow-phase responses that were greater than 50 ms and less than 500 ms (Knapp et al., 2008) in duration. The upper limit of 500 ms was added to exclude any voluntary pursuits of the stimulus. Figure 2 shows an example of a typical OKN response to the 10 deg/s stimulus.

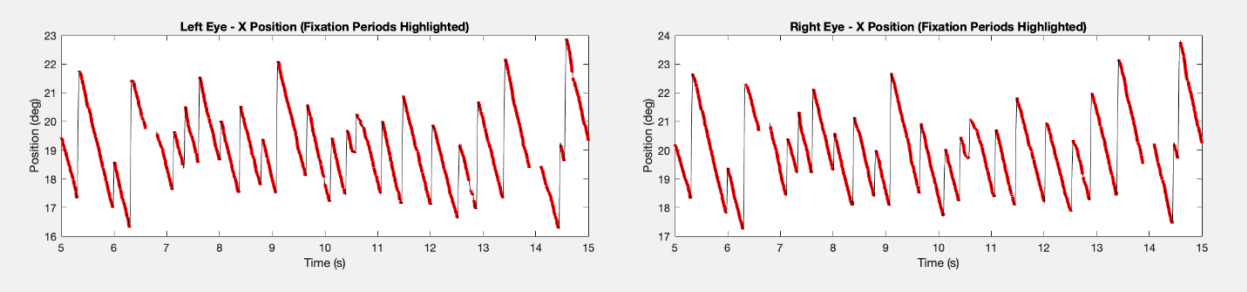


Figure 2. Horizontal eye position for a control participant of the a) left eye and b) right eye when the OKN stimulus is moving right (nasalward for the left eye and temporalward for right eye).

The OKN response was quantified by calculating the gain of the slow-phase and the horizontal asymmetry index. The gain of the slow phase was calculated by the ratio of the eye velocity and target velocity (10 deg/s). The mean slow-phase velocity (MSPV) was first extracted from each trial and then the gain was calculated using the following formula: MSPV/stimulus velocity. In addition to this, the number of OKN cycles per second were also quantified as the OKN frequency, and a horizontal asymmetry index for the frequency across nasalward and temporalward trials was calculated. The following equation was then used to determine the horizontal asymmetry index for each participant (Knapp et al., 2008). A horizontal asymmetry index close to 0.5 indicates a symmetrical response, a nasalward bias is evident if the index is greater than 0.5, and a temporalward bias is evident if the index is less than 0.5.

$$Horizontal\ Asymmetry\ index = \frac{Nasalward\ MSPV}{Nasalward\ MSPV + Temporalward\ MSPV}$$

Each trial was also visually inspected to determine any differences in the visual appearance of the nasalward and temporalward trials.

3. Results

3.1 Fixation Stability

The aim of the first experiment was to determine the effects of viewing condition and visual feedback on fixation stability as quantified by BCEA, microsaccade rate and amplitude, and slow drift velocity in both the control and patient groups.

Out of a total of 162 trials across the 18 control participants, 36 trials were removed because of missing data due to blinks or the eye tracker not recording eye movements. Table 3 summarizes the number of trials that were included for the patient data. Some trials were removed due to technical difficulties during the recording, specifically, the calibration of the eye tracker.

Table 3. *Summary of the number of trials that were included for each patient across viewing conditions (maximum number of trials per condition was 3).*

Participant	Binocular Fellow	Binocular Amblyopic	Closed-loop Fellow	Closed-loop Amblyopic	Open-loop Fellow	Open-loop Amblyopic
P1	0	0	2	2	2	2
P2	2	2	2	2	1	1
P3	3	3	0	2	2	0
P4	3	3	3	3	3	3
P5	3	3	2	1	1	2
P6	2	0	2	2	0	0
P7	2	0	2	2	2	0

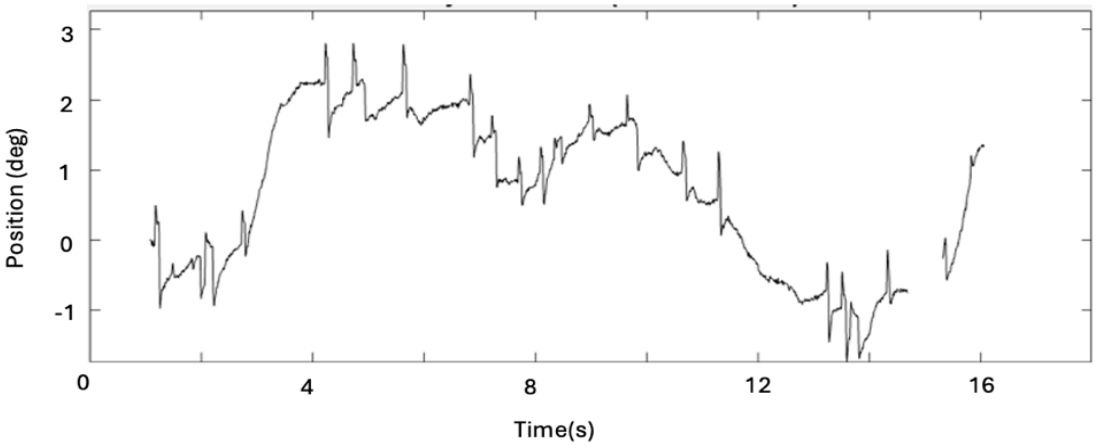
The first step was to calculate the BCEA, microsaccade amplitude, microsaccde rate and slow drift velocity. All outcome measures were tested to ensure assumption of normality and

homogeneity of variance were met, which is required for parametric testing. The Shapiro-Wilk normality test was used to confirm normality. The Mauchly's test of sphericity was used to assess whether the assumption of sphericity is violated.

All outcome measures analysed for the control group met the assumptions for a parametric analysis. Therefore, a 2x3 repeated measures ANOVA was conducted for BCEA, microsaccade amplitude and slow drift velocity across the 3 viewing conditions (binocular, left eye, and right eye) and 2 eyes (left eye and right eye). A one-way ANOVA was conducted to determine any difference in microsaccade rate across the 3 viewing conditions (binocular viewing, left eye viewing, and right eye viewing).

Due to the sparse patient data, low sample size and not normal data, z-scores were calculated for each of the outcome measures relative to the mean and standard deviations of the control data.

A) Horizontal Eye Position of Amblyopic Eye during Binocular Viewing



B) Horizontal Eye Position of Fellow Eye during Binocular Viewing

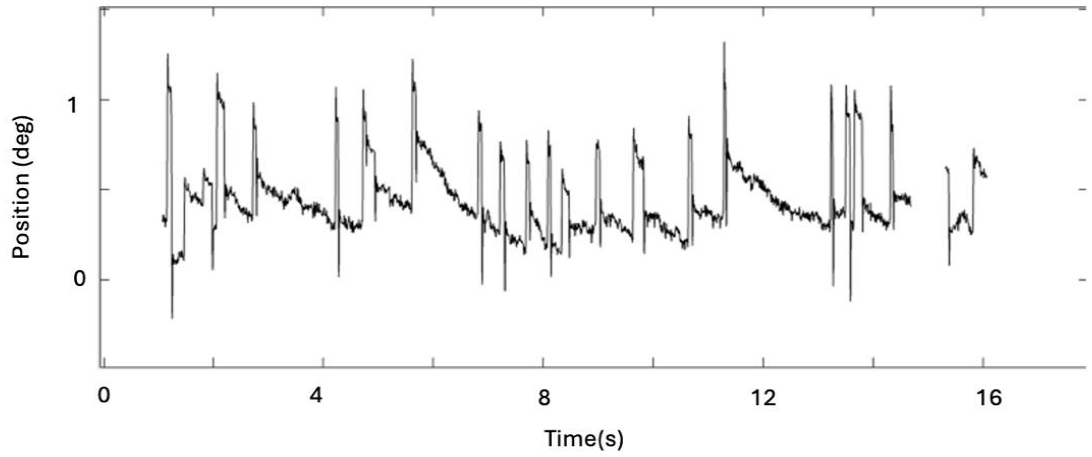
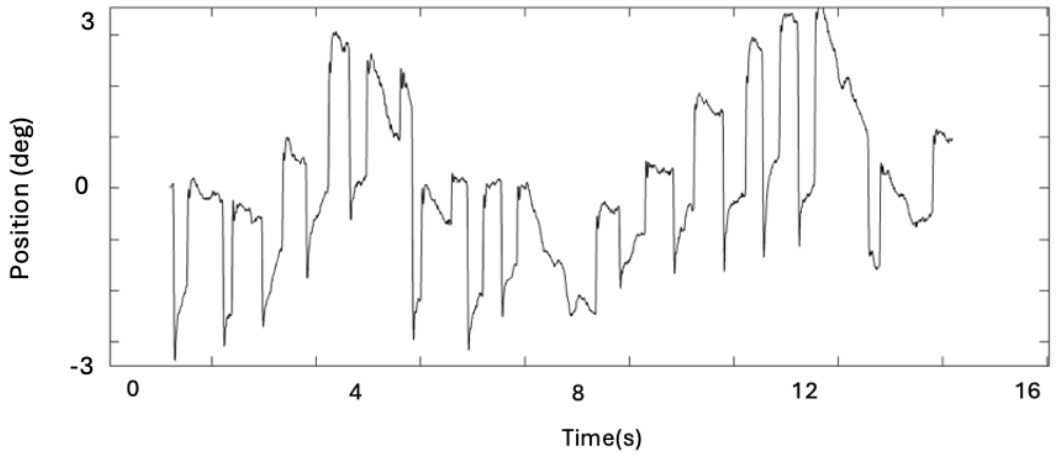


Figure 3. Eye position recording during binocular viewing of the amblyopic (A) and fellow eye (B) for patient P4 showing higher amplitude microsaccades during binocular viewing for both eyes. Increase in slow drift velocity was the driver of increased dispersion in the amblyopic eye.

A) Horizontal Eye Position of Amblyopic Eye under Closed-loop Viewing.



B) Horizontal Eye Positions of Fellow Eye under Open-loop Viewing.

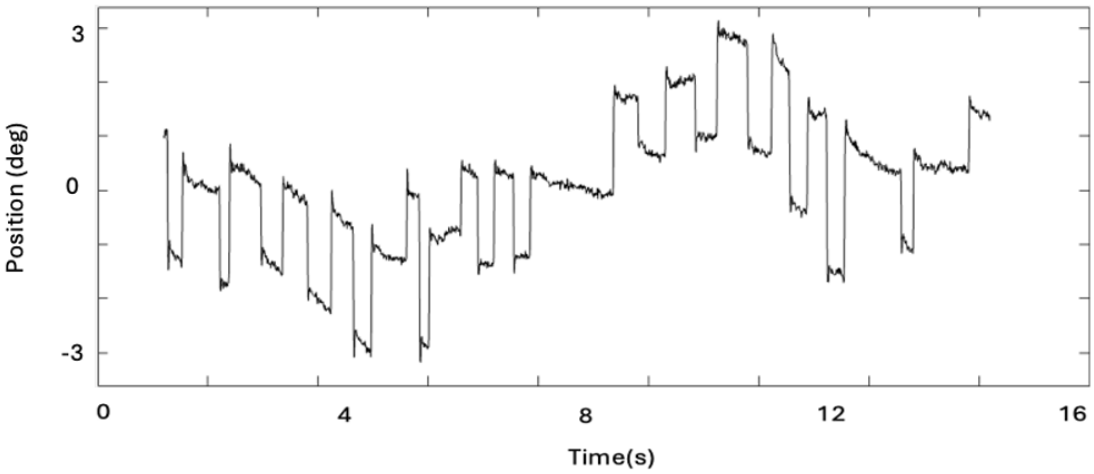
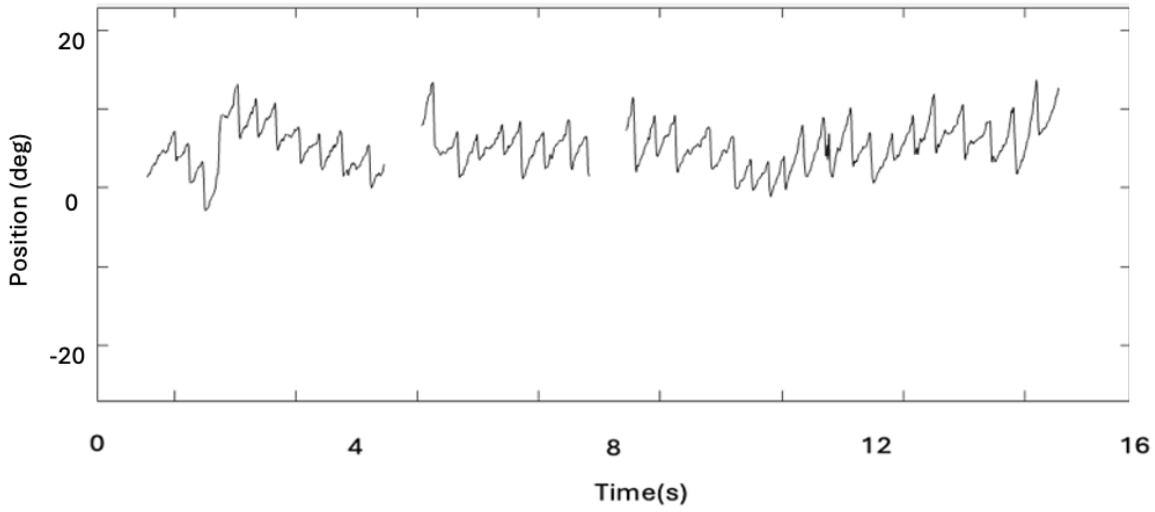


Figure 4. Eye position recording for the amblyopic eye under closed-loop viewing (A), and the fellow eye under open-loop viewing (B) for P4 showing high amplitude microsaccades. Square wave jerk response is evident in both eyes.

A) Horizontal Eye Position of Amblyopic Eye under Closed-loop Viewing.



B) Horizontal Eye Position of Fellow Eye under Open-loop Viewing.

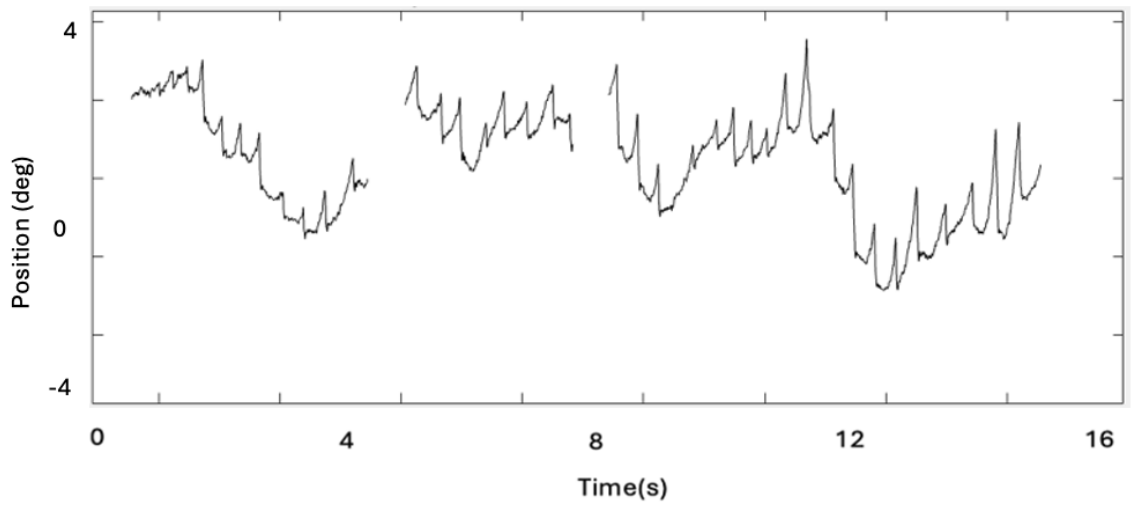


Figure 5. Eye position recording for the amblyopic eye during closed-loop viewing (A), and fellow eye during open-loop viewing (B) for P7 which demonstrates an FMNS response that resulted in a higher rate of microsaccades, larger microsaccade amplitude and increased slow drift velocity for both the amblyopic and fellow eyes.

3.1.1 Global BCEA

Figure 6 summarizes the BCEA results for the 18 control participants across the viewing conditions. Both left and right eye were summarized into one boxplot as there was no difference between the eyes. Individual patient data points for both fellow and amblyopic eye have been plotted relative to the control data.

For the control group, the ANOVA revealed a significant main effect of viewing condition; $F_{(2,34)}= 126.34$, $p < 0.001$, partial $\eta^2 = 0.28$, and a significant viewing condition by eye interaction; $F_{(2,34)}= 96.45$, $p < 0.001$, partial $\eta^2 = 0.20$.

Bonferroni pairwise post-hoc comparisons were used to decompose the main and interaction effects. Fixation stability, as indicated by $\log_{10}$BCEA, was significantly poorer ($p<0.001$) during monocular compared to binocular viewing (-0.619 ± 0.11 deg^2 vs -0.813 ±0.20 deg^2, respectively). In addition to this, fixation stability was significantly poorer ($p<0.001$) during an open-loop in comparison to a closed-loop recording (-0.372 ± 0.12 deg^2 vs -0.619 ± 0.11 deg^2, respectively).

For the patients, the amblyopic eye during binocular viewing exhibited an increase in dispersion in comparison to the fellow eye (0.44 ±0.28 deg^2 vs -0.57 ± 0.28, respectively). The $\log_{10}$BCEA of the amblyopic eye of four patients was greater than 4 standard deviations away from the control mean. The fellow eye of five patients remained within 1 standard deviations of the control group, while the fellow eye of P7 was within 3 standard deviations of the control mean. Overall, $\log_{10}$BCEA during binocular viewing for the fellow eye of most patients was similar to controls, except for P7. In contrast, the amblyopic eye showed very large fixation instability in most patients.

During closed-loop monocular viewing, the fellow eye $\log_{10}$BCEA for four patients was 1.5 standard deviations of the control dataset, while one patient was approximately 3 standard deviations away, and one patient deviated by 6 standard deviations. The amblyopic eye exhibited an increase in dispersion in comparison to the fellow eye (0.43 ±0.29 deg^2 vs -0.30 ± 0.31 deg^2, respectively). The amblyopic eye $\log_{10}$BCEA for all patients was greater than 7 standard deviations away from the control mean.

During open-loop monocular viewing, the fellow eye $\log_{10}$BCEA for two patients was within 1 standard deviation of the control data set, one patient was 3 standard deviations away, and three patients were 7 standard deviations away from the control group. The amblyopic eye during open-loop viewing exhibited greater dispersion in comparison to the fellow eye (0.31 ± 0.31 deg^2 vs 0.26 ±0.51 deg^2). The amblyopic eye of one patient was within 2 standard deviations of the control data set, while three patients were 5 standard deviations away from the control data set.

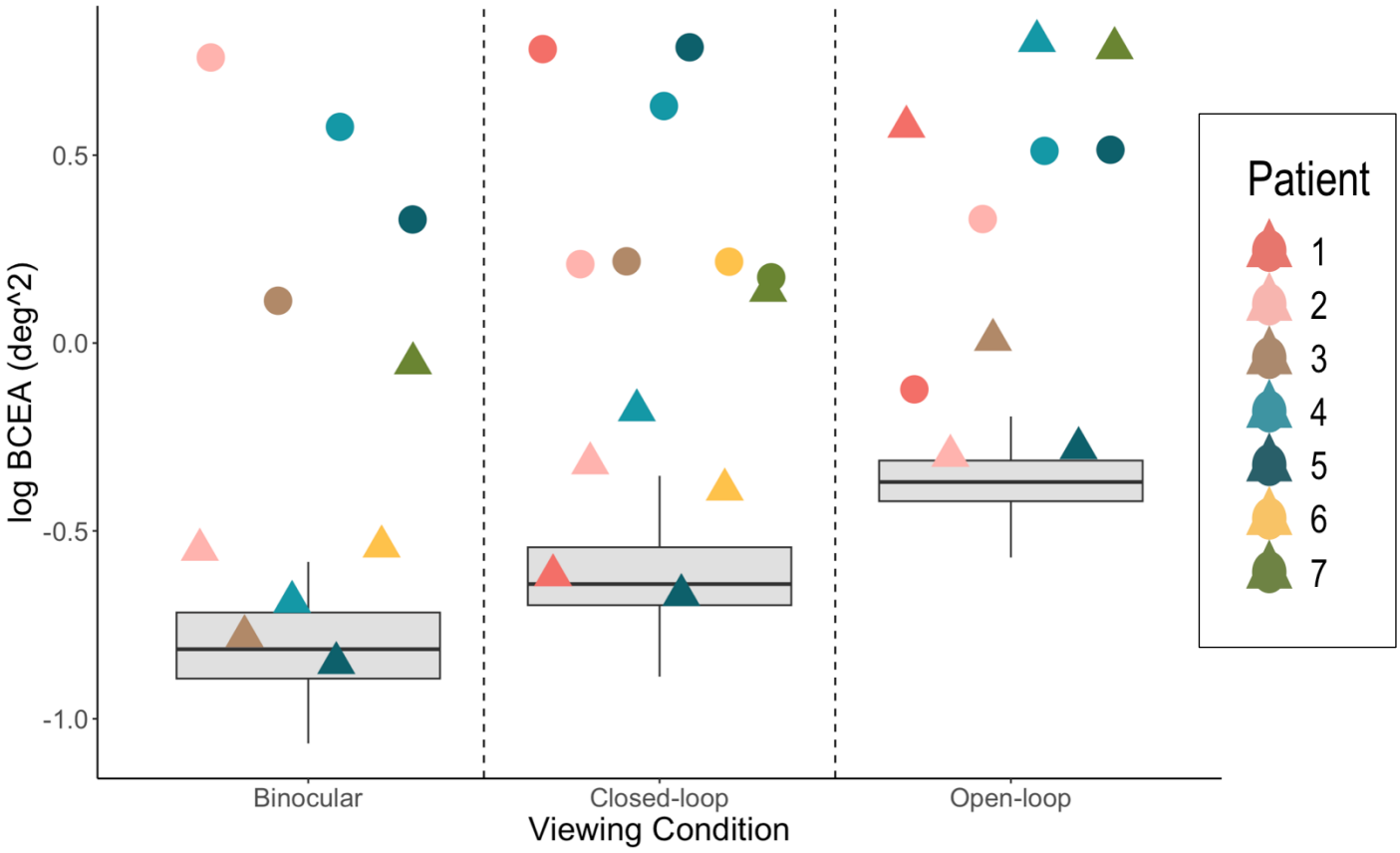


Figure 6. Boxplot depicting fixation dispersion plotted as $\log_{10}$BCEA across different viewing conditions. **Each b**oxplots represent the distribution of the control group across viewing conditions. Each patient has been color coded with circles representing their amblyopic eye and triangles representing their fellow eye.

3.1.2 Microsaccade Rate

Figure 7 summarizes the microsaccade rate results for the control group across the viewing conditions. Individual patient data points for both the amblyopic and fellow eye have been plotted relative to the control data.

Results from the ANOVA for the control group demonstrated a significant main effect of viewing condition on microsaccade rate; $F_{(2,34)} = 63.74$, $p < 0.001$, partial $\eta^2 = 0.16$. Post-hoc comparisons showed significantly ($p<0.001$) more microsaccades per second during monocular in comparison to binocular viewing (0.94 ±0.27 microsaccades/s vs 0.67 ±0.26 microsaccades/s, respectively).

For the patient group, results revealed a similar microsaccade rate during binocular viewing for the amblyopic and the fellow eye (1.14 ±0.3 microsaccades/s vs 1.07 ±0.3 microsaccades/s, respectively). The amblyopic and fellow eye of four patients were within 2 standard deviations of the control group. The fellow eye of P7 was 4 standard deviations away from the control group due to a manifest nystagmus.

During the closed-loop condition, the fellow eye of all patients was within 2 standard deviations of the control mean. The amblyopic eye had a slightly higher microsaccade rate in comparison to the fellow eye (1.91 ±0.30 microsaccades/s vs 1.31 ± 0.27 microsaccades/s, respectively). The amblyopic eye microsaccade rate of four patients was within 3 standard deviations of the control mean. The amblyopic eyes of P6 and P7 were >7 standard deviations away because they exhibited a FMNS response that had more frequent microsaccades in the temporalward direction.

During open-loop viewing, the fellow eye exhibited a slightly higher microsaccade rate in comparison to the amblyopic eye (1.76 ±0.21 microsaccades/s vs 1.21 ±0.23 microsaccades/s, respectively). The amblyopic and fellow eyes of four patients were within 2 standard deviations of the control mean, while the fellow eyes of P1 and P7 were 3 and 7 standard deviations away from the control mean, respectively. The fellow eye of P7 exhibited a FMNS response that had more frequent microsaccades in the temporalward direction.

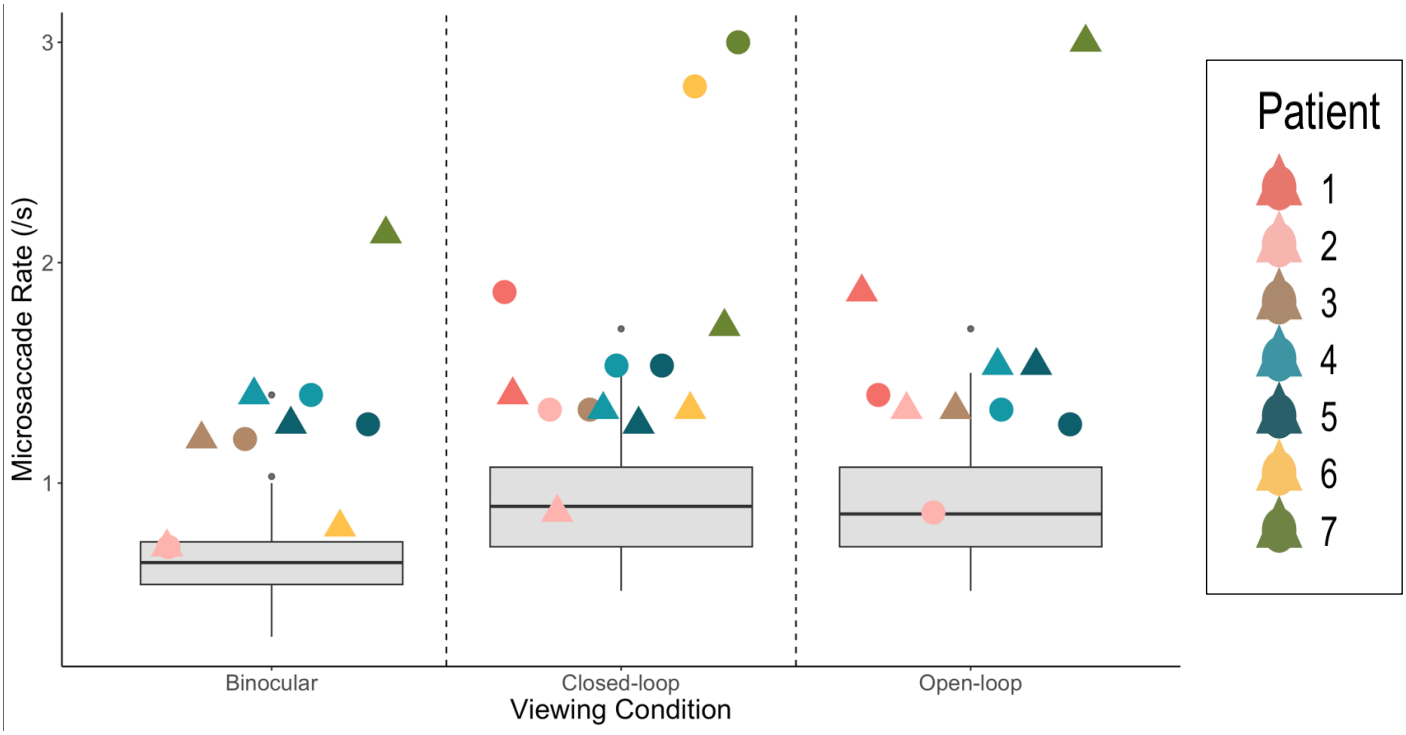


Figure 7. Boxplot depicting the microsaccade rate across different viewing conditions. Each of the boxplots represent the distribution of the control group. Each patient has been color coded with circles representing the amblyopic eye and triangles representing the fellow eye.

3.1.3 Microsaccade Amplitude

Figure 8 summarizes the microsaccade amplitude results for the control group. Results for the left and right eyes have been collapsed as there were no difference between the eyes. Individual patient data points for both fellow and amblyopic eyes have been plotted relative to the control data. P7 has been excluded from the plot due to extremely high values. Their results are discussed in the section below.

Results from the ANOVA for the control group revealed a significant main effect of viewing condition; $F_{(2,34)} = 25.19$, $p < 0.001$, partial $\eta^2 = 0.04$, and a significant viewing

condition by viewing eye interaction; $F_{(2,34)} = 10.47$, $p<0.001$, partial $\eta^2 = 0.11$. Bonferroni pairwise post-hoc comparisons were used to decompose the main and interaction effects. Microsaccade amplitude was not significantly different ($p > 0.05$) between binocular and closed-loop viewing (0.21 ±0.12 vs 0.23 ±0.12, respectively). Microsaccade amplitude during open-loop recording was significantly greater ($p < 0.05$) when compared to closed-loop recording (0.27 ± 0.08 deg vs 0.23 ±0.12, respectively).

For the patient group during binocular viewing, the amblyopic eye exhibited higher amplitude microsaccades in comparison to the fellow eye (0.46 ± 0.16 deg vs 0.36 ± 0.16 deg, respectively). The amblyopic eye of P2, P3 and P5 fell between one and two standard deviations away from the control group, while P4 was 4 standard deviations away. The fellow eye of three patients remained within 0.5 standard deviation from the control group, while the fellow eye of P4 and P7 was 3 standard deviations away from the control mean. Overall, the microsaccade amplitude of the amblyopic eye and fellow eye did not greatly deviate from the control dataset, except for P4 and P7.

During closed-loop viewing, the amblyopic eye exhibited higher amplitude microsaccades in comparison to the fellow eye (0.74 ±0.17 deg vs 0.41 ±0.17 deg, respectively). The amblyopic eye of P7 has been excluded from this mean measure due to a high amplitude of 5.65 deg, which was 42 standard deviations away from the control mean. P7 exhibited a characteristic FMNS eye movement in the amblyopic eye, which produced high amplitude microsaccades. The amblyopic eye microsaccade amplitude of one patient was approximately 1 standard deviation away from the control group, while five patients were greater than 3 standard deviations away from the control group. The fellow eye microsaccade amplitude of four patients was within a half standard deviation of the control group, while P4 was greater than 2.5 standard

deviations away. P4 exhibited a horizontal square wave jerk during both fellow and amblyopic eye closed-loop viewing. P1 exhibited this type of eye movement during amblyopic eye closed-loop viewing, which contributed to the increase in microsaccade amplitude.

During open-loop viewing, the amblyopic and the fellow eyes exhibited similar microsaccade amplitudes (0.53 ±0.12 deg vs 0.51 ± 0.19 deg). The fellow eye of P7 was excluded from the average calculation because of a high amplitude of 2.5 deg caused by a nystagmus. The amblyopic eye of four patients fell within 3 standard deviations of the control group. The fellow eye of three patients was within 2 standard deviations from the control group. The fellow eye of P4 and P1 under open-loop viewing exhibited a horizontal square wave jerk that contributed to the increase in microsaccade amplitude causing them to be 4 standard deviations away from the control mean.

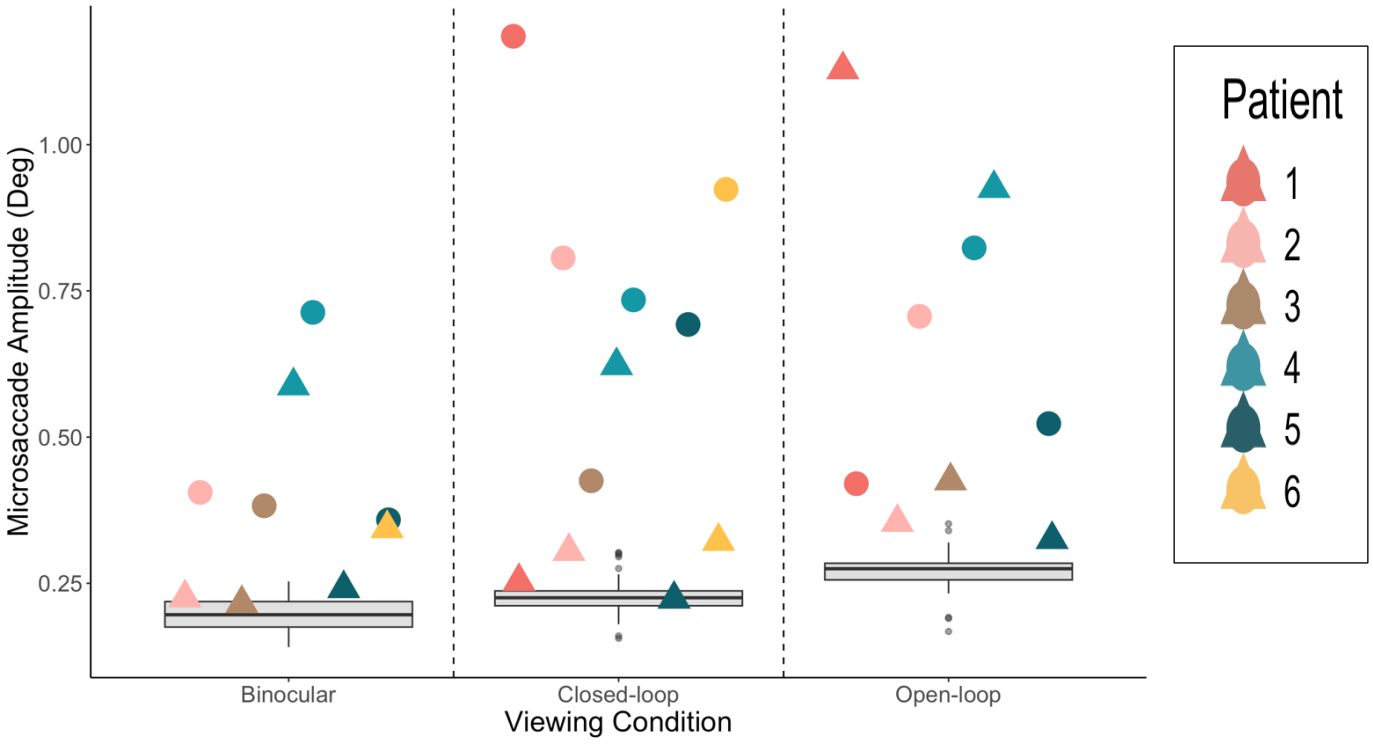


Figure 8. Boxplot depicting the microsaccade amplitude (deg) across different viewing conditions. Each of the boxplots represent the distribution of the control group. Individual patients have been plotted with circles representing their amblyopic eye and triangles representing their fellow eye.

3.1.4 Ocular Slow Drift Velocity

Figure 9 summarizes the ocular slow drift results for the control group. Left and right eyes have been summarized into a single box as there were no differences between the eyes. Individual data points for each patient for both the fellow and amblyopic eye have been plotted relative to the control data. P7 has been excluded from the plot due to extremely high values, their results will be discussed in this section.

The ANOVA revealed a significant main effect of viewing condition; $F_{(2,34)} = 30.59$, $p < 0.001$, partial $\eta^2 = 0.24$ and a significant viewing condition by eye interaction; $F_{(2,34)} = 28.32$, $p < 0.001$, partial $\eta^2 = 0.04$. Bonferroni pairwise post-hoc comparisons were used to decompose the main and interaction effects. Slow drift velocity was significantly greater ($p < 0.05$) during closed-loop monocular viewing in comparison to binocular viewing (0.65 ±0.12 vs 0.46 ±0.12 deg/s, respectively). Open-loop monocular viewing had the highest slow drift velocity (0.76 ±0.15 deg/s), however, it was not significantly greater than closed-loop recording.

For the patient group, the amblyopic eye under binocular viewing exhibited higher slow drift velocity than the fellow eye under binocular viewing (1.48 ±0.43 deg/s vs 0.62 ± 0.18 deg/s). The amblyopic eye of P4 was 7 standard deviations away, one patient was 4 standard deviations away, and three patients were 2 standard deviations away from the control mean. The ocular drift in the fellow eye of four patients was within one standard deviation of the control

mean and one patient was within two standard deviations. In contrast, the fellow eye of P7 exhibited a slow drift velocity of 0.85 deg/s, which was 3 standard deviations away from the control mean.

The amblyopic eye under closed-loop viewing exhibited a higher slow drift velocity than the fellow eye under closed-loop viewing (1.68 ±0.50 deg/s vs 0.95 ±0.31 deg/s). The amblyopic eye of P7 was excluded from this calculation due to an extremely high slow drift velocity of 22.9 deg/s, which was 181 standard deviations away from the control mean. P7 experienced FMNS, involving a nasalward drift that had a high slow phase velocity. The ocular drift of the amblyopic eye of four patients was > 9 standard deviations away from the control dataset, while P2 and P3 were 2 and 4 standard deviations away, respectively. The amblyopic eye of P1 and P4, during closed-loop viewing exhibited a horizontal square wave jerk which increased the slow drift velocity, while P6 exhibited FMNS, which also increased the slow drift velocity. The fellow eye ocular drift of four patients was within 2 standard deviations of the controls, while P6 was 4 standard deviations away. The fellow eye of P7 exhibited a slow drift velocity of 1.47 deg/s, which was 6 standard deviations from the control mean.

The amblyopic eye under open-loop viewing exhibited higher slow drift velocity than the fellow eye under open-loop viewing (1.50 ±0.41 deg/s vs 1.25 ±0.58 deg/s). The fellow eye of P7 under amblyopic eye open loop viewing was excluded from this calculation because of a high slow drift velocity of 4.23 deg/s, which was 22 standard deviations away from the control mean. The amblyopic eye of P2 and P5 were 2.5 standard deviations away from the control mean, P1 was 4 standard deviations away and P4 was 8 standard deviations away. P7 exhibited a FMNS that had a nasalward drift which was of a high velocity. The fellow eye ocular drift of 3 patients

was within one standard deviation of the control mean. P1 was 4 standard deviations away and P4 was 8 standard deviations away which was due to a square wave jerk.

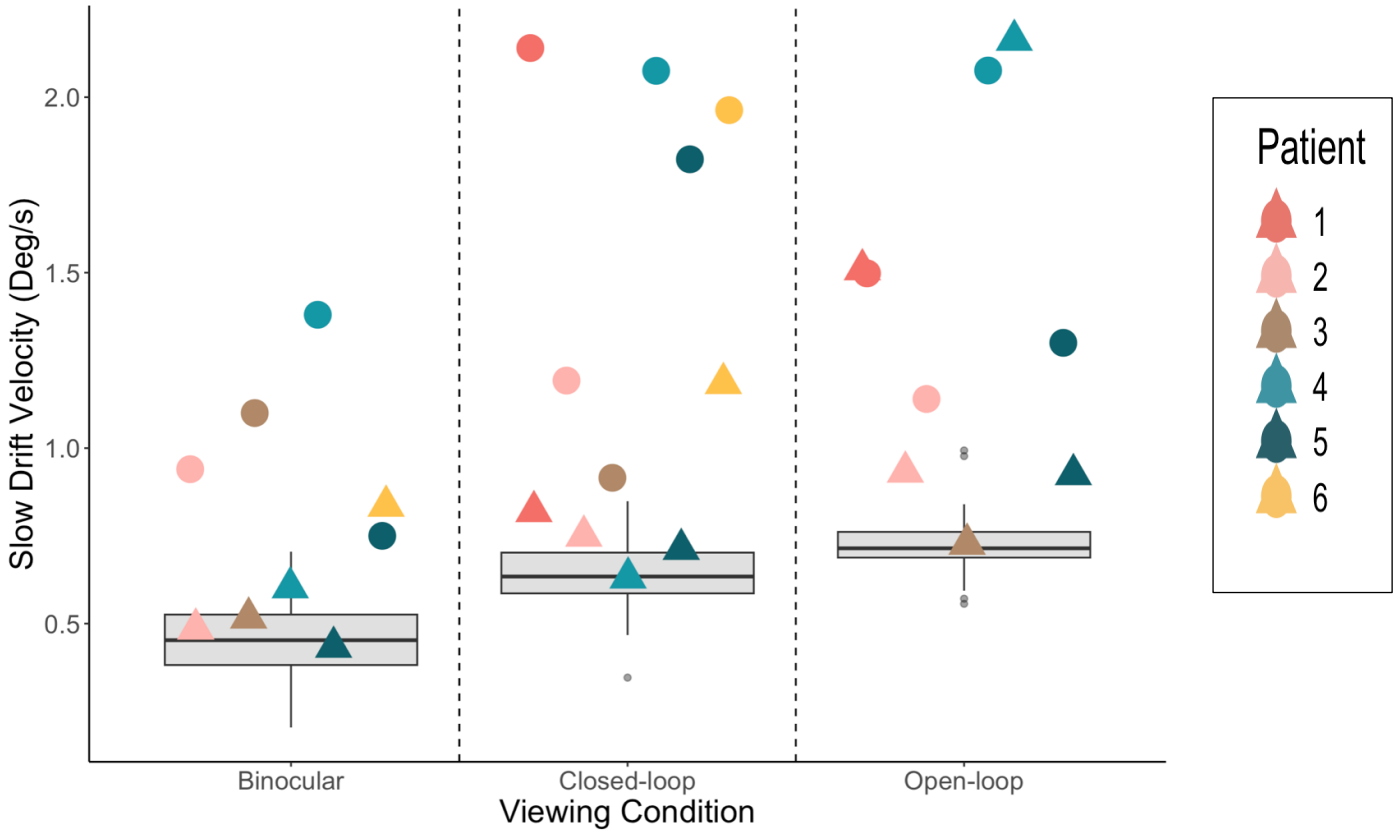


Figure 9. Boxplot depicting the ocular slow drift velocity across different viewing conditions. Each of the boxplots represent the distribution of the control group. Each individual patient has been plotted with circles representing their amblyopic eye and triangles representing their fellow eye.

In summary, fixation stability results for the control group demonstrated no difference in BCEA, microsaccade amplitude or slow drift velocity between the left and right eyes during binocular viewing. However, fixation stability was poorer during monocular closed- and open-loop viewing, as reflected by an increase in BCEA, a higher microsaccade rate, and increased

slow drift velocity. During open-loop viewing, an even higher BCEA and increase in microsaccade amplitude showed that fixation was worst when there was no visual feedback.

In the patient group, results showed that the amblyopic eye had poorer fixation stability than the fellow eye across both binocular and closed-loop viewing conditions, represented by higher BCEAs, higher microsaccade amplitude, and a higher slow drift velocity. During open-loop viewing, both amblyopic and fellow eye had poorer fixation stability than the control group across all measures.

3.2 Optokinetic Nystagmus (OKN)

The aim of this experiment was to determine the effects of stimulus direction (nasalward and temporalward) on the gain and frequency of the OKN reflex. For the control group, out of a total of 108 trials, 18 nasalward and 12 temporalward trials were removed due to technical difficulties with the eye tracker. Table 4 summarizes the number of trials included (out of maximum of 3) for each individual patient. Table 5 summarizes the OKN outcome measures for the control group and Table 6 summarizes the results for each patient. The asymmetry indices for both the gain and frequency have been calculated and plotted in figure 12.

Table 4. *Summary of the number of trials included in the OKN analysis for each stimulus motion direction (maximum of 3 trials per stimulus direction).*

Participant	Number of Trials	
	Temporalward	**Nasalward**
P1	3	3
P2	2	2
P3	2	2
P4	2	2
P5	2	2
P6	2	2
P7	2	2

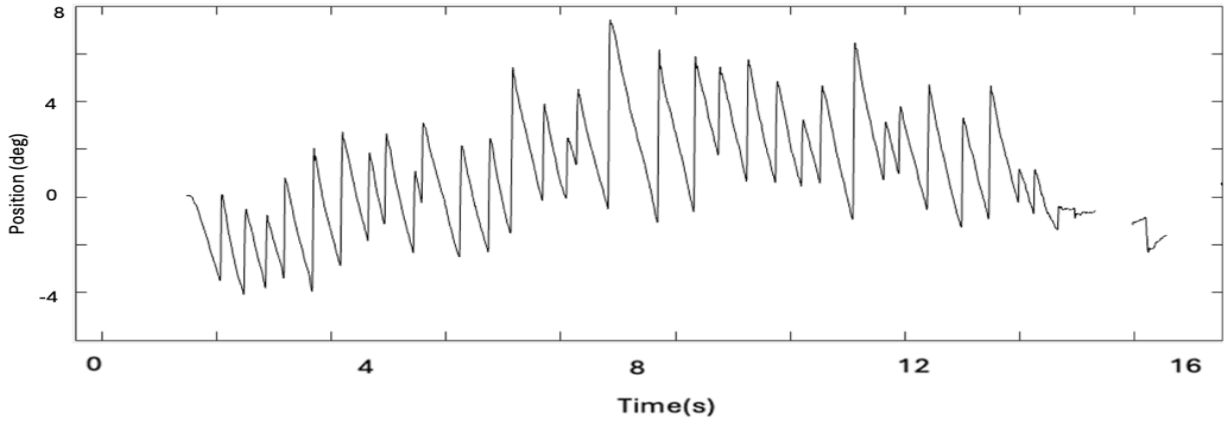
The outcome measures gain and frequency were first tested to ensure that the assumption of normality and homogeneity of variance were met, which is required for parametric testing. The Shapiro-Wilk normality test and Levine's test for homogeneity were used. For the control group, paired t-tests were conducted to determine if there was a difference between the nasalward and temporalward conditions for the OKN gain and frequency measures.

Figure 10 shows an example of the symmetrical OKN response of P1, with nasalward direction (A) and temporalward (B) direction. Figure 11 shows an example of the asymmetrical OKN response of P5. Due to the small sample size of the patient group, z-scores of the gain and frequency asymmetry indices were calculated based on the control means and standard deviations to determine how each individual patient differed from the control group.

Table 5. *Mean, standard deviation (SD) and range for temporalward and nasalward OKN frequency and gain for control group.*

	Frequency (cycles/s)		**Gain**	
	Temporalward	**Nasalward**	**Temporalward**	**Nasalward**
Mean ± SD	1.82 ± 0.36	1.62 ±0.38	0.79 ±0.09	0.82 ±0.09
Range (min – max)	0.9 – 2.4	1 – 2.26	0.66-0.94	0.68-0.92

A) OKN Response of P1 in Nasalward Direction



B) OKN Response of P1 in Temporalward Direction

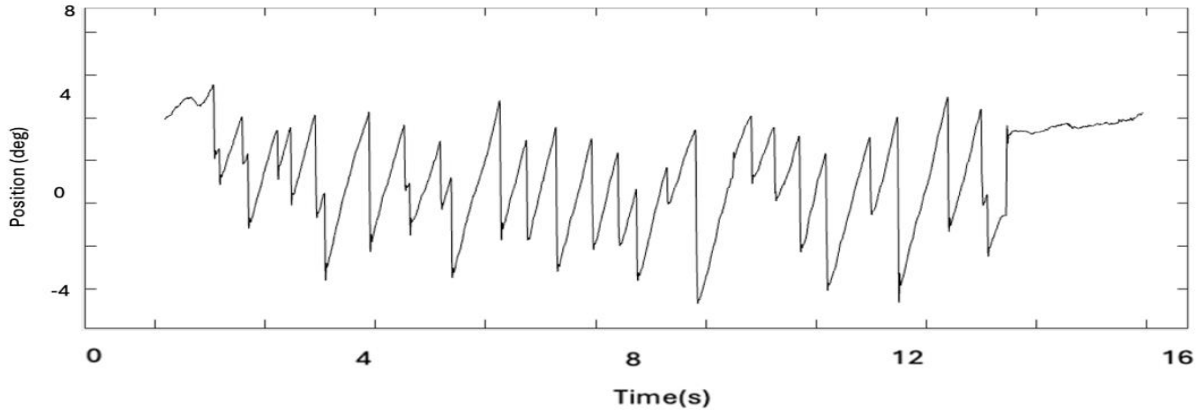
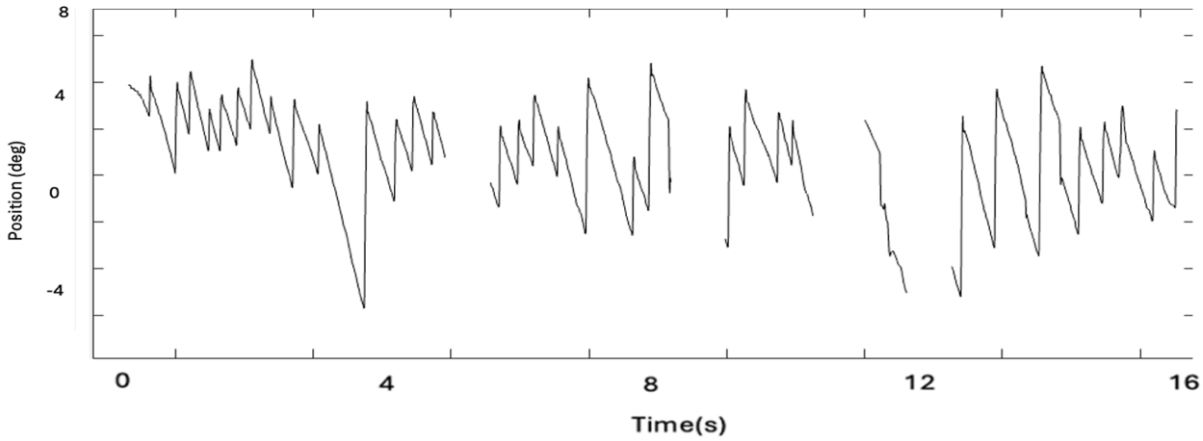


Figure 10. OKN response of the fellow eye of P1 showing a symmetrical response across (A) nasalward and (B) temporalward trials.

A) OKN Response of P5 in Nasalward Direction



B) OKN Response of P5 in Temporalward Direction

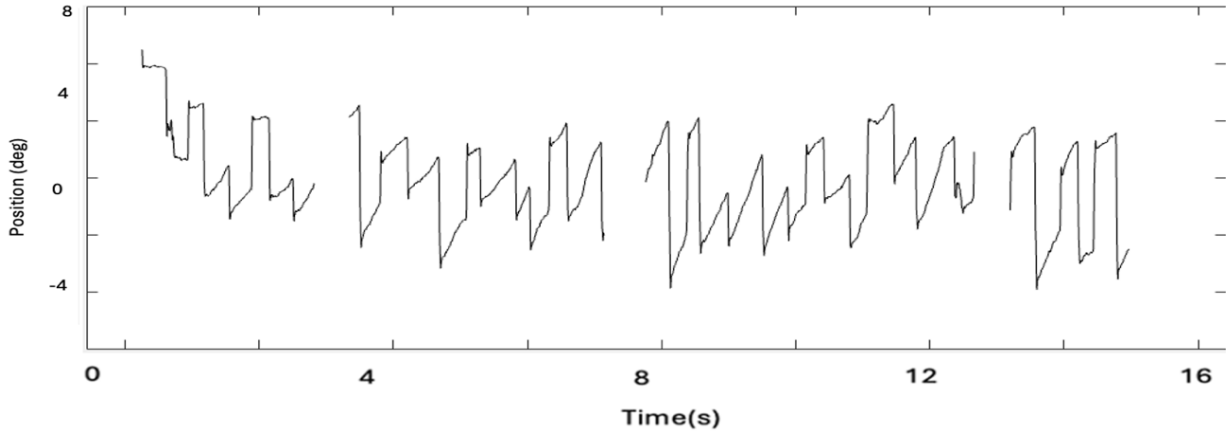


Figure 11. OKN response of the fellow eye of P5 showing an asymmetrical response across (A) nasalward and (B) temporalward trials illustrating a nasalward bias.

Table 6. *Summary of the outcome measures for the 7 patients, along with the group mean and standard deviation (SD)*

	Frequency (cycles/s)		Gain	
	Temporalward	**Nasalward**	**Temporalward**	**Nasalward**
P1	1.7	2.1	0.81	0.89
P2	1.52	2.13	0.66	0.96
P3	0.66	1.2	0.69	0.72
P4	1.53	1.86	0.80	0.84
P5	1.0	1.4	0.72	0.92
P6	1.76	1.86	0.82	0.88
P7	N/A	0.86	N/A	0.88
Mean ± SD	**1.36 ±0.43**	**1.67 ±0.48**	**0.72 ±0.08**	**0.86 ±0.07**

N/A indicated no measurable OKN response was detected.

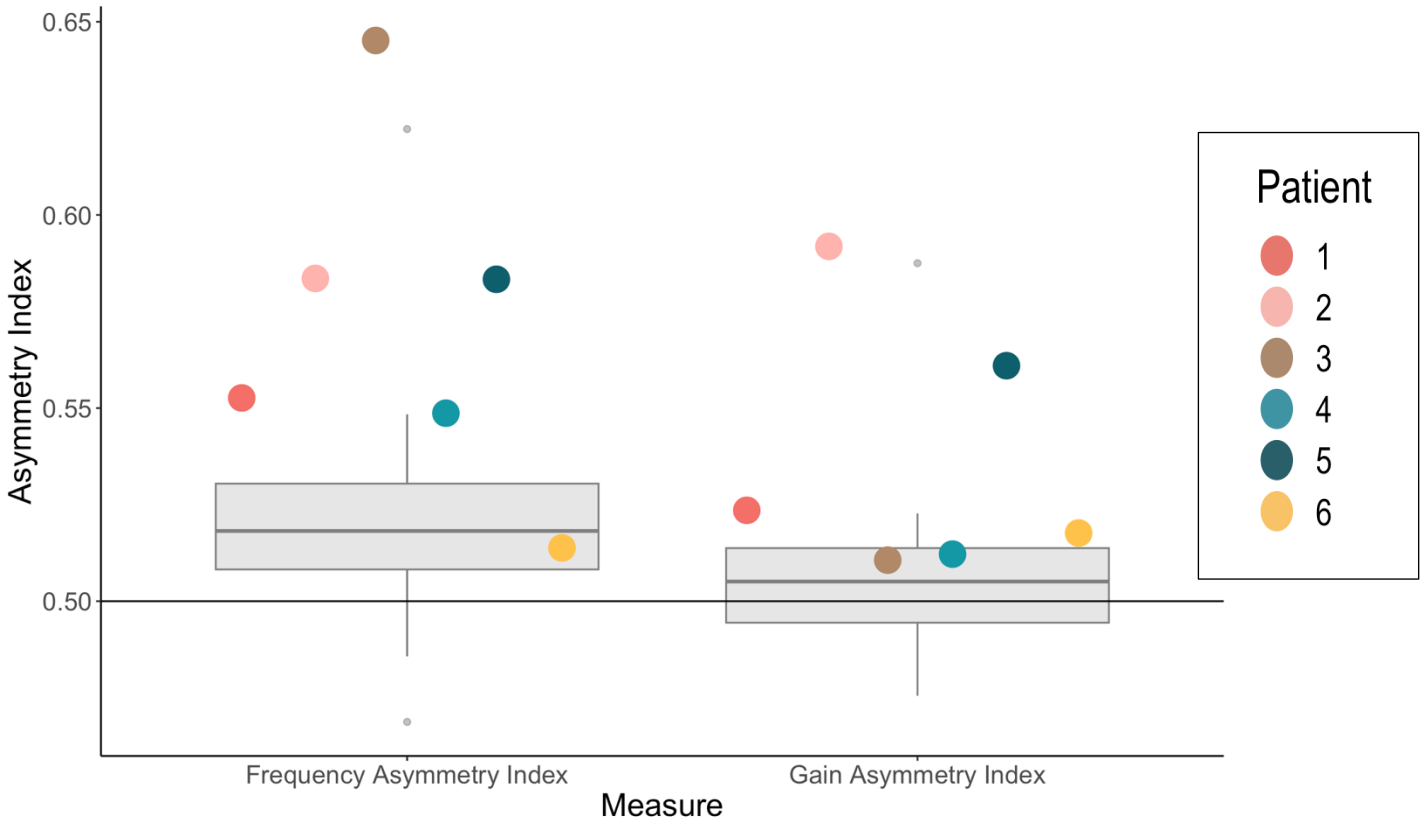


Figure 12. Distribution of the frequency asymmetry index and gain asymmetry index for the control group shown by the boxplot. Each patient has been color coded. P7 has been excluded because this participant exhibited no OKN response in the temporalward direction.

For the control group, the paired t-test revealed that there was no significant difference in gain between the nasalward and temporalward directions; $t_{(17)} = 1.31$, $p = 0.20$. Similarly, there was no significant difference in the nasalward and temporalward directions for frequency; $t_{(17)} = 2.21$, $p = 0.08$.

For the patient group, z-scores were used to assess OKN performance. The gain asymmetry index of four patients fell within one standard deviations of the control group, while two patients were >2 standard deviations away. The frequency asymmetry index for three patients was within one standard deviations of the control group, while two patients were 2

standard deviations away, and P3 was 4 standard deviations away. P7 has been excluded from the asymmetry index plot in Figure 11 because results indicated no reliable OKN response in the temporalward direction. For the nasalward direction, P7 showed a mean gain of 0.88 ± 0.08 and a frequency of 0.86 cycles/s ± 0.09.

4. Discussion

The objective of this thesis was to characterize the effects of unilateral deprivation amblyopia on oculomotor control. More specifically, the study evaluated fixation stability for the fellow and amblyopic eyes across viewing conditions including binocular, open-loop and closed-loop monocular, as well as the OKN response for the fellow eye for motion in the nasalward and temporalward direction. The major findings of this study are as follows: (1) fixation stability in the control group was reduced during the open-loop condition; (2) patients with deprivation amblyopia exhibited a decrease in fixation stability in the amblyopic eye in all viewing conditions; (3) the fixation stability of the fellow eye was dependent on viewing condition; 4) the OKN response was present and symmetrical for four patients. These findings and the implications are discussed in detail below.

Fixation Stability Performance in the Control Group

As expected, the results showed that fixations stability was best during binocular viewing, as indicated by the lowest dispersion (lowest BCEA values). Fixation stability was poorer during closed-loop recording and increasingly worse during open-loop recording (i.e., no visual feedback). The poorer fixation stability during closed loop recording was attributed to an increase in the rate of microsaccades and higher slow drift velocity. The poorer fixation during open-loop recording was attributed to larger amplitude of microsaccades. These results for the control group are comparable to previous literature. For example, Gonzalez et al. (2012) found that fixation stability, measured by BCEA, was best during binocular viewing, poorer during closed-loop monocular viewing, and even worse during the open-loop recording. It was also found that in comparison to binocular viewing, monocular viewing was associated with an increase in microsaccade rate, which is consistent with findings in the current study. Gonzalez et

al. (2012) also analyzed microsaccade amplitude and found that it was similar across binocular and monocular viewing, with an average amplitude of 0.42 +-0.16 deg across controls. The current study also found that microsaccade amplitude was similar across binocular and monocular viewing however, the amplitude was higher when visual feedback was blocked (i.e., open-loop recording). The velocity of slow drifts has not previously been investigated; thus, the current study provides a novel contribution by showing that fixation instability during monocular viewing is due to the increase in slow drift velocity in both, open- and closed-loop viewing conditions.

The phenomenon where binocular viewing is superior to monocular viewing across a range of visual tasks has been well documented in the literature (Blake & Fox, 1973). This is known as binocular summation and the benefit of utilizing both eyes as opposed to just one has been explained by probability summation (Pineles et al., 2013) and/or neural summation (Chino et al., 1994). Probability summation claims that each eye operates independently, and the visual system combines information from both eyes statistically, producing more reliable signals, while neural summation claims that binocular vision exceeds probability summation through the integration of signals from both eyes at the neural level. It is important to note that binocular summation decreases when there is an increase in the interocular difference in visual acuity (Martino et al., 2021). The difference in fixation stability during closed- and open-loop viewing helps to understand the effectiveness of visual feedback, and the idea of there being fixation control signals being received form the viewing eye. During the open-loop condition when the eye did not have visual feedback, fixation stability was reduced as shown by a significant increase in microsacccade amplitude. In contrast, in a closed-loop condition, visual feedback was used by the oculomotor system to improve the accuracy and stability of fixation. Now that

fixation stability in the control population has been established, the next section will discuss the results of the patient group.

Overall Fixation Stability Performance in the Patient Group

The amblyopic eye under binocular viewing exhibited an increase in dispersion in all the patients (only 4 patients had usable results for this viewing condition). This increase in dispersion can be explained by an increase in the microsaccade amplitude and ocular slow drift velocity. Contrary to this, the fellow eye under binocular viewing had similar dispersion to the control group for three patients, which was attributed to a similar microsaccade amplitude, microsaccade rate, and slow drift velocity. Another patient had similar dispersion to the control group, however, exhibited higher amplitude microsaccades. In addition to this, the fellow eye of one patient exhibited a manifest nystagmus that increased the dispersion, microsaccade amplitude, and slow drift velocities beyond the range of the control data.

The amblyopic eye under closed-loop viewing exhibited an increase in dispersion in comparison to the control group. For three patients, there was an increase in slow drift velocity and microsaccade amplitude that contributed to the increase in dispersion and poorer fixation stability. For two patients, it was the presence of a horizontal square wave jerk that increased dispersion by increasing the microsaccade rate, microsaccade amplitude and slow drift velocity. Finally, two patients showed the FMNS response that increased the fixation dispersion by increasing the microsaccade amplitude, microsaccade rate, and slow drift velocity. The fellow eye of four patients under closed-loop viewing exhibited similar dispersion to the controls. This similar dispersion was attributed to similar microsaccade amplitude, microsaccade rate and slow drift velocity. Contrary to this, the fellow eye of one patient exhibited increased dispersion due to

large amplitude microsaccades, and the fellow eye of one other patient had increased dispersion due to a FMNS response.

The amblyopic eye under open-loop viewing exhibited an increase in dispersion in comparison to the control group. This increase in dispersion was attributed to an increase in slow drift velocity and microsaccade amplitude for four patients. The fellow eye under open-loop viewing performed similarly to the control group for two patients, while two patients had an increase in dispersion because of an increase in microsaccade rate, microsaccade amplitude and slow drift velocity due to horizontal square wave jerks. In addition to this, two participants also had an increase in dispersion due to an increase in microsaccade rate, microsaccade amplitude and slow drift velocity because of FMNS.

In summary, it was clear that the amblyopic eye exhibited poorer fixation stability across viewing conditions, while the fellow eye's fixation stability was dependent on the viewing conditions and the characteristics of that patient. The next section will discuss the broader implications of these findings.

Under binocular and closed-loop viewing, the amblyopic eye's poorer performance in comparison to the fellow eye and controls can be attributed to the increase in random internal noise within the visual system. It has been shown that patients with amblyopia exhibit increased positional uncertainty and random internal noise (Levi et al., 2008) (Levi et al., 1987). Due to visual deprivation during the critical period, the development of the visual system has been disrupted leading to reduced visual function. The visual signal from the amblyopic eye may exhibit abnormal sensory processing, which can include variability in neural firing patterns in response to visual stimuli (Levi et al., 2008) (Levi et al., 1987). The increase in noise can increase the variability in the neural signals being generated, making it more difficult to localize

the target and thus impacting oculomotor control. In addition to this, previous studies have shown a correlation between visual acuity and fixation stability (Chung et al., 2015). The amblyopic eye of the patients in the current study had very poor visual acuity, making this another factor that may have made it more difficult for the eye to localize the target resulting in reduced fixation stability.

Another factor that impacted fixation stability in the amblyopic eye during closed-loop viewing was the FMNS and the horizontal square wave jerk. FMNS presents in patients who lack binocular fusion. The FMNS caused large increases in microsaccade amplitude, microsaccade rate and slow drift velocity in 2 patients in this study. Based on the Worth 4 dot test, both patients exhibiting FMNS also suppressed their amblyopic eye during clinical assessment. The horizontal square wave jerk is an involuntary, horizontal, saccadic intrusion that can occur during fixation, typically consisting of a saccade away from a target, and then a saccade back towards the target after approximately 100-300 ms (Phillipou et al., 2014). This eye movement resulted in higher amplitude microsaccades and increased slow drift velocities for both patients that exhibited it. In summary, during binocular and closed-loop viewing, the amblyopic eye's inferior performance could be linked to an increase in random internal noise, disrupted visual system development and reduced visual acuity, while factors such as FMNS and horizontal square wave jerk further impact fixation stability.

The relatively preserved fixation stability of the fellow eye during binocular and closed-loop viewing can be attributed to its normal visual acuity. Thus, the fellow eye is able to better localize the target and fixate on it with less dispersion or uncertainty. The manifest nystagmus of the fellow eye of P7 increased all dispersion measures, decreasing fixation stability, while P4 did have slightly more dispersion than controls due to high amplitude microsaccades.

Under open-loop viewing, the poorer performance of the fellow eye can be attributed to poor visual signals being received form the amblyopic eye. Careful examination of the eye position results revealed that the fellow eye was exhibiting similar fixational eye movements as the viewing eye (amblyopic eye). For example, when the patient's amblyopic eye under closed-loop viewing exhibited an FMNS or a square wave jerk, the fellow eye under open-loop viewing showed a similar pattern. This informs us that there is some level of communication between the two eyes, which was not seen during binocular and closed-loop viewing when the fixation stability of the fellow eye greatly exceeded the amblyopic eye. This communication can be influenced by retinal or extraretinal feedback (Ostendorf et al., 2015). As mentioned earlier, the amblyopic eye during closed-loop viewing had poor fixation stability due to the random internal noise and poor visual acuity. This means that the retinal feedback is compromised in the amblyopic eye, and this signal cannot be used to influence the fixation stability of the fellow eye. Extraretinal feedback, in the form of an efference copy could also influence the responses in the fellow eye. The efference copy is an internal copy of motor innervation and can provide extraretinal signals about voluntary and involuntary eye movements, including saccades and nystagmus (Bridgeman, 1995). It can be speculated that the efference copy from the amblyopic eye is being used to influence the position of the fellow eye, which is resulting in the fellow eye under open-loop exhibiting similar eye movements to the amblyopic eye under closed-loop viewing. The amblyopic eye under open-loop viewing had poorer fixation stability than the control group, however, contrary to what we saw in the fellow eye under open-loop viewing, it did not exhibit similar fixational eye movements to the viewing eye (fellow eye). It has previously been proposed that the contribution of fixation signals from the fellow eye to the amblyopic eye is not as strong in comparison to those with normal binocular vision (Gonzalez et

al., 2012). Therefore, it can be speculated that sensorimotor integration between the two eyes may not have developed normally resulting in poorer fixation signals. All of the participants in this study showed no measurable stereopsis or fusion, which may be further indicative of limited communication between the fellow eye to the amblyopic eye.

The fixation stability performance and characteristics across viewing conditions indicate that amblyopia is not only associated with sensory deficits, but it also impacts oculomotor control. Overall, this study showed that fixation stability in individuals with unilateral deprivation amblyopia is more disperse and has poorer fixation stability due to an increase in the velocity of slow drifts in the amblyopic eye, however, the fellow eye's performance was dependent on viewing condition. There were cases of increased microsaccade amplitudes, however, these cases were due to additional deficits, such as the presence of FMNS, a manifest nystagmus, or a horizontal square wave jerk.

OKN Performance in Controls

Previous literature has shown that healthy adults exhibit a symmetrical OKN response to nasalward and temporalward stimulus motion (Knapp et al., 2008). This means that the symmetrical horizontal index for the gain is close to 0.5. The control participants in this study generally exhibited a symmetrical OKN response in terms of the frequency and the gain. Previous literature has shown that an asymmetric OKN response is linked to abnormal development of binocular vision (Westall et al., 1989). Participants in this study had stereopsis, therefore, they exhibited a symmetrical OKN response with a similar gain for the nasalward and temporalward directions.

OKN Performance in Patients

The OKN asymmetry index for frequency and gain varied across the seven patients. Since gain is the commonly used method to describe OKN asymmetry response, this measure will be prioritized when determining which participants had an asymmetric response.

Deprivation amblyopia disrupts visual development which is associated with loss of acuity and binocularity. Processing of motion in the temporalward direction has been suggested to activate the visual pathway which projects ipsilaterally to the NOT via the binocular cortical neurons (Braddick, 1961). If binocular cortical neurons are disrupted in cases of unilateral deprivation at birth, it was hypothesized that there would be no response in the temporalward direction. Thus, it was surprising that four out of the seven patients in this current study exhibited a symmetric OKN response, which is in contrast to the results from Lewis et al. (1986). Results from one patient supported the hypothesis of there not being a response in the temporalward direction, and two patients had a lower gain for temporalward in comparison to the nasalward response. Such results are consistent with Westall et al. (1989) who investigated OKN in other types of amblyopia and found a nasalward bias, but there was still a response in the temporalward direction.

Despite the strong links between binocularity and symmetrical OKN in previous studies, the OKN results indicates that the pathway supporting neural processing of motion in the temporalward direction may only be partially dependent on binocular neurons. This allows for a speculation that there may be additional compensatory mechanisms, and OKN may rely on a distributed network of neurons spanning both cortical and subcortical regions. For example, in other types of amblyopia, such as in strabismus, in addition to the OKN asymmetry, there is also a marked asymmetry for the smooth pursuit eye movements (Braddick, 1996). Based on this information, Tyschen & Lisberger. (1986) have proposed that the asymmetry is not only due to

the lack of development of the oculomotor pathway but may also be related to basic mechanisms of motion processing in the cortex (Tychsen & Lisberger, 1986). Therefore, it could be proposed that although the patients in the current study had deficits in the oculomotor pathway for the temporalward response (due to limited binocular fusion), compensatory mechanisms may be present in the middle temporal or medial superior temporal area, which contain directionally sensitive neurons that could support an adequate response to a temporalward stimulus.

In summary, the patients in this study produced a range of OKN responses. Further investigation is needed to gain a better understanding for what compensatory mechanisms may develop in individuals with deprivation amblyopia to allow for a symmetrical OKN response without binocular fusion.

4.1 Limitations

Although this study has shed light on the effect of unilateral deprivation amblyopia on oculomotor control, there are some limitations related to the resources available and the methodology. This study encountered limitations related to sample size, heterogeneity within the patient population, and technical challenges with eye tracking.

The small sample size of patient participants (n = 7) is the main limitation in this study. Due to the lack of access to interested patients and given the fact that unilateral deprivation amblyopia is a rare condition, it was difficult to schedule more patients. A small sample size may mean that the results from this study may not accurately measure characteristics of the broader population undermining the external validity of the results. In addition, all individual patients with unilateral deprivation amblyopia had poor visual acuity in the amblyopic eye; however, they presented with different oculomotor problems such as FMNS or strabismus. This makes it even

more important to have more patients presenting with a variety of signs to get a better understanding of oculomotor control in this patient population.

Second, due to technical difficulties with calibrating patients with unilateral deprivation amblyopia with the eye tracking device, some viewing conditions for individual patients could not be recorded. For example, two patients presented with manifest strabismus during the binocular viewing condition, which made it difficult to track the deviated eye during binocular viewing (i.e., it was outside the range of the eye tracker recording). This sparse data may affect the conclusion drawn by limiting the generalizability and introducing uncertainty.

A limitation of the OKN procedure was that the amblyopic eye viewing data were removed from the experiment. Upon visual inspection of the amblyopic eye viewing data, it was unclear whether some patients lacked an OKN response in both the temporalward and nasalward directions because of pathological reasons or because their poor visual acuity was a limiting factor. In a future study, it would be beneficial to move the stripes closer to the patient to ensure that visual acuity does not limit their ability to respond to the stimulus.

This study encountered limitations related to sample size, heterogeneity within the patient population, and technical challenges with eye tracking. Addressing these limitations in the future endeavours is crucial for advancing our understanding of oculomotor control in patients with unilateral deprivation amblyopia and improving patient care.

5. Conclusion

Understanding oculomotor abnormalities in deprivation amblyopia is crucial for developing targeted interventions to improve visual function and quality of life in affected individuals. The observed patterns of fixation instability, abnormal microsaccade characteristics, and variability in slow drift velocity highlights the complex interplay between sensory and motor aspects of amblyopia. The OKN component of this investigation has provided insight into neuroplasticity and the presence of compensatory mechanisms. Further research needs to be done into the OKN response in this population to better understand what additional mechanisms could be driving the response in the temporalward direction in patients who lack binocular fusion. In addition, this study may have uncovered signs of hidden binocularity, such as a symmetrical OKN response that prioritizes the need for future investigations into this population to better understand the neural circuitry and neuroplasticity that results from visual deprivation at birth. Future research exploring the underlying mechanisms driving this oculomotor behaviour may lead to novel therapeutic approaches aimed at optimizing visual outcomes in amblyopic patients.

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